Research

Analysis of N-Terminal Fragment B Type Natriuretic Peptide Serum In Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) is a condition of decreased kidney function due to chronic and irreversible renal parenchymal damage. Chronic kidney disease is one of the world's health problems due to its high prevalence of the disease, increasing morbidity and mortality rates and expensive treatment costs. Cardiovascular complications have been recognized as the leading cause of death in CKD. Left ventricular hypertrophy (LVH), systolic and diastolic dysfunction are the most common cardiovascular complications found in CKD. NTproBNP is an early diagnostic and prognostic biomarker of cardiovascular diseases, hence it can distinguish between acute and chronic cardiovascular diseases. Therefore, this examination is recommended to monitor patient treatment. NTproBNP levels circulating in the circulations of cardiovascular patients are about six times higher than other biomarkers including BNP. This study aims to assess serum NTproBNP levels in various degrees of CKD. This research is an observational analytic study with cross sectional approach. It was conducted between June and August 2019 at Dr. Wahidin Sudirohusodo hospital with total sample of 86 patients diagnosed with CKD who met the inclusion and exclusion criteria. Based on the Kruskal Wallis test, which were used due to abnormal data distribution, a significant difference was found in serum NTProBNP levels based on the degree of CKD with the initial increase occured in grade III CKD with mean value of 4,653 ng/L. Serum NTproBNP levels were not significantly different based on the degree of hypertension. Serum NTProBNP levels were significantly correlated with urea and creatinin levels and GFR value based on the Rho Spearman correlation test with a p value <0.05.

Keyword: *Chronic Kidney Disease, NTProBNP, Glomerular Filtration Rate, Hypertension*

Introduction

Chronic kidney disease is a condition of decreased kidney function that is chronic and irreversible. A person is diagnosed with CKD if there is an abnormality and damage to his the kidneys for approximately 3 months which is characterized by a decrease in kidney function with or without an abnormality of the kidneys. Chronic kidney disease is one of the world's health problems due to its high prevalence, increased morbidity and mortality rates and it requires expensive treatment costs. The increased prevalence of CKD is in line with the increased incidence of obesity, diabetes mellitus (DM), dyslipidemia and high blood pressure as the risk factors for CKD.[1,2]

About 20 million (10.8%) of the population of the United States experience CKD and 400,000 (0.1%) of them are categorized as ESRD which must be treated with dialysis (hemodialysis or periotenal dialysis) or kidney transplantation. Based on the data compiled from the 9th Annual Report of the Indonesian Renal Registry, the number of deaths of CKD patients in 2016 in Indonesia was 2,221 with cardiovascular complications

as the highest cause of death with the prevalence of left ventricular hypertrophy (49%) and coronary heart disease was 40%.[3]

Over the past decade, cardiovascular complications have been recognized as the leading cause of death in CKD. Left ventricular hypertrophy (LVH), systolic and diastolic dysfunction are the most common cardiovascular complications found in CKD. Most researchers report cardiovascular complications starting at the onset of decreased LFG. For CKD patients, especially at grade V, the decrease in LFG causes the disruption of water, electrolyte, and urea regulation. This leads to an increase in extracellular volume and vascular volume due to the retention of sodium and water by the kidneys. Increased vascular volume causes cardiac burden and strain increase resulting in cardiovascular diseases.[4]

Clinical manifestations experienced by CKD patients such as anemia, hyperkalemia, malnutrition, inflammation and impaired calcium and folate metabolism are involved in accelerating the process of heart damage. Hemodialysis is a therapy commonly experienced by CKD patients to control uremia, excess of fluid, and maintain electrolyte balance. Actions of hemodialysis repeatedly cause new problems with the emergence of various kinds of comorbidities, especially cardiovascular disease (68.4%). The slow identification of asymptomatic cardiovascular complications is a major cause of death in patients with CKD.[5,6,7]

