Prognostic Value of B-type Natriuretic Peptide for Assessment of Left Ventricular Function in Patients With Chronic Kidney Disease

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Introduction. Since the level of B-type natriuretic peptide (BNP) increases in heart failure, elevated plasma BNP concentration is used as a predictor in the diagnosis and management of heart failure. Due to the diminished renal clearance of BNP, its level is above normal in kidney failure. This study evaluated the BNP prognostic value for assessing ventricular function in patients with chronic kidney disease.

Materials and Methods. All the participants were diagnosed with chronic kidney disease. Echocardiography was employed to assess ejection fraction. Body mass index, serum creatinine, and BNP were measured for all the patients. Prognostic value of BNP was assessed for ventricular function measured by ejection fraction.

Results. Forty-four patients, including 34 men and 10 women, participated in the study. Level of BNP had a significant correlation with body mass index, ejection fraction, age, and gender. The sensitivity and specificity of BNP levels of 150 pg/mL and 705 pg/mL were 93.3% and 28.6% and 50.0% and 85.7%, respectively, for the diagnosis of ventricular dysfunction in the patients with chronic kidney disease.

Conclusions. These findings suggest that a level of BNP of 705 pg/mL is a rather acceptable predictive factor for heart failure in patients with chronic kidney disease. The participants' height and weight, which were associated with BNP as body mass index, contributed to this level.

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INTRODUCTION

Synthesis of B-type natriuretic peptide (BNP) is done mainly by myocytes in the cardiac ventricles in response to excessive cardiac ventricular stretch and pressure overload. B-type natriuretic peptide was originally isolated from porcine brain tissue, but it is also secreted from the heart and the ventricles, in particular.[1,2] Age, sex, and body mass index (BMI) affect plasma BNP concentration[3]; therefore, it is much elevated in women and old people, while plasma BNP concentration is lowered in the patients with a high BMI.[4-9] Since the level of BNP increases in patients with heart failure, plasma BNP concentration and its serial analysis is used as a predictor not only in the diagnosis, prognosis, and management, but also in assessment

of the severity of heart failure. Furthermore, BNP levels are elevated in the plasma of patients with diminished left ventricular ejection fraction (EF), given the clear association between the increase in the BNP concentration and reduction of EF.[10-17]

The other essential diagnostic value of serum BNP is its ability for assessment of patients with acute dyspnea.[18-22] Plasma BNP concentration can be applied in order to differentiate between dyspnea due to heart failure and dyspnea caused by other diseases.[23] Because of helping to shorten the time to initiating appropriate treatment of heart failure as well as the duration of intensive care and hospitalization,[24] the use of BNP as a prognostic and diagnostic value for dyspnea in the emergency departments can be cost-effective and improve clinical outcomes.[25]

Although most often used in patients with acute dyspnea and those with established heart failure, plasma BNP may have a value in a variety of other settings. Plasma BNP concentration reveals a diagnostic or prognostic value in the patients with stable angina,[26] chronic mitral regurgitation,[27] restrictive cardiomyopathy (for distinguishing it from constrictive pericarditis, in which wall stretch is minimized by the thickened pericardium),[28] primary or secondary pulmonary hypertension,[29] and sepsis.[30,31] It is a predictor of mortality rate in heart failure and acute coronary syndromes,[17,26,32] and also it was found to be a prognostic marker in patients who undergo cardiac surgery for coronary revascularization and correction of valve defects or inborn dysplasia of the heart.[33,34]

