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Plasma NT-pro BNP Concentrations in Patients with Hypertensive Chronic Kidney Disease

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Abstract

Background and Aims: Plasma N-amino terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP) is produced and released from cardiac ventricles; it is elevated in patient with heart failure, hypertension and chronic kidney disease (CKD). This study aims to examine the plasma levels of NT-proBNP and their relationship in hypertensive patients with or without CKD.

Methods: Our study population consisted of 129 patients with hypertensive CKD (stage 1-4) (Group 1) and 41 controls with hypertensive normal kidney function (Groups 2). Patients with CKD were divided into two groups. Group 1A (n=89) with diabetes mellitus, Group 1B (n=40) without diabetes mellitus. Serum creatinine, NT-proBNP concentrations and proteinuria were analyzed and glomerular filtration rate, blood pressure, weight, height were measured.

Results: The patients with hypertensive CKD were older compared to the controls (p=0.047), BMI was not statistically significant (p>0.05). NT-pro BNP concentrations were significantly elevated in the group 1, compared to the group 2 (p=0.007). Notably, there was no significant difference between Group 1A and Group 1B (p>0.05). NT-proBNP concentrations correlated positively with longer diabetes duration (r=0.34, p=0.001), proteinuria (r=0.30, P=0.001) and negatively with BMI (r=-0.20, p=0.02) and GFR (r=-0.29, p=0.001).

Conclusions: In patients with hypertensive CKD, levels of NT-proBNP concentrations are increased. There was no significant difference between diabetic and non diabetic patients with CKD. Because of the relationship between proteinuria and Pro-BNP, increased plasma NT-proBNP concentrations may be a risk factor for the progression of renal disease. The relationship between elevated NT-proBNP and proteinuria should be further investigated.

Keywords: Kidney Disease, Hypertension, Natriuretic Peptide

Introduction

The N-amino terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP) is released from myocytes in response to ventricular wall stretch and wall tension. As such, the circulating level of NT-proBNP serves as a sensitive marker of both left ventricular hypertrophy and volume expansion. Chronic kidney disease (CKD) is associated with impaired salt regulation and extracellular fluid volume expansion. Therefore, NT-pro-BNP concentrations may be altered in renal failure (1-3).

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The kidney is an important filtration organ for circulation. NT-proBNP levels are elevated in individuals with reduced kidney function, although it remains unknown whether this is solely due to the increased left ventricular mass and prevalence of heart failure in this population or whether reduced clearance of NT-proBNP, volume overload, or other factors are directly related to uremia that may play a role (4, 5). We hypothesize that plasma NT-pro BNP concentrations may reflect an increased volume load of heart as a consequence of volume expansion due to impaired renal function.

This study aims to examine the plasma levels of NT-proBNP and their relationship in hypertensive patients with and without chronic kidney disease.

Materials and Methods

Our study population consisted of 129 patients with hypertensive CKD (stage 1-4) (Groups 1) and 41 controls with hypertensive normal kidney function (Groups 2) were recruited at the Unit of Nephrology of the Bagcılar Education and Research Hospital between December 2008 and September 2009. CKD patients were divided into two groups. Group1A (n=89); with diabetes mellitus, Group 1B (n=40); without diabetes mellitus.

All blood samples were taken after 10 hours of overnight fasting. Fasting blood glucose, serum creatinine, NT-proBNP concentrations were analyzed. Serum creatinine was measured by an autoanalyser and creatinine clearance was calculated using the Cockcroft–Gault formula. NT-proBNP concentrations were analysed by an electrohemiluminiscence immunoassay using an automated instrument (Roche Diagnostics). Urinary proteinuria concentration was determined by an immunoturbidimetric method. Proteinuria was defined as ≥300mg/day.

Renal function was defined according to the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) definitions (6). Chronic kidney disease was defined according to the presence or absence of kidney damage and level of kidney function. Kidney damage was defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. Among individuals with chronic kidney disease, the stage was defined by the level of GFR (stage 1-5). Hypertension was defined as one or more of systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg and use of antihypertensive medication, known history of diabetes mellitus (fasting plasma glucose ≥ 7.0 mmol/l or use of anti-diabetic medications).

The control subjects had normal renal function (estimated glomerular filtration rate (GFR) ≥ 90 ml/min per 1.73 m^2), no glucose tolerance (fasting plasma glucose <6.1 mmol/l and 2 h plasma glucose <7.8 mmol/l) and proteinuria < 300 mg/day.

The Gault-Cockcroft formula: Kcr (mL/min) = (140-age) × Weight (kg) / (plasma Cr × 72). The obtained value was multiplied by 0.85 in women. Body mass index (BMI = Weight (kg) / Height (m^2)) was obtained from height and weight.

