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Estimation of GFR using β-trace protein in children

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Estimation of GFR Using β-Trace Protein in Children

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Abstract

Background and objectives Sex may affect the performance of small molecular weight proteins as markers of GFR because of differences in fat mass between the two sexes. The hypothesis was that the diagnostic performance of β-trace protein, a novel marker of GFR, would be significantly better in boys than in girls.

Design, setting, participants, & measurements GFR, height, weight, serum creatinine, and β-trace protein were measured in 755 children and adolescents (331 girls) undergoing ^{99}technetium diethylenetriamine penta–acetic acid renal scans from July of 1999 to July of 2006. Boys and girls were separated into formula generation cohorts (284 boys and 220 girls) and formula validation cohorts (140 boys and 111 girls). GFR-estimating formulas on the basis of β-trace protein, creatinine, and height were derived using stepwise linear regression analysis of log-transformed data. The slope of the regression lines of the sex-specific eGFRs were compared. Bland–Altman analysis was used for testing agreement between ^{99}technetium diethylenetriamine penta–acetic acid GFR and calculated GFR both with this equation in boys and girls as well as previously established Benlamri, White, and Schwartz formulas.

Results In the stepwise regression analysis, β-trace protein (R^2=0.73 for boys and R^2=0.65 for girls) was more important than creatinine (which increased R^2 to 0.81 for boys and R^2 to 0.75 for girls) and height (which increased R^2 to 0.88 for boys and R^2 to 0.80 for girls) in the data generation groups. GFR can be calculated using the following formulas:

$$GFR_{boys} = 10^{\left(2.824 - 0.461 \times \log BTP\left[\frac{mg}{L}\right] - 0.679 \times \log\left[88.4 \times Cr\left[\frac{mg}{L}\right]\right] + 0.00259 \times \text{height[cm]}\right)}$$

and

$$GFR_{girls} = 10^{\left(2.772 - 0.433 \times \log BTP\left[\frac{mg}{L}\right] - 0.661 \times \log\left[88.4 \times Cr\left[\frac{mg}{L}\right]\right] + 0.00256 \times \text{height[cm]}\right)}.$$

Bland–Altman analysis showed better performance in boys than in girls. The new formulas performed significantly better than the previous Benlamri, White, and Schwartz formulas with respect to bias, precision, and accuracy.

Conclusions Improved and sex-specific formulas for the estimation of GFR in children on the basis of β-trace protein, serum creatinine, and height are now available.

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Introduction

Although measuring inulin clearance is the gold standard surrogate for GFR, an important marker of renal function (1), it is a time-consuming and complex procedure requiring a bolus injection, continuous infusion, repetitive blood sampling, and meticulously timed urine collection (2). Consequently, nuclear medicine tests, such as the ^{99m}technetium diethylenetriamine penta–acetic acid (^{99m}Tc DTPA) renal scan, are often used to measure GFR (3), although these pose other drawbacks, because they are cumbersome, are invasive, and expose patients to radiation (2). Endogenous markers for estimating GFR, such as serum creatinine (Cr), cystatin C (CysC), and β-trace protein (BTP), carry no radiation risk but can be imprecise (4–8). Of these, Cr is the most commonly used marker in clinical practice, but the significant influence of muscle mass (9) on this marker results in substantial interpatient variability (10). Cr-based formulas, such as the Modification of Diet in Renal Disease (11) and the CKD Epidemiology Collaboration (12) equations, have compensated for this limitation by accounting for age and sex. However, these formulas were generated using data from patients older than 18 years of age and have not been validated in pediatric populations (13). Although the Cr-based Schwartz formula (14) was specifically derived for pediatric populations, researchers have been investigating alternative

