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EDITORIAL COMMENTARY

Can the new CKD-EPI BTP-B2M formula be applied in children?

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Abstract Although measuring creatinine to determine kidney function is currently the clinical standard, new markers such as beta-trace protein (BTP) and beta-2-microglobulin (B2M) are being investigated in an effort to measure glomerular filtration rate more accurately. In their recent publication, Inker et al. (Am J Kidney Dis 2015; 67:40–48) explored the use of these two relatively new markers in combination with some commonly available clinical characteristics in a large cohort of adults with chronic kidney disease. Their research led them to develop three formulae using BTP, B2M, and a combination of the two. The combined formula is particularly attractive as it removes all gender bias, which applies to both serum creatinine and cystatin C. Using data from a cohort of 127 pediatric patients from our center, we sought to determine whether these formulae would be equally as effective in children as in adults. Unfortunately, we found that the formulae cannot be applied to the pediatric population.

Keywords Glomerular filtration rate · Beta-trace protein · Beta-2-microglobulin · Chronic kidney disease

Introduction

In a recent edition of the *American Journal of Kidney Diseases*, Inker et al. explore the role of the unconventional endogenous filtration markers beta-trace protein (BTP) and beta-2 microglobulin (B2M) in estimating glomerular filtration rate (GFR) [1]. Using data from 3551 subjects in three large adult populations with chronic kidney disease (CKD), they developed and validated a robust formula to estimate GFR using these biomarkers and commonly available clinical characteristics. Inker et al.'s study [1] carefully adjusted for covariates such as gender, ethnicity, and age. We were particularly interested in the fact that there was no bias induced by gender. There is a significant difference in body fat between the genders during puberty [2]. An adjustment for gender must be made in order to accurately estimate GFR in children when using creatinine [2, 3], cystatin C [4], and BTP [2, 5]. A formula that would be independent of gender would greatly improve the practice of estimating GFR in children. Unfortunately, the mean age of the relatively homogenous patient population in Inker et al.'s study was 54.0 ± 22.7 years, with relatively few young adults and no children. It should be noted that each formula works best in the population type and within the GFR range in which it was generated [6].

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Table 1 Chronic Kidney Disease Epidemiology Collaboration equations for the estimation of glomerular filtration rate based on the endogenous filtration markers beta-trace protein and beta-2 microglobulin alone and in combination

CKD-EPI equations [1]	Formulae
BTP	$GFR = 55 \times BTP^{-0.695} \times 0.998^{age}$ x 0.899 if female
B2M	$GFR = 133 \times B2M^{-0.852}$
BTP-B2M	$GFR = 96 \times BTP^{-0.278} \times B2M^{-0.588}$

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; BTP, beta-trace protein; B2M, beta-2-microglobulin; GFR, glomerular filtration rate

The Inker formulae

To study the usability of the new Inker formulae in children and adolescents, we applied the formulae using a post-hoc analysis of previously published data [7]. A total of 127 pediatric patients with various renal diseases underwent simultaneous measurements of GFR using a ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) renal scan, BTP and B2M, as outlined in our previous publication [7]. The median age was 11.9 [interquartile range (IQR) 8.5–14.9] years and the mean ^{51}Cr-EDTA GFR was 100.6 ± 32.1 ml/min/1.73 m^2, which was significantly higher than that of Inker et al.'s pooled population [1]. GFR distribution was normal (Kolmogorov–Smirnov test) and, as such, a linear regression analysis was used to assess the relationship between the calculated estimated GFR (eGFR) and the measured GFR. The agreement of the various formulae was assessed using the Bland & Altman analysis. All statistical tests were performed using GraphPadPrism 5.0f for Mac (GraphPad Software Inc., La Jolla, CA). The formulae for BTP, B2M and BTP-B2M combined are listed in Table 1.

