International Journal of Children and Adolescents

Original Article
IJCA, Vol. 1, No. 2, Oct, 2015.25-28.

Beta trace protein as GFR marker in children

Rama Naghshizadian: *Pediatric Nephrologist, Pediatric Transplantation and Dialysis Research Center, Iran University of Medical Sciences, Tehran, Iran.*
Sepideh Hekmat: *Radionuclide Scan Specialist, Pediatric Transplantation and Dialysis Research Center, Iran University of Medical Sciences, Tehran, Iran.*
Nakyssa Hooman: *Pediatric Nephrologist, Pediatric Transplantation and Dialysis Research Center, Iran University of Medical Sciences, Tehran, Iran.*
Nahid Rahimzadeh: *Pediatric Nephrologist, Pediatric Transplantation and Dialysis Research Center, Iran University of Medical Sciences, Tehran, Iran.*

Received: 11 April 2015 Accepted: 13 May 2015

Abstract

Background and Objective: Serum creatinine is the most used endogenous marker of glomerular filtration rate (GFR), but it also has multiple limitations. Therefore, some surrogate GFR markers, such as beta trace protein, have been introduced for GFR estimation. The aim of our study was to estimate GFR by serum beta trace protein using three available equations and compare them to DTPA GFR as the gold standard and Schwartz GFR.

Methods: The three beta trace protein (BTP)-related GFR formulas were the White formula (1): GFR=167.8×BTP-0.758×creatinine-0.204, Pöge formula (2): GFR=974.31×BTP-0.2594×creatinine-0.647, and Benlamri formula (3): GFR=10^ (1.902+ (0.9515×LOG (1/BTP)). Twenty seven children were included in this study. All patients had a Schwartz and DTPA GFR more than 50 cc/min/1.73m2.

Results: We showed that there was no significant correlation between DTPA GFR and Schwartz-estimated GFR (r= -0.1, Pv= 0.5). There also was not any association between GFR estimated by Pöge and Benlamri formulas and DTPA scans. In contrast, there was a significant association between DTPA GFR and White BTP formula-estimated GFR (r=0.77 r=0.00).

Conclusion: This study showed that GFR estimated by serum beta trace protein and White formula had accuracy over Schwartz formula in children with normal or mild reduced GFR; however, this result needs to be confirmed by additional studies with more cases.

Keywords: Beta trace protein, GFR marker, Children

Introduction

The measurement of glomerular filtration rate (GFR) is the best method for renal function assessment. Inulin clearance is the gold standard test for GFR measurement. Nuclear medicine scans, while accurate, are expensive and involve radiation exposure. Serum creatinine concentration and creatinine clearance are currently used for estimating GFR. However, serum creatinine as a GFR marker has some problems: the level depends on the body's muscle mass, and its concentration is insensitive to early changes of GFR. Additionally, serum creatinine, which can overestimate GFR, can be eliminated by several non-renal routes in children with chronic kidney disease. Thus, it appears that Schwartz-estimated GFR cannot be accurate in patients with low muscle mass or chronic kidney disease (1). Many investigators have tried to reduce these problems by using other GFR markers or by modifying the traditional GFR formulae based on serum creatinine. Beta trace protein, an endogenous marker, has recently been introduced for this aim and has been used with success in recent studies.

The aim of this study was to assess serum beta trace protein as a GFR marker. We estimated GFR based on serum BTP and serum creatinine, and compared them with gold standard GFR.

Methods

We obtained serum samples from 27 children with various renal involvement referred for nuclear medicine assessment. Patients' ages ranged from 0.2 to 15 years, with a mean of 4.9±3.9

years. DTPA scan was performed on all patients, and serum creatinine and beta trace protein were also measured concurrently. Serum creatinine was measured by Jaffe reaction, and Schwartz formula was used for GFR estimation. GFR estimation by serum BTP was performed by three equations:

White formula (1):
$GFR=167.8\times BTP^{-0.758}\times creatinine^{-0.204}$
Pöge formula (2):
$GFR=974.31\times BTP^{-0.2594}\times creatinine^{-0.647}$
Benlamri formula (3):
GFR=10^(1.902 + (0.9515×LOG(1/BTP)).