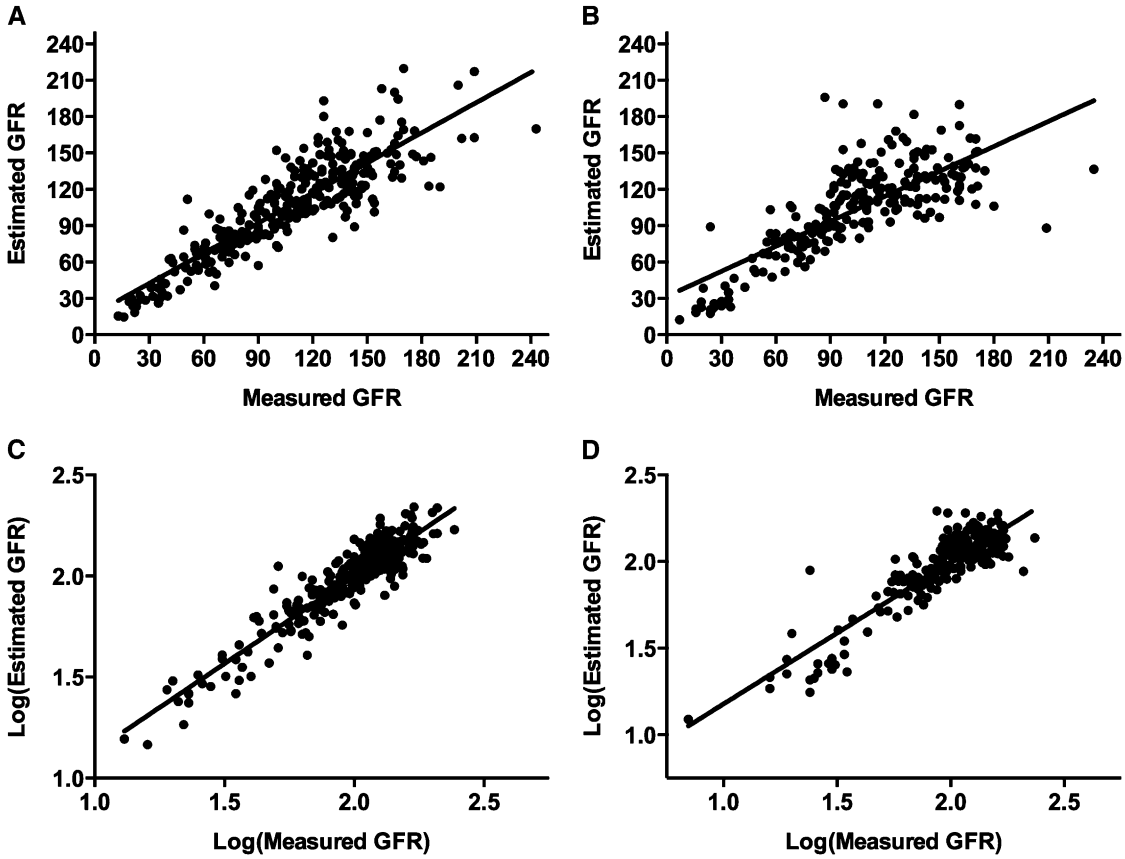

Figure 1. | Scatter plots of estimated versus measured GFR in girls and boys. The original data for eGFR versus measured GFR is shown in the upper panels (A and B), whereas the log-transformed data is depicted in the lower panels (C and D) for the total study population. Scatter plots for all boys are shown in the left panels (A and C), and scatter plots for all girls are shown in the right panels (B and D). Linear regression lines have been included. GFR was measured in milliliters per minute per 1.73 m^2.

endogenous markers, because the formula tends to overestimate GFR in patients with advanced CKD (15).

BTP, a 23- to 29-kD enzyme (16) consisting of 168 amino acids (17), is a promising new marker of renal function. Because its concentration seems to be independent of age, it forms an attractive alternative to Cr in pediatric populations (5). BTP is also reportedly more sensitive in detecting impaired GFR than Cr in this population (5,18). However, the effect of sex on BTP remains controversial (6,19,20). Although little is known about the volume of distribution of BTP in the body, a pharmacokinetic study of recombinant human BTP in canines found evidence to suggest that BTP is distributed in plasma (21). Noting the relationship between lean body mass and plasma volume (22) and differences in the proportions of lean body mass between boys and girls (23), we hypothesized that sex would influence BTP. The purposes of our study were to investigate if sex affects BTP and if so, develop new formulas to calculate GFR in boys and girls on the basis of our BTP measurements.

Materials and Methods

Study Population

The study adhered to the Declaration of Helsinki. The Children's Hospital of Eastern Ontario Institutional Review Board provided approval for both the previously published studies (20,24,25) and a *post hoc* analysis of the data from the initial study. Written consent was obtained for every patient. We performed a *post hoc* analysis on the complete set of data obtained from 755 pediatric patients between 24 months and 18 years of age (331 girls [43.8%]; median age=11.3 years; age range=2–17.9 years) with various renal pathologies referred for a nuclear medicine scan to measure GFR between July of 1999 and July of 2006 at a single institution. We excluded patients outside of the specified age range and those with incomplete data.

Experimental Methods

Patients underwent a ^{99m}Tc DTPA GFR scan with a three-point sampling approach at 2, 3, and 4 hours postinjection according to the work by Russell (26). Height, weight, serum Cr, and BTP were recorded for all patients. BSA was calculated according to the Haycock formula (27), and ^{99m}Tc DTPA GFR was normalized to a BSA of 1.73 m^2. Specifics regarding the enzymatic assay used to measure Cr (Ortho Clinical Diagnostics) and the methods used to determine nuclear GFR and BTP (Siemens Health Care) are described in a previous publication (5).