Plasma BNP concentration is elevated in patients with chronic kidney disease (CKD).[25,35] B-type natriuretic peptide is cleared by the receptor-mediated binding and removal, neutral endopeptidase,[35,36] as well as by passive excretion. Thus, diminished glomerular filtration rate (GFR) in CKD is related to elevated BNP concentrations.[5,26] Such elevations may result from volume expansion due to renal retention or from left ventricular hypertrophy, which increases its cardiac release,[35] and monitoring plasma BNP does not appear to facilitate management of these patients.[37] Since patients with CKD are at extremely high cardiovascular risk and frequently experience coronary events and heart failure, this increase of BNP levels has initially been considered an unwanted confounder in the diagnosis of congestive heart failure. However most recent studies have shown that BNP is also a suitable diagnostic and prognostic biomarker of heart failure in patients with CKD,[5,36,38-40] requiring, however, higher diagnostic cutoffs, whether or not they have clinically diagnosed heart failure.[35-37,41]

There is a consensus that the measurement of cardiac peptides is clinically useful and could be a cost-effective method of screening for left ventricular systolic dysfunction in the general population, especially if its use is targeted to individuals at high risk.[42] Although serial echocardiography is an approved method to identify and treat alterations in the left ventricular mass and function in CKD patients, echocardiography services are often available in hospitals and not in daily out-patient clinics.[43] There is much need to some simple and validated methods to clinically diagnose these abnormalities in CKD patients. In this way, BNP has been reproduced by many investigators and seems that it would be more useful in the follow-up of cardiac complications in patients with kidney disease.[5,36,38-40] In addition, its serial measurements guides the prognosis and severity of therapy.[14]

There is no overall agreement on the accurate cutoff of BNP in diagnosis of left ventricular dysfunction in patients suffering CKD. Therefore, we designed this study to evaluate the variations of serum BNP and to investigate the sensitivity and specificity of serum BNP in the diagnosis of left ventricular dysfunction in CKD patients.

MATERIALS AND METHODS

Patients

To determine the prognostic value of BNP in assessing ventricular function in the patients with kidney disease, we enrolled 60 patients referred to nephrologists complaining about kidney disease after obtaining informed consent. Patients with valve or congenital disorder (according to their angiography) and those with a level of BNP above 5000 ng/mL were excluded from the study (6 patients). In 5 patients, no serum sample was available for subsequent measurement of BNP. Three patients underwent dialysis and 2 were lost to follow up. Consequently, the remaining 44 patients were included in the study.

The causes of CKD were diabetes mellitus (n = 31), hypertension (n = 9), and chronic

glomerulonephritis, obstruction, and renal cell carcinoma (n = 4). Our criterion for CKD was a GFR less than 60 mL/min calculated from the equation of Cockcroft-Gault, as follows: [(140 - age) × weight in kilogram]/serum creatinine, multiplied by a constant of 1.25 for men and 1.03 for women. The EF based on echocardiography measured using the Simson method was set as an indicator for detecting heart failure; the patients were referred to a cardiologist for echocardiography. Based on the rate of EF, the patients were divided into 2 groups: one with heart failure (EF < 45%) and the other without heart failure (EF ≥ 45%). Also the patients were classified according to the New York Heart Association Functional Classification.[44] Demographic data such as height, weight, age, and gender were also collected.

Laboratory Analysis

Two milliliters of blood samples taken from each patient and kept at a temperature of 2°C to 8°C were sent to the laboratory within 24 hours. All the tests were done using double-blinded method in a single laboratory, under supervision of an experienced person, using a single machine. Patients' sera were poured into the cuff and plasma level of BNP was measured via a commercially available immunoassay based on the Sandwich technique (Elecys pro-BNP, Roche Diagnostics, Basel, Switzerland) after 25 minutes in the laboratory. A level of BNP less than 100 pg/mL was regarded as normal.

Statistical Analysis

The data were analyzed by means of the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). Initially, the *t* test or its nonparametric equivalent, the Mann-Whitney test, was used for univariable comparisons. Linear regression was employed to study the effects of nuisance variables and modeling, where a P value less than .05 was considered significant. The sensitivity and specificity of the plasma BNP in diagnosing ventricular dysfunction was assessed using a receiver operating characteristic (ROC) curve. The area under the curve represents the overall accuracy of the BNP measurement; the larger the area, the greater the accuracy of plasma BNP. A *P* value less than .05 was considered to be statistically significant.

