Exp Biomed Res 2020; 3(1): 30-36 DOI: 10.30714/j-ebr.2020157451

EXPERIMENTAL BIOMEDICAL RESEARCH
http://www.experimentalbiomedicalresearch.com

Original Article

Role of N-terminal pro b-type natriuretic peptide (NT-pro-BNP) in compensated chronic kidney disease

Tuba T. Duman[1] · Hikmet Tekce[2] · Buket Kin Tekce[3]

[1]*Department of Internal Medicine, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey*
[2]*Department of Nephrology, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey*
[3]*Department of Medical Biochemistry, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey*

ABSTRACT

Aim: To evaluate the role of N-terminal pro b-type natriuretic peptide (NT-pro-BNP) in the evaluation of hypervolemia in chronic kidney disease (CKD) and its relationship with CKD.

Methods: Sixty compensated chronic kidney disease patients enrolled in this study. NT-pro BNP levels and other routine biochemical laboratory parameters are studied. The associations between results were analyzed.

Results: NT-pro BNP levels were correlated with urea *($r = 0.66$, $p < 0.01$)*, creatinine *($r = 0.69$, $p < 0.01$)* and phosphorus *($r = 0.36$, $p < 0.01$)* values and were negative correlated with hemoglobin *($r = -0.32$, $p = 0.01$)*, hematocrit *($r = -0.36$, $p < 0.01$)*, albumin *($r = -0.29$, $p = 0.02$)* and glomerular filtration rate (GFR) values *($r = -0.35$, $p < 0.01$)*.

Conclusion: The positive correlation between NT-pro BNP levels and urea and creatinine values in our study and the negative correlation with GFR support that the severity of hypervolemia increases as the CKD stage progresses. BNP and NT-pro BNP are strong predictors of all-cause cardiovascular mortality in asymptomatic CKD patients. In the light of all these data, it is possible to suggest that NT-pro BNP is associated with hypervolemia and therefore increased cardiovascular mortality in subjects with CKD.

Keywords: Chronic kidney disease, NT-pro BNP, hypervolemia.

✉ *Dr. Tuba T Duman, Department of Internal Medicine, Faculty of Medicine, Bolu Abant Izzet Baysal University, Bolu, Turkey.*
E-mail: doktortuuba@gmail.com
Received: 2019-11-14 / Accepted: 2019-12-03
Publication Date: 2020-01-01

Introduction

Chronic kidney disease (CKD) is a disease that causes significant morbidity and mortality and associated cardiovascular diseases are common [1]. Left ventricular hypertrophy (LVH), one of the cardiovascular problems, is a strong predictor of mortality in CKD [2,3]. Therefore, early detection of LVH in this population is of great importance in preventing mortality and in determining CVD risk. LVH is caused by prolonged exposure to increased volume load in CKD patients and can be detected by echocardiography. However, some serum markers have been shown to play a role in

determining LVH. For example, the N-terminal pro-brain natriuretic peptide (NT-pro BNP) has been reported in many studies as an important predictor of LVH in CKD patients [4-7].

Increased extracellular volume, myocardial strain and increased left ventricular pressure are among the main causes of elevation of NT-pro BNP levels in CKD patients [8]. This hormone is a member of the family of natriuretic peptides, known as vasoactive hormones, and when activated via neurohumoral pathways, plays a role in regulating blood pressure and maintaining volume balance by acting directly on the kidneys and systemic vessels [9,10].

In the light of current literature, in this study, we aimed to evaluate the role of NT-pro BNP in the evaluation of hypervolemia in CKD and its relationship with CKD.

