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ORIGINAL ARTICLE

Development of a beta-trace protein based formula for estimation of glomerular filtration rate

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Abstract Beta-trace protein (BTP) is a novel marker of glomerular filtration rate (GFR). To date, no pediatric formula for calculating GFR based on BTP has been developed. We measured GFR, serum creatinine and BTP in 387 children who underwent 474 ^{99m}Tc-diethylene triamine pentaacetic acid renal scans. A BTP-based formula for estimating GFR was derived using stepwise linear regression analysis. A separate control group of 116 measurements in 99 children was used to validate the novel formula. A formula was also developed for each gender. The novel formula is: GFR = 10^(1.902 + (0.9515xLOG(1/BTP))). The Spearman rank correlation coefficient between the BTP-derived GFR estimate and the measured GFR was 0.80 [95% confidence interval (CI) 0.76–0.83], which is substantially better than that derived with the Schwartz formula (r=0.70, 95% CI 0.65–0.74). The Bland–Altman analysis revealed a mean bias of 1.21% [standard deviation (SD) 28%] in the formula development dataset, which was virtually identical to the 1.03% mean bias (29.5% SD) in the validation group and no different from the Schwartz formula bias. The percentage of values within 10% (33.0 vs. 28.3%) and 30% deviation (76.8 vs. 72.6%) were better for BTP-based formula than for the Schwartz formula. Separate formulas according to gender did not perform better than that for the pediatric population. This BTP-based formula was found to estimate GFR with reasonable precision and provided improved accuracy over the Schwartz GFR formula.

Keywords Agreement · Beta-trace protein · Bland–Altman analysis · eGFR · Glomerular filtration rate · Schwartz formula

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Introduction

Inulin clearance forms the gold standard for measuring glomerular filtration rate (GFR). However, due to the lack of availability of inulin, this practice has been replaced by nuclear medicine GFR scans [1]. Although accurate, the latter are expensive and cumbersome, involve radiation exposure, and can only be performed infrequently. Consequently, for frequent monitoring, surrogate markers of GFR have to be utilized [2]. The most commonly used marker of GFR is serum creatinine, although more recently cystatin C (CysC) has been gaining popularity. In children, serum creatinine level varies with muscle mass. To account for this variability, creatinine-based GFR estimates are usually calculated using height/creatinine ratios, as muscle mass correlates very closely with height. The most commonly used formula, the Schwartz formula [3], is hampered by several limitations, including the non-renal elimination of creatinine and the substantial over-estimation of GFR in patients with advanced renal failure [4]. The Schwartz formula also becomes inaccurate in patients with altered muscle mass, such as children with spina bifida [5].

Beta-trace protein (BTP), also known as prostaglandin D synthase, is a 23- to 29-kDa enzyme that has been traditionally used as a marker of cerebrospinal fluid leakage [6, 7]. It is expressed in all tissues except the ovaries [8], and its biological actions include vasodilatation, bronchoconstriction, inhibition of platelet aggregation, and recruitment of inflammatory cells. Beta-trace protein has recently been presented as a promising surrogate marker for the GFR measurement [9, 10]. As BTP is a small molecular weight protein that is freely filtered by the glomerulus, its serum concentration depends on the GFR; consequently, it reflects the GFR status. Preliminary studies have confirmed a good correlation between serum BTP levels and the GFR measurement based on inulin clearance and nuclear medicine methods [10, 11].

As a tool for GFR measurement, BTP has been found to have a few distinct advantages. It has been reported that serum BTP levels do not have a significant relationship with C-reactive protein [12] and that they are unaffected by body composition [11, 13]. During the third trimester of pregnancy, BTP, but not CysC, has been shown to adequately reflect the GFR [14]. Unlike CysC, thyroid function [15] has not been reported to affect the concentration of BTP. Another possible advantage would be the lack of effect of corticosteroid administration on BTP concentrations. However, there is conflicting evidence on this property [16, 17].

In clinical practice, the applicability of a surrogate marker needs an appropriate formula by which to calculate the estimated GFR (eGFR) from a corresponding serum concentration. At the time this manuscript was being prepared, a formula for the estimation of GFR based on serum BTP had been established only in adults [17]. Here, we report on the development and the validation of a novel formula for the estimation of GFR in children based on BTP. We hypothesized that BTP-based GFR estimates would determine the GFR more accurately than serum creatinine measurements or the Schwartz formula.