Various biomarkers have been recommended as markers of cardiovascular diseases such as troponin, natriuretic peptides (BNP), N-terminal fragments of B-type natriuretic peptide (NTproBNP), C-reactive protein (CRP), Creatin Kinase (CK), Lactate dehydrogenase (LDH), homocysteine and plasminogen activator inhibitor 1 (PAI-1). Biomarkers that are considered to be clinically useful should have high sensitivity and specificity for detecting diseases with coefficient of low enough variation so that small changes in biomarkers reflect actual changes in the patient's clinical condition. N-terminal fragment B-type natriuretic peptide is an early diagnostic and prognostic biomarker of cardiovascular diseases, is able to differentiate between acute and chronic cardiovascular disease and is recommended for examination in follow-up therapy. NTproBNP levels circulating in the circulation of cardiovascular patients are about six times higher than other biomarkers including BNP. NT-proBNP levels increase along with increasing severity of heart failure and serve as a screening test for heart failure and asymptomatic left ventricular dysfunction.[8,9]

Methods

This study is an observational analytic study with cross sectional approach analyzing NTproBNP as an early diagnostic and prognostic biomarker of cardiovascular disease. The study was conducted during Juny until August 2019 at Clinical Pathology Laboratory of Dr. Wahidin Sudirohusodo Hospital Makassar. The study sample was all CKD patients diagnosed by Internists based on Glomerular Filtration Rate (GFR) by using cockroft-Gault formula. Patients who have been diagnosed with heart disease, obesity and patients who have undergone HD for more than 3x were excluded. All subjects were tested for serum NTproBNP, ureum, creatinine levels in Hasanuddin University Faculty of Medicine Research Unit/Hasanuddin University Hospital. NTproBNP assay was carried out with the Cat. No E-EL-H090296T ELISA kit.

Data were analyzed statistically by Kruskal Wallis test to determine the differences in NTproBNP levels of CKD in various degrees and hypertension. Spearman correlation tests was performed to analyze the correlation of NTproBNP levels with ureum creatinine levels and GFR. The results were considered significant if $p<0.05$.

Results

The study samples obtained were 86 CKD patients who met the inclusion criteria. The characteristics of the study samples can be seen in table 1 that shows male subjects were more than female. Most study subjects were found in the 36-59 years-old group. Most of the study subjects had a history of hypertension and DM with a percentage of 44.2% and 22.1%, respectively.

Table 1. Sample characteristics

Sample characteristics	N (%)	Mean ± SD	p
Gender			
Male	57 (66.3)		
Female	29 (33.7)		
Age (years)		47.19 ± 11.88	0.036
NTProBNP (ng/L)		7.57 ± 8.29	0.013
Ureum (mg/dL)		89.01 ± 47.69	0.200*
Creatinine (mg/ dL)		3.51 ± 2.37	0.010
GFR (mm/menit/1.73 m2)		32 ± 22.7	0.200*
Platelet (x103/mm3)		273.65 ± 123.16	0.077*
Haemoglobin (gr/dL)		10.32 ± 2.19	0.083*
Blood Pressure			
Pre Hypertension	44 (51.2)		
Hypertension I	29 (33.7)		
Hypertension II	13 (15.1)		
Basic Diseases			
Hypertension	38 (44.2)		
Diabetes Mellitus	19 (22.1)		
Other diseases	19 (22.1)		
More than one diseases	10 (11.6)		

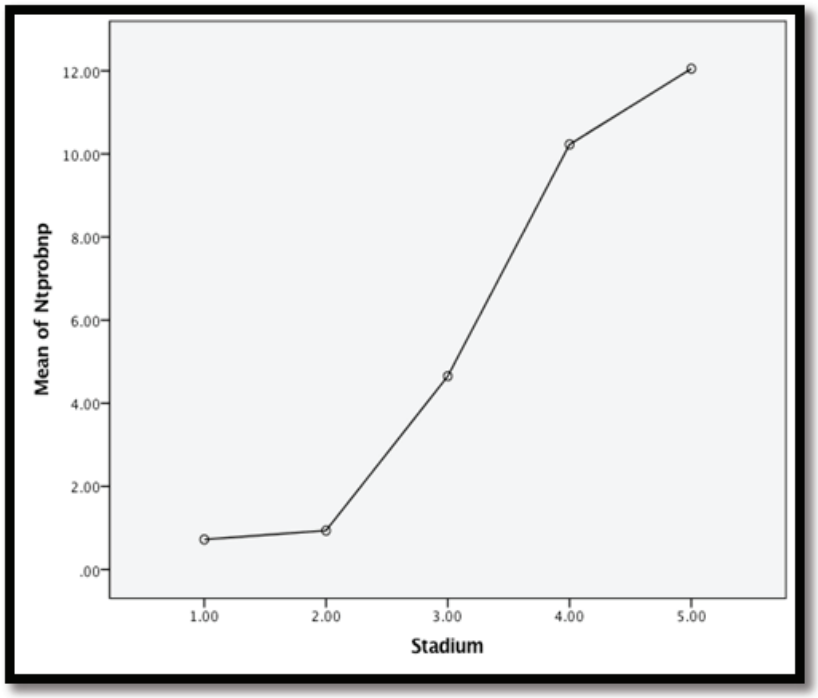
Table 2. Comparison of NTproBNP levels based on various degrees of CKD