Scintigraphic measurement of GFR was performed using an ADAC single-headed gamma camera. Patients were advised to drink adequate water to be well hydrated. After an IV injection of 185-259 Mbq Tc-DTPA, sequential 2sec/frame images were obtained for the first 1 minute of the study as the blood flow phase. The 1min/frame images were acquired after that up to 30 minutes. If retention of activity was noted in the collecting system at the 20th min, 1 mg/kg Lasix was also injected. Pre- and post- injection syringes were counted for 1 min at a standard distance from the detector. Renal graft depth was determined by a sonographist colleague. Regions of interest (ROI) were drawn manually around the renal graft on the 1-3 frames and also as a background area inferolateral to the graft. GFR was calculated by the modified Gates method with the following formula:

Total renal uptake percent (%) = $(k-b)/e^{-\mu x}$/ Pre-post

K: kidney count
b: background count
x: renal depth
μ: attenuation coefficient of ^{99m}Tc in soft tissue (0.153/cm)
e: constant

GFR= Total renal uptake percent (%) ×100 ×9.81270 – 6.82519

We compared GFRs estimated by BTP equations and Schwartz formula with DTPA GFR as the gold standard.

Statistical analysis

Statistical analysis was performed with SPSS for Windows, version 13. Descriptive results were expressed as mean ± standard deviation. Associations between variables (GFRs) were assessed with the Pearson or Spearman correlation coefficient. Pearson correlation was used for quantitative variables with normal distribution, and Spearman correlation was used for those without normal distribution. $P\leq 0.05$ was considered statistically significant.

Results

27 patients were assessed in this study. 15 patients (55.6%) were male. The mean age of patients was 4.9±3.9 years, and the mean height was 102.6±28.5. The mean GFR estimated by Schwartz formula was 88.8±22.4 cc/min/1.73 m^2 (58-141 cc/min/1.73m^2). The mean GFR measured by DTPA scan was 161.7±76.4 cc/min/1.73 m^2 (51-357 cc/min/1.73 m^2). GFR estimated by BTP formulas 1, 2, and 3 were 98.37±21.8, 182.4±152.4, and 264.13±66.6 cc/min/1.73m^2, respectively. Regarding DTPA GFR, 5 patients had DTPA GFR less than 90 cc/min/1.73m^2, and other patients had DTPA GFR≥100 cc/min/1.73 m^2.

We determined the correlation between DTPA GFR with reverse BTP and GFRs estimated by Schwartz and BTP formulas. The correlation coefficients between DTPA GFR and Schwartz GFR, reverse BTP and BTP GFR formulas 1, 2, and 3 were r=-0.1 (P=0.5), r=0.5 (P=0.007), r=0.77 (P=0.00), r=0.3 (P=0.12), and r=-0.1 (P=0.54), respectively (Figure 1).

We also designed a GFR formula based on the serum creatinine and beta trace protein:

GFR= -244.4 × BTP-169.17 × creatinine + 364.6 (P=0.002) (r=0.55, Pv= 0.002).

Discussion

Beta trace protein (BTP) is a 23 to 29 KDa protein. This low molecular weight enzyme is freely filtrated by the glomerulus without secretion and/or reabsorption in renal tubules. Consequently, serum beta trace protein level correlates with GFR. BTP has some benefits as a GFR marker. Serum BTP concentration is not associated with C-reactive protein and inflammation (2). This marker is not changed by body composition changes (3). It reflects GFR status in the third trimester of pregnancy (4). The serum BTP concentration is unaffected by thyroid function (5). Its serum levels are possibly unaffected by corticosteroid administration. However a recent study has shown the effect of high corticosteroid level on serum BTP concentration (6) unlike most other studies (7). It appears that BTP may have roles in GFR estimation in the future, especially in

