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Serum Beta-Trace Protein versus Glomerulus Filtration Rate as a Predictor for Kidney Function among Hypertensive Patients

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ABSTRACT

Beta-Trace Protein (BTP) is a low-molecular-weight glycoprotein that can convert prostaglandin H2 into prostaglandin D2 and is associated with the vascular function's alteration. Serum beta-trace protein has been proposed as a promising marker in predicting kidney function in hypertensive patients. This study aimed to analyze the correlation between BTP and glomerulus filtration rate, particularly in hypertensive patients. A cross-sectional survey was conducted on 70 hypertensive participants admitted to Dr. Wahidin Sudirohusodo Hospital from July-August 2019. Beta-trace protein, serum urea, creatinine, blood pressure, and anthropometric were measured. The Glomerulus Filtration Rate (GFR) with Cockcroft Gault was graded using GFR stages. The hypertension was graded according to the category of the European Society of Cardiology (ESC) 2018. A descriptive test, Kruskal-Wallis test, Fisher exact test, Spearman correlation test, and logistic regression test were performed at a confidence level of 95%. Significant differences were found between the age, systole, diastole, blood urea, creatinine, and GFR ($p=< 0.05$). There was a significant difference between GFR and the degree of hypertension ($p=< 0.001$), but no differences were found in the mean value of BTP and the degree of hypertension ($p=0.348$). A significant negative correlation was found between GFR and BTP ($p=0.028$, $r_s= -0.263$). Logistic regression test showed that the increased BTP led to 2.591 times greater possibility of end-stage renal disease with GFR < 15 mL/min/ 1.73 m^2 (crude odds ratio 95% CI 1.168-5.475). Serum beta-trace protein possesses a prognostic ability of glomerulus filtration rate and can be used to predict the odd of end-stage renal disease in hypertensive patients.

Keywords: Serum beta-trace protein, glomerular filtration rate, hypertension

INTRODUCTION

Hypertension or high blood pressure increases the systolic blood pressure of more than 140 mmHg and diastolic blood pressure of more than 90 mmHg on two measurements with an interval of 5 minutes in a resting state. The World Health Organization (WHO) in 2015 showed that approximately 1.13 billion people in the world suffer from hypertension.[1] The American Heart Association defines hypertension as systolic blood pressure equal to or more than 130 mmHg and diastole greater than or equal to 80 mmHg.[2] European Society of Cardiology (ESC) or the European Society of Hypertension (ESH) in 2018 explains that normal hypertension is the blood pressure of 120-129 mmHg and/or diastolic blood pressure of 80-84 mmHg, normal-high is the systolic blood pressure of 130-139 mmHg and diastolic blood pressure of 85-89 mmHg. Hypertension is further classified into Grade 1, 2, and Grade 3.[3,4]

Hypertension can have both mechanical effects and wall shear stress on artery walls. Wall Shear Stress (WSS) is the lateral biomechanical force determined by blood flow, vessel geometry, and fluid viscosity. Shear stress is essential for endothelial cell stimulation and vascular function. Active and reactive endothelial cells participate in hemostasis, immune reactions, inflammation, and regulate blood vessel tone through the production of nitric oxide, endothelin, and prostaglandins.[5] Laminar shear stress via protein I activator in vascular endothelial cells induces the expression of lipocalin-type Prostaglandin D Synthase (PGDS-L), which is further synthetically expressed by smooth muscle cells in intimal atherosclerotic lesions. Lipocalin-type prostaglandin D synthase or known as Beta-Trace Protein (BTP), is a low-molecular-weight glycoprotein (23,000-29,000 Daltons), which converts Prostaglandin H2 (PGH2) into Prostaglandin D2 (PGD2) and plays an essential role in the maintenance of vascular function.[6]

Beta-trace protein can predict cardiovascular injury in humans. Beta-trace protein resides in myocardial cells, endocardial cells atria and ventricles, coronary arteries, smooth muscle cells,

and atherosclerotic plaque. Serum and urine BTP levels may be elevated in patients with renal impairment.[7,8]