*Kruskall Wallis Test

Table 2 showed the comparison of NTproBNP levels in various degrees of CKD patients. This study showed a significant difference NTproBNP levels in various degrees of CKD patients with p=0.000.

Degree	NTproBNP Levels (ng/L)		
	N	Median (Min – Max)	P value
I	4	0.68 (0,58- 0.95)	
II	8	0.67 (0.36- 1.99)	
III	28	2.72 (0.34 – 30.45)	0.000*
IV	24	7.5 (0.60 – 34.93)	
V	22	9.67 (0.60 – 35.28)	

As shown on graph 1, the average level of NTproBNP began to increase at degree III with a mean of 4.65 ng / L and reached the highest level at degree V (mean = 12.05 ng / L).



Graph 1. Average Ntprobnp Levels Based on PGK Degrees

Table 3. Comparison of NTproBNP levels based on the degree of hypertension

Degree	NTproBNP Levels		
	N	Median (Min – Max)	P value
Pre Hypertension	44	3.79 (0,36- 35.28)	
Hypertension I	29	7.67 (0.34- 23.95)	0.708
Hypertension II	13	2.72 (0.58 – 15.53)	

*Kruskal Wallis Test

Table 3 showed the majority of the subjects was in the pre hypertension group, counted for 44 subjects. There was no significant difference in NTproBNP level at various degrees of hypertension (p = 0.708) based on the results of the Kruskall Wallis test.

Table 4. Correlation of NTproBNP levels with serum urea and creatinine levels

		Ureum	Creatinine
NTproBNP	N	86	86
	p	*0.019	*0.007
	r	0.253	0.289

*Correlation Spearman Rho test

Statistical analysis showed a positive correlation of NTproBNP levels with the ureum and creatinine levels with a weak correlation (r=0.50) as shown in Table 4

Table 5. Correlation of NTproBNP levels with GFR degrees

		GFR degrees
NTproBNP	N	86
	p	0.000
	r	-0. 579

*Correlation Spearman Rho test

Statistical analysis showed a negative correlation of NTproBNP levels with the GFR degrees levels with a medium correlation (r=-0.579) as shown in Table 5

Discussion

This study was conducted at Dr. Wahidin Sudirohusodo Hospital Makassar during the June-August 2019 period, involving 86 patients, including male (66.7%) and female (33.7%). Most patients with CKD were found in the average age of 47 years-old with the most common underlying disease is hypertension (38%). This is in line with the Indonesian Renal Registry (IRR) data (2016), showing that the highest prevalence of kidney failure found in male (0.5%) and female (0.2%) of all patients who are generally caused by diabetic nephropathy (52%), hypertension (24%), kidney stones, ureteric stones (6%), gout (1%), lupus disease (1%) and others (IRR, 2016). This result is dissimilar with what has been described by Kamelia that the number of CKD is not different between male and female.