To investigate the effect of sex on BTP, study participants were divided into two groups: boys and girls. Patients within each group were ranked according to ^{99m}Tc DTPA-derived GFR. Starting with the first record, measurements

from every third record were used for the data validation cohort; remaining records were used for the data generation cohort. As a result, two thirds of the patients from each sex were used to generate the formulas, and one third of the patients from each sex were used to validate the formulas, with a similar distribution of GFR in both subgroups.

To evaluate our eGFR formulas, we calculated the correlation, bias, precision, and accuracy of the formulas with respect to ^{99m}Tc DTPA GFR for both sexes and in both groups. To compare our equations with existing formulas, eGFR was calculated using the Benlamri (20), White (19), and updated Schwartz (28) equations as follows:

$$GFR_{Benlamri} = 10^{\left(1.902+\left(0.9515\times\log\left(\frac{1}{BTP}\right)\right)\right)}$$

$$GFR_{White} = 167.8\times BTP^{-0.758}\times Cr^{-0.204}$$

$$(\times 0.871 \text{ if patient is a girl})$$

$$GFR_{Schwartz} = 41.6\left[\frac{\text{height}}{Cr}\right]^{0.599}\times\left[\frac{1.8}{CysC}\right]^{0.317}$$

Of note, the units for Cr are milligrams per deciliter in the Schwartz (28) formula and micromoles per liter in the White (19) formula, height was measured in meters, and BTP was measured in milligrams per liter. Bias, precision, and accuracy of the three formulas were compared, which was recommended by the National Kidney Foundation (29). Bias is the mean difference between ^{99m}Tc DTPA GFR and eGFR, whereas relative bias is the mean percentage difference. Relative bias is calculated by finding the mean of 100%(eGFR−^{99m}Tc DTPA GFR)/GFR_{AVE}, where GFR_{AVE} is the mean of eGFR and ^{99m}Tc DTPA GFR. The SD of the bias was used as a marker for precision, where an increase in SD represented a decrease in precision. Relative SD is the SD of relative bias. Finally, accuracy is the percentage of eGFR values within 10% and within 30% of the respective ^{99m}Tc DTPA GFR measurements.

Statistical Analyses

Simple descriptive statistics were used wherever possible. Contiguous data were tested for normal distribution using the Shapiro–Wilk normality test. Parametric methods were used to assess normally distributed data (mean, SD, unpaired *t* test, and Pearson coefficient); otherwise, nonparametric methods were applied (median, range, Mann–Whitney *t* test, and Spearman coefficient). We used stepwise linear regression analysis on log-transformed data with an inclusion criterion of P value ≤0.05 and an exclusion criterion of P value ≥0.20 to generate the GFR models. Log-transformed data were used, because although both datasets were non-normally distributed, the relationship of the log-transformed data was more linear (Figure 1). Bland–Altman analysis was used to assess agreement between the nuclear-measured GFR and the eGFR (on the basis of our equation). Analysis of covariance was used to assess whether BTP was affected by sex after accounting for GFR. P values <0.05 were considered statistically significant. GraphPad Prism Software for Science, Version 5.0c (San Diego, CA) and SPSS for Mac, Version 21.0 (International Business Corporation Inc., Amonk, NY) were used for all statistical analyses.

Results

Patient Demographics

All girls participating in the study had the following underlying diagnoses: congenital anomaly of the kidneys and urinary tract (CAKUT; 23%), GN (21%), renal hypodysplasia/dysplasia (10%), hereditary nephropathy (9%), spina bifida (8%), cancer survivor (7%), urinary tract infection (4%), transplant recipient (4%), tubulopathy (4%), diabetic nephropathy (4%), AKI (2%), and other (2%). All boys had the following underlying diagnoses: CAKUT (20%), GN (16%), renal hypodysplasia/dysplasia (21%), hereditary nephropathy (14%), spina bifida (3%), cancer survivor (3%), urinary tract infection (1%), transplant recipient (8%), tubulopathy (2%), diabetic nephropathy (3%), AKI (1%), and other (8%). As expected, boys and girls significantly differed in their underlying diagnoses as a result of the high prevalence of congenital renal anomalies (composed of CAKUT and hypodysplasia/dysplasia) in boys (P<0.001, chi-squared test). The median age of patients was 11.3 years (range=2–17.9 years), median height was 142 cm (range=75–193 cm), median weight was 38 kg (range=10–120 kg), median ^{99m}Tc DTPA GFR was 110 ml/min per 1.73 m^2 (range=7–243 ml/min per

