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NT-proBNP levels in nephropathy cases with and without diabetes, echocardiographic abnormality, and hypertension

Müslüm Güneş[1], **Ali Kemal Kadiroğlu**[2]

1 Internal Medicine Department, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye

2 Nephrology Department, Memorial Hospital, Diyarbakır, Türkiye

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Abstract

Objective: Increased NT-proBNP level is a diagnostic sign for heart failure and is associated with cardiovascular mortality. It is related to chronic kidney disease (CKD) in also cases without heart failure. In this study, the authors aimed to investigate NT-proBNP levels in CKD cases with and without diabetes, echocardiographic abnormality, and hypertension.

Methods: Sixty-four cases (26 diabetic and 38 non-diabetic) with stage 3-4 CKD were investigated in the study. Blood pressure values were measured on the right arm after resting for at least 5 minutes. M-mode two-dimensional echocardiography device and ultrasonography were used to evaluate cardiac and renal findings. Blood samples were taken for biochemical, hematological, hormonal and serological parameters of the patients after 12 hours of fasting. Nt-proBNP levels were measured by Elecys ProBNP sandwich immunoassay method in the Biochemistry laboratory.

Results: NT-proBNP levels were not statistically different according to the presence and absence of diabetes (p=0.821) in CKD cases. However, stage-4 CKD had significantly higher NT-proBNP level than stage-3 CKD in both diabetic (p<0.001) and non-diabetic cases (p<0.001). NT-proBNP levels showed similarity in cases with and without echocardiographic abnormality in both diabetics (p=0.135) and non-diabetics (p=0.531). Similarly, CKD cases with and without hypertension were not different in NT-proBNP levels in both diabetics (p=0.412) and non-diabetics (p=0.432).

Conclusion: The present findings suggest that NT-proBNP level is related to the severity of CKD rather than the presence of diabetes and cardiovascular disorders.

Keywords: NT-proBNP, kidney disease, diabetes mellitus, echocardiography.

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Correspondence / Yazışma Adresi: *Müslüm Güneş, Internal Medicine Department, Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye e-mail: muslumgunes21@yahoo.com*

Diyabet, ekokardiyografik anormallik ve hipertansiyon bulunan ve bulunmayan nefropati vakalarında NT-proBNP düzeyleri

Öz

Giriş: Artmış NT-proBNP düzeyi kalp yetmezliği için tanısal bir işarettir ve kardiyovasküler mortalite ile ilişkilidir. Kalp yetmezliği olmayan vakalarda da kronik böbrek hastalığı (KBH) ile ilişkilidir. Bu çalışmada yazarlar diyabet, ekokardiyografik anormallik ve hipertansiyonu olan ve olmayan KBH vakalarında NT-proBNP düzeylerini araştırmayı amaçlamışlardır.

Yöntemler: Çalışmada evre 3-4 KBH'li 64 vaka (26 diyabetik ve 38 diyabetik olmayan) incelendi. Kan basıncı değerleri en az 5 dakika dinlendikten sonra sağ koldan ölçüldü. Kardiyak ve renal bulguları değerlendirmek için M-mod iki boyutlu ekokardiyografi cihazı ve ultrasonografi kullanıldı. Hastaların 12 saatlik açlıktan sonra biyokimyasal, hematolojik, hormonal ve serolojik parametreleri için kan örnekleri alındı. Nt-proBNP düzeyleri Biyokimya laboratuvarında Elecys ProBNP sandwich immunoassay yöntemi ile ölçüldü.

Bulgular: NT-proBNP düzeyleri KBH vakalarında diyabetin varlığına ve yokluğuna göre istatistiksel olarak farklı değildi ($p=0.821$). Ancak, evre-4 KBH'nin NT-proBNP düzeyi hem diyabetli ($p<0.001$) hem de diyabetli olmayan vakalarda ($p<0.001$) evre-3 KBH'den anlamlı derecede daha yüksekti. NT-proBNP düzeyleri hem diyabetlilerde ($p=0.135$) hem de diyabetli olmayanlarda ($p=0.531$) ekokardiyografik anormalliği olan ve olmayan vakalarda benzerlik gösterdi. Benzer şekilde, hipertansiyonu olan ve olmayan KBH vakaları hem diyabetlilerde ($p=0.412$) hem de diyabetli olmayanlarda ($p=0.432$) NT-proBNP düzeylerinde farklı değildi.

