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Diagnostic Efficacy of Natriuretic Peptide: NT-ProBNP in Hemodialysis Patients with Left Ventricular Failure

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Abstract

Objective

In the general population, plasma concentrations of natriuretic peptides such as brain natriuretic peptide (BNP), are useful markers to predict left ventricular hypertrophy and left ventricular (LV) systolic dysfunction. Left ventricular hypertrophy in dialysis patients is exceedingly frequent and predicts mortality in these patients. LV systolic dysfunction is also frequent due to high coronary artery disease (CAD) prevalence in this population. The present study aimed to evaluate the clinical diagnostic potential of N-terminal pro-brain natriuretic peptide (NT-proBNP); as an indicator for left ventricular (LV) systolic dysfunction and left ventricular mass (LVM), in chronic hemodialysis patients.

Material and Method

76 patients with end-stage renal disease (54 males and 22 females, mean age 60.51±13.96 years) who had been on regular hemodialysis treatment twice or three times a week were enrolled in this study. Patients were divided into two groups based on left ventricular ejection fraction (LVEF). Left ventricular systolic dysfunction was defined as LVEF ≤40%. Basic biochemical parameters, NT-proBNP, and echocardiographic parameters including left ventricular mass (LVM) and left ventricular mass index (LVMI) were measured.

Results

Mean concentration of serum NT-proBNP was 8333 (208-35000) pg/ml, and this parameter was not significantly different between the two groups (13136 (361-35000) pg/ml vs. 6617 (20-33805) pg/ml, p:0.16). Multivariate analysis results of logarithmic transformed NT-proBNP showed correlation only with RVEF. The left ventricular end-systolic diameter was significantly lower in the normal LV systolic function group (35.4±8.2 vs. 31.3±7.1 mm, p:0.04).

Conclusion

Our findings suggest that NT-proBNP is inadequate to determine LV systolic dysfunction in chronic hemodialysis patients.

Keywords: Hemodialysis, left ventricular systolic dysfunction, NT-proBNP

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Introduction

Across the whole population, plasma concentrations of natriuretic peptides like BNP are beneficial in predicting LV dysfunction and LVH. BNP is more often produced by ventricular myocytes (1). BNP release is increased by ventricular dysfunction or LVH (1-3). BNP is first produced as inactive pro-hormone and splits up into two fragments. The first is c-BNP, which is an active fragment, and the second is the NT-proBNP. Both can be measured in plasma or serum (4-6).

Chronic kidney disease (CKD) is a common clinical condition in which ANP and BNP are usually elevated (7). Only a few clinical studies have demonstrated the clinical diagnostic potential of NT-proBNP, particularly in CKD patients with LV dysfunction and LVH who require hemodialysis. (7-9). In addition, LVH is extremely common in dialysis patients and predicts mortality in these patients (10).

Because of this history, we hypothesized in the present study that NT-proBNP is a beneficial serum biomarker predicting LV dysfunction and LVM in CKD patients on hemodialysis (HD) treatment.

Material and Method

This study included 76 CKD patients (54 males and 22 females; mean age 60.51±13.96 years) receiving regular hemodialysis treatment two/three times a week. All participants had admitted to the Suleyman Demirel University Dialysis Center; Isparta/Turkey, between March 2023 and April 2023.

The patients were divided into two groups according to their LV ejection fraction (LVEF). LV systolic dysfunction was defined as LVEF ≤40%. Patients participating in this study had no rhythm disturbances during the follow-up period. Our study exclusion criteria were; patients on peritoneal dialysis treatment, acute decompensated heart failure (NYHA Class III-IV), chronic liver disease, chronic obstructive airway disease (COPD), mild or severe valvular heart dysfunction, and patients who refused to give study constent.

