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BETA-TRACE PROTEIN AS A MARKER OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE: COMPARISON WITH OTHER RENAL MARKERS

BETA-TRACE PROTEIN KAO MARKER RENALNE DISFUNKCIJE KOD PACIJENATA SA HRONIČNOM BUBREŽNOM BOLEŠĆU: POREĐENJE SA DRUGIM RENALNIM MARKERIMA

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Summary: Beta-trace protein (BTP), also known as prostaglandin D synthase, is a low-molecular-mass protein which belongs to the lipocalin protein family. It was found to be increased in the serum of patients with renal diseases. The aim of this study was to compare the clinical usefulness of serum levels of beta-trace protein for the detection of renal dysfunction in patients with chronic kidney disease (CKD) with levels of other renal markers: creatinine, cystatin C and β_2-microglobulin (B2M). The study included 134 patients with a wide range of renal dysfunction that encompassed all five CKD stages. Obtained data showed that beta-trace protein highly correlated (Spearman test) with creatinine ($r = 0.890$), cystatin C ($r = 0.904$) and B2M ($r = 0.933$) and its levels in serum significantly increased from CKD stage 1 to 5. Furthermore, the values of glomerular filtration rate (GFR) estimated from a BTP-based formula significantly correlated with GFR calculated from creatinine-based and cystatin C-based formulas. ROC analyses showed that BTP had similar diagnostic accuracy for detection of reduced renal function in CKD stages as other renal markers, for estimated GFRs of < 30, < 60 and < 90 mL/min/1.73 m^2. The areas under the ROC curves (AUC) for BTP, for these GFR limits, were from 0.983 to 0.917 and they were not significantly different from AUCs for other renal markers. The results of this study showed that BTP may be a useful and reliable serum marker for identifying the magnitude of renal dysfunction in patients with CKD and may have its place beside serum cystatin C and creatinine as an alternative endogenous GFR marker.

Keywords: beta-trace protein, creatinine, cystatin C, β_2-microglobulin, chronic kidney disease

Kratak sadržaj: Beta-trace protein (BTP), takođe poznat kao prostaglandin D sintaza, je protein male molekulske mase koji pripada familiji lipokalinskih proteina. Pronađeno je da je povećan u serumu pacijenata sa renalnim bolestima. Cilj ovog rada je bio da se uporedi klinička korisnost serumskih nivoa beta-trace proteina u detekciji renalne disfunkcije kod pacijenata sa hroničnom bolešću bubrega (CKD) sa nivoima drugih renalnih markera: kreatinina, cistatina C i β_2-mikroglobulina (B2M). Studija je uključila 134 pacijenta sa širokim opsegom renalne disfunkcije koji obuhvata svih 5 CKD stadijuma. Dobijeni podaci su pokazali da beta-trace protein veoma dobro koreliše (Spearmanov test) sa kreatininom ($r = 0,890$), cistatinom C ($r = 0,904$) i B2M ($r = 0,933$) i da se njegovi nivoi u serumu značajno povećavaju od (1. do 5.) CKD stadijuma. Osim toga, vrednosti jačine glomerulske filtracije (GFR) procenjene iz formule bazirane na BTP značajno korelišu sa GFR izračunatom iz formula baziranih na kreatininu i cistatinu C. ROC analiza je pokazala da BTP ima sličnu dijagnostičku tačnost za detekciju redukovane renalne funkcije u CKD stadijumima kao drugi renalni markeri, pri procenjenim GFR od < 30, < 60 i < 90 mL/min/1,73 m^2. Površine ispod ROC krivih (AUC) za BTP, za ove nivoe GFR, bile su od 0,983 do 0,917 i one se nisu značajno razlikovale od AUC za druge renalne markere. Rezultati ove studije su pokazali da BTP može biti koristan i pouzdan serumski marker za identifikaciju obima renalne disfunkcije kod pacijenata sa CKD i može se koristiti uz serumski cistatin C i kreatinin kao alternativni endogeni GFR marker.