No patient presented significant cardiac history based on clinical examination, electrocardiography recording, and chest radiography. All those who were studied had sinus rhythm on a 12-lead electrocardiogram with no signs of hypertrophy according to either the Cornell product criteria or the Sokolow-Lyon voltage criteria (7). The exclusion criteria were age <20 or >75 years, secondary hypertension, serious systemic disease or end stage renal disease (estimated GFR < 15 ml/min per 1.73 m^2).

Statistics

Data were performed using SPSS 13.0 software. All data were expressed as mean ± standard deviation. Unpaired Student's t test was used to determine differences in continuous variables between groups. Multiple linear regression analysis was used to determine all correlations. The P values were considered

significant at P < 0.05.

Results

The patients with hypertensive CKD were 72 females, mean age 55.±10 years, median BMI= 29.8.±4.8 kg/m². The control patients were 19 females, mean age 52.±9 years, BMI 29.6.±3.9 kg/m². The patients were older compared to the control group (p=0.047), however, the BMI was not significantly different (p>0.05). The clinical characteristics of the hypertensive patients with and without CKD are summarized in Table 1.

CKD patients were divided into two groups. Group1A (n=89); with diabetes mellitus (47 female, mean age 57±8 years median GFR=67.9±39.1/1.73m² ml/mýn, BMI=30.7±4.6kg/m²), group 1B (n=40); without diabetes mellitus (25 female, mean age 52.±11 years, median GFR=59.1±34./1.73m² ml/mýn, BMI=27.7±4.5 kg/m²). The Group 1A patients were older (p=0.023) and higher BMI (p=0.001) compared to the Group 1B, and GFR was not significantly different (p>0.05).

All controls were without CKD, while 9.5 % patients had CKD stage 1, 25.6 % patients stage 2, 44.6 % patients stage 3, 13.2 % patients stage 4. NT-pro BNP concentrations were significantly elevated in the Group 1 (415±804.4 pg/dl), compared Group 2 (191.6±254.6 pg/dl) (p=0.007). Notably, there was no significant difference between Group 1A (502.2±933.7 pg/dl) and Group 1B (472.9±1086 pg/dl) patients with CKD (Table 2).

NT-proBNP concentrations correlated positively with longer diabetes duration (r=0.34, p=0.001), proteinuria (r=0.30, P=0.001), negatively with BMI (r=-0.20, p=0.02) and GFR (r=-0.29, p=0.001).

Table 1. Clinical and biochemical data of patients

Characteristics	CKD (+) DM (+)	CKD (+)DM (-)	CKD(-)
Age (years)	57±8	52±11	52±9
BMI (kg/m²)	30.7±4.6	27.8±4.5	29.6±3.9
GFR (ml/min)	65.9±39.1**	59.3±34.1**	95.3±32.1
Systolic BP (mmHg)	135.8±15.7	138.4±16.3	134.8±15.8
Diastolic BP (mmHg)	77.8±8.1	82.8±9.2	82.6±10.2
Urinary protein exrcretion (mg/24h)	1819.5±2572**	476.1±647**	182.29±48.1
NT-proBNP (pg/ml)	502.2±933.7*	472.9.±1086*	191.6±254.2*

* Not statistically significant p>0.05

** Statistically significant p<0.05

Table 2. Clinical and biochemical data in patients with/without CKD

Characteristics	CKD (+)	CKD (-)	P
Age (years)	55±10	52±9	0.047
BMI (kg/m²)	29.8±4.8	29.6±3.9	NS
GFR (ml/min)	65.2±37.7	95.3±32.1	0.001
Systolic BP (mmHg)	136.6±15.9	134.8±15.8	NS
Diastolic BP (mmHg)	79.4±8.7	82.6±10.2	NS
Urinary protein exrcretion (mg/24h)	1410.24+2257.1	182.29±48.1	0.001
NT-proBNP (pg/ml)	415.1±804.4	191.6±254.2	0.007

Discussion

We show that in patients with hypertensive CKD, levels of NT-proBNP concentrations were increased. There was no significant difference between diabetic patients and non diabetic patients with CKD. There are an inverse correlation between NT-proBNP and GFR, and a positive correlation with proteinüria proteinuria.

The reason for increased BNP and NT-proBNP concentrations in patients with impaired renal function has not been clarified. The most frequently used explanation is the renal retention of both BNP and NTproBNP. In accordance with this explanation are the strong correlations of GFR with BNP and NT-proBNP concentrations. Surprisingly, increased rather than decreased urinary concentrations of BNP have been found in patients with renal impairment compared with healthy controls. Furthermore, urinary NT-proBNP significantly correlated with NT-proBNP and creatinine concentrations in plasma of healthy individuals. Lower GFR and and higher urinary protein excretion may be associated with volume expansion in CKD. These processes may be associated with increased NT-proBNP in CKD.