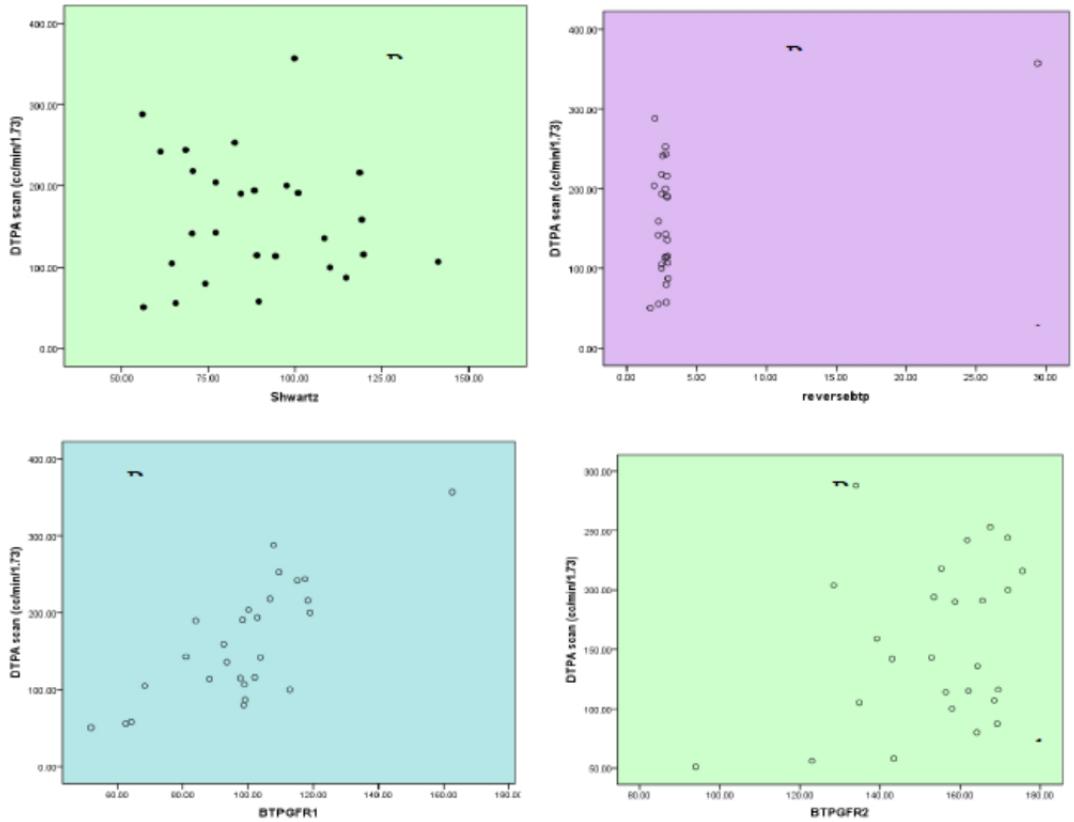

Fig 1. The correlation between DTPA GFR with Schwartz GFR (a), reverse BTP (b), BTP GFRs based on formulas 1(c) and 2 (d)

conditions in which serum cystatin C cannot be used, such as in neonates or pregnant females (8).

Filler et al. assessed serum samples from 225 children with various renal pathologies. They showed that the correlations of nuclear medicine clearance with the reciprocals of BTP, Cys-C, and the Schwartz GFR were significant (r=0.653, 0.765, and 0.706, respectively; P<0.05). These correlations were higher than the reciprocal of creatinine or beta-2 microglubolin (r=0.500 and 0.557, respectively). BTP increased the diagnostic sensitivity by 30% in comparison with serum creatinine, but BTP was not more sensitive than serum cystatin C or GFR estimated by Schwartz formula in this study (9).