Ključne reči: beta-trace protein, kreatinin, cistatin C, β_2-mikroglobulin, hronična bolest bubrega

Introduction

Chronic kidney disease (CKD) is a world-wide public health problem with adverse outcomes of kidney failure. Early diagnosis and treatment may delay or even prevent the onset of nephropathy in CKD. The Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation (NKF) published guidelines for the diagnosis and classification of CKD. These guidelines define chronic kidney disease by either a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 or the presence of kidney damage, manifested by either pathological abnormalities or abnormal renal markers in blood or urine, for 3 or more months (1).

Beta-trace protein (BTP) was primarily isolated as prostaglandin D2 synthase (EC 5.3.99.2.) from cerebrospinal fluid and has a molecular weight of 23–29 kDa depending on the degree of glycosylation. It has also been detected in serum, urine, amniotic fluid, and seminal plasma. BTP catalyses the conversion of prostaglandin H_2 to prostaglandin D_2 and is a lipocalin transporter protein that binds retinoid, thyroid hormones, and bile pigments. The half-life of BTP is approximately 1.2 hours and it is almost completely excreted via the kidneys (2). Because of its low molecular mass, its constant production rate and its stability, BTP has been proposed as a new endogenous marker of glomerular filtration rate (3). A few formulas for estimating GFR based on serum BTP have also been proposed (4).

Creatinine is the most widely used endogenous marker of GFR in routine clinical practice. Creatinine (113 Da) is freely filtered at the glomerulus and secreted in urine by the proximal tubule. The serum creatinine alone fails to identify patients in the early stage of CKD, therefore NKF-K/DOQI guidelines recommend reporting an estimated GFR (eGFR), calculated from prediction formulas, in addition to the serum creatinine value. Abbreviated Modification of Diet in Renal Disease (MDRD) study formula for eGFR is the current recommendation (1). In May 2009, a new CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula was published (5). It was developed in effort to produce more accurate estimation of GFR than the MDRD formula.

Cystatin C is a small (12.8 kDa) non-glycosylated protein synthesized by all nucleated cells that functions as a cysteine protease inhibitor. It has been proposed as an alternative filtration marker to creatinine. Cystatin C is produced at a constant rate, with a half-life of approximately 2 hours, but several publications suggest an influence of thyroid hormone. Several formulas for estimating GFR based upon serum cystatin C determination have been introduced (6, 7).

$Beta_2$-microglobulin (B2M) is a low-molecular-weight (11.8 kDa) protein found on the cell surface of all nucleated cells. High plasma levels of B2M occur in renal failure, inflammation and tumors. It has been shown that B2M may be a more sensitive marker of renal function than serum creatinine, but it is overly affected by non-renal factors. B2M may be useful as a renal marker in specific situations such as renal transplant monitoring (8).

The aim of this study was to investigate the clinical usefulness of the serum levels of beta-trace protein for the detection of renal dysfunction in patients with chronic kidney disease and to compare them with the levels of other renal markers.

Materials and Methods

Subject samples

The study was performed in a population of 134 patients (72 females and 62 males) with chronic kidney disease. Serum samples were collected from each patient. Serum concentrations of creatinine, cystatin C and β_2-microglobulin were measured on the day of blood collection, and β-trace protein was measured later in serum samples stored at –70 °C. All study participants gave written informed consent.

Methods

BTP was measured by a latex particle-enhanced immunonephelometric assay on a Behring Nephelometer II analyzer (Dade Behring, Marburg, Germany). Interassay imprecision was assessed using N/A Protein Control LC® (Dade Behring) and a CV of 3.2% at 1.87 mg/L (n = 20) was obtained. BTP was also measured in the sera of 50 healthy volunteers (25 females and 25 males) with age ranging from 20 to 70 years and the mean concentration (± SD) was 0.646 (±0.1129; range 0.368–0.827) mg/L.

A Behring Nephelometer II analyzer was also used to measure cystatin C and B2M by immunonephelometry. Creatinine was determined by a kinetic alkaline picrate method on an ARCHITECT *ci*8200 analyzer (Abbott Diagnostics, Wiesbaden, Germany).

The creatinine clearance was calculated using the standard formula (9). Glomerular filtration rate (GFR) was estimated using the creatinine-based MDRD study (10) and CKD-EPI (2) formulas and cystatin C-based Hoek's formula (11). Estimated GFR (eGFR) was also calculated from serum BTP concentrations according to the formula published by White et al. (8): GFR (mL/min/1.73 m^2) = $167.8 \times BTP^{-0.758} \times creatinine^{-0.204} \times 0.871$ (if the patient is female).

