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ORIGINAL ARTICLE

The Relationship Between Nt-ProBNP and Volume Overload in Diabetic Nephropathy Progression

Diyabetik Nefropati Progresyonunda Nt-Pro BNP ve Volüm Yükü Arasındaki İlişki

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Abstract

Objectives: The early diagnosis of volume overload in chronic kidney disease (CKD) is very important. N-terminal pro-brain natriuretic peptide (NT-proBNP) is a valuable biomarker for this purpose. Our study aimed to detect the relationship between NT-proBNP and left ventricular hypertrophy (LVH), hypertension (HT), GFR, and proteinuria among diabetic patients with stage 3-4 CKD.

Methods: 160 diabetic patients with stage 3-4 CKD [80 patients in stage 3 CKD (group 1) and 80 patients in stage 4 CKD (group 2)] were enrolled. NT-proBNP levels were evaluated in serum, and proteinuria was determined from 24-hour collected urine. Left ventricular hypertrophy was evaluated by M-mode echocardiography. NT-proBNP levels were compared according to their left ventricular hypertrophy, hypertension, and proteinuria levels.

Results: NT-proBNP levels was significantly higher, and GFR was lower in group 2 compared to group1 ($p < 0.05$). NT-proBNP was higher in patients with LVH (+) HT (+) and proteinuria ≥ 1gr/d than patients with LVH (-), HT (-), and proteinuria < 1g/d ($p < 0.05$). We found a significant correlation between NT-proBNP levels and left ventricular posterior wall thickness, diastole (LVPWTd), proteinuria, SBP, and DBP. Proteinuria was the major contributor to increased NT-proBNP levels among the independent variables.

Conclusion: We detected that NT-proBNP levels are increased during the progression of CKD, and proteinuria is the major cause of increased NT-proBNP levels among the independent variables.

Key words: NT-proBNP, chronic kidney disease, hypertension, left ventricular hypertrophy, proteinuria

Özet

Amaç: Kronik böbrek hastalığında (KBH) volüm yükünün erken tanısı çok önemlidir. NT- Pro BNP bunu gösteren değerli bir biyomarkırdır. Çalışmamızda diyabetik nefropati zemininde KBH gelişen evre 3-4 hastalarda NT-Pro BNP'nin sol ventrikül hipertrofisi, kan basıncı, glomerüler filtrasyon hızı ve proteinüri ile ilişkisini değerlendirmeyi amaçladık.

Yöntemler: Diyabetik nefropati zemininde kronik böbrek hastalığı gelişen evre 3, 80 hasta ile evre 4, 80 hasta çalışmaya dahil edildi. NT-Pro BNP serumda, proteinüri 24 saatlik idrarda çalışıldı. Hastaların M-Mode ekokardiyografi ile sol ventrikül hipertrofisi belirlendi. KBH evrelerine göre iki gruba ayrılan hastaların T Pro BNP değerleri, sol ventrikül hipertrofisi, hipertansiyon ve proteinüri ile karşılaştırıldı.

Bulgular: Diyabetik nefropatide hastalığın progresyonu ile birlikte NT- Pro BNP anlamlı olarak artmaktaydı. Ancak NT Pro BNP, sol ventrikül hipertrofisi, yüksek kan basıncı 1gram/gün üzerinde proteinürisi olanlarda daha yüksekti. Bununla beraber NT- Pro BNP ile sol ventrikül duvar kalınlığı arasında da pozitif korelasyon vardı. Bağımsız değişken olarak proteinüri, sistolik ve diyatolik kan basıncı NT- Pro BNP artışı ile ilişkilidir.

Sonuç: Kronik böbrek hastalığının progresyonu ile NT Pro BNP artmaktadır. Bu artışa en büyük katkıyı proteinüri yapmaktadır.

Anahtar kelimeler: NT-proBNP, kronik böbrek hastalığı, hipertansiyon, sol ventrikül hipertrofisi, proteinüri, Türkiye

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INTRODUCTION

Chronic kidney disease (CKD) is described as gradual loss of renal functions that occurs in months or years. Several factors can contribute to CKD including diabetic nephropathy, which is the leading cause of CKD in the majority the patients. Nephropathy due to diabetes mellitus is characterized by increasing proteinuria (accompanied with elevated blood pressure), a gradual decline in GFR, and an increased risk of cardiovascular disease (CVD). CVD is one of the leading causes of mortality and morbidity in CKD patients, and the prevalence of CVD increases as CKD progresses. Therefore, early diagnosis of CKD is very important. Brain natriuretic peptide (BNP) and NT-proBNP are beneficial markers for diagnosis and prognosis of CVD patients. The most important determinant for BNP and NT-proBNP release to the circulation is myocardial stretch [1]. Increased BNP levels have been documented as a prognostic marker for cardiovascular mortality in CKD patients in several studies [2,3]. In addition, NT-proBNP and BNP are approved as precious markers in cardiovascular disease [4].