Materials and Methods

This prospective study was conducted after approval by the local ethics committee (Decision no: B.30.2. ABÜ.0.20.05.04-050.01.04-08). Patients who were referred to our Internal Medicine-Nephrology clinic and diagnosed as compensated chronic renal failure were included in the study on a voluntary basis. Laboratory parameters were evaluated with blood samples taken at least eight hours after fasting were taken according to routine procedures in patients with compensated chronic renal failure. Complete blood count parameters were recorded on Mindrey BC-5380 analyzer; Glucose, urea, creatinine, sodium, potassium, total protein, albumin, calcium, phosphorus, parathormone, C-reactive protein (CRP) parameters were studied in Abbott C-8000 clinical chemistry autoanalyser. Plasma NT-pro BNP measurements; Electrochemiluminescence immunoassay method was used with Elecsys 2010 analyzer. Cockcroft-Gault formula, which is the most commonly used glomerular filtration rate (GFR) in clinical practice for the determination of CKD stage [Creatinine clearance = (140-Age) x (Ideal weight) (ml / min) / Serum creatinine (mg / dl) X 72 (female x 0.85)] was used [11].

Exclusion criteria were follows: Patients with congestive heart failure, heart valve diseases, coronary artery disease, cardiac operation history or cardiac pacemaker, cardiomyopathy, sick sinus syndrome, chronic obstructive pulmonary disease, morbidly obese and overweight, hypo / hyperthyroidism and chronic liver disease. Cases without consent to participate in the study were also excluded.

Statistical analysis

All statistical analyzes of the data were performed by SPSS (15.0 IBM Co., Chicago, Illinois, USA) program. The Pearson test was used to analyze the correlation coefficients and statistical significance between the clinical parameters whose normal distribution was demonstrated by analytical methods (using Kolmogorov Smirnov and Shapiro-Wilk tests). Spearman's correlation test was used for the relationship between at least one of the variables which did not show normal distribution or ordinal variables. The statistical difference between the independent parameters, whose normal distribution was shown by the tests mentioned above, was investigated by independent groups t test (Student's t test) and expressed as mean ± standard deviation. Kruskal Wallis test was used to compare the data with abnormal distribution and the results were expressed as median (min-max). Statistical significance level was accepted as $p < 0.05$.

Results

The study population consisted of 31 (51%) male and 29 (48%) female patients. The age of

Table 1. The clinical and laboratory findings of the study.

Parameter		Mean ± SD
Age (year)		60.8 ± 12.4
Gender	Female	29 (% 48)
	Man	31(% 51)
Weight (kilogram)		72.2 ± 11.1
Size (meter)		1.63 ± 0.1
BMI(weight/size²)		26.8 ± 3.6
DM time (year)		12 ± 5.7 *
Smoking cigarette	Yes	9 (% 15)
	No	51 (% 85)
Using Anti-HT	Yes	53 (% 88)
	No	7 (% 12)
Systolic blood pressure (mmHg)		136 ± 21
Diastolic blood pressure (mmHg)		79 ± 12
Heart rate (beat/min)		70 ± 7
Leukocyte (/mm³)		7163 ± 1955
Hemoglobin (g/dl)		11.7 ± 2.3
Hematocrit (%)		35.6 ± 6.9
Thrombocyte (/mm³x1000)		246 ± 71
Glucose (mg/dl)		122 ± 57
Urea (mg/dl)		84 ± 37
Creatinine (mg/dl)		2.36 ± 1.2
Sodium (mmol/l)		137 ± 4
Potassium (mmol/l)		4.6 ± 1.0
Total protein (g/dl)		6.8 ± 1.0
Albumin (g/dl)		3.8 ± 1.0
Calcium (mg/dl)		8.8 ± 1.0
Phosphorus (mg/dl)		3.9 ± 1.2
Parathyroid hormone (pg/ml)		130 ± 85.1
C-reactive protein (mg/l)		13.7 ± 19.1*
NT-pro BNP (pg/ml)		1181. 1 ± 2198.6
		473.7 * (min:37,5-max:14541)
GFR (Cocroft-Gault) (ml/min.)		36.3 ± 14.5
		33.6 * (min:12,1-max:73)

*Median value.