NTproBNP levels were found to differ at each CKD levels and began to increase in the third grade CKD with a decrease in LFG <60 mm / min / 1.73 m2 with a median value and a minimum-maximum value of 2.72 (0.34 - 30.45). This study is in line with research conducted by Horii et al in Japan, BNP and NTproBNP levels were associated with cardiomyocyte damage in patients with CKD grade IV and V compared to the grade with the I-III grade. In a Chinese study, NTproBNP was the cause of death in patients with LFG <60 ml / min per 1.73 m2. In addition, the limit of NTproBNP associated with mortality is higher in patients with CKD (2584 pg / ml) than in people without CKD (370 pg / ml).[10,11]

Several studies conducted in the United States concluded that an increase in NTproBNP had a four times higher risk of cardiovascular complications than patients without CKD. The increasing prevalence of CKD is one of the main problems related to the incidence of heart failure as a complication which is 56% asymptomatic. Therefore, new parameters are needed to help in the identification and early detection of heart failure in CKD. The NTproBNP parameter is one of the molecules synthesized in cardiac myocytes in response to stress by stretching the left ventricular wall. Apart from being more stable in shape, a longer half-life is a better biomarker for chronic volume expansion or stress than BNP.[12,13]

The results of this study showed no significant difference between blood pressure (TD) and serum NTproBNP levels based on the degree of hypertension. This is not in line with research conducted by Supriati W, 2018 who found the opposite, showed that there is a significant difference in NTproBNP levels in the degree of BP increase associated with the duration of hypertension. [14]This study uses research samples with various causes of CKD such as HT, DM, ureteric stones, pyelonephritis and other diseases so that the blood pressure in patients varies greatly and is influenced by several factors such as therapy, duration of disease and etiology of more than 2 diseases.

Hypertension is one of the main risk factors for cardiovascular diseases, such as heart failure, acute myocardial infarction and even sudden death. Patients with hypertension can experience cardiac arrhythmias and abnormalities such as left ventricular hypertrophy (LVH) and left ventricular systolic dysfunction (LVSD), due to the induction effect by the left ventricular hypertrophic response to increase post cardiac load. Detection of this condition is very important in the management of hypertensive patients. Therefore, NTproBNP is used as a marker for the detection of heart failure.[15,16]

This study found a significant correlation between serum NTproBNP levels with urea levels (p = 0.019) and creatinine (p = 0.007) with a weak correlation. This is in line with research conducted by Astor BC in 2008, concluding that there is a significantly stronger correlation in CKD patients with proteinuria associated with impaired renal filtration function with a p value = 0.05. This study is different with research conducted by Fabio et al, 2011 NTproBNP levels is correlated with urea and creatinine and GFR with a p value> 0.05. Patients with CKD who undergo HD, have a higher cardiovascular risk of suffering from heart disease than non-HD patients. Left ventricular hypertrophy and left ventricular dysfunction are currently considered the strongest predictors of cardiovascular diseases and total mortality in the dialysis population. Left ventricular hypertrophy is a widespread complication of end-stage renal disease with prevalence rates ranging from 60 to

80%. [12,17]

This study found higher levels of NTproBNP in HD patients compared to patients without HD even though the patients were asymptomatic. NTproBNP levels are going to increase as a result of decreased renal excretion and fluid volume and due to several other factors such as uremic syndrome, blood contact with the dialysis membrane and progression to decrease LFG. NTproBNP can routinely be used as a diagnostic tool to detect LVD in CKD patients.

This study has several limitations, This study did not analyze the length of continuation of the underlying disease and the given treatment, the history of other risk factors causing cardiovascular disease such as smoking and not evaluating the cardiovascular diseases by echocardiography.

Conclusion and Suggestion

This study concluded that there were differences in NTproBNP levels in various degree of CKD and begin to increase in the third stage. There was no difference in NTproBNP levels in the degree of hypertension. There was a weak positive correlation between NTproBNP levels and ureum creatinine levels and medium negative correlation with GFR. Patients with CKD, it can be considered NTproBNP examination to prevent further cardiovascular complications. Beside that, further researches that measures NTproBNP levels in CKD by considering echocardiography examination to establish a definitive diagnosis of cardiovascular complications.

Ethical Clearance- Taken from Health Research Ethics Commission, Medical Faculty, Hasanuddin University – RSPTN UH – RSUP Dr. Wahidin Sudirohusodo Makassar

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Conflict of Intereset- nil

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