Sonuç: Mevcut bulgular, NT-proBNP düzeyinin diyabet ve kardiyovasküler bozuklukların varlığından ziyade KBH'nin şiddetiyle ilişkili olduğunu düşündürmektedir.

Anahtar kelimeler: NT-proBNP, böbrek hastalığı, diabetes mellitus, ekokardiyografi.

INTRODUCTION

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is an amino acid fragment originated from stretched cardiomyocytes and its increased secretion is an indicator for heart failure and cardiovascular mortality[1]. It is known that NT-proBNP is related to chronic kidney disease (CKD) in also cases without heart failure[2]. It has been demonstrated that the ratio of cardiac NT-proBNP to peripheral NT-proBNP is remarkably reduced in cases with CKD[3]. In addition, it has been found that circulating NT-proBNP is higher in diabetic cases with cardiovascular morbidity and associated with greater deterioration in cardiac and renal functions[4]. These findings suggest that elevated NT-proBNP level is related to renal and cardiac dysfunctions and diabetes mellitus-related problems.

Therefore, the potential clinical roles and implications of NT-proBNP may be more clearly observed in diabetic cases experiencing cardiac and renal dysfunctions and problems. In this line, the authors aimed to test that NT-proBNP may be higher in cases with diabetes than those without, in cases with echocardiographic abnormality than those without, and in cases with hypertension than those without. For this purpose, it was planned to perform statistical comparisons between cases with and without these conditions in terms of NT-proBNP levels. Additionally, it was planned to compare NT-proBNP levels between stage-3 and stage-4 CKD cases.

METHODS

In this cross-sectional study, sixty-four patients (26 diabetic and 38 non-diabetic) with stage 3-4 CKD were investigated at the Department of Nephrology. Ethics committee approval (The Ethics Committee of Dicle University, no: 079, date: 28 December 2009) and informed

consents of the patients were obtained. The study was performed in accordance with the Declaration of Helsinki including ethical principles regarding biomedical investigations. The criteria for inclusions and exclusions of the study were conducted as follows. Inclusion criteria were 18-65 years of age, diabetic or non-diabetic stage 3-4 CKD, ejection fraction >50%, presence of consent to participate in the study, and cooperative patients. Exclusion criteria were congestive heart disorder, acute coronary disease, chronic obstructive pulmonary disorder, non-renal edema or vasculitis, and cerebrovascular disease. These inclusion/exclusion criteria were applied to provide homogeneity and to minimize potential influencers on NT-proBNP levels.

Demographic characteristics of the patients were obtained from themselves and their patient files. Blood pressure values of all patients were measured using a pneumatic manometer on the right arm after resting for at least 5 minutes.

Blood samples were taken for biochemical, hematological, hormonal and serological parameters of the patients after 12 hours of fasting. Without waiting for the samples; urea, creatinine, Na, K, Ca, P, glucose, albumin, total cholesterol, triglyceride (TG), low-density lipoprotein (LDL), uric acid, C-reactive protein (CRP), parathyroid hormone (PTH), hemoglobin values were studied. Nt-proBNP levels in the patients were measured by Elecys ProBNP sandwich immunoassay method in the Biochemistry laboratory.

The patients' left ventricular end-diastolic and end-systolic diameters, apical four-chamber left ventricular ejection fraction with the modified Simpson method, septum interventriculare and left ventricular posterior wall thickness, left atrial diameter, mitral early deceleration time, and isovolumetric relaxation time were measured using an M-mode two-dimensional echocardiography device. In addition, the patients were evaluated with renal ultrasonography.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows version 11.0. The Student t-test was used to compare continuous variables between groups and between subgroups. The Fisher's exact test was used to analyze categoric variables. Data were shown as mean value ± standard deviation or frequency (percentage). If the p value was <0.05, it was accepted as significant.