The patients were classified into the CKD stage according to the American National Kidney Foundation guidelines (1) using eGFR from MDRD formula; CKD stages 1–5 correspond to GFR of >90, 60–89, 30–59, 15–29 and <15 mL/min/1.73 m^2.

Statistical analysis

Adherence to Gaussian distributions was assessed using the Kolmogorov-Smirnov test, taking $P < 0.05$ as a significant result. Mean and standard deviation (SD) were used for descriptive statistics of variables with normal distribution; median and range for variables with nonparametric distribution. Gaussian-distributed variables were analyzed between the groups using Student's t-test and Pearson's test. Mann-Whitney *U*-test and Spearman's test were used for comparison and correlation of nongaussian-distributed variables in the groups. A P value less than 0.05 was considered statistically significant. A 95% confidence interval (CI) was also shown in reported data.

The diagnostic value of serum BTP, creatinine, cystatin C and B2M for identifying renal dysfunction was evaluated using receiver operating characteristic (ROC) curve analysis, and the data are expressed as areas under the curve (AUC; 95% confidence interval, 95% CI; standard error, SE). AUC for these variables were compared for estimation of renal function for eGFR of < 30, < 60 and < 90 mL/min/1.73 m^2, with $P < 0.05$ taken as a significant result.

Statistical analyses were performed using MedCalc for Windows, version 9.5.2.0. (MedCalc software, Mariakerke, Belgium).

Results

The patient characteristics are summarized in *Table I*. The patients had a wide range of renal dysfunction that encompassed all five stages of the K/DOQI chronic kidney disease classification system.

In the investigated population, the median (range) serum concentrations of BTP, creatinine, cystatin C and B2M were 1.060 (0.368–8.840) mg/L, 104 (55–892) μmol/L, 1.16 (0.56–5.02) mg/L, and 2.78 (0.99–29.00) mg/L, respectively. Concentrations of BTP were significantly higher than in healthy individuals (medians: 1.06 vs. 0.64 mg/L; $P < 0.0001$). Beta-trace protein correlated significantly (Spearman test, $P < 0.0001$) with creatinine, cystatin C and B2M in serum (creatinine, $r = 0.890$, 95% CI 0.849–0.921; cystatin C, $r = 0.904$, 95% CI 0.868–0.931; B2M, $r = 0.933$, 95% CI 0.907–0.952).

Patients were stratified into 5 groups according to the CKD stage (K/DOQI classification). The mean (SD) serum concentrations of BTP in CKD stages 1–5 were: 0.6098 (0.1528) mg/L, 0.8595 (0.2347) mg/L, 1.6715 (0.6582) mg/L, 3.0580 (0.9174) mg/L and 6.0158 (1.5028) mg/L. The mean (SD) serum concentrations of creatinine in CKD stages 1–5 were: 73.1 (11.2) μmol/L, 88.5 (16.0) μmol /L, 135.6 (30.5) μmol/L, 250.7 (56.2) μmol/L and 610.3 (169.5) μmol /L. The mean (SD) serum concentrations of cystatin C in CKD stages 1–5 were: 0.748 (0.118) mg/L, 0.966 (0.216) mg/L, 1.629 (0.529) mg/L, 2.861 (0.703) mg/L and 4.358 (0.494) mg/L. The mean (SD) serum concentrations of B2M in CKD stages 1–5 were: 1.699 (0.447) mg/L, 2.260 (0.665) mg/L, 4.361 (2.346) mg/L, 10.723 (6.038) mg/L and 18.808 (6.842) mg/L. A comparison of these data showed that serum concentrations of BTP, creatinine, cystatin C and B2M significantly increased from CKD stage 1 to stage 5; P value was less than 0.0001 for all groups (*Figure 1*).

Table I Population characteristics (n = 134).