BTP and B2M were not normally distributed. The median BTP concentration was 0.76 (IQR 0.62–0.98) mg/L, and the median B2M concentration was 1.93 (IQR 1.52–2.69) mg/L. The mean measured ^{51}Cr-EDTA-GFR was 100.6 ± 32.1 ml/min/1.73 m^2 compared to a BTP-eGFR of 61.93 ± 14.11 ml/min/1.73 m^2, a B2M-eGFR of 76.95 ± 31.93 ml/min/1.73 m^2, and a BTP-B2M-eGFR of 70.13 ± 23.52 ml/min/1.73 m^2, whereas the absolute measured GFR was 75.27 ± 31.09 ml/min. As such, the results are only comparable to the absolute (non-adjusted to body surface area) GFR. While all three new eGFR results significantly correlated with the absolute GFR, the Pearson R^2 values were <0.3 (Table 2). Bland & Altman analysis of the unadjusted absolute GFR with the combined BTP-B2M-based eGFR formula revealed a bias of −5.151 ± 27.06 ml/min with a 95 % confidence interval between −58.19 and +47.90 ml/min (Fig. 1).

Conclusions

While the bias of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) BTP-B2M-based eGFR formula was acceptable in this pediatric cohort, small, and similar to that observed in the training and validation cohort, the 95 % confidence interval was unacceptable. However, it is possible that including B2M can reduce the effect of gender. Cystatin C is produced by all nucleated cells in the body with the exception of adipocytes [8]. The volume of distribution of cystatin C is most likely the extracellular volume (ECV), which correlates better with lean body mass than body surface area [9]. While BTP is produced in the coronary arteries (reviewed recently by Filler et al. [10], the differing fat mass between the genders has been shown to affect BTP-based GFR estimates [2]. Its volume of distribution is unknown [10]. B2M is a component of MHC class I molecules, which are present on all nucleated cells. Its volume of distribution is also considered to be the ECV [11], which suggests body fat mass should affect its use in estimating GFR. Interestingly, Inker et al. found that including gender in B2M-based GFR estimation

Table 2 Linear regression analysis of the measured unadjusted glomerular filtration rate for body surface area and the CKD-EPI equations from Table 1

Linear regressio analysis	BTP-GFR	B2M-GFR	BTP-B2M-GFR
Best-fit values			
Slope	0.2371 ± 0.03460	0.4849 ± 0.08067	0.4072 ± 0.05703
Y-intercept when *X* = 0.0	43.53 ± 2.816	40.45 ± 6.566	39.48 ± 4.642
X-intercept when *Y* = 0.0	−183.6	−83.40	−96.96
1/slope	4.217	2.062	2.456
R^2	0.2731	0.2243	0.2897
P value	<0.0001	<0.0001	<0.0001
Deviation from zero?	Significant	Significant	Significant
Data			
Total number of values	127	127	127
Number of missing values	0	0	0

BTP beta trace protein, *B2M* beta-2-microglobulin, *GFR* glomerular filtration rate, *CKD* chronic kidney disease

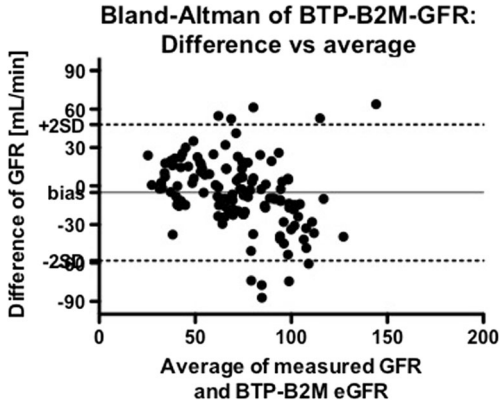

Fig. 1 Bland & Altman analysis of the absolute glomerular filtration rate (*GFR*) (unadjusted for body surface area) of 127 children and adolescents with the new beta trace protein-beta-2 microglobulin-estimated GFR (*BTP-B2M eGFR*) formula by Inker et al. [1]. *SD* Standard deviation

did not improve results. This phenomenon should be subject to additional study. Following our analysis, we conclude that the new CKD-EPI BTP-B2M-based eGFR formula cannot be used in children.

Compliance with ethical standards

Disclosure The authors have no conflicts of interest to disclose.

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