Subjects and methods

Patients and methods

After obtaining approval from the Institutional Review board, we analyzed 474 nuclear GFR scans in 387 pediatric patients (172 girls, 44.4%; mean age 10.7±7.1 years) with various renal pathologies who had been referred for a nuclear renal scan between July 1999 and September 2002. The data were derived in association with a previously published study [11], which continued to enroll patients after the initial publication. We included patients from the Children's Hospital of Eastern Ontario who underwent a ^{99m} technetium diethylene triamine pentaacetic acid (^{99m}Tc DTPA) GFR scan, with a three-point sampling approach at 2, 3, and 4 h post-injection according to Russell [18]. To ensure a homogenous patient selection in our analysis, we omitted the patients enrolled from Berlin in the previous study. In total, 298 patients were included in the study protocol, with 387 patients available for the generation of the data set. Body surface area was calculated using the Haycock formula [19], and GFR was normalized to a body surface area (BSA) of 1.73 m^2. This set of measurements will be referred to hereafter as the formula generation dataset.

Upon completion of the initial study, BTP became available for routine clinical practice. To validate the formula derived from the generation dataset, one of the authors (RN) retrieved a new dataset based on simultaneously determined serum BTP levels and ^{99m}Tc DTPA renal scans. From the initial list of 264 BTP measurements, we compiled a new validation dataset based on 125 BTP measurements in 103 patients with concomitant nuclear GFR and serum creatinine estimations. The validation group had a similar gender and age distribution as the formula generation dataset (40 females, 38.8%, not significantly different from the formula generation group, p= 0.28, Fisher's exact test; mean gold standard GFR 95.6± 44.6, not significantly different from the formula generation group, p=0.052; mean age 10.3±5.1 years, not significantly different from the original group, p=0.94, unpaired t test), and the validation of the formulas was performed between December 2002 and July 2006.

The methods for the determination of BTP (Dade Behring, Milton Keynes, UK) and creatinine (Ortho Clinical Diagnostics, Tilburg, the Netherlands) have been described in our previous study [11]. The creatinine-GFR/BSA value was calculated with the Schwartz formula [3]:

$$\text{GFR estimate} = \frac{\text{Height [cm]} \times \text{constant}}{\text{serum creatinine } [\mu\text{mol/L}]}$$

The constants used for the Schwartz formula were 49.9 for adolescent boys and 46.2 for all other children [20].

To address the question of whether separate formulas are required for boys and girls, we also developed separate formulas for both genders and compared the agreement between GFR and estimated GFR (eGFR) using gender-specific formulas, with the agreement for the formula derived for the group as a whole.

Statistics

Wherever possible, simple descriptive statistics were used. Contiguous data were tested for normal distribution using the Shapiro–Wilks normality test. Normally distributed data were analyzed using parametric methods (mean, standard

deviation, *t* test, Pearson correlation); in all other cases, non-parametric methods were used (median, range, Wilcoxon′s matched pairs test and Spearman rank correlation). For the development of the BTP formula, we used a similar multiple stepwise linear regression analysis as in our previous study after log–log transformation [21]. For the evaluation of the newly derived formula for the estimation of GFR based on BTP, we used Bland–Altman analysis [22]. All statistical analyses were performed using the commercially available software GraphPad Prism software, ver. 4.02 (GraphPad, San Diego, CA).

Results

Testing by the Shapiro–Wilk test revealed that all of the parameters under study were not normally distributed. Following log transformation of the data, however, all log-transformed variables became normally distributed. The median age of patients was 11.01 years (range 0.21–18.9), median height was 137.0 cm (range 55.00–192.6), median weight was 34.70 kg (range 5.1–116.2), median GFR was 105.5 mL/min/1.73 m^2 (range 7.0–414.0), median creatinine level was 61 μmol/L (range 23–530), and median BTP level was 0.775 mg/L (range 0.24–5.56).

The Spearman rank correlation coefficient between measured GFR and 1/BTP was 0.80 with a 95% confidence interval (CI) of 0.76–0.83, which was significant at $p<0.0001$ (Fig. 1). The correlation coefficient for BTP was superior to that between measured GFR and the Schwartz formula (correlation coefficient 0.70, 95% CI 0.65–0.74).

To generate the formula for the estimation of GFR based on BTP, we used a previously proposed modeling method [21] with log–log transformation of both parameters in the formula generation dataset:

$$\mathrm{GFR} = 10\text{^}(1.902 + (0.9515 \ \mathrm{x} \ \mathrm{LOG}(1/\mathrm{BTP})))$$

(Fig. 1).