Table 1. Demographic information

Parameter	Boys		Girls	
	Data Generation (n=284)	Data Validation (n=140)	Data Generation (n=220)	Data Validation (n=111)
Age (yr)	11.2 (2.0–17.8)	11.3 (2.0–17.9)	11.4 (2.2–17.9)	11.7 (2.3–17.9)
Height (cm)	140 (75–189)	138 (75–193)	147 (78–172)	148 (82–176)
Weight (kg)	37 (10–120)	35 (10–87)	41 (10–100)	43 (11–94)
GFR (ml/min per 1.73 m^2)	111 (13–243)	111 (13–209)	108 (7–235)	107 (7–209)
Creatinine (mg/L)	0.71 (0.19–3.91)	0.66 (0.27–3.19)	0.63 (0.21–6.00)	0.62 (0.16–6.00)
β-Trace protein (mg/L)	0.80 (0.34–4.47)	0.84 (0.35–4.21)	0.74 (0.27–5.56)	0.79 (0.24–5.56)

There was no statistically significant difference between the data generation and data validation groups in boys or girls for any of the above parameters (data not shown).

Table 2. Bland–Altman analysis for the agreement of measured ^{99m}technetium diethylenetriamine penta–acetic acid GFR and the β-trace protein eGFR in four subgroups

Subgroup	Bias	SD of Bias	Relative Bias (%)	Relative SD of Bias (%)	95% Confidence Interval	Accuracy (%)	
						10%	30%
Boys: data generation	−1.2	19.9	0.003	17.6	−40.3 to37.9	44.0	90.5
Boys: data validation	−0.4	21.5	0.8	19.9	−42.4 to 41.7	37.9	88.6
Girls: data generation	−2.1	25.8	−0.01	22.6	−52.8 to 48.5	36.8	87.7
Girls: data validation	−0.6	25.8	0.4	24.8	−59.2 to 58.1	33.3	80.2

Accuracy is the percentage of values within 10% or 30%. Bias, SD of bias, and 95% confidence interval are shown in milliliters per minute per 1.73 m^2.

1.73 m^2), median Cr level was 0.67 mg/L (range=0.16–6.00 mg/L), and median BTP level was 0.79 mg/L (range=0.24–5.56 mg/L). Patient demographic information for boys and girls in data generation and data validation groups is summarized in Table 1.

Effect of Sex

Analysis of covariance revealed a significant effect of sex on logBTP after controlling for the effect of logGFR (P=0.001). The 95% confidence interval of the difference in logBTP between boys and girls (corrected for logGFR) was 0.01 to 0.04. This is compared with the absolute difference between median logBTP in boys and girls, which was 0.030. Sex differences with respect to logBTP led to the creation of separate equations for girls and boys.

The effect of sex on the correlation between GFR and BTP was also assessed after separating children on the basis of age to determine whether puberty affects the relationship between GFR and BTP in boys and girls. In children <13 years of age, the Spearman correlation was r=−0.80