RESULTS

Table I presents statistical comparisons between diabetic and non-diabetic cases with stage 3-4 CKD in terms of the parameters evaluating in this study. There were no differences in age (p=0.974), disease duration (p=0.538), NT-proBNP (p=0.821), systolic and diastolic blood pressure values (p=0.722 and p=0.741, respectively), hemoglobin (p=0.446), CRP (p=0.197), urea (p=0.101), Na (p=0.630), Ca (p=0.703), albumin (p=0.127), triglyceride (p=0.514), total cholesterol (p=0.270), LDL (p=0.116), PTH (p=0.094), echocardiographic abnormalities (p=0.207), and hypertension (p=1.0). However, the two groups were different in creatinine (p=0.006), K (p=0.039), and P (p=0.013) levels (Table 1).

Table I: Comparisons between diabetic and non-diabetic patients with CKD.

Parameters	Diabetic patients (n=26)	Non-diabetic patients (n=38)	p
Age, years	50.03±15.63	50.16±15.70	0.974
Disease duration, years	2.78±1.83	3.08±1.96	0.538
NT-proBNP, pg/mL	796.00±128.18	724.80±121.77	0.821
Systolic blood pressure, mmHg	129.28±11.84	130.83±20.33	0.722
Diastolic blood pressure, mmHg	78.92±8.31	79.72±10.27	0.741
Hemoglobin, g/dL	11.76±1.62	12.13±2.12	0.446
CRP, mg/L	4.91±3.02	7.48±1.00	0.197
Urea, mg/dL	76.25±27.26	90.77±39.38	0.101
Na, mmol/dL	137.10±3.28	137.61±4.67	0.630
Ca, mg/dL	8.93±0.69	8.86±0.67	0.703
Albumin, g/dL	3.24±0.65	3.52±0.76	0.127
Triglyceride, mg/dL	172.21±73.14	188.55±114.79	0.514
Total cholesterol, mg/dL	187.00±57.92	172.92±43.30	0.270
LDL, mg/dL	114.39±48.28	98.00±33.93	0.116
PTH, pg/mL	92.45±54.30	139.72±62.13	0.094
Creatinine, mg/dL	1.92±0.73	2.53±0.94	0.006
K, mmol/dL	4.84±0.78	4.46±0.63	0.039
P, mg/dL	4.33±0.53	3.77±1.07	0.013
Abnormal echocardiography, n (%)	18 (69.23)	20 (52.63)	0.207
Hypertension, n (%)	8 (30.77)	13 (34.21)	1.0

Abnormal echocardiography: Left ventricular hypertrophy, heart valve disease, left atrial dilatation.

Table II presents statistical comparisons between the subgroups of diabetic patients including stage-3 (n=14) and stage-4 (n=12) CKD. Accordingly, the two subgroups were similar in terms of most parameters evaluating in this study (p>0.05). However, diabetic cases with stage-4 CKD had significantly increased NT-proBNP (p<0.001) and K (p<0.001) levels than those with stage-3 CKD (Table 2).

Table II: Comparisons between stage-3 and stage-4 CKD in diabetic patients.