Characteristics	Value
Mean (±SD) age, years	47.5 (±17.0)
Mean (±SD) body mass index, kg/m^2	24.4 (± 4.2)
Cause of kidney disease	n (%)
Focal segmental glomerulosclerosis	17 (13)
Other glomerulosclerosis	6 (4)
Membranous glomerulonephritis	24 (18)
Other glomerulonephritis	11 (8)
Systemic lupus erythematosus	17 (13)
Hypertension	19 (14)
Diabetic nephropathy	9 (7)
Nephrolithiasis	5 (4)
Polycystic kidney disease	7 (5)
Other	19 (14)
Glomerular filtration rate (GFR)	n (%)
≥ 90 mL/min per 1.73 m^2	21 (16)
60–89 mL/min per 1.73 m^2	50 (37)
30–59 mL/min per 1.73 m^2	36 (27)
15–29 mL/min per 1.73 m^2	15 (11)
< 15 mL/min per 1.73 m^2	12 (9)

The mean value (±SD) of creatinine clearance in the study population was 75.92 (±47.13) mL/min. The means (±SD) of estimated GFR calculated using MDRD and CKD-EPI creatinine-based formulas were 59.8 (±30.1) mL/min/1.73 m^2 and 62.1 (±32.8) mL/min/1.73 m^2, respectively. The means (±SD) of eGFR calculated from cystatin C and BTP concentrations were 65.1 (±33.0) mL/min/1.73 m^2 and 58.2 (±30.7) mL/min/1.73 m^2, respectively. BTP-based eGFR correlated significantly (Pearson test, $P < 0.0001$) with creatinine clearance and all calculated eGFRs. The concentrations of BTP were also in significant negative correlation (Pearson test, $P < 0.0001$) with creatinine clearance and all calculated eGFRs (*Table II*).