BNP is eliminated by kidneys through a specific receptor mediated degradation as well as enzymatically by a neutral endopeptidase [5]. NT-proBNP is not cleared by these mechanisms, and its clearance has been primarily dependent to renal excretion. In CKD patients, both of these peptides levels are elevated. Therefore, it is thought that accumulation of these peptides is associated with the decline in the GFR [6]. This hypothesis has been confirmed by observational studies [7]. Often, the impact of NT-proBNP levels on these patients is much more important [8]. Our study intended to identify the relationship between NT-proBNP and LVH, HT, GFR, and proteinuria among diabetic patients with stage 3 and 4 CKD.

METHODS

From 2008 to 2012, 160 patients with diabetes mellitus and stage 3-4 CKD that: (i) were treated in clinic of nephrology or (ii) consulted to nephrology for their routine follow-up and treatments were accepted to the study. Our study design was cross sectional. The patients were divided into 2 groups with respect to the baseline stages of eGFR as described by the Disease Outcomes Quality Initiative of the National Kidney Foundation [9]. Group 1, included patients with CKD stage 3 and eGFR levels of 30–59 mL/min/1.73 m2, while group 2 was composed of CKD stage 4 patients with eGFR levels of 15-29 mL/min/1.73 m2. The serum levels of NT-proBNP from these groups were compared between patients with LVH (+) and LVH (-), with hypertensive and normotensive, and patients who has proteinuria ≥1 g/day and proteinuria < 1g/day.

The study protocol was approved by the Dicle University Local Human Ethics Committee and informed consent was obtained from all patients at the time of study acceptance. The inclusion criteria were as follows: patients aged between 18-65 years, those with diabetes, and stage 3 and 4 CKD, and left ventricular systolic ejection fraction (LVEF) greater than 50%.

The exclusion criteria were as follows:

1. LVEF less than or equal to 50%,
2. Cardiac arrhythmias,
3. History of cerebrovascular disease, any malignant disease and coronary artery disease,
4. Patients that underwent renal replacement treatment,
5. Acute intercurrent illness,
6. Patients that did not want to participate into the study.

Demographic characteristics of patient's were taken from patient's files. Systolic and diastolic blood pressure measurements of patients were obtained from the right arm by sphingomanometry after 5 minutes resting. Hypertension was diagnosed according to the

guidelines presented in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [10]. Hypertension was defined as diastolic blood pressure (DBP) ≥ 90 mmHg and/or systolic blood pressure (SBP) ≥140 mmHg on at least three measurements performed in a medical office and/or use of antihypertensive drugs. A 24-hour urine sample was collected to assess the level of proteinuria in the urine. GFR was measured by modification of the diet in renal disease (MDRD) formula [11]. Blood samples were obtained after 12 hours of fasting for biochemical, hematological, and serological analysis. NT-proBNP was measured by Elecsys proBNP sandwich immunoassay (Mannheim, Germany, Roche Diagnostics). A 2D-guided M-mode echocardiography (Siemens, Sonoline G60S; Siemens AG, Munich, Germany) was used to assess left ventricular hypertrophy (LVH) by a single experienced cardiologist. The thickness of the left ventricle as visualized using the echocardiography and was correlated with its actual mass. LVH was diagnosed if the left ventricular posterior wall thickness in diastole (LVPWTd) was ≥ 11 mm in thickness [12].

Statistical analysis

SPSS 11.0 was utilized to analyze data. Student t-test was performed to compare independent variables with normal distribution. Independent variables without normal distribution were compared with Mann-Whitney U test. Pearson's correlation test was utilized for the analysis of the relationship between independent and dependent variables. A stepwise multiple linear regression analysis was used to show independent predictors of NT-proBNP. Stepwise method of multiple linear regression tests was used to analyze the major determinant of dependent variable (NT-proBNP) among the independent variables (LVPWTd, SBP, DBP, proteinuria, and GFR). Data were expressed as mean ± standard deviation (SD) or median (min-max).