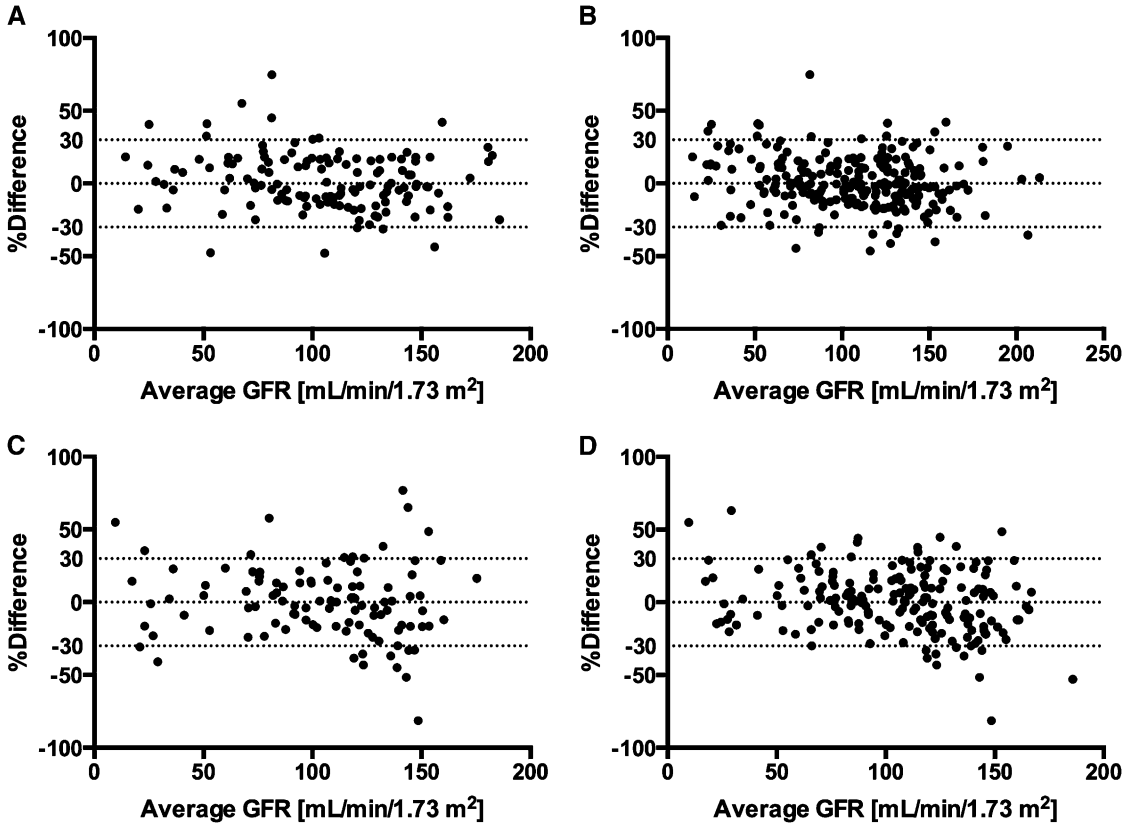

Figure 2. | Relationship between the percentage difference of the eGFR equation and average GFR in boys and girls in both the data generation and validation subgroups. The panels are arranged as follows: data validation group of boys (A), data generation group of boys (B), data validation group of girls (C), and data generation group of girls (D). Percentage difference=(eGFR−measured GFR)/(average GFR)×100. Average GFR=(measured GFR + eGFR)/2. Dotted lines are used to visualize which values are within 30% of measured GFR. The greater the number of values within the lines, the more accurate the equation.

($P<0.001$) in boys and $r=-0.74$ ($P<0.001$) in girls. In those 13 years old and older, the Spearman correlation between GFR and BTP was $r=-0.79$ ($P<0.001$) in boys and $r=-0.73$ ($P<0.001$) in girls.

Formula Generation

We used a previously proposed modeling method (19,20,30) with log-log transformation of both parameters to generate the formulas used to estimate GFR. In the stepwise regression analysis of the data generation groups, the model using logBTP alone had a coefficient of determination (R^2) of 0.73 for boys and 0.65 for girls. The R^2 was increased to 0.81 for boys and 0.75 for girls when logCr was added to the model. The addition of height further increased R^2 to 0.88 for boys and 0.80 for girls in the data generation cohort.

Stepwise multivariate regression analysis using logGFR as the dependent variable and logBTP, logCr, and height as the independent variables generated the following equations:

$$GFR_{boys} = 10^{(2.824 - 0.461 \times \log BTP - 0.679 \times \log(88.4 \times Cr) + 0.00259 \times \text{height})},$$

and

$$GFR_{girls} = 10^{(2.772 - 0.433 \times \log BTP - 0.661 \times \log(88.4 \times Cr) + 0.00256 \times \text{height})}.$$

The GFR models were expressed in original units (milliliters per minute per 1.73 m^2) to aid in interpretation. In the formulas, BTP is expressed in milligrams per liter, Cr is expressed in milligrams per deciliter, and height is expressed in centimeters.

Formula Evaluation

Figure 1 depicts the relationship between our eGFR and measured ^{99m}Tc DTPA GFR for boys and girls for both the raw and log-transformed data in our total study population. Boys had a higher value of R^2 than girls (0.77 compared with 0.59 for raw data and 0.86 compared with 0.80 for log-transformed data in the total study group).

The results of the Bland–Altman analysis for the data generation and data validation groups in both boys and girls are summarized in Table 2. The Bland–Altman plots depicting the accuracy of each group are shown in Figure 2. The equation for boys performed better than the formula for girls in all domains (bias, SD, and accuracy) in both the data generation and validation groups.

Comparison between Formulas

Table 3 summarizes the Bland–Altman analysis for the agreement between measured ^{99m}Tc DTPA GFR and eGFR on the basis of four equations (these formulas as well as the Benlamri [20], White [19], and Schwartz [28] formulas) in the validation groups for both boys and girls. Figure 3 depicts these results graphically. The eGFR equation derived from our study performed better than the Benlamri (20), White (19), and Schwartz (28) equations in all domains (bias, SD, and accuracy) in both boys and girls. In the boys validation group, our equation had a relative bias of 0.83% and a relative SD of 19.94%. Our new formula was very accurate in these boys, with 38% of values within 10% and 89% of values within 30% of measured GFR. In the girls validation group, the relative bias was 0.40%, with a relative SD of 24.76%. With respect to the accuracy of the equation in these girls, 33% of values were within 10% and 80% of values within 30% of measured GFR.