RESULTS

Forty-four patients, including 34 men (77.3%) and 10 women (22.7%), participated in the study. The mean weight and age of the patients were 68.45 kg and 66.77 years, respectively. The mean BMI and serum creatinine were 25.05 kg/m^2 and 1.69 mg/dL, respectively. The mean EF was 39.36%, and the mean BNP level was 747.69 pg/mL (Table).

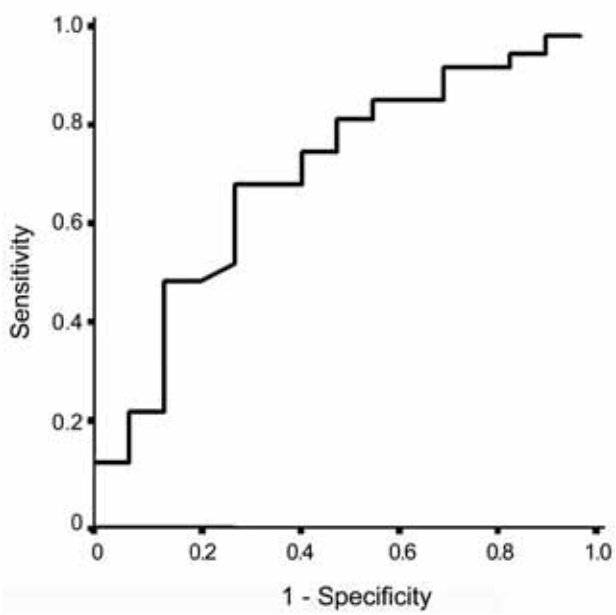
Thirty-four patients (77.3%) had an abnormal ventricular function (EF < 45%), while 10 (22.7%) had a normal ventricular function. In patients with a normal EF, CKD stage was 1 in 5.8%, 2 in 11.8%, 3 in 70.6%, and 4 in 11.8%, and in those with a low EF, zero, 14.8%, 59.3%, and 25.9% had CKD stages 1 to 4, respectively. Based on the New York Heart Association Functional Classification, 35.3% of the patients with a normal EF were in stage 1, 58.8% were in stage 2, 5.9% were in stage 3, and none were in stage 4. Of the patients with a low EF, 18.5%, 40.7%, 29.6%, and 11.1% were in stages 1 to 4 of functional class, respectively.

The mean of the age, weight, and height were 66.5 years, 70.4 kg, and 165.8 cm for patients with low EF and 69.4 years, 73.9 kg, and 164.9 cm for those with normal EF, respectively. The mean BNP level was 879.42 pg/mL for patients with low EF, while it was 465.40 pg/mL for those with normal EF (P = .03). The mean serum creatinine levels were 1.50 mg/dL and 1.76 mg/dL, respectively. There was a significant correlation between BNP and BMI (P = .047). However, BNP level was not significantly associated with gender (P = .91), serum creatinine (P = .19), or age (P = .94). In the multivariate analysis using a regression model, only BMI and EF were significantly linked with BNP levels.

To determine the cutoff of BNP for predicting low EF, the ROC curve was used. The area under the curve was 0.711 (Figure). A BNP level of 584 pg/mL had a sensitivity of 70.0% and a specificity

Characteristics of Patients With Chronic Kidney Disease

Variable	Mean (Range)
Age, y	66.8 ± 11.9 (42 to 88)
Weight, kg	68.4 ± 12.2 (43 to 95)
Height, cm	165.3 ± 8.9 (150 to 185)
B-type natriuretic peptide, pg/mL	747.69 ± 744.67 (26.1 to 3721.2)
Ejection fraction, %	39.4 ± 15.7 (15 to 70)
Serum creatinine, μmol/L	1.69 ± 0.48 (0.9 to 3.3)
Body mass index, kg/m^2	25.1 ± 4.0 (14.5 to 34.0)



The receiver operating characteristic curve in assessing the diagnostic accuracy of B-type natriuretic peptide for left ventricular dysfunction.

of 71.4% and a BNP of 705 pg/mL had a sensitivity of 50.0% and a specificity of 85.7% to predict ventricular dysfunction in the patients with CKD, as measured by EF through echocardiography.