All study populations were anuric (24-hour urine volume ≤ 200 mL/day) and they all were on standard bicarbonate dialysis treatment (Na 138 mmol/L, HCO3 35mmol/L, K 1.5 mmol/L, Ca 1.25 mmol/L, Mg 0.75 mmol/L) or by high-flux HD with cuprophan or other semisynthetic membranes (dialysis filters surface area: 1.1 to 1.7 m2) two or three times weekly. Thirty-three patients were habitual smokers (43.4%).

The participants were given detailed information about our research. Then, an informed consent form was signed by the participants. The study was prepared per the Declaration of Helsinki and was approved by the ethics committee for clinical research at Suleyman Demirel University Medical Faculty (Date: 06/03/2023, No: 39). All studies were performed during a day without dialysis.

Echocardiography

2-D echocardiography examinations were done by a single cardiologist. The clinician was blinded to all clinical data of patients. While echocardiography was performed, participants were lying in the left decubitus position. GE-VingMed System 5 echocardiography machine (GE-VingMed Sound AB, Horten, Norway) with a 2.5 MHz FPA probe was used during the examination.

Fluid status or volume overload was not evaluated at enrollment. However, for all patients, TTE was performed on an interdialytic day in the evaluation phase for standardization. LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), thickness of interventricular septum (IVS), left ventricular posterior wall (LVPW) and LV mass (LVM) were calculated according to the guidelines of the American Society of Echocardiography (11-12).

LV systolic dysfunction was defined as LVEF of ≤40%. LVM was measured by the Devereux Formula and indexed to height2.7 to calculate the LVM index (LVMI) (13). LVM was indexed by height rather than body surface area to minimize possible disruption from extracellular volume overload. LVH was stated if LVMI was higher than 47 g/m2.7 in women and 50 g/m2.7 in men. LVEF was achieved from apical two and four-chamber views using a modified biplane Simpson's method (14).

Biochemical Analysis

At enrollment, a 5-ml blood sample was collected into a plastic tube containing potassium EDTA (1 mg/ml blood). Within five hours, the samples were centrifuged at 1,000 relative centrifugal force for 15 minutes at 4 °C then plasma samples were protected in plastic bottles at -70 °C to assess NT-proBNP, albumin, hemoglobin, and C-reactive protein (CRP).

Serum NT-proBNP was measured with radio-immunoassay kits (Roche Diagnostics GmbH, D-68298 Mannheim) by electrochemiluminescence immunoassay on the Immulite 2000 analyzer

(Siemens, USA) and in a range of 5 to 35,000 pg/ml. If NT-proBNP sample concentrations are above the higher measuring range, will be taken as 35,000 pg/ml. Measurements of CRP quantified by micro ELISA (Enzyme-Linked Immunosorbent Assay) on Immulite 2000 analyzer (Siemens, USA).

Statistical Analysis

Statistical analysis was performed by using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as means ± standard deviation or as median. Student's t-test and x2 test were used to compare continuous and discontinuous variables between the two groups, respectively.

Regression analysis was used to measure the correlation of other patient characteristics with NT-proBNP and it was log-transformed for skewed distribution before entering the linear regression model. The correlation between serum NT-proBNP and echocardiographic parameters was compared between groups. p-value < 0.05 was considered to be statistically significant.

Results

Patient's Characteristics

The basic demographic characteristics of all study patients are detailed in Table 1. Fifty-five patients (72%) were treated with erythropoietin, and fifty-six patients (74%) were taking angiotensin-converting enzyme (ACE) inhibitors monotherapy, angiotensin II type I (AT1) antagonists, and calcium channel blockers. Twenty patients (26%) were on combination therapy with various compositions of these drugs.