Parameters	Stage-3 (n=14)	Stage-4 (n=12)	p
Age, years	48.78±12.75	56.83±12.99	0.125
Disease duration, years	2.57±1.15	3.25±2.45	0.365
NT-proBNP, pg/mL	186.13±144.36	521.12±265.30	<0.001
Systolic blood pressure, mmHg	129.28±14.91	130.00±8.52	0.885
Diastolic blood pressure, mmHg	77.14±8.25	80.00±8.52	0.395
Hemoglobin, g/dL	12.26±1.70	11.48±1.43	0.223
CRP, mg/L	5.85±3.19	4.30±2.68	0.200
Urea, mg/dL	76.14±34.57	77.58±20.02	0.125
Na, mmol/dL	136.64±3.43	137.16±3.27	0.250
Ca, mg/dL	9.10±0.58	8.68±0.80	0.885
Albumin, g/dL	3.31±0.56	3.22±0.81	0.200
Triglyceride, mg/dL	178.35±83.41	170.91±68.07	0.807
Total cholesterol, mg/dL	188.00±73.41	188.00±42.82	1.0
LDL, mg/dL	116.07±63.17	112.66±31.57	0.867
PTH, pg/mL	55.94±39.76	145.21±120.50	0.223
Creatinine, mg/dL	1.62±0.32	2.32±0.94	0.365
K, mmol/dL	4.67±0.86	4.96±0.74	<0.001
P, mg/dL	4.39±0.47	4.16±0.57	0.395
Uric acid, mg/dL	7.00±2.49	6.03±1.40	0.246
Glucose, mg/dL	244.21±136.73	170.25±57.61	0.094
HbA1c	9.12±2.71	8.06±1.65	0.250
Abnormal echocardiography, n (%)	9 (64.29)	9 (75.0)	0.683
Hypertension, n (%)	6 (42.86)	2 (16.67)	0.216

Abnormal echocardiography: Left ventricular hypertrophy, heart valve disease, left atrial dilatation.

Table III presents statistical comparisons between the subgroups of non-diabetic patients including stage-3 (n=20) and stage-4 (n=18)

CKD. Accordingly, the two subgroups were similar in terms of most parameters evaluating in this study (p>0.05). However, non-diabetic cases with stage-4 CKD had significantly higher levels of NT-proBNP (p<0.001), urea (p=0.002), creatinine (p=0.001), PTH (p=0.044) than those with stage-3 CKD (Table 3).

Table III: Comparisons between stage-3 and stage-4 CKD in non-diabetic cases.

Parameters	Stage-3 (n=20)	Stage-4 (n=18)	p
Age, years	43.50±16.60	54.00±15.93	0.055
Disease duration, years	3.10±1.58	2.88±2.32	0.743
NT-proBNP, pg/mL	133.58±111.08	488.87±253.36	<0.001
Systolic blood pressure, mmHg	130.00±23.16	131.11±16.04	0.866
Diastolic blood pressure, mmHg	81.00±11.19	78.88±9.00	0.529
Hemoglobin, g/dL	12.43±2.29	11.57±1.87	0.221
CRP, mg/L	6.48±12.04	7.97±6.94	0.647
Urea, mg/dL	72.20±29.90	109.00±38.63	0.002
Na, mmol/dL	138.15±3.43	137.27±5.66	0.565
Ca, mg/dL	9.02±0.52	8.73±0.76	0.183
Albumin, g/dL	3.62±0.66	3.35±0.84	0.289
Triglyceride, mg/dL	174.95±108.64	197.94±118.06	0.536
Total cholesterol, mg/dL	172.95±46.20	173.00±38.40	0.997
LDL, mg/dL	97.51±34.17	100.22±32.96	0.806
PTH, pg/mL	96.90±10.42	175.27±12.66	0.044
Creatinine, mg/dL	2.03±0.67	3.01±0.92	0.001
K, mmol/dL	4.58±0.70	4.43±0.59	0.480
P, mg/dL	3.70±0.69	3.99±1.39	0.408
Uric acid, mg/dL	6.61±1.75	7.78±2.09	0.068
Glucose, mg/dL	116.30±55.98	100.44±18.20	0.259
Abnormal echocardiography, n (%)	11 (55.0)	9 (50.0)	1.0
Hypertension, n (%)	6 (30.0)	7 (38.89)	0.734

Abnormal echocardiography: Left ventricular hypertrophy, heart valve disease, left atrial dilatation.

In NT-proBNP levels, there were not differences between CKD patients with and without echocardiographic abnormality in both diabetics (393.17±285.87 versus 222.78±177.37; p=0.135) and non-diabetics (327.53±261.50 versus 273.37±265.08; p=0.531). Similarly, CKD patients with and without hypertension were not different in NT-proBNP levels in both diabetics (274.96±165.39 versus 369.98±299.88; p=0.412) and non-diabetics (348.83±287.32 versus 277.46±248.95; p=0.432).