These inverse correlations between renal function and urinary BNP or NT-proBNP indicate that renal retention is not the only reason for increased plasma concentrations of BNP and NT-proBNP in patients with impaired renal function (8, 9).

Progression of CKD is associated with impaired salt regulation and extracellular fluid volume expansion. Therefore, the inverse relationship between GFR and plasma BNP or NT-proBNP concentrations may reflect an increased volume load of the heart as a consequence of volume expansion due to restricted GFR. Fagugli et al investigated the reationship between plasma BNP and volume load by using bioimpedance. These authors reported an association between BNP and extracellular volume and indicated that the increased synthesis and release of BNP from the ventricular (10, 11).

Plasma BNP and NT-proBNP concentrations were independently affected by eGFR and left ventricular mass index. Vickery et al demonstrated that mean BNP concentration increased by 20.6% per 10 mL/min/1.73 m2 reduction in eGFR, while mean NT-proBNP concentrations increased 37.7% (12). The mechanisms underlying these associations may be postulated to reflect impaired renal clearance of natriuretic peptides. NT-proBNP concentration had been found to be increased in patients with impaired renal function (13, 14). Median NT-proBNP concentration increased in parallel with decrease in renal function. Moreover, increased NT-proBNP concentration indicated an increased risk for accelerated progression of CKD to ESRD and may prove to be valuable biomarker for the assessment of prognosis in patients with CKD (15).

In our study, serum NT-proBNP concentrations are inversely related with GFR; NT-proBNP concentrations increased in patients with hypertensive chronic kidney disease patients. Additionally, the BNP levels in urine and volume load by using bioimpatence were not investigated. However, we believe that increased NT-proBNP concentrations in renal failure reflected not only impaired glomerular filtration but also a counterregulatory response of the heart to the changes in hemodynamics and water homeostasis.

In previous clinical studies, patients with Type 2 diabetes, albuminuria or diastolic dysfunction were associated with increased levels of BNP in the absence of heart failure. Moreover, in type 2 diabetes mellitus patients with macro- and/or micro-vascular complications exhibit an elevation of plasma NT-proBNP levels compared to corresponding patients without evidence of vascular disease (16-18).

In our study, NT-proBNP concentrations increased in patients with hypertensive CKD, but no difference was found between non diabetic and diabetic patients.

Especially in obese patients, BNP and NT-BNP

levels decreased in correlation with BMI and also a decrease in cut-off levels was shown while their weight increeased. Obesity caused water and salt retantion and so volume overload. In large cohort studies of patients with or without heart failure, greater obesity or BMI was significantly associated with lower natriuretic peptide concentrations compared with concentrations in leaner cohort members. In our study, inverse relation was found between BMI and NT-pro BNP concentrations (19, 20).

The relation between the levels of BNP and microalbuminuria remains unclear. A number of factors might explain the increased plasma levels of BNP in patients with albuminuria. Firstly, intravenous infusion of BNP has been shown to increase urinary albumin excretion in previously normoalbuminuric individuals, which suggests that higher proteinuria among those with elevated NT-proBNP may be an indicator of past NT-proBNP levels (21, 22).

Secondly, the elevation of BNP can be mediated by down-regulation of A-type guanylate cyclase-coupled natriuretic peptide receptor (NPR-A). NPR-A found in target tissues such as renal tubules and atrial natriuretic peptide (ANP), a close relative of BNP, exerts a vasodilatory effect on afferent arterioles and a vasoconstrictive effect on efferentarterioles of glomeruli, thereby increasing glomerular hydraulic pressure. Because both ANP and BNP bind to the same receptor and have the same biological activity, it is conceivable that abnormally elevated levels of BNP also cause increased glomerular hydraulic pressure and thus induce increased albumin excretion (23, 24).

In our study, there is a positive correlation between the increase in NT-proBNP levels and proteinuria. We believe that the pressure overload and volume expansion due to impaired glomerular filtration may be stimulated BNP secretion from cardiac ventricles. The elevation of BNP may lead to increased glomerular hydraulic pressure and thus induce increased albumin excretion. Because of the relationship between proteinuria and Pro-BNP, increased NT-proBNP plasma concentrations may be a risk factor for the progression of renal disease.

Conclusions

NT-proBNP concentrations increased in patients with hypertensive chronic kidney disease. However, there is no significant difference between diabetic and non diabetic patients with CKD.

Because of the relation between proteinuria and NT-Pro-BNP, increased NT-proBNP plasma concentrations may be a risk factor for the progression of renal disease. The relationship between elevated NT-proBNP and proteinuria should be further studied.

Conflict of Interest

None declared.

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