We also investigated the performance of our equation relative to the other three established formulas at GFR values <60 ml/min per 1.73 m^2. Although our equation continued to outperform the Benlamri (20) and White (19) formulas, the Schwartz (28) equation had a more favorable relative bias, SD, and accuracy compared with our equation at this lower GFR range in the data validation group. In boys, our equation had a relative bias of 17.20% and a relative SD of 23.28%, and 73.68% of eGFR values were within 30% of the measured GFR. In contrast, the Schwartz (28) equation had a relative bias of 8.89% and relative SD of 17.49%, and 84.21% of eGFR values were within 30% of the measured GFR. Similarly, in the data validation group of girls, our equation had a relative bias of 5.41% and a relative SD of 28.84%, and 68.75% of eGFR values were within 30% of measured GFR. In the same subgroup, the Schwartz (28) equation had a relative bias of 6.36% and a

Table 3. Bland–Altman analysis for the agreement of measured ^{99m}technetium diethylenetriamine penta–acetic acid GFR and eGFR values from three equations in boys and girls

Equation	Bias	SD of Bias	Relative Bias (%)	Relative SD of Bias (%)	95% Confidence Interval	Accuracy (%)	
						10%	30%
Boys: validation group							
Our formula	−0.4	21.5	0.8	19.9	−42.4 to 41.7	37.9	88.6
Benlamri formula	−9.5	24.8	−6.7	25.5	−58.1 to 39.2	30.7	69.3
White formula	−21.3	22.8	−18.9	23.3	−66.0 to 23.5	24.3	60.0
Schwartz formula	−27.5	25.7	−24.5	23.0	−77.9 to 23.0	14.8	55.6
Girls: validation group							
Our formula	−0.6	25.8	0.4	24.8	−59.2 to 58.1	33.3	80.2
Benlamri formula	0.9	41.3	0.6	31.0	−80.0 to 81.8	26.1	71.2
White formula	−25.6	30.0	−25.7	26.7	−84.4 to 33.1	13.5	44.1
Schwartz formula	−22.4	28.4	−19.2	25.2	−78.1 to 33.3	25.2	62.2

Accuracy is the percentage of values within 10% or 30%. Bias, SD of bias, and 95% confidence interval are shown in milliliters per minute per 1.73 m^2.