The clinical characteristics of the two groups are presented in Table 2. The mean age was 62.3±9.9 years in patients with LV systolic dysfunction and 59.9±15.1 years in patients with normal LV systolic function group; this finding was not statistically significant. The mean systolic blood pressure was 136 ± 24 mmHg, and the mean diastolic blood pressure was 87 ± 10 mmHg in the total patient population. There was no significant difference in systolic and diastolic blood pressure between groups (139 ± 20 mmHg vs. 135 ± 25 mmHg, p=0.54, and 90 ± 11 mmHg vs. 87 ± 10

Table 1 Demographic, anthropometric and hemodynamic characteristics of all study population

Characteristic	Values , n= 76
Age (Year)	60.5±13.9
Men / Women	54/22
BMI (kg/m²)	26±5
Duration of dialysis treatment (Months)	67±39
Hypertansion (%)	28 (%37)
Diabetes Mellitus (%)	26 (%34)
Hyperlipidemia (%)	24 (%31)
Systolic blood pressure (mmHg)	136±24
Diastolic blood pressure (mmHg)	87±10
Heart rate (b.p.m)	78±10
Myocardial infarction (%)	19 (%25)
Stroke (%)	15 (%20)
Peripheral vascular disease (%)	8 (%10)
Drug therapy	
Erythropoietin	55 (%72)
ACE inhibitors	24 (%32)
Calcium channel blockers	17 (%22)
β blockers	21 (%28)
AT1 antagonist or α blockers	16 (%21)
Double or triple therapy	20 (%26)

Unless specified otherwise, data are means ± SD. Percentages may not add up to 100 due to rounding off of decimal places.

Table 2 Demographic, anthropometric and hemodynamic characteristics of two study groups

Characteristic	EF≤40, n= 20	EF>40, n=56	P value
Age (Year)	62.3±9.9	59.9±15.1	0.50
Men / Women	16/4	38/18	0.39
BMI (kg/m²)	25±5	26±5	0.31
Duration of dialysis treatment* (Months)	56 (14-108)	71 (16-231)	0.48
Hypertansion (%)	6 (%30)	22 (%39)	0.59
Diabetes Mellitus (%)	6 (%30)	20 (%36)	0.78
Hyperlipidemia (%)	10 (%50)	14 (%25)	0.05
Systolic blood pressure (mmHg)	139±20	135±25	0.54
Diastolic blood pressure (mmHg)	90±11	87±10	0.60
Heart rate (b.p.m)	79±11	75±10	0.23
Myocardial infarction (%)	15 (%75)	4 (%7)	<0.01
Stroke (%)	4 (%20)	11 (%20)	0.99
Peripheral vascular disease (%)	5 (%25)	3(%5)	0.02
Drug therapy Erythropoietin	14 (%70)	41 (%73)	0.77
ACE inhibitors	11 (%55)	13 (%23)	0.01
Calcium channel blockers	4 (%20)	13 (%23)	0.99
β blockers	8 (%40)	13 (%23)	0.16
AT1 antagonist or α blockers	7 (%35)	9 (%16)	0.10
Double or triple therapy	7 (%35)	13 (%23)	0.37

Data are expressed as mean ±SD or as median *(interquartile range), as appropriate.

Table 3 Main laboratory findings of patients

Characteristic	Total, n= 76	EF<40, n= 20	EF>40, n=56	P value
NT-pro BNP (pg/ml) *	8333 (208-35000)	13136 (361-35000)	6617 (20-33805)	0.16
Log-transformed NT-pro BNP	3.61±0.57	3.79±0.60	3.55±0.54	0.10
Serum albumin (g/dL)	3.8±0.4	3.7±0.4	3.8±0.4	0.72
Serum C-reactive protein (mg/L)*	1.96 (0.02-20.4)	1.68 (0.28-4.10)	2.07 (0.02-20.44)	0.46
Serum cholesterol (mg/dl)	175±34	191±38	169±34	0.04
Serum phosphate (mg/dl)	4.7±1.0	4.5±0.8	4.8±1.0	0.24
Serum calcium (mg/dl)	9.1±1.0	9.4±0.9	9.0±1.0	0.05
Serum iPTH (pg/ml)*	473 (16-2500)	454 (101-1051)	480 (16-2500)	0.75

Data are expressed as mean ±SD or as median *(interquartile range), as appropriate.