The Bland–Altman analysis, which was then applied to compare the nuclear GFR and the BTP-based eGFR from the generating dataset, revealed a mean bias of 1.21%, a standard deviation (SD) of 27.97%, and a 95% CI of −53.61 to 56.01% (Fig. 2). Using the same approach, the formula was then validated in the validation dataset, revealing a mean bias of 1.03%, which is almost identical to that of the generating set, with a SD of 29.51% and a 95% CI of −56.81 to 58.87%. Bland–Altman analysis for the comparison between nuclear GFR and Schwartz GFR in the generating set further revealed a bias of −0.97%, a SD of 35.11% and a 95% CI of −69.79 to 67.85%. The Bland–Altman results using the validating data set revealed a bias of −7.17%, a SD of 27.85% and a 95% CI of −61.75 to 47.42%. The results for each separate dataset are given in Table 1. We also compared the percentage error for BTP and for the Schwartz GFR. There were consistently more measurements within 10% (33.0 vs. 28.3%) and 30% (76.8 vs. 72.6%) using the BTP-based eGFR than using the Schwartz GFR. The results of the percentage error in the formula generation dataset and the validation dataset are given in Table 2.

Thereafter, we analyzed the formula generation dataset separately for males (n=258) and females (n=216). The two new gender-specific datasets did not differ significantly for age, height, weight, BSA, creatinine, Schwartz GFR, GFR, BTP, and 1/BTP. The formula for boys reads:

$$\mathrm{GFR} = 10\text{^}\left(1.92 + (0.98 \ \mathrm{x} \ \mathrm{LOG}(1/\mathrm{BTP}))\right), \mathrm{r}^2 = 0.792.$$

Similarly, the formula for girls reads:

$$\mathrm{GFR} = 10\text{^}(1.90 + (0.89 \ \mathrm{x} \ \mathrm{LOG}(1/\mathrm{BTP}))), \mathrm{r}^2 = 0.723.$$

The Bland–Altman analysis for agreement between the specific male formula and the formula derived for both genders revealed a slight underestimation of the bias at 4.46% with a SD of 1.50% and a 95% CI 1.50–7.38%. Conversely, the Bland–Altman analysis between the specific female formula and the formula derived for both genders shows a slightly overestimating bias of −0.04% with a standard deviation of 1.61% and a 95% CI 3.20–3.11%. We also compared the percentage error using both the formula for both genders as well as the gender-specific formulas. The differences were not significant (Table 3).

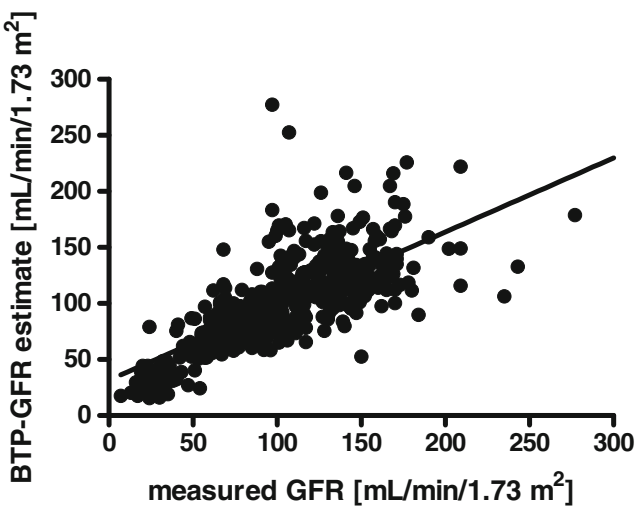

Fig. 1 Relationship between measured glomerular filtration rate (*GFR*) and GFR based on the novel beta-trace protein (*BTP*) formula GFR = 10^(1.902 + (0.9515xLOG(1/BTP))) in 474 GFR measurements from the formula generation dataset used to derive the formula. The regression correlation coefficient was 0.7994 with a 95% confidence interval of 0.7632 to 0.8306, which was significant ($p<0.0001$)