Hypertension with renal impairment is associated with a further increase in BTP concentrations in serum and urine. Increased serum BTP is related to urinary BTP excretion. Urinary BTP precedes the increased excretion of urinary albumin. This increase may represent injury in the renal tubules and arterioles caused by hypertension.[7-9]

Hirawa *et al.* reported that serum BTP levels and excretion of BTP in the urine were significantly higher in patients with essential hypertension than patients with normotensive subjects. Hypertension with kidney injury is associated with increased concentrations of BTP in serum and urine. Chronic kidney disease can be detected by assessing the kidneys' excretory function according to the calculation of the glomerular filtration rate.[8-10] Beta-trace protein levels can predict the prognosis of end-stage renal disease better than other markers such as glomerular filtration rate, cystatin C, and serum creatinine.[11]

This study aimed to analyze the correlation between serum BTP and glomerular filtration rate in hypertensive patients at Dr. Wahidin Sudirohusodo Hospital, Makassar.

METHODS

This study was cross-sectional research using primary data on patient serum and secondary data from patient medical records. Sampling was performed at the Laboratory of Clinical Pathology at Dr. Wahidin Sudirohusodo Hospital, Makassar, patients' data were collected from Installation of Medical Records, and research procedure was carried out at the Hasanuddin University Faculty of Medicine research unit of Faculty of Medicine, Hasanuddin University/Hasanuddin Hospital from July to August 2019.

Serum beta-trace protein was measured by Enzyme-Linked Immunosorbent Assay (ELISA) using a human lipocalin-type prostaglandin D synthase kit (Bioassay Technology Laboratory Technology, China), and the results were expressed in mg/L.

This study's sample was collected from July to August 2019 from Outpatients and Inpatients who met the inclusion criteria consisting of patients diagnosed with hypertension and underwent a creatinine urea test. The degree of hypertension was determined according to the European Society of Cardiology (ESC) 2018. The National Kidney Foundation recommends that the Glomerular Filtration Rate calculation (GFR) is based on serum creatinine, age, body weight, and gender using the Cockcroft and Gault equation.

The glomerular filtration rate is divided into several categories. The GFR values ≥ 90 mL/min/1.73m^2, GFR 60-89 mL/min/1.73m^2, GFR 30-59 mL/min/1.73m^2, GFR 15-29 mL/min/1.73m^2, and GFR < 15 mL/min/1.73m^2. This category would be further correlated with serum BTP levels. Statistical Package for the Social Sciences (SPSS) was used for statistical analysis. Data were statistically analyzed with the Spearman correlation test, The Kruskal-Wallis test, the Fisher exact test, and the logistic regression test, $p < 0.05$.

This study was approved by the Health Research Ethics Committee of Faculty of Medicine, Hasanuddin University/Dr. Wahidin Sudirohusodo Hospital, Makassar, with number 567/UN4.6.4.5.31/PP36/2019, considers respect for subject, beneficence, non-maleficence, and justice.

RESULTS AND DISCUSSIONS

This study involved 70 patients who met the inclusion and exclusion criteria. Inclusion criteria in this study were patients diagnosed with hypertension by clinicians, both patients with a recent diagnosis of hypertension or current treatment in Outpatient and Inpatient Clinics. Patients with the icteric and lipemic serum were excluded. Urine and creatinine levels were measured at the same time as the intake of serum BTP intake. Complete patients' identity, including medical record, blood pressure, and body weight, were recorded.

Table 1 shows the subjects' characteristics classified by gender, age, body weight, systolic blood pressure, diastolic blood pressure, urea, creatinine, BTP, and GFR.

There was a significant difference between the mean GFR with age, systolic blood pressure, diastolic blood pressure, urea, and creatinine levels with p-value < 0.05 (Table 2).

Table 3 generally explains that there was a significant difference between the degree of hypertension according to ESC 2018 classification with the mean value of filtration rate (p= < 0.001); however, based on the degree of hypertension, there was no significant difference with the mean value of BTP (p=0.348).

