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Serum levels of beta-trace protein and glomerular filtration rate—preliminary results

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Abstract

The aim of this study was to evaluate the relationship between serum levels of beta-trace protein (BTP), a low molecular weight (MW) protein, and glomerular filtration rate (GFR). GFR and serum levels of BTP, and for comparison creatinine (Creat), cystatin C (Cys) and β2-microglobulin (β2M), were measured in 60 patients, with renal function ranging from normality to advanced renal failure. Serum levels of BTP progressively increased with the reduction of GFR. A good correlation was found between GFR and serum levels of BTP ($r = 0.918$), Creat ($r = 0.932$), Cys ($r = 0.937$), and β2M ($r = 0.924$). Furthermore, no statistically significant difference was found between BTP and Creat, Cys, β2M, as indicators of a moderate GFR impairment. These preliminary data indicate that BTP might be suitable as an indicator of GFR.

Keywords: Beta-trace protein; Prostaglandin D synthase; Cystatin C; β2-Microglobulin; Creatinine; Glomerular filtration rate

1. Introduction

The measurement of plasma concentration of creatinine (Creat) is the most commonly used test to evaluate an impairment of glomerular filtration rate (GFR). However, plasma Creat lacks sensitivity to identify patients with moderate impairment in renal function.

Many low molecular weight (MW) proteins are cleared from the plasma mainly by the kidneys via glomerular filtration, followed by complete tubular reabsorption and complete catabolism inside tubular cells [1–3]. Due to such renal handling, the measurement of plasma concentration of various low MW proteins has been proposed as a useful tool to evaluate an impairment of GFR, possibly more sensitive than Creat [4–17].

Beta-trace protein (BTP), known also as prostaglandin D synthase, is a low MW protein (MW ≈ 18.5 kDa) isolated primarily from cerebrospinal fluid. Highly elevated serum levels of

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BTP have been found in patients with end-stage renal failure [18]. Furthermore, other data suggest that BTP could be an indicator of reduced GFR [19,20].

The aim of this study was to evaluate the relationship between serum levels of BTP and GFR, as a preliminary step in the assessment of the reliability of BTP as indicator of GFR impairment.

2. Patients and methods

2.1. Patients

Sixty adult renal patients (28 males and 32 females; aged 20–82 years, mean 53; body weight 40.7–112 kg, mean 72.6) with various kidney diseases and different degree of functional impairment (plasma Creat 0.5–8.4 mg/dl, mean 1.92) participated in this study. All patients needed the measurement of GFR for the assessment of renal function or to evaluate the progression of kidney disease. The study was performed according to the Helsinki declarations.

2.2. Methods

2.2.1. Measurement of blood concentration of beta-trace protein, creatinine, cystatin C, and β2-microglobulin

2.2.1.1. Beta-trace protein (BTP). Particle enhanced immune-nephelometry (N Antiserum to human BTP, Dade Behring). Reference intervals for serum BTP were calculated in 120 normal subjects (60 males and 60 females), aged 18–59 years, mean 32.2.

2.2.1.2. Creatinine (Creat). Autoanalyzer methods (Crea Abbott/Hitachi automated analysis for Hitachi 717/911; reference intervals 0.50–0.90 mg/dl in females and 0.70–1.20 mg/dl in males).

2.2.1.3. Cystatin C (Cys). Particle enhanced immune-nephelometry (N Latex Cys, Dade Behring; reference intervals 0.50–0.96 mg/l in females and 0.57–0.96 mg/l in males).

2.2.1.4. β2-Microglobulin (β2M). Immune-enzymic method (AxSym β2M, Abbott; reference intervals 0.8–2.5 mg/l, without differences between males and females).

2.2.2. Measurement of renal function

GFR was measured, with a radio-isotopic method, as the renal clearance of ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA) [21,22]. The results were adjusted, as usual, to the standard body surface of 1.73 m^2.