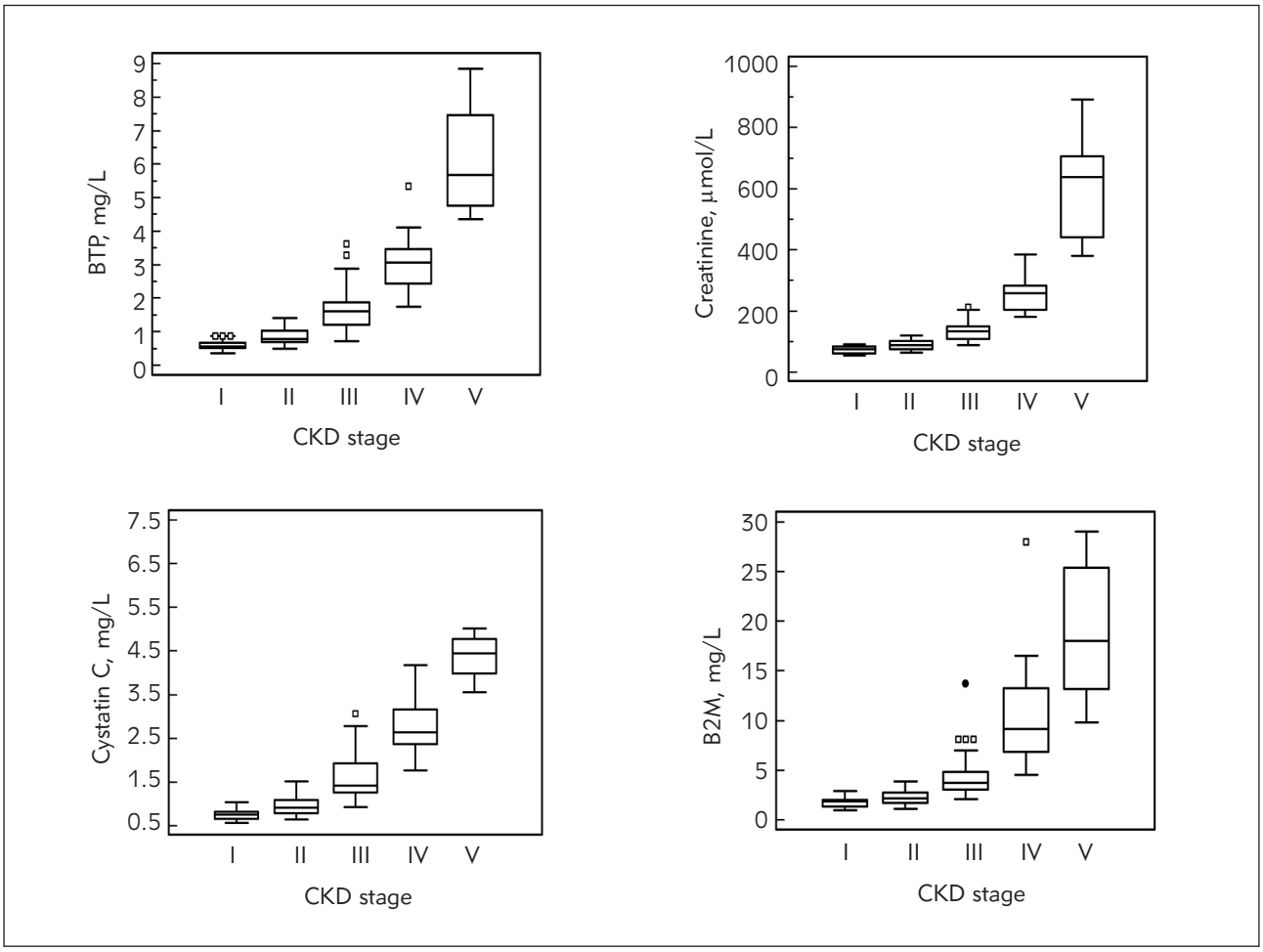

Figure 1. Serum values of beta-trace protein (BTP), creatinine, cystatin C and β_2-microglobulin (B2M) in groups of patients stratified according to the Chronic Kidney Disease (CKD) stage. Data are presented as box-plots, showing the 10th, 25th, 50th, 75th and 90th percentiles.

Table II Correlation between beta-trace protein (BTP) and BTP-based estimated glomerular filtration rate (eGFR), and creatinine clearance, creatinine-based eGFRs (MDRD and CKD-EPI) and cystatin C-based eGFR (Pearson test, $P < 0.0001$). Data are presented as the correlation coefficients (95% CI).

	BTP	BTP-based eGFR
Creatinine clearance	–0.673 (–0.756 to –0.568)	0.818 (0.752–0.867)
MDRD eGFR	–0.793 (–0.848 to –0.720)	0.928 (0.901–0.949)
CKD-EPI eGFR	–0.785 (–0.842 to –0.709)	0.926 (0.898–0.947)
Cystatin C-based eGFR	–0.756 (–0.821 to –0.673)	0.902 (0.865–0.929)
BTP-based eGFR	–0.785 (–0.842 to –0.709)	

MDRD – Modification of Diet in Renal Disease study formula
CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration formula

In order to determine the diagnostic accuracy of BTP and other analytes for the detection of renal impairment, various ROC plots were calculated, with GFR limits at 90, 60 and 30 mL/min/1.73 m^2, which correspond to the borders of CKD stages. CKD stages were combined, because of a small number of patients in the stages. The data from ROC analyses are presented in *Table III*. The areas under the curves (AUCs) were not significantly different (*Figure 2*).

Table III ROC analyses data at GFR limits of 90, 60 and 30 mL/min/1.73 m^2 for beta-trace protein, creatinine, cystatin C and β_2-microglobulin in serum of patients with CKD (cutoff values represent optimum concentrations at different GFR limits).

ROC analysis parameters						
eGFR	AUC	SE	95% CI	Sensitivity	Specificity	Cutoff value
BETA-TRACE PROTEIN						
< 90	0.917	0.0249	0.856–0.957	92.9	76.2	0.65 mg/L
< 60	0.964	0.0170	0.917–0.989	84.1	97.2	1.27 mg/L
< 30	0.983	0.0179	0.943–0.997	96.3	92.5	1.88 mg/L
CREATININE						
< 90	0.895	0.0288	0.831–0.941	73.5	100.0	91 μmol/L
< 60	0.970	0.0155	0.926–.992	84.1	98.6	116 μmol/L
< 30	0.996	0.0088	0.965–.998	100.0	96.3	170 μmg/L
CYSTATIN C						
< 90	0.919	0.0244	0.859–0.933	77.9	95.2	0.85 mg/L
< 60	0.967	0.0164	0.902–0.982	88.9	87.3	1.13 mg/L
< 30	0.985	0.0166	0.942–0.997	96.3	94.4	2.06 mg/L
BETA-2-MICROGLOBULIN						
< 90	0.884	0.0308	0.818–0.933	77.9	95.2	2.13 mg/L
< 60	0.953	0.0196	0.902–0.982	88.9	87.3	2.82 mg/L
< 30	0.982	0.0183	0.942–0.997	96.3	94.4	5.48 mg/L

