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Research Article

EFFECTS OF DIABETES ON THE AMINO TERMINAL PROBRAIN TYPE NATRIURETIC PEPTIDE (NT-PROBNP) LEVELS IN ELDERLY PATIENTS

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ABSTRACT
The Amino terminal portion of the precursor of brain natriuretic peptide (NT-proBNP) has been reported to be elevated in left ventricular dysfunction. The NT-proBNP is a split product from the proBNP molecule, and its level in the circulation is not, as the mature Brain type natriuretic peptide, dependent on the peripheral number of brain natriuretic peptide (BNP) receptors. We aimed to test the hypothesis that asymptomatic left ventricular dysfunction (ALVD), as estimated by NT-proBNP, would be more prevalent in patients with type 2 diabetes without overt cardiovascular disease in comparison with matched control subjects. The study population consisted of [N=100] out of which 75 patients including Type-II diabetes and 25 matched control subjects aged 40–70 years heart disease from OPD Escorts Heart Institute and Research centre Okhla New Delhi. NT-proBNP was measured in plasma by competitive enzyme immunosorbent assay. Patients with type-II diabetes were shown to have higher NT-proBNP values than control subjects. NT-proBNP levels were independently related to diabetes after adjustment for age, sex, systolic and diastolic blood pressure, BMI, heart rate, drug treatment, serum creatinine, and cystatin-C. The secretion of NT-proBNP is increased in type-II diabetic patients, suggesting that type 2 diabetes is associated with a higher prevalence of ALVD. NT-proBNP may thus serve as a screening tool to select patients with type-II diabetes who could benefit from an echocardiographical examination.
Key words: ALVD, asymptomatic left ventricular dysfunction, BNP, brain natriuretic peptide, LVD, left ventricular dysfunction, NT-proBNP, Amino terminal Brain Natriuretic Peptide, SBP, systolic blood pressure

INTRODUCTION

The major causes of morbidity and mortality in the patients with diabetes are cardiovascular disease and angiopathies. Screening for kidney and retinal complications is already an established part of routine diabetes care today. The most evident cardiac complication is coronary atherosclerosis, it becomes clinical earlier and is more generalized in the coronary tree compared with the subjects without diabetes[1].Diabetes is also more prevalent among patients with heart failure. It has been reported in the Framingham study, male patients with diabetes had twice the risk and female patients five times the risk of a control population to develop heart failure[2]. These patients with diabetes also have an increased collagen content[3]. Patients with diabetes have a disproportional increase in left ventricular mass independent of blood pressure[4-6]. All of these factors contribute to an increased myocardial stiffness. This is especially important because left ventricular hypertrophy in a meta-analysis has been associated with a 1.5- to 3.5-fold increased risk of future cardiovascular morbidity and a 1.5- to 6.8-fold increase of all-cause mortality[7]. Thus, taken together, patients with diabetes have a higher cardiac morbidity and mortality, beside the more aggressive atherosclerosis. Brain Natriuretic Peptide (BNP) is a 32–amino acid peptide[8], synthesized predominantly in the left ventricle of the heart as 108–amino acid pro hormone-preproBNP [9-11]. The hormone is a potent vasodilator and a natriuretic factor regulating salt and water homeostasis. The circulating plasma forms of BNP are BNP-32 and the NH_2-terminal portion proBNP (NT-proBNP) (1-76)[12-13]. Increased secretion of NT-proBNP occurs mainly with increased tension in the ventricular walls, decreased oxygen supply, acute myocardial infarction, chronic cardiac heart failure, and in hypertrophy of the heart[14-15]. In a head-to-head comparison study[16], BNP and NT-proBNP were found to be superior markers to NT-pro atrial natriuretic peptide in detecting left ventricular dysfunction (LVD). Cardiovascular death accounts for more than 75% of the deaths among subjects with diabetes. The treatment of Left Ventricular Dystrophy, even when asymptomatic, is associated with a better prognostic outcome[17]. This study was performed to establish whether asymptomatic LVD (ALVD), as estimated by NT-proBNP, is represented in patients with type-II diabetes compared with nondiabetic subjects for both groups with cardiovascular disease.

MATERIALS AND METHODS

In this study 75patients with left side heart failure, who were referred to Escorts Heart hospitals and Research Centre, Okhla, New Delhi, consecutively, were selected. Diagnosis of heart failure in these patients was done through clinical evaluation and echocardiographic procedures. The severity of heart failure was determined according to New York heart association (NYHA) classification for each patient. 5-6 ml venous blood from each patient was drawn. NT-proBNP level in all samples was measured by ELISA (Boehringer Mannahiem, Hitachi902) in Biochemistry Lab. A careful medical history was taken to obtain information about the diseases particularly hypertension, coronary heart disease, myocardial infarction, stroke, peripheral vascular disease, and endocrine disorders and medication. Body weight and height were measured with subjects in light clothing without shoes. Three blood pressure recordings were obtained from the right arm while in the supine position after 30 min of rest at 5-min intervals, and their mean value was calculated. Blood samples were drawn into vacutainer tubes containing EDTA. Plasma was frozen at –80°C for the measurement creatinine, cystatin C, and NT-proBNP. Patients with lung disease, liver cirrhosis, primary