Table 4 Echocardiographic findings of patients

Characteristic	EF≤40, n= 20	EF>40, n=56	P value
LVEF (%)	34.9±5.8	58.5±5.2	<0.01
LVEDD (mm)	48.1±7.0	48.5±6.2	0.84
LVESD (mm)	35.4±8.2	31.3±7.1	0.04
LVPW (mm)	14.2±2.4	14.0±2.4	0.65
IVS (mm)	13.6±2.4	12.8±2.3	0.20
LVMI (g/height$^{2.7}$)	272.6±51.9	267.0±82.7	0.77
LVM (g)	73.7±14.0	74.0±24.6	0.95
LA (mm)	35±7.1	31±5.2	0.04
TR jet velosity (m/s)	3.1±0.9	2.8±0.7	0.7
PAPs (mmHg)	38±7.6	31±6.9	0.06

LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LVPW: Left ventricular posterior wall thickness, IVS: Interventricular septum thickness, LVMI: Left ventricular mass index, LVM: Left ventricular mass, LA: Left atrium diameter, TR: Tricuspid regurgitation, PAPs: estimated pulmonary artery peak systolic pressure

mmHg, p=0.60). The history of myocardial infarction and antihypertensive therapy with ACEi were more common in the LV systolic dysfunction group; and these differences were statistically significant (p<0.01 and p=0.01, respectively).

Laboratory Findings

Table 3 summarizes the main laboratory findings of two study populations. There was no significant difference in mean serum levels of the following parameters groups, respectively; hemoglobin (11±1.1 g/dL vs. 11±1.2 g/dL; p:0.72), serum albumin (3.7±0.4 g/dL vs 3.8±0.4 g/dL, p:0.72), serum phosphate concentration (4.5±0.8 mmol/L vs. 4.8±1.0 mmol/L, p:0.24), serum iPTH concentration (454 (101-1051) pg/ml vs. 480 (16-2500) pg/ml, p:0.75) and serum C-reactive protein (1.68 (0.28-4.10) mg/L vs. 2.07 (0.02-20.44) mg/L, p:0.46). Serum total cholesterol (191±38 mg/dl vs. 169±34 mg/dl, p:0.04) and serum calcium (9.4±0.9 mmol/L vs. 9.0±1.0 mmol/L, p:0.05) levels were significantly higher in the LV systolic dysfunction group.

The mean concentration of serum NT-pro-BNP was 8333 (208-35000) pg/ml, and this parameter was not significantly different between the two groups (13136 (361-35000) pg/ml vs. 6617 (20-33805) pg/ml, p:0.16). NT-pro-BNP is not a significant predictor of a history of MI, peripheral vascular disease, ACEi usage, total cholesterol concentrations, LVEF, or LV end-systolic diameter (LVESD) in either univariate and the multivariable Cox regression models. In multivariate analysis, log-transformed NT-pro-BNP correlated only with RVEF (β = 0.390, P = 0.001).

The echocardiographic findings of the patients are presented in Table 4. The ejection fraction (EF) was significantly lower in the LV dysfunction group than the normal LV systolic function group (34.9±5.8% vs. 58.5±5.2%, respectively, p<0.01). There were no statistically significant differences between the two groups concerning LVEDD, IVS, LVPW, LVM, and LVMI. However, LVESD was significantly lower in the normal LV systolic function group than in the LV systolic dysfunction group (35.4±8.2 vs. 31.3±7.1 mm, p:0.04).

Discussion

Previous studies showed that BNP and NT-proBNP are mean diagnosting parameters in ventricular dysfunction (15-17). They also predict prognosis in heart failure (HF) (18-21). These parameters are also useful in excluding HF in the general population. They are highly sensitive and specific (over 85%) and increase the diagnostic precision of heart failure from 73% to 84% (15, 22, 23). In addition, the measurement of the plasma concentrations of cardiac natriuretic peptides, such as NT-proBNP, in patients with CKD proved to be beneficial for the diagnosis

of LVH and LV dysfunction. LVH and LV dysfunction are recently recognized as the strongest predictors of cardiovascular and total mortality in the dialysis population (24, 25). Volume overload and higher LV filling pressures are the main factors of LVH in both healthy subjects and renal insufficiency patients (26). Since elevated ventricular mass and pressure load independently increase natriuretic peptide synthesis, the plasma values of these peptides are strongly correlated with cardiac mass and function (27-32).