DISCUSSION

In this cross-sectional study, comparisons between diabetic and non-diabetic cases and between stage-3 and stage-4 CKD patients were performed in terms of NT-proBNP levels, echocardiographic findings, and blood pressure. As a result, there was similarity between the diabetic and non-diabetic patients in NT-proBNP, echocardiographic findings, and blood pressure. In both diabetics and non-diabetics, cases with stage-4 CKD exhibited significantly higher levels of NT-proBNP than cases with stage-3. Accordingly, it is possible that NT-proBNP may be used to facilitate diagnosis, differential diagnosis, prognosis and treatment monitoring in patients with CKD. However, the limitations of the study should be into consideration.

Recent studies have reported that higher circulating NT-proBNP is an indicator for progression and prognosis of kidney disease in diabetic patients[5-7]. Similarly, the present study showed that diabetic patients have higher levels of NT-proBNP than non-diabetic patients, but this was not statistically significant. On the other hand, the present study revealed that cases with stage-4 CKD have significantly increased level of NT-proBNP than those with stage-3 CKD in both diabetics and non-diabetics. Thus, the present study confirmed previous

findings suggesting an association of NT-proBNP with progression and prognosis in diabetic patients with kidney disease[5-7], but also showed that this association also valid in non-diabetic cases.

The association of NT-proBNP with heart failure has been discussed and demonstrated in previous studies[8-10]. It has been found that NT-proBNP is more relevant for predicting adverse outcomes in case of heart failure and decreased kidney function[9]. Therefore, it is important to evaluate NT-proBNP status in cases with CKD in terms of cardiac and renal findings. For this reason, the present study addressed NT-proBNP in potential relation with also echocardiographic findings and blood pressure. However, the current results did not clearly support such relationship at a significant level. Because no significant association was found between NT-proBNP and echocardiographic findings and blood pressure in this study. These results seem compatible with previous finding that NT-proBNP is related to CKD in also cases without heart failure[2]. However, the present results were not compatible with previous finding that NT-proBNP concentration was related to left ventricular systolic dysfunction in CKD patients[11-14].

Given the strong interactions between CKD and heart failure[14-17], it was reasonable to expect NT-proBNP to be associated with both conditions. Indeed, the present study manifested that stage-4 was associated increased serum NT-proBNP concentration than stage-3 in both diabetic and non-diabetic cases. Another reasonable expect in this study was that NT-proBNP may be associated with diabetes mellitus and cardiovascular disorders. However, this expect was not proven according to the results of the study. In general, the current study not find a significant association between NT-proBNP and cardiovascular disorders, contrary to previous research. This may be due to small sample size, especially when comparing subgroups in this study.

This study has some limitations that should be into consideration. Various features of the study such as small sample size, single-centered nature, cross-sectional design. The cross-sectional design of this study has disadvantages, including risk of bias and inability to determine causal and influential factors and relationships. In addition, the choice to focus on stage 3-4 CKD instead of a broader spectrum (e.g., stages 1-5), the exclusion of mild CKD (stages 1-2) patients, and inclusion of age range (18-65 years) are potential limitations that may affect the generalizability of the findings.

CONCLUSION

In this study, the findings suggest that serum NT-proBNP concentration is associated with the severity of CKD rather than the presence of diabetes and cardiovascular disorders. These findings can be used to improve diagnostic, differentiative and therapeutic processes of CKD. Longitudinal studies to explore the causal relationships between NT-proBNP levels and CKD progression are needed.

Ethics Committee Approval: Ethics committee approval (The Ethics Committee of Dicle University, no: 079, date: 28 December 2009) and informed consents of the patients were obtained. The study was performed in accordance with the Declaration of Helsinki including ethical principles regarding biomedical investigations.

Declaration of Conflicting Interests: The authors have no conflicts of interest to declare.

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