DISCUSSION

Our findings suggest that BNP level is a rather acceptable predictive factor for the rate of heart failure in the CKD patients. In the general population, using serum BNP as a screening test in asymptomatic patients, a BNP concentration of 17.9 pg/mL (5.2 pmol/L) or greater, yielded a sensitivity of 77% and a specificity of 87% in all participants for a diagnosis of left ventricular systolic dysfunction.[45] In another study of newly diagnosed patients with symptomatic heart failure, a BNP greater than 22.2 pmol/L yielded sensitivity, specificity, and positive predictive value for the diagnosis of heart failure of 97%, 84%, and 70%.[45] The findings of our study demonstrated that BNP level in the patients with CKD and abnormal ventricular function was more elevated than that in the CKD patients with a normal ventricular function. Our results were consistent with many such as those obtained by Clerico and colleagues.[16] They measured plasma levels of atrial natriuretic peptide, BNP, pro-atrial natriuretic peptide, and pro-BNP-related peptides in patients with kidney failure on long-term hemodialysis. They found that only BNP levels significantly increased according to the degree of ventricular hypertrophy and/or ventricular function. Therefore, BNP would be more useful for the follow-up of cardiac complications in patients with end-stage renal disease on regular hemodialysis.

Nonetheless, the accuracy of BNP in diagnosing left ventricular dysfunction in CKD patients has been inconsistent. Mark and associates reported a cutoff of 42 pmol/L for BNP with a sensitivity of 82.5% and a specificity of 29.6% in CKD patients.[46] Zeng and colleagues[47] and Francesca and coworkers[48] determined a cutoff of 152 pg/mL with a sensitivity of 81% and a specificity of 29.6% and a cutoff of 38.9 pmol/L with a sensitivity of 74% and a specificity of 76% in dialysis patients, respectively. The reasons for these discrepancies are some confounders affecting in determining serum BNP, including GFR, albumin, hemoglobin, beta blockade, drug therapy, and age. These confounders limit the application of BNP in the detection and monitoring of cardiac dysfunction in patients with CKD.[46] In the present study, a different level of BNP along with its sensitivity and specificity was determined. The sensitivity and specificity are 93% and 14% for a BNP of 100 pg/mL, respectively. Troughton and coworkers reported a sensitivity and specificity of 90% and 86%, respectively.[14] The sensitivity given by these authors was rather identical to that of ours, but their specificity was elevated. In another study conducted by Takami and colleagues, a BNP of 150 pg/mL was inaugurated as a suitable criterion for diagnosing abnormal ventricular function in CKD patients. This level had a sensitivity and specificity of 93% and 28%, respectively.[41]

Given the role of BNP level in predicting heart and kidney failure, as mentioned in the previous studies, this criterion can be used in the cases above. In our study, a BNP of 705 pg/mL with a sensitivity of 50% and a specificity of 85.7% seemed to be rather acceptable and can be used as an appropriate cutoff to detect ventricular dysfunction in the patients with CKD. However, a BNP of 150 pg/mL, identified in most of the studies, seems to have a poor specificity despite its elevated sensitivity. Since this study was performed on 44 patients, further studies are advised to be done on a larger sample size. Another limitation

of our study is not considering some confounding factors such as serum albumin, haemoglobin, and beta blockade that may counteract with serum BNP levels.

CONCLUSIONS

Our findings suggested that level of BNP can be an appropriate predictive factor for \heart failure in the CKD patients. We proposed a BNP of 705 pg/mL with a sensitivity of 50% and specificity 85.7% as an appropriate cutoff to detect ventricular dysfunction in the patients with CKD.

CONFLICT OF INTEREST

None declared.

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