Discussion

Markedly increased serum levels of beta-trace protein have been reported in patients with various renal diseases (12, 13). In this study, the median BTP concentrations were: 0.64 (0.37–0.83) mg/L and 1.06 (0.37–0.8) in healthy individuals and CKD patients, respectively. The reference interval of 0.40–0.74 mg/L was found in adults, using the same assay (14).

Serum creatinine is a crude marker of GFR; major limitations to its use to estimate GFR are interaction with age, sex, muscle mass, exercise, certain drugs, and nutritional status, and insensitivity in detection of early stages of CKD (15). Several studies have suggested that serum cystatin C is superior to creatinine for the estimation of GFR, whereas others have questioned this (16–18). Cystatin C is particularly well suited to detect early renal function impairment (19). Cystatin C started to increase as GFR fell below about 80 mL/min/1.73 m^2 compared with about 40 mL/min/1.73 m^2 for serum creatinine (9). However, the glucocorticoid administration and thyroid disorders have been described as nonrenal factors influencing serum cystatin C concentrations (20, 21). B2M has been advocated as a better predictor of GFR, but its serum concentrations can increase as an acute-phase reactant in disorders such as lupus nephritis (22).

We found that elevated BTP concentrations in the serum of patients with CKD highly significantly correlated with the concentrations of creatinine, cystatin C and B2M; correlation coefficients were from 0.890 to 0.933. Similar correlation was reported (14) between BTP and creatinine ($r = 0.86$) and BTP and cystatin C ($r = 0.80$). Serum levels of BTP, similar to levels of other renal markers, were highly associated with renal impairment in CKD stage; its concentrations significantly increased from stage 1 to 5 (*Figure 1*). Investigations showed that BTP and cystatin C had significantly greater proportional increase at all GFR stages and they detected a diminished GFR earlier than creatinine (14, 23). It was reported that BTP, like cystatin C, is independent of age and gender (23, 24). However, nonrenal factors influencing cystatin C and B2M levels, such as corticosteroid therapy, also influence BTP levels (25–27). BTP concentrations may be increased in the cerebrospinal fluid of patients with various neurological conditions (2). The effects of other pathological conditions on the serum BTP have not been well established.

Measurement of clearance of exogenous filtration markers, such as inulin, is the most accurate method for GFR determination. The measurement of