Based on analysis using the Spearman correlation test, there was a weak negative correlation between BTP as the dependent variable and GFR as the

Table 1. Characteristics of research subjects

Variable		Value (%)	Mean±SD
Gender			
Male		48 (68.6)	
Female		22 (31.4)	
Age (years)	Min-Max	19-81	55.16±0.20
Bodyweight (kg)	Min-Max	31-85	56.91±10.76
Systolic pressure (mmHg)	Min-Max	102-197	143,89±2.04
Diastolic pressure (mmHg)	Min-Max	59-117	85.3±9.92
Urea (mg/dL)	Min-Max	8-286	80.74±6.09
Creatinine (mg/dL)	Min-Max	0.5-22.39	3.54±3.91
Beta-trace protein(mg/L)			
Male			1.22±0.97
Female			0.94±0.37
Total			1.13±0.84
	Min-Max	0.68-5.20	
GFR (mL/min/1.73 m^2)	Min-Max	0.48-192.81	40.32±3.64
Normal LFG ≥ 90mL/min/1.73m^2		9 (12.9)	
GFR 60 -89 mL/min/1.73m^2		10 (14.3)	
GFR 30-59 mL/min/1,73m^2		13 (7.1)	
GFR 15-29 mL/min/1.73m^2		17 (18.5)	
GFR < 15mL/min/1.73m^2		21 (30)	
Blood pressure (ESC 2018)			
Normal–high (130-139) and/or (85-89)		26 (37.1)	
Grade 1 (140-159) and/or (90-99)		26 (37.1)	
Grade 2 (160-179) and/or (100-109)		11 (15.8)	
Grade 3 (≥ 180) and/or ≥ 110		7 (10)	

Table 2. Difference of variables mean value based on the mean value of GFR

Variable	Mean of Glomerular Filtration Rate					p-value
	≥ 90mL/ min/1.73m^2	60-89 mL/ min/1.73m^2	30-59 mL/ min/1.73m^2	15-29 mL/ min/1.73m^2	< 15 mL/ min/1.73m^2	
Age (years)[a]	39.22±16.57	34.6±13.06	60.61±14.64	55.76±15.68	54.42±12.84	0.013*
Gender[b]						
Male	7	8	10	9	14	0.726
Female	2	2	3	8	7	
Body weight[a]	62.23±12.16	61.5±10.07	58.92±9.95	50.29±11.92	56.52±7.61	0.057
Systolic[a]	126.89±12.5	141.9±27.49	141,15±17.26	143.17±19.33	154.38±17.41	0.006*
Diastolic[a]	81.44±7.73	77.8±8.94	85±7.86	86.64±11.81	89.62±8.65	0.023*
Urea	23.3±8.48	34.6±13.06	59±30.64	93.41±35.60	130,52±74.48	< 0.001*
Creatinine	0.76±0.22	0.88±0.11	1.49±0.58	2.56±0.84	8.05±4.50	< 0.001*

a. Kruskal-Wallis test b. Fisher exact test * Significant at confidence interval of 95%, p < 0.05 was significant

Table 3. ESC 2018 classification of hypertension with mean GFR and mean BTP

Classification of Hypertension	Mean GFR	p	Mean BTP	p
Controlled	60.05±41.82		0.94±0.36	
Grade 1	36.78±28.83	<0.001	0.76±0.57	0.348
Grade 2	13.15±18.83		1.82±1.55	
Grade 3	22.81±21.58		1.26±0.99	

* Kruskal-Wallis test. Significant at confidence interval of 95%, p < 0.05 was significant
GFR=Glomerular Filtration Rate; BTP= Beta-Trace Protein

independent variable with r = -0.263 and p=0.028. It was shown in this study that a higher GFR led to a lower BTP. Contrastingly, a lower GFR led to a higher BTP.

A logistic regression test was used to analyze the probability of changes in BTP values for the incidence of chronic renal failure or GFR < 15 mL/min/1.73 m^2. The results of this test indicated that the increased BTP led to 2.591 times greater risk (crude odds ratio) to the incidence of chronic renal failure (95% CI 1.168-5.745) (p=0.019).