2.2.3. Statistical analysis

The correlation between GFR and serum concentrations of BTP, Creat, Cys, and β2M, and the correlation between serum concentration of BTP, and Creat, Cys, β2M were evaluated from the value of correlation coefficients r.

The diagnostic accuracy of BTP as indicator of GFR impairment, in comparison with Creat, Cys, and β2M, was tested using receiver-operating characteristic (ROC) analysis.

The significance of the differences among the mean values of blood levels of BTP, Creat, Cys, and β2M, in different groups of patients was assessed using Student's t-test.

3. Results

Reference intervals (2.5–97.5%) for BTP in the 120 normal subjects were 0.39–0.76 mg/l, mean 0.56 mg/l, median 0.54 mg/l. In males, the reference intervals were 0.37–0.77 mg/l, mean 0.58 mg/l, median 0.57 mg/l, while in females reference intervals were 0.40–0.70, mean 0.54 mg/l, median 0.53 mg/l. Mean values of BTP in males and females resulted significantly different ($P = 0.043$).

Serum concentrations of BTP (Fig. 1) linearly correlated with serum concentrations of Creat ($r = 0.921$), Cys ($r = 0.890$) and β2M ($r = 0.884$).

Serum concentrations of BTP increased progressively with the reduction of GFR (Fig. 2). The best correlations between GFR and serum levels of BTP, Creat, Cys, and β2M were logarithmic. A high correlation coefficient was found between BTP and GFR, very similar to the correlation coefficients found for Creat, Cys, and β2M. The

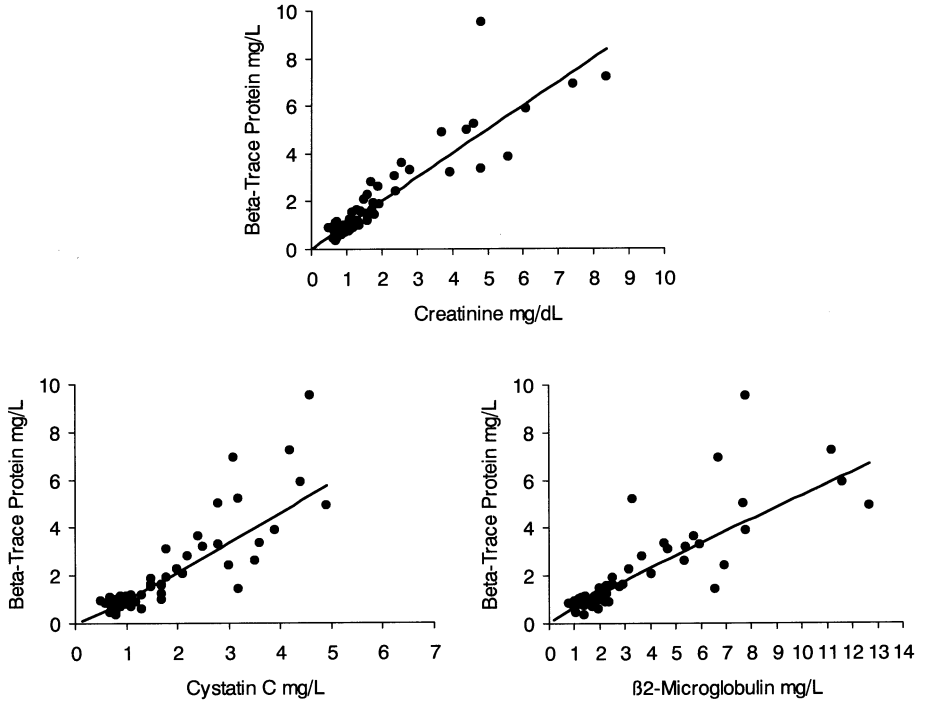

Fig. 1. Correlation plots between serum concentrations of BTP, Creat, Cys, and β2M. The linear correlation lines are plotted; the coefficients of correlation r were 0.921 with Creat, 0.890 with Cys, and 0.884 with β2M.

upper limits of values found in the group of 15 patients with GFR > 75 ml/min per 1.73 m^2 (mean + 2S.D.) were 1.2 mg/l for BTP, 1.2 mg/dl for Creat, 1.0 mg/l for Cys, and 2.0 mg/l for β2M. These limits intersect the four correlation lines at a similar value of GFR, of approximately 60 ml/min per 1.73 m^2.