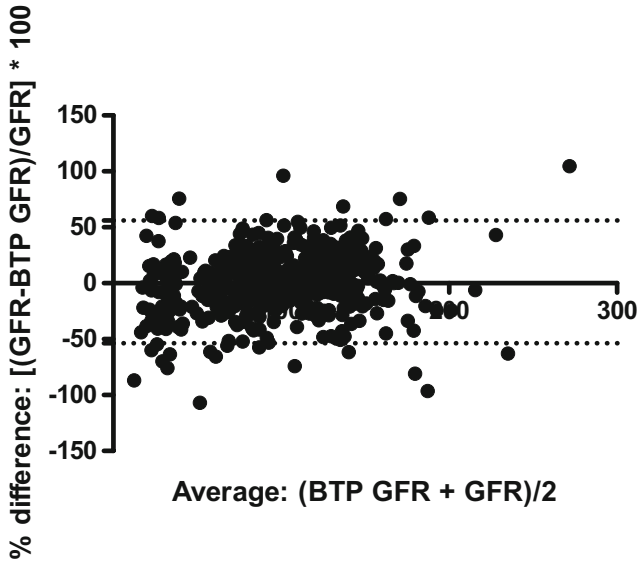

Fig. 2 The Bland–Altman analysis to test agreement between the newly derived formula for calculating GFR from the serum BTP concentration using GFR = 10 ^(1.902 + (0.9515xLOG(1/BTP))). Differences were plotted as percentages of the average. The mean difference was 1.21% with a standard deviation (SD) of 27.97%. The 95% confidence interval (CI) was –53.6 to 56.0% and is indicated by the *dashed lines* on the graph. The slope of the regression line was not significantly non-zero. This analysis was performed on the formula generation dataset (n=474)

Discussion

The main objective of our study was to develop a formula for estimating GFR based on serum BTP levels. Utilizing the GFR measurements obtained with ^{99m}Tc DTPA renal scans and simultaneous serum BTP levels, we were able to derive a novel formula after logarithmic transformation of the measured GFR and the reciprocal of the serum BTP level.

The GFR based on the nuclear renal scan showed a better agreement with the BTP-estimated GFR than with the creatinine-based GFR, based on calculations with the Schwartz formula. The agreement was acceptable, with a mean bias of −1.4% (SD 28%) for the entire group. In addition, validation in a reasonably sized control group generated almost identical results.

In terms of the validation, it has recently been suggested that a reasonably sized control group should comprise at least 40 measurements [23], as a smaller control group can introduce a bias. By these standards, our observations from a sample size of 125 measurements in 103 patients improved the validity of our observation.

For the clinical applicability of a formula, the degree of agreement that should be considered acceptable remains an important question. The literature provided us with the guidelines. For serum creatinine, an agreement of ±0.3 mg/dL or 26.5 µmol/L is considered to be acceptable; for other markers, an acceptable variation is 25–30% [23]. The agreement of 28% with our BTP-estimated GFR formula met these criteria. Of note, the BTP-based formula also performed better than the Schwartz formula. Therefore, our results provide evidence that BTP is a better surrogate marker for GFR estimation than serum creatinine, even when the old Schwartz formula is used.

However, our derived BTP formula may not perform as well as a recently derived formula that uses urea, creatinine and CysC measurements [24]. With this so-called "CKiD" method, 87.7% of the eGFR was within 30% of the isotopic (i) GFR, and 45.6% was within 10%. These results are superior to those found using the BTP-based formula derived here. Thus, while this newly derived BTP formula performs better than the creatinine-based Schwartz formula, it may be inferior to formulas based on both creatinine and CysC. As urea was only collected in a subset of the patients who participated in our study, we were unable to compare the diagnostic performance of the modified Schwartz formula in our own data. There are some concerns with CysC, especially in pregnancy [14] while the BTP-based formula was accurate in predicting eGFR in pregnancy. The verdict on whether or not CysC is affected by inflammation remains to be made. BTP is independent of inflammation [12]. As such, there may be a clinical role for a BTP-based eGFR. Furthermore, the performance of the CKiD formula has not yet been tested under conditions that affect serum creatinine levels, such as spina bifida and muscle disorders, while it is known that serum BTP levels are not affected under such clinical conditions.

A BTP-based estimation is more expensive than serum creatinine testing. At this point in time, a single BTP estimation costs CDN$22 and therefore compares unfavorably with the creatinine-based estimation of CDN$4.00, although it is comparable to the costs of a CysC-based estimation. However, it is expected that with more frequent utilization, the costs of the BTP tests will decrease.