the patients was 60.8 ± 12.4 years. The mean GFR value of the CKD patients included in the study was 36.3 ± 14.5 ml / min. According to CKD stage, 5 (9%) patients were classified as stage 2, 31 (51%) patients as stage 3 and 24 (40%) patients as stage 4 CKD. Twenty-six (43%) patients were diagnosed with diabetes mellitus (DM) and the mean duration of diabetes was 12.0 ± 5.7 years. Nine (85%) people were smoking cigarette and 88% (53 cases) of the patients were using anti-hypertensive (anti-HT) treatment due to hypertension. The clinical and laboratory findings of the cases included in the study are presented in Table 1.

The mean NT-pro BNP values of the patients included in the study were 1181.1 ± 2198.6 pg / ml and the median value was 473.7 (min:37,55pg/ml-max: 14541pg / ml).

There was a positive correlation between NT-pro BNP levels and urea *(r = 0.66, p <0.01*), creatinine *(r = 0.69, p <0.01)* and phosphorus *(r = 0.36, p <0.01)* values and then negative correlation with hemoglobin *(r = -0.32, p = 0.01)*, hematocrit *(r = -0.36, p <0.01)*, albumin *(r = -0.29, p = 0.02)* and GFR values *(r = -0.35, p <0.01*). There was no correlation between age, height, weight, body mass index (BMI), smoking cigarette, use of anti-HT agents, DM time, blood pressures, heart rate and other laboratory findings and NT-pro BNP levels. The results of the analysis showing the correlation between NT-pro BNP level and clinical and laboratory parameters are shown in Table 2.

Discussion

The most important results of this study were that NT Pro BNP had a positive correlation with serum creatinine and phosphorus levels, which are important markers of renal function, and a

negative correlation with hemoglobin, hematocrit, albumin and GFR levels.

Table 2. The correlation between NT-pro BNP level and clinical and laboratory parameters.

Parameter	*p*	*r*
Age (year)	0.95	0.01
Size (meter)	0.20	0.16
Weight (kg)	0.27	0.14
BMI (weight/size²)	0.64	0.06
DM time (year)	0.19	0.27
Systolic blood pressure (mm Hg)	0.20	0.11
Diastolic blood pressure (mm Hg)	0.17	-0.17
Heart rate (Beat/min)	0.92	-0.01
Leukocyte (/mm³)	0.17	0.17
Hemoglobin (g/dl)	0.01	-0.32
Hematocrit (%)	<0.01	-0.36
Thrombocyte (mm³ x 1000)	0.15	-0.18
Glucose (mg/dl)	0.69	-0.05
Urea (mg/dl)	<0.01	0.66
Creatinine (mg/dl)	<0.01	0.69
Sodium (mmol/l)	0.43	-0.1
Potassium (mmol/l)	0.75	-0.41
Albumin (g/dl)	0.02	-0.29
Total protein (g/dl)	0.16	-0.18
Calcium (mg/dl)	0.58	-0.73
Phosphorus (mg/dl)	<0.01	0.36
Parathyroid hormone (pg/ml)	0.67	0.05
C-Reactive Protein (mg/dl)	0.09	0.25
GFR (ml/min.)	<0.01	-0.35

CKD is an important public health problem in the world and in our country (1). According to the data of the CREDIT study the prevalence of CKD from all causes in Turkey was estimated at 15.7% [12]. The main problem with this large group of patients is the inability to effectively control the complications as well as the disease. Cardiovascular diseases, commonly seen in patients with chronic renal failure, are a major cause of morbidity and mortality [1]. Cardiovascular diseases seen in CKD have a broad spectrum and these are mainly left ventricular hypertrophy, ischemic heart disease, heart failure, peripheral vascular diseases, cardiac arrhythmias and sudden death [13].