This study used a cross-sectional design involving 70 patients who met the inclusion and exclusion criteria. Table 1 shows that samples in this study consisted of a higher number of males (68.6%) than females (31.4%), suggesting a similar result to a study by Bhavsar *et al.*, which involved predominant males samples. Hormonal factors play an important role due to the production of female estrogen. The incidence of hypertension in females will increase after menopause. The mean age and body weight in this study was 55.16±0.20 years and 56.91±10.76 kg, respectively. Serum BTP was 1.131±0.84 mg/L and was higher in males compared to females. This result was in line with a study by Mohammed *et al.*, which suggested that the serum BTP in males was higher than in females with a mean serum BTP of 1.36±0.36 mg/L.[12] Normal BTP for males and females is 0.33-0.77 mg/L and 0.40-0.70 mg/L, respectively.[7] The mean urea and creatinine in this study were 80.74±6.09 mg/dL and 3.54±3.91 mg/dL, while the normal value of urea and creatinine in males is 10-50 mg/dL and < 1.3 mg/dL. Normal creatinine levels in females < 1.1 mg/dL. The GFR was calculated using the Cockcroft and Gault equation.[7]

The difference in mean variables based on the classification of GFR is described in Table 2. The variables consisting of age, systolic blood pressure, diastolic blood pressure, urea, and creatinine had significant differences in GFR. The results of this study were in line with a study by Donadio *et al.* and Bhavsar *et al.*, which showed a significant relationship between age, systolic blood pressure, diastolic blood pressure, urea, and creatinine with the mean GFR.[7,11]

According to ESC 2018 classification of hypertension with mean GFR and mean BTP (Table 3), there was a significant difference in the degree of hypertension with the mean value of filtration rate (p= < 0.001). However, based on the analysis of the degree of hypertension, there was no significant difference with the mean value of BTP (p=0.348).

The European Society of Cardiology (ESC) or the European Society of Hypertension (ESH), in 2018, classified hypertension into optimal, normal, high-normal, Grade I hypertension, Grade II hypertension, and Grade III hypertension.[3,4] This study found 26 patients (37.1%) with normal blood pressure, 26 patients (37.1%) with Grade 1 hypertension, 11 patients (15.8%) with Grade 2 hypertension, and seven patients (10%) with Grade 3 hypertension.

Blood pressure control is an essential factor to slow down the progression of chronic renal failure and cardiovascular disease because kidneys are the main target for organ damage in hypertension and long-term exposure to elevated blood pressure.[12] The results obtained in this study were not in line with a study by Bhavsar *et al.*, which suggested that serum BTP was found higher in patients with hypertension. Hirawa *et al.* stated that hypertension could be associated with kidney injury characterized by a decrease in the GFR.[9,11] A study by Mohammed *et al.* found a highly significant correlation between BTP in the serum of patients with chronic renal failure with creatinine and Cystatin C.[13] Beta-trace protein can play a role in the pathophysiology of cardiovascular disease and has a predictive value as a marker of kidney function.[14]

There was a weak negative correlation between the GFR and the BTP (p=0.028). A higher GFR led to a lower BTP. Contrastingly, a lower GFR led to a higher BTP. This study's results were similar to research by Donadio *et al.*, which showed that BTP reabsorption decreases along with the stage of GFR.[7] A study by Pinero *et al.* showed that BTP could be used as a prognostic marker for GFR.[15]

A logistic regression test was performed to explain the probability of changes in BTP values for the incidence of chronic renal failure or GFR < 15 mL/min/1.73m^2. The results of this test indicated that the increase in the value of BTP contributed to 2.591 times of greater possibility (crude odds ratio) to the incidence of chronic renal failure (95% CI 1.168-5.745) (p-value = 0.019). Beta-trace protein diagnostic markers can be used to detect the severity of impaired kidney function. These markers can predict risk for kidney disease progression in patients with chronic renal failure or end-stage renal failure, indicating consistency with a study by Spannaus *et al.*[16]

CONCLUSIONS AND SUGGESTIONS

In hypertensive patients, there was a significant correlation between the degree of hypertension and the GFR. A higher GFR rate led to a lower BTP.

Beta-trace protein has the prognostic ability to predict the GFR and the probability of end-stage renal failure or GFR < 15 mL/min/1.73 m^2 as many as 2.591 times in hypertensive patients.

Beta-trace protein is one of the renal function tests, which can be measured, and other kidney function tests in hypertensive patients to prevent complications leading to end-stage renal failure.

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