RESULTS

The clinical, demographic and laboratory characteristics of the patients are demonstrated in Table 1. A total of 160 patients, with 80 patients in group 1 (stage 3 CKD) and 80 patients in group 2 (stage 4 CKD), were enrolled into the study. NT-proBNP, GFR, urea, and creatinine levels were significantly higher in group 2 than in group 1 ($p < 0.05$).

Table 1: Clinical, demographic and laboratory characteristics of patients

Parameters	Group 1 (n = 80)	Group 2 (n = 80)	p
Gender (Male/Female)	41/39	45/35	0.53
Age (years)	48.78 ± 12.75	56.83 ± 12.99	0.135
Duration (years)	2.57 ± 1.15	3.25 ± 2.45	0.37
GFR (ml/min)	46.57 ± 8.51	27.83 ± 11.76	**<0.001**
Proteinuria (gr/day)	0.60 (0.50 - 7.00)	1.20 (0.65 - 13.00)	0.44
SBP (mmHg)	129.28 ± 14.91	130.00 ± 8.52	0.89
DBP (mmHg)	77.14 ± 8.25	80.00 ± 8.52	0.4
Hemoglobin (gr/dl)	12.26 ± 1.70	11.48 ± 1.43	0.23
Urea (mg/dl)	73.00 (52.00-173)	112.00 (71.00 - 175.00)	**<0.001**
Creatinine (mg/dl)	1.59 ± 0.32	2.90 ± 0.80	**<0.001**
Glucose (mg/dl)	115.00 (60.00-600)	110.00 (73 - 294)	0.51
LDL-C (mg/dl)	100.00 (6.30-282.00)	110.00 (58.00 - 177.00)	0.29
Na (mg/dl)	136.64 ± 3.43	137.16 ± 3.27	0.25
Albumin (g/L)	3.31 ± 0.56	3.22 ± 0.81	0.20
LVPWTd	10.09 ± 0.21	11.20 ± 0.18	0.71
NT-proBNP (pg/ml)	211.90 (9.70 – 6,443.00)	520.00 (62.00 - 5,666.00)	**<0.001**

GFR: Glomerular Filtration Rate, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, Na: Sodium, LDL-C: low density lipoprotein-cholesterol, LVPWTd: Left ventricular posterior wall thickness, diastole

The NT-proBNP levels in patients with LVH were significantly greater than those in patients without LVH. In addition, plasma levels of NT-proBNP were significantly greater in patients with hypertension than without hypertension, and significantly greater in patients with proteinuria ≥1gr/day than proteinuria < 1 gr/day (Table 2).

Table 2: The levels of NT-proBNP according to the left ventricular hypertrophy, blood pressure, and proteinuria.

	Parameters		
	LVH(+)	**LVH(-)**	**p**
NT-proBNP	430.17 ± 285.87	222.78 ± 177.37	0.032
	Hypertension (+)	**Hypertension (-)**	**p**
NT-proBNP	409.98 ± 299.88	274.96 ± 165.39	0.023
	Proteinuria ≥ 1 g/day	**Proteinuria < 1 g/day**	**p**
NT-proBNP	473.53 ± 289.30	226.92 ± 187.43	0.015

In the present study, we found significantly positive correlation between NT-proBNP levels and LVPWTd (r = 0.205, p = 0.008), SBP (r = 0.124, p = 0.025), DBP (r = 0.351, p = 0.018) and proteinuria (r = 0.502, p < 0.001, and negative correlation with GFR (r = - 0.298, p < 0.001) levels (Table 3).

Table 3: Correlations between NT-proBNP with LVPWTd, SBP, DBP, proteinuria, and GFR

Parameters	**R**	**p**
NT-proBNP& LVPWTd	0.205	**0.008**
NT-proBNP & SBP	0.124	**0.025**
NT-proBNP&DBP	0.351	**0.018**
NT-proBNP & Proteinuria	0.502	**<0.001**
NT-proBNP & GFR	- 0.298	**<0.001**

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; GFR, Glomerular filtration rate; LVPWTd: Left ventricular posterior wall thickness, diastole

Using a stepwise method of multiple linear regression analysis, proteinuria was found to be the major determinant among the independent variables {NT-proBNP = 285.525+ [(0.220 x proteinuria) + (-0.112 x diastolic blood pressure) + 0.032 x systolic blood pressure) + (0.056 x left ventricular posterior wall thickness, diastole)+(-.00064 x glomerular filtration rate)]; (R2 = 0.241, p < 0.001)}.