BNP is a peptide hormone that is secreted in response to muscular relaxation in the left ventricle and is converted to two biologically active forms: c-BNP and N terminal proBNP. N-terminal proBNP has a prolonged half-life and is more biologically stable than c-BNP, and it has greater clinical significance (1).

In our study, we demonstrated that NT-pro-BNP level was numerically higher in the LV systolic dysfunction group than in the normal LV systolic function group, however, it did not reach to statistical significance level (13136, 6617; P = 0.16). Log-transformed NT-pro-BNP concentration was also similar between the two study groups. In addition, LVM (g) and LVMI (g/m 2.7) were also similar between the two groups. There is a significant interaction between systolic dysfunction and total cholesterol levels, and it was higher in the systolic dysfunction group.

Many recent studies have been conducted on correlations between BNP level, cardiac function, and patient prognosis. Kim et al. (33) and Goto et al. (34) published that serum BNP concentration was inversely proportional to LV ejection fraction. Nitta et al. (35) showed that the mean serum BNP concentration in hemodialysis patients was higher than in normal healthy individuals, and there was an inverse correlation between serum BNP concentration and LV function.

There are few studies evaluating the diagnostic utility of NT-proBNP, in hemodialysis patients with LV dysfunction (2-4). In a recent study, Wang et al. (8) also reported that NT-proBNP levels were significantly related to acute decompensated heart failure, in chronic peritoneal dialysis patients with end-stage renal disease as in our study. This study also indicated that cardiovascular congestion was strongly related to LVMI, however, we did not find any significant interaction between LVMI and NT-proBNP concentration. Another study suggests that a serum NT-proBNP cut-off value of>/=7200 ng/L discriminates CKD stage 5 patients without LV dysfunction (LVD) from those with LVD (36). In our study, we also evaluated NT-proBNP values but did not find a correlation between LV functions. This may be related to the stringent exclusion criteria we used on echocardiography. To the best of our knowledge, our study is one of the first-line studies to evaluate the diagnostic utility of NT-proBNP, in hemodialysis patients with LV dysfunction.

Several limitations of this study should be considered. First, the number of patients was small, because it was conducted at a single hemodialysis center. This decreases the statistical power of the study. However after exclusion criteria were performed, limited patients were eligible and underwent the analysis. Second, we only evaluated the diagnostic utility of NT-proBNP in hemodialysis patients, but we don't know how this parameter changes in peritoneal dialysis or in chronic kidney disease patients who do not receive dialysis treatment. Third, fluid status or volume overload was not evaluated at enrollment. This may have allowed us to evaluate the higher NT-proBNP concentration in baseline volume overload or cardiovascular obstruction.

NT-proBNP is an important indicator of LV systolic dysfunction in the general population. However, our findings suggest that NT-proBNP levels are inadequate to determine LV systolic dysfunction in patients with chronic kidney disease on hemodialysis treatment.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
In this study, we undertake that all the rules required to be followed within the scope of the ''Higher Education Institutions Scientific Research and Publication Ethics Directive'' are complied with, and that none of the actions stated under the heading ''Actions Against Scientific Research and Publication Ethics'' are not carried out.The study was prepared by the Declaration of Helsinki and was approved by the ethics committee for clinical research at Suleyman Demirel University Medical Faculty (Date: 06/03/2023, No: 39). The study was conducted in accordance with the principles set forth in the Declaration of Helsinki.

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all participants included in the study.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
ŞT: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing-original draft.

BAU: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing-original draft.

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