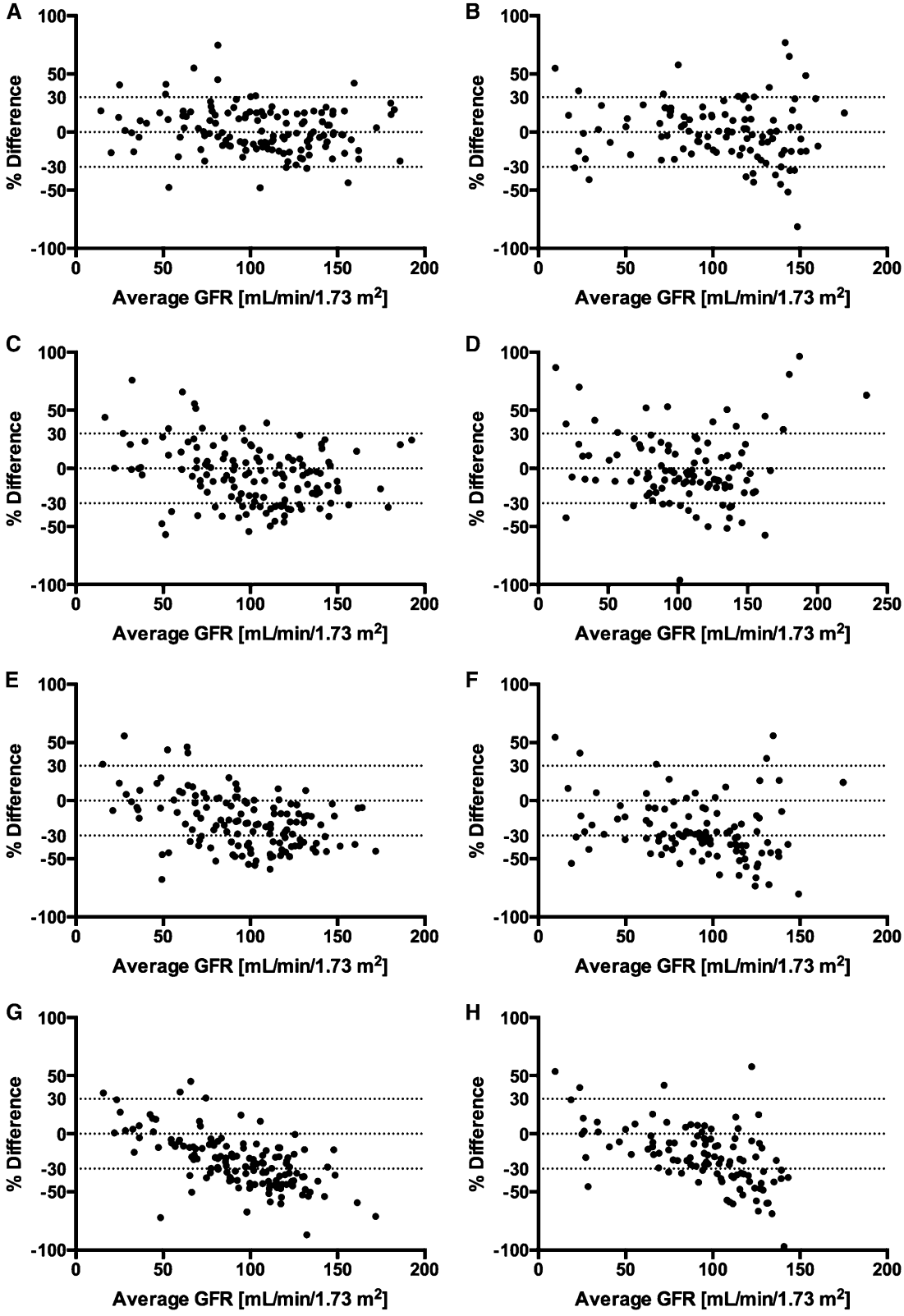

Figure 3. | **Relationship between the percentage difference of the eGFR equations and average GFR in the validation groups.** The data from boys is shown on left (A, C, E, and G) and girls on the right (B, D, F, and H). From top to bottom, the panels are as follows: our current eGFR equation (A and B), the Benlamri equation (C and D), the White equation (E and F), and the Schwartz equation (G and H). Percentage difference=(eGFR−measured GFR)/(average GFR)×100. Average GFR=(measured GFR+eGFR)/2. Dotted lines are used to visualize which values are within 30% difference. The greater the number of values within the lines, the more accurate the equation.

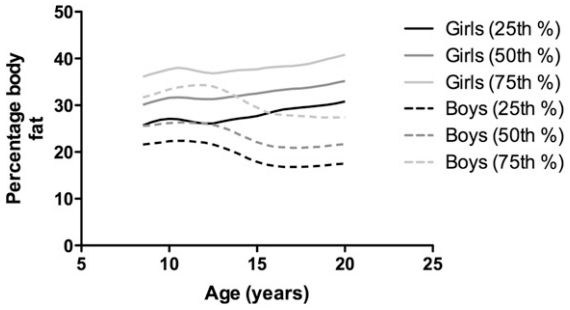

Figure 4. | Percentage body fat by age for boys and girls. The relationship between the percentage body fat in children stratified by sex. Values modified from ref. 23, with permission.

relative SD of 25.49%, and 75.00% of eGFR values were within 30% of measured GFR. Our equation outperformed all other equations in the 60–150 ml/min per 1.73 m^2 GFR range in every domain in both boys and girls in the data validation group, with the exception of improved relative bias with the Benlamri (20) equation compared with our equation in girls (0.87% versus 4.28%).

Discussion

Our study aimed to improve the performance of eGFR methods by developing BTP-based, sex-specific GFR estimates. Our BTP-based formulas for boys and girls performed better than both previously published adult (19) and pediatric (20) BTP equations and the pediatric Cr-based (28) formula using the total data validation cohort. The Cr-based Schwartz formula performed best at GFR levels <60 ml/min per 1.73 m^2.

Although our study found a significant effect of sex on the performance of BTP-based eGFR, existing literature on the topic is conflicting (6,19,20). For example, a pediatric study by Benlamri *et al.* (20) did not find improved performance with sex-specific formulas compared with a single sex-independent formula (20), whereas adult studies showed opposing results (6,19). Of the three studies cited above, only the formula by White *et al.* (19) used a correction factor for girls, whereas the other two did not find a significant improvement in formula performance when accounting for sex (6,20). A previously published article by Filler *et al.* (5) on the basis of the same study as this manuscript also did not find an effect of sex on BTP. Although the same assays were used, there were differences in the age and number of patients. The cutoff age of this analysis was 2 years old, whereas the previous analysis included children as young as 0.2 years of age. The original investigation by Filler *et al.* (5) also consisted of fewer patients (225 children). This analysis was likely better powered to detect the effect of sex on BTP relative to previous studies as a result of its superior sample size of 755 pediatric patients.

To date, few studies have investigated the effect of sex-associated differences in lean body mass in childhood and adolescence on BTP, and little is known about the volume of distribution of BTP. Some evidence suggests that it is distributed in plasma volume (21), which is correlated to lean body mass and therefore, closely related to height (22). The proportion of lean body mass varies between boys and girls in that, on average, girls have higher body fat percentages than their boy counterparts (23). This effect is seen in both pre- and postpubertal children, although the effect is more dramatic in the older age groups (Figure 4) (23). The relationship between BTP and lean body mass may partially explain the poorer performance that we found in the linear regression between nuclear GFR and serum BTP in girls relative to boys. We were, however, surprised to find that the correlation between GFR and BTP differed between the sexes in both upper and lower age groups. Regardless, the decreased performance of GFR-estimating BTP formulas in girls compared with boys was consistent with results from Benlamri *et al.* (20). This observation is in agreement with the better performance of CysC- (31) and Cr-based (11) formulas in boys compared with girls. We believe that indexing GFR to calculated BSA on the basis of height and weight may be suboptimal, because calculated BSA is not closely related to the volumes of distribution of endogenous markers of GFR. We propose indexing GFR to height or extracellular volume instead, because both are more consistent with lean body mass.