A significant increase in blood levels of BTP and of the other markers of renal function was already observed in the group of patients with GFR < 75 ml/min per 1.73 m^2 (Table 1). In patients with advanced renal failure (GFR < 25 ml/min per 1.73 m^2), serum levels of BTP were 5.8 times the values found in patients with GFR > 75 ml/min per 1.73 m^2; a similar increase was found for Creat (5.5) and β2M (5.7), while Cys increased only 4.4 times (Table 1).

Diagnostic accuracy of BTP, Creat, Cys and β2M, as indicators of a GFR < 70 ml/min per 1.73 m^2 resulted similar. In fact, the areas under the curve (AUC) of the ROC plot were similar, and the criterion values were as follows. BTP: AUC = 0.892, criterion = 1.1 mg/l; Creat: AUC = 0.929, criterion 1.0 mg/dl; Cys: AUC = 0.936, criterion 1.1 mg/l; β2M: AUC = 0.889, criterion 1.72 mg/l. The differences among the values of AUC were not statistically significant.

4. Discussion

Inulin is the gold standard for the measurement of GFR [23]. However, the measurement of renal clearance of inulin is not feasible in clinical practice, due to the necessity of constant IV infusion of the tracer and of bladder catheterization to ensure an adequate urine collection. ^{99m}Tc-DTPA is an adequate and widely used tracer for the assessment of GFR. We measured GFR from the increase in bladder radioactivity after IV injection of ^{99m}Tc-DTPA, thus avoiding both IV infusion and bladder catheterization [21].

The results of this study, performed in patients with renal function ranging from normality to

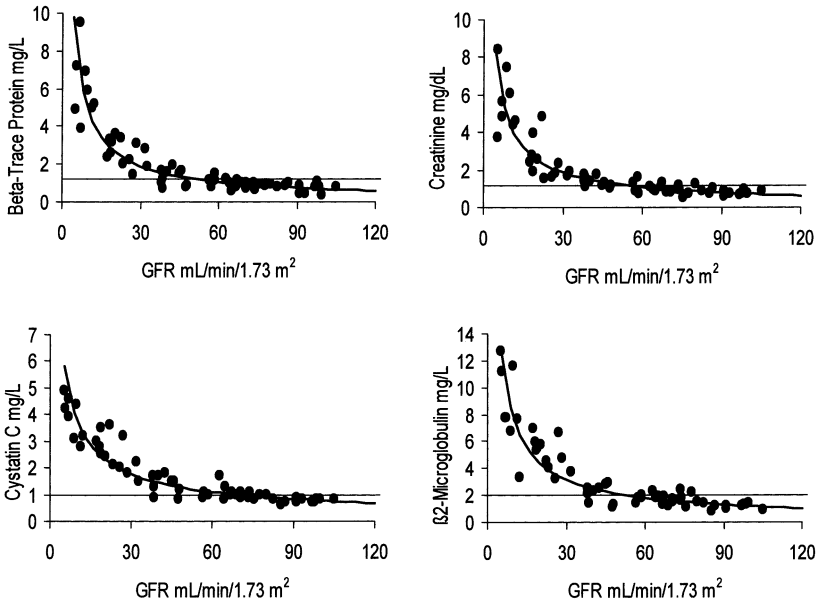

Fig. 2. Serum concentrations of BTP, Creat, Cys, and β2M plotted vs. GFR. The straight lines represent the upper limit of values found in the group of 15 patients with GFR > 75 ml/min per 1.73 m^2 (mean+2S.D.): 1.2 mg/l for BTP, 1.2 mg/dl for Creat, 1.0 mg/l for Cys, and 2.0 mg/l for ß2M. The curve lines represent the logarithmic correlation with GFR. BTP = $33.367 \times GFR^{-0.8445}$, $r = 0.9179$; Creat = $27.320 \times GFR^{-0.7915}$, $r = 0.9323$; Cys = $18.255 \times GFR^{-0.6868}$, $r = 0.9371$; β2M = $49.406 \times GFR^{-0.8097}$, $r = 0.9238$.