LVH is a strong predictor of mortality in CKD [13]. There are many studies in the literature that NT-pro BNP is a strong predictor of left ventricular hypertrophy. In a study by Satyan et al. [4] in asymptomatic HD patients, a significant relationship was found between NT-pro BNP and left ventricular mass index. In another study, it was shown that there is a direct relationship between NT-pro BNP and left ventricular hypertrophy in patients with end-stage renal disease (ESRD) [5]. Wang et al. [6] found that NT-pro BNP levels were significantly higher in patients with left ventricular dysfunction and severe left ventricular hypertrophy in a CKD cohort undergoing dialysis treatment. In another study performed by the same team, the association of NT-pro BNP with cardiovascular congestion, mortality and cardiac events was examined in a group of 230 patients with chronic peritoneal dialysis [7]. In this study, echocardiographic measurements were performed concurrently with basal NT-pro BNP value and all patients were followed up to 3 years. As a result of the study, a strong relationship was found between left ventricular EF, left ventricular mass index

and residual GFR and NT-pro BNP. NT-pro BNP has been shown to be an important predictor of cardiovascular congestion, mortality and cardiovascular side effects.

Studies have shown that left ventricular hypertrophy was detected at the beginning of dialysis treatment in more than 70% of CKD patients and that the frequency of left ventricular hypertrophy increased in this patient group over time [14,15]. The positive correlation between NT-pro BNP levels and urea and creatinine values in our study and the negative correlation with GFR support that the severity of hypervolemia increases as the CKD stage progresses. Deflippe et al. [16] found positive and significant correlation between NT pro BNP and LVH in asymptomatic compensated CKD patients and was consistent with GFR. In another study performed on the diagnostic values of natriuretic peptides in CKD, a negative correlation was found between BNP and GFR and it was reported that the increase in phosphorus values and anemia-related values were related to the progression of CKD stage [17]. In the evaluation of this group, hypoalbuminemia in patients was associated with CKD-induced urinary protein loss and malnutrition, and its association with natriuretic peptides was attributed to extracellular volume increase and hypervolemia. In our study, a positive correlation was found between the NT-pro BNP and phosphorus, and a negative correlation between NT-pro BNP and hemoglobin, hematocrit, albumin values. This suggests that as the degree of renal failure progresses in compensated CKD, it may show increased anemia and metabolic imbalance disturbances as well as a reflection of increased hypervolemia. In addition, hypoalbuminemia is an important indicator of inflammation and CRP elevation and hypoalbuminemia in CKD are two independent and strong predictors of mortality [18, 19]. In a study performed in patients with ESRD, it was shown that there was a 4.6-fold increase in deaths related to all diseases and 5.5-fold increase in CVD-related deaths due to the increase in CRP level [20]. Studies have shown that inflammation markers are significantly reduced in patients with euvolemia, where hypervolemia causes inflammation and cardiovascular morbidity and mortality in CKD patients [18,19]. In our study, there was a negative correlation between NT-pro BNP and albumin, which is consistent with the above-mentioned literature. In addition, we found a significant relationship between NT-pro BNP and CRP *(p=0.09)*. However, this value was above the level of statistical significance. We thought that this might be related to the scarcity of our patients.

Limitations of present study are lack of echocardiographic evaluation and relatively small study population. However, our results showing significant association between NT pro BNP and compensated CKD.

Conclusion

Among the main causes of BNP and NT-pro BNP increase in CKD patients are factors such as increased extracellular volume, myocardial strain and increased left ventricular pressure (9). In addition, causes such as left ventricular hypertrophy, endothelial dysfunction in advanced CKD, systolic and diastolic left ventricular insufficiency, and ischemic cardiac disease also contribute to this increase. In conclusion, BNP and NT-pro BNP are strong predictors of all-cause cardiovascular mortality in asymptomatic CKD patients. In the light of all these data, it is possible to say that NT-pro BNP is associated with hypervolemia and therefore increased cardiovascular mortality in CKD.