DISCUSSION

Release of NT-proBNP and BNP due to increased myocardial wall stress cause the vasorelaxation and natriuresis, fibrosis prevention, negative effect on of renin, aldosterone and sympathetic nervous activity and amelioration in myocardial muscle relaxation [13]. BNP and NT-pro-BNP levels are commonly found increased in patients with CKD [14-17]. NT-proBNP and GFR were inversely correlated in a study by Anwaruddin et al. [18] Multinational, observational study of 177 nondiabetic patients with mild-to-moderate CKD showed that both NT-proBNP and BNP plasma concentrations were compatible with CKD progression. This suggested that increased NT-proBNP and BNP concentrations demonstrate an increased risk for CKD progression [19]. An independent negative correlation was found between NT-proBNP and GFR in asymptomatic stage 3 and 4 CKD patients by Tagore et al. [20]. Van Kimmenade et al. showed BNP and NT-proBNP concentrations correlated similarly to GFR [4]. Our results confirmed the previous studies that showed an adverse correlation between GFR and NT-proBNP levels in CKD stage 4 patients, which had significantly greater NT-proBNP levels than CKD stage 3 patients. Our studies show that NT-proBNP levels were adversely linked to the progression of CKD.

It is thought that NT-proBNP is eliminated by renal excretion although a mechanism for this is not exactly known [21,22]. NT-proBNP accumulation occurs in kidney disease, so decreased renal elimination may be accountable for increased plasma levels of NT-proBNP in CKD. Most patients with CKD have cardiac abnormalities including LVH, left ventricular dilatation (LVD), or systolic dysfunction [23]. CVD were frequently encountered at the beginning of ESRD. Echocardiography of these patients demonstrated systolic dysfunction (15%), left

ventricular dilatation (32%), and left ventricular hypertrophy (74%) [24]. An association of BNP and NT-pro-BNP levels with LVH has been reported previously. In a study of 213 predialysis patients with CKD by Vickery et al [14], plasma BNP and NT-proBNP concentrations were statistically significantly higher in patients with LV hypertrophy. Cataliotti et al. reported that BNP can be used as an important biomarker for ventricular hypertrophy in dialysis patients with ESRD [2]. In a study which carried out by 994 hypertensive African-American with a glomerular filtration rate of 20 to 65 ml/min, it is found that patients with increased NT proBNP levels were associated with higher CVD risk [25].In a study by Struthers et al. they found that BNP and NT-proBNP are indicators of asymptomatic cardiac target organ damage [26].

LVH is a frequently observed among ESRD patients and is also thought to be a predictor of death [27]. Compatible with the findings of the studies mentioned above, we showed that the plasma levels of NT-proBNP were statistically significantly higher in patients with LVH than in patients without LVH. Besides, we found positive correlation between NT-proBNP levels and LVPWTd. We did not find any statistically significant difference in the SBP and DBP between groups. NT-proBNP levels were significantly higher in patients with hypertension than in patients without hypertension, and a statistically significant correlation between NT-proBNP levels and SBP ($p = 0.025$) and DBP ($p = 0.018$) were found. Gradual reductions in creatinine clearance were seen in diabetic patients who progress to ESRD. [28]. It has been shown that BNP plasma levels were significantly higher in microalbuminuric diabetic patients than those normoalbuminuric diabetic patients. In addition, they found a positive correlation between plasma BNP levels and urinary albumin excretion rate [29].

Similar findings were found in our study, NT-proBNP levels were significantly higher in patients with proteinuria ≥1gr/day than patients with proteinuria < 1 gr/day. Moreover, we found statistically significant positive correlation between NT-proBNP levels and proteinuria. The major determinant of NT-proBNP levels was proteinuria in the multiple linear regression analysis by stepwise method among the independent variables. Patients with greater baseline proteinuria had faster decline in glomerular filtration rate and had the increased risk for both kidney disease progression and CVD [30]. In addition, patients with proteinuria can have raised plasma volume as a result of sodium retention due to primary defect in the ability of the distal nephron to excrete sodium. The relationship between proteinuria and NT-proBNP can be explain by the tubulotoxic effect of proteinuria progress chronic renal disease worsen, and causing plasma volume to increase.

In conclusion, NT-proBNP levels were statistically higher in diabetic patients with stage 4 CKD than diabetic patients with stage 3 CKD. In association with chronic kidney disease progression, NT-proBNP levels were increased, and it was significantly higher in patients with LVH, hypertension, and proteinuria ≥1gr/day. There was a statistically significant positive correlation between NT-proBNP levels with LVPWTd, proteinuria, SBP and DBP, whereas a negative correlation with GFR was observed. Proteinuria was the major determinant for high levels of NT-proBNP among the independent variables.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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