Limitations of this study include the use of ^{99m}Tc DTPA to measure GFR rather than inulin, the gold standard. Although nuclear medicine tests replaced inulin clearance worldwide in the 1970s, all nuclear medicine methods use tracers that have some plasma protein binding. This binding is low on average but shows significant variability (32). The results from this study were also formed as part of a *post hoc* analysis of a study that was designed for a different purpose, namely to show the superiority of CysC versus Cr as a surrogate endogenous GFR marker (33). Furthermore, our CysC and BTP measurements were only validated internally, and certified CysC reference materials were not available at that time (34). We were limited in terms of sample size in our subgroup analyses. In particular, the validation group at GFR levels of <60 ml/min per 1.73 m^2 consisted of 16 girls and 19 boys. Additionally, separating patients into those <13 years of age and those ≥13 years of age does not accurately divide children into pre- and postpubertal age groups because of the large intervariability in the onset of puberty. We were also unable to include the updated Schwartz formula that contains BUN, because this information was not collected from our patients (28). However, the updated Schwartz formula that we evaluated is a Cr-based pediatric formula that uses isotope dilution mass spectrometry traceable enzymatic Cr assays and therefore, applicable to our sample. Previous literature has also shown reasonable performance with a coefficient of determination (R^2) of 69.4%, and 84.0% of values were within 30% of measured GFR in pediatric populations (28). Another limitation of our study is the lack of data on race, which has been shown to affect Cr. Finally, there are also limitations to using BTP as a marker of GFR: BTP is costly to measure compared with Cr, and there is a lack of international standardization between BTP measurement techniques across laboratories. These factors may limit the practicality of BTP as a marker of renal function at this time.

A strength of the study is our rigorous adherence to the Russell (26) method when measuring ^{99m}Tc DTPA GFR. Many centers only use two sampling points instead of three and start sampling before the intravascular and extravascular spaces are equilibrated (32). Other strengths of

the study include its large sample size (755 patients), broad age range of pediatric patients (2–17.9 years old), wide variety of renal pathologies, and wide range of GFR values within the cohort. These new estimated BTP GFR formulas are, therefore, generalizable to pediatric patients with various renal pathologies. Another strength of this study is that BTP and Cr were measured on the same day as the ^{99m}Tc DTPA GFR test was performed, reducing confounding factors secondary to intrapatient variability. Finally, this study used a robust method for selecting the data validation group. This group consisted of 251 patients, with no significant differences in demographic characteristics between the generation and validation groups.

In summary, this study provides evidence that either formulas used to calculate GFR on the basis of BTP should include a correction factor for sex or separate sex-specific formulas should be used. Future studies investigating the volume of distribution of BTP and the effect of sex on that volume may help in clarifying the mechanism through which BTP is affected by sex.

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Correction

Witzel SH, Huang SH, Braam B, Filler G. Estimation of GFR using β-trace protein in children. *Clin J Am Soc Nephrol* 10: 401–409, 2015.

Because of author error, incorrect units for creatinine in the formulas appeared within the abstract and Table 1. The units were incorrectly reported as milligrams per liter instead of as milligrams per deciliter. Additionally, the authors did not explicitly indicate that the base for the logarithmic transformation was 10. To circumvent the use of logarithms and provide interpretation to the constant multipliers, the equations should be re-expressed as

$$eGFR_{boys} = 110.04 \times \left(\frac{BTP\left[\frac{mg}{L}\right]}{0.7}\right)^{-0.461} \times \left(\frac{Cr\left[\frac{mg}{dl}\right]}{0.7}\right)^{-0.679} \times 10^{0.00259 \times (height[cm] - 140)}$$

and

$$eGFR_{girls} = 103.10 \times \left(\frac{BTP\left[\frac{mg}{L}\right]}{0.7}\right)^{-0.433} \times \left(\frac{Cr\left[\frac{mg}{dl}\right]}{0.7}\right)^{-0.661} \times 10^{0.00256 \times (height[cm] - 140)},$$

where for a child with a β-trace protein (BTP) of 0.7 mg/L, a creatinine (Cr) of 0.7 mg/dl, and a height of 140 cm, the eGFR of a boy would be 110.04 ml/min per 1.73 m^2 and the eGFR of a girl would be 103.10 ml/min per 1.73 m^2.

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