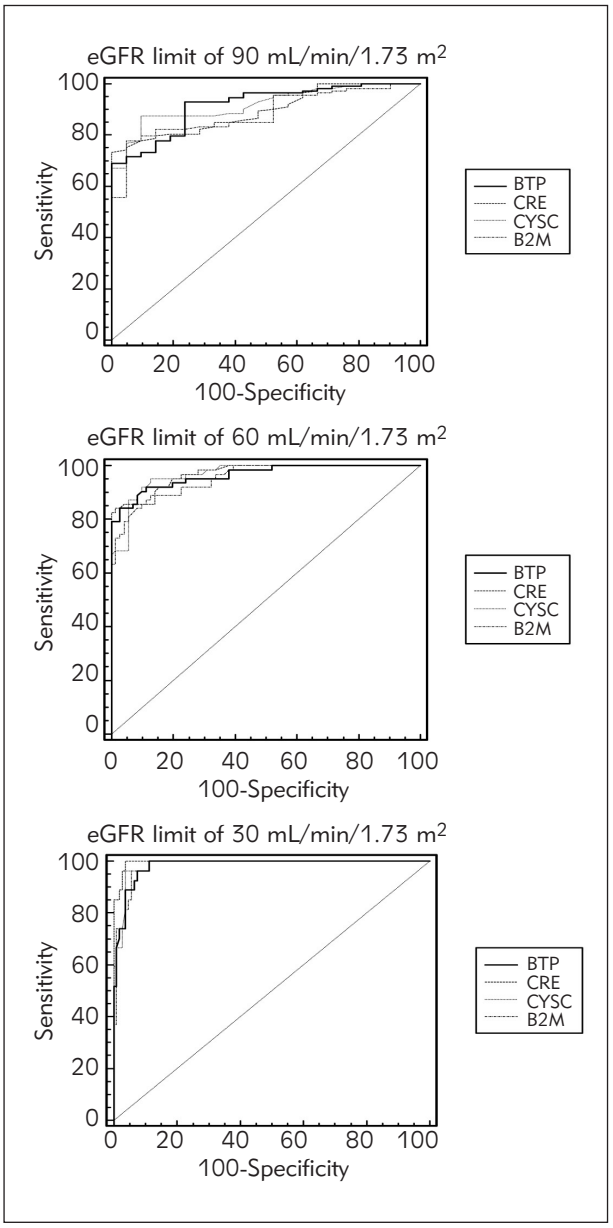

Figure 2. ROC analysis plots at GFR limits of 90, 60 and 30 mL/min/1.73 m^2 for beta-trace protein (BTP), creatinine (CRE), cystatin C (CYSC) and β_2-microglobulin (B2M) in the serum of patients with CKD. The areas under the curves (AUCs) were not significantly different ($P > 0.05$).

creatinine clearance may be useful for the clinical conditions, other than kidney disease, that affect GFR, but it remains inaccurate because of collection errors and changes in creatinine excretion (27). Various creatinine-based formulas have been developed in an attempt to improve the estimation of GFR from serum creatinine, and the MDRD formula is the current recommendation. Recently, it has been reported that the CKD-EPI formula performed better than the MDRD formula, especially at higher GFR, with less bias, improved precision and greater accuracy (5).

In this study, GFR was estimated using one of the BTP-based formulas proposed by White et al. (4). These authors reported that this formula had low bias, good precision and accuracy, with 42% within 10% of the measured GFR (by technetium-diethylenetriamine pentaacetic acid clearance). The bias was lower and the accuracy was higher than for the MDRD formula. Another investigation showed that the performance of these formulas is comparable to that of the reexpressed MDRD formula in kidney transplant recipient patients (29). In this study, the BTP concentrations, as well as eGFRs calculated from White's formula, significantly correlated with creatinine clearance and eGFRs calculated from the MDRD formula, CKD-EPI formula and cystatin C-based formula. The highest correlation coefficients were obtained with eGFRs from creatinine-based formulas, and the lowest with creatinine clearance (the coefficients were from 0.928 to 0.673). Similar significant correlations between GFR, estimated by an exogenous filtration marker clearance, and the reciprocal concentrations of BTP were reported (3, 14).

In order to determine the diagnostic accuracy of BTP and other renal markers for the detection of reduced renal function in CKD stages, ROC analysis was done. Beta-trace protein showed almost the same diagnostic value as other renal markers for eGFRs of < 30, < 60 and < 90 mL/min/1.73 m^2 (*Table III*). The areas under the ROC curves for BTP for these eGFR limits were from 0.983 to 0.917 and they were not significantly different from AUCs for other renal markers. The sensitivities and specificities of BTP for the optimum cutoff values (0.65 mg/L, 1.27 mg/L, 1.88 mg/L) at these eGFR limits were also very similar to the sensitivities and specificities of other markers. The highest sensitivity for BTP (96.3%) was for detecting a GFR of 30 mL/min/1.73 m^2 with serum BTP of 1.88 mg/L. The highest specificity for BTP (97.2%) was for detecting a GFR of 60 mL/min/1.73 m^2 with serum BTP of 1.27 mg/L. The limitation of this analysis was that GFR values from the MDRD formula were used for establishing the CKD stage instead of directly measured GFR values. In published data, where GFR was determined by measuring the exogenous filtration marker clearance, serum BTP and cystatin C had higher diagnostic accuracy than serum creatinine for the identification of reduced GFR values in adults and children (3, 23, 24, 30).

Therefore, the results of our study support other reported data that BTP may be a useful and reliable marker of renal dysfunction and may have a place beside serum cystatin C and creatinine as an alternative endogenous GFR marker in patients with chronic kidney disease.

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