Benlamri et al. determined a formula based on the serum BTP in 387 children who underwent 99mTc-diethylene triamine pentaacetic acid renal scans. This formula was GFR=10^ (1.902 + (0.9515×LOG(1/BTP)). The correlation between this new BTP-related GFR and DTPA GFR was significant (r=0.8). GFR estimated by BTP in this study had accuracy over Schwartz GFR formula (r=0.8 vs r=0.7) (10).

In another study, White et al. assessed the validation of four BTP equations in 54 children with impaired kidney function. These BTP equations included:

White equation:

$GFR= 167.8\times BTP^{-0.758}\times creatinine^{-0.204}\times$ (0.871 if female)

Pöge equation:

$GFR= 974.31\times BTP^{-0.2594}\times creatinine^{-0.647}$

They found that White equation had a low median bias and high accuracy rate. In contrast, Schwartz equation had high median bias and reduced accuracy in this study (11).

We also found that GFRs estimated by White formula correlated significantly with DTPA GFR, while this correlation was not found between GFR estimated by Pöge, Benlamri, and Schwartz formulas with DTPA GFR.

We also previously found an insignificant correlation between BTP GFR and Schwartz GFR in 110 children with a Schwartz GFR more than 60 cc/min/1.73m^2 in an unpublished paper (in press). As most patients in this study also had normal GFR, these finding may indicate the superiority of BTP as a GFR marker in comparison with serum creatinine in children with normal renal function. However, these results need confirmation by

further studies.

References

1. Pham-Huy A, Leonard M, Lepage N, Halton J, Filler G. Measuring glomerular filtration rate with cystatin C and beta-trace protein in children with spina bifida. J Urol. 2003;169:2312–2315.
2. Kanaoka Y, Urade Y. Hematopoietic prostaglandin D synthase. Prostaglandins Leukot Essent Fatty Acids 2003; 69:163–167.
3. Huber AR, Risch L. Recent developments in the evaluation of glomerular filtration rate: is there a place for beta-trace? Clin Chem. 2005; 51:1329–1330.
4. Akbari A, Lepage N, Keely E, Clark HD, Jaffey J, MacKinnon M, et al. Cystatin-C and beta trace protein as markers of renal function in pregnancy. Br J Obstet Gynaecol. 2005;112:575–578
5. Manetti L, Pardini E, Genovesi M, Campomori A, Grasso L, Morselli LL, et al. Thyroid function differently affects serum cystatin C and creatinine concentrations. J Endocrinol Invest. 2005; 28:346–349
6. Abbink FC, Laarman CA, Braam KI, van Wijk JA, Kors WA, Bouman AA, , et al. Beta-trace protein is not superior to cystatin C for the estimation of GFR in patients receiving corticosteroids. Clin Biochem. 2008;41:299–305
7. Pöge U, Gerhardt TM, Stoffel-Wagner B, Palmedo H, Klehr HU, Sauerbruch T, et al. β-Trace protein is an alternative marker for glomerular filtration rate in renal transplantation patients. Clin Chem. 2005; 51:1531–1533
8. Filler G, Yasin A, Medriros M. Methods of assessing renal function, Pediatr Nephrol. 2013; [Epub ahead of print]
9. Filler G, Priem F, Lepage N, Sinha P, Vollmer I, Clark H, et al. Beta-trace protein, cystatin C, beta (2)-microglobulin, and creatinine compared for detecting impaired glomerular filtration rates in children. Clin Chem. 2002;48(5):729-36.
10. Benlamri A, Nadarajah R, Yasin A, Lepage N, Sharma AP, Filler G. Development of a beta-trace protein based formula for estimation of glomerular filtration rate, Pediatr Nephrol. 2010; 25:485–490.
11. White CA, Akbari A, Doucette S, Fergusson D, Hussain N, Dinh L, et al. Estimating GFR using serum beta trace protein: accuracy and validation in kidney transplant and pediatric populations. Kidney Int. 2009;76(7):784-91.