Of interest, the estimated BTP-GFR showed a better correlation with the measured GFR in our male pediatric

Table 1 Agreement between the GFR estimates based on BTP or the Schwartz formula and the measured GFR

Marker	Bias (%)	SD of Bias	95% CI
Dataset used for formula (n=474)			
Schwartz GFR	−0.97	35.11	−69.79 to 67.85
BTP GFR	1.21	27.97	−53.61 to 56.02
Dataset used for validation (n=125)			
Schwartz GFR	−7.17	27.85	−61.75 to 47.42
BTP GFR	1.03	29.51	−56.81 to 58.87

GFR, Glomerular filtration rate; BTP, beta-trace protein; SD, standard deviation; CI, confidence interval

Table 2 Percentage of agreement within 10, 30, and 50% between the GFR based on the surrogate marker and measured GFR. For both the original dataset and the validation set, BTP-based GFR estimates showed a higher proportion of agreement

Marker	Number/percentage of dataset	Within 10% error	Within 30% error	Within 50% error
Dataset used for formula (n=474)				
Schwartz GFR	n	134	343	413
	%	28.3	72.4	87.1
BTP GFR	n	156	363	434
	%	32.9	76.6	91.6
Dataset used for validation (n=125)				
Schwartz GFR	n	33	82	103
	%	28.4	70.7	88.8
BTP GFR	n	37	84	105
	%	31.9	72.4	90.5

cohort than in our female one. This observation matches the data on CysC, where a better correlation between measured GFR and estimated CysC-GFR was observed in males [25]. Creatinine-based formulas, such as the modification of diet in renal disease (MDRD), modified MDRD, and Cockcroft–Gault formula, in adults also perform better in males than in females [26–28]. The need of a different formula in girls is not unexpected considering their higher fat mass across all ages [29, 30]. However, we found an acceptable agreement between the eGFR based on the formula for both genders and each of the gender-specific formulas. As such, we feel that a differentiation for gender is not necessary in young children and adolescents. This is in contrast to the BTP eGFR formula that we recently published for adult patients where the results have to be multiplied by 0.88 for females [17]. However, Pöge et al. recently published an adult BTP eGFR formula that was also independent of gender [31].

Importantly, the Schwartz-derived GFR accounted for 70% of the variability of the GFR, whereas BTP alone accounted for 80% of the variability of the GFR. This was slightly better than the 75.6% variability that was reported for BTP alone in adult patients [17]. The data of Pöge et al. [31] and from our study are in contrast to the data of Solichova et al. who, based on their measurement of BTP in 25 volunteers, concluded that BTP was not a useful tool for estimating GFR [32]. This difference is likely explained by the much larger number of subjects in our study.

An adult formula was very recently evaluated in children [33] in a study involving a mixed cohort of adult and pediatric patients. The BTP formula performed well in the relatively small cohort of 54 pediatric patients. We applied this formula to our dataset but found its performance somewhat inferior to our specific pediatric formula (data not included in the Results). While 95% of the BTP-based estimated GFR were within a 50% error interval and 68% were within a 30% error window, only 18.3% were within a 10% error window. It is therefore not surprising that a specifically developed pediatric formula would perform better in the pediatric setting.

There are some limitations to this study. It is important to note that we did not control for corticosteroid use. A recent study suggests that high levels of corticosteroids may influence BTP concentrations [16]. In contrast, other studies have not demonstrated any effect of high-dose glucocorticoid therapy on BTP concentrations [9, 16].

Table 3 Percentage of agreement within 10, 20, 30, and 50% between the GFR based on the surrogate marker and the measured GFR in five groups based on gender and formula (gender-specific or not)

Five categories of analysis	Within 50%	Within 30%	Within 20%	Within 10%
All patients–formula for both genders	91.6% (434)	76.8% (363)	56.5% (268)	32.9% (156)
male patients–formula for both genders	93.8% (242)	80.6% (208)	58.9% (152)	34.5% (89)
female patients–formula for both genders	88.4% (191)	71.7% (155)	53.7% (116)	30.6% (66)
Male patients–male formula	93.0% (240)	79.1% (204)	58.9% (152)	33.7% (87)
Female patients–female formula	89.8% (194)	71.7% (155)	54.2% (117)	29.2% (63)

The formula generation dataset (male: n=258; female: n=216) was used.

Values are given in percentages with the number of patients in parenthesis

In summary, the BTP formula proposed here performed significantly better than the Schwartz formula. We conclude that this BTP formula, which has been validated, can be used to predict the true GFR with a higher accuracy than the Schwartz formula. Until more studies test the performance of BTP-based estimated GFR, BTP could have a role in the clinical conditions that affect serum CysC levels.

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