advanced renal failure, suggest that BTP is an indicator of GFR impairment with a behavior similar to Creat, Cys and β2M. In fact, serum levels of BTP correlated closely with serum Creat, Cys and βM. Furthermore, the logarithmic correlation of serum BTP with GFR was very high and similar to that of Creat, Cys and β2M. Finally, the diagnostic accuracy of BTP, as indicator of a GFR < 70 ml/min per 1.73 m^2, was also very similar to that of Creat, Cys and β2M. Other authors, in a group of patients with a lower incidence of advanced renal failure than our study, reported a significantly higher diagnostic accuracy of BTP in comparison with both Creat and β2M [19].

In patients with reduced renal function, serum concentrations of BTP, Creat, β2M, and particularly of Cys increase to a lesser extent than an ideal marker of GFR (Fig. 3). Various factors may affect the relationship with GFR of the different markers of renal function [24,25]. First of all, in patients with advanced renal failure, Creat has an extra-renal route of elimination [26]. Furthermore, in these patients, muscle mass is reduced, thus Creat production is probably reduced [27]. Data in rat indicate that Cys has a significant extra-renal clearance [28,29]. β2M is generally believed to be eliminated solely by the kidneys [7]. However, a glomerular sieving coefficient lesser than 1 for this protein has been reported [30], and the rate of production of β2M in renal failure patients could be lower than in normal subjects [31]. All these factors may determine the lower than expected increase in plasma concentration of Creat, Cys and β2M in patients with renal failure. Some of these factors could hypothetically influence also the relationship between BTP and GFR. This will be object of further studies.

In conclusion, serum levels of BTP increase progressively with the reduction of renal function. However, further studies are necessary to assess its diagnostic accuracy and reliability, in comparison with Creat, Cys and β2M. For this purpose, it is also necessary to evaluate imprecision of measurements, and influence of sex, age and other anthropometric data on serum concentrations of BTP.

Table 1
Mean values (±S.D.) of serum concentrations of BTP, Creat, Cys, and β2M

GFR (ml/min per 1.73 m^2)	N	BTP (mg/l)	Mean increase	Creat (mg/dl)	Mean increase	Cys (mg/l)	Mean increase	β2M (mg/l)	Mean increase
< 25	15	4.60 ± 2.08***	5.8	4.33 ± 1.98***	5.5	3.40 ± 0.85***	4.4	7.13 ± 2.79***	5.7
25–50	15	1.62 ± 0.69***	2.1	1.53 ± 0.37***	1.9	1.65 ± 0.57***	2.1	2.85 ± 1.50***	2.3
50–75	15	0.97 ± 0.24*	1.2	1.02 ± 0.24**	1.3	1.07 ± 0.22***	1.4	1.77 ± 0.33***	1.4
> 75	15	0.79 ± 0.21		0.79 ± 0.20		0.77 ± 0.13		1.26 ± 0.35	

Patients were divided in groups according to their GFR. The significance of the difference with mean values found in patients with GFR > 75 ml/min per 1.73 m^2 is indicated by asterisks (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). The mean increases in plasma concentrations with respect to values found in the patients with GFR > 75 ml/min per 1.73 m^2 are also reported.

Fig. 3. Normalized values of serum concentrations of BTP, Creat, Cys, β2M vs. GFR. Patients were clustered in four groups according to their GFR: < 25, 25–50, 50–75, and > 75 ml/min per 1.73 m^2. The mean values of each group were normalized for the mean values found in the patients with GFR > 75 ml/min per 1.73 m^2. For comparison, the behavior of an hypothetical ideal marker (ideal) of GFR is plotted.

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