Funding: *There is no financial support and sponsorship*

Conflict of Interest: *The authors declare that they have no conflict of interest.*

ORCID iD of the author(s)

Tuba T. Duman / 0000-0002-3836-2125

Hikmet Tekce /0000-0002-4542-4064

Buket Kin Tekce /0000-0002-5924-7476

References

[1]Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003; 42(5): 1050–65.

[2]Amann K, Rychlík I, Miltenberger-Milteny G, et al. Left ventricular hypertrophy in renal failure. Kidney Int Suppl.1998; 68:78-85.

[3]Krane V, Heinrich F, Meesmann M, et al. Electrocardiography and outcome in patients with diabetes mellitus on maintenance hemodialysis. Clin J Am Soc Nephrol. 2009; 4(2): 394-400.

[4]Satyan S, Light RP, Agarwal R. Relationships of N-terminal pro-B-natriuretic peptide and cardiac troponin T to left ventricular mass and function and mortality in asymptomatic hemodialysis patients. Am J Kidney Dis. 2007; 50(6): 1009–19.

[5]Madsen LH, Ladefoged S, Corell P, et al. N-terminal pro brain natriuretic peptide predicts mortality in patients with end-stage renal disease in hemodialysis. Kidney Int. 2007; 71(6): 548–54.

[6]Wang AY, Lam CW, Wang M, et al. Diagnostic potential of serum biomarkers for left ventricular abnormalities in chronic peritoneal dialysis patients. Nephrol Dial Transplant. 2009; 24(6):1962– 69.

[7]Wang AY, Lam CW, Yu CM, et al. N-terminal probrain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. J Am Soc Nephrol. 2007; 18: 321–30.

[8]Wang AY. Clinical utility of natriuretic peptides in dialysis patients. Semin Dial. 2012;25(3):326–333.

[9]Baughman KL. B-type natriuretic peptide -- a window to the heart. N Engl J Med. 2002;347(3):158–59.

[10]de Lemos JA, McGuire DK, Drazner MH: B-type natriuretic peptide in cardiovascular disease. Lancet. 2003; 362 (9380): 316–22.

[11]Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

[12]Süleymanlar G, Utaş C, Arinsoy T, et al. A population-based survey of Chronic REnal Disease In Turkey--the CREDIT study. Nephrol Dial Transplant. 2011;26(6):1862–71.

[13]Ausma J, Litjens N, Lenders MH, et al. Time course of atrial fibrillation-induced cellular structural remodeling in atria of the goat. J Mol Cell Cardiol. 2001; 33(12): 2083–94.

[14]Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995; 47(1):186-92.

[15]Wang AY, Wang M, Woo J, et al. Inflammation, residual kidney function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk of peritoneal

dialysis patients. J Am Soc Nephrol. 2004; 15(8): 2186–94.

[16] De Filippi CR, Fink JC, Nass CM, et al. N-terminal pro- B-type natriuretic peptide for predicting coronary disease and left ventricular hypertrophy in asymptomatic CKD not requiring dialysis. Am J Kidney Dis. 2005; 46(1): 35–44.

[17] Patrick B. Mark, Graham A. Stewart, et al. Jardin. Diagnostic potential of circulating natriuretic peptides in chronic kidney disease. Nephrol Dial Transplant. 2006; 21(2): 402–10.

[18] Ortega O, Gallar P, Muñoz M, et al. Association between C-reactive protein levels and N-terminal pro-B-type natriuretic peptide in pre-dialysis patients. Nephron Clin Pract. 2004; 97 (4):125-30.

[19] Yılmaz R. Ultrafiltrasyon ve hemodiyaliz sıklığının BNP ve CRP üzerine etkisi: Kardiyak fonksiyon bozukluğu, inflamasyon ve hipervolemi ilişkili mi? 22. Ulusal Nefroloji, Hipertansiyon, Diyaliz ve Transplantasyon Kongresi Özet Kitabı, 2005; s: 8.

[20] Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C. Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. Kidney Int. 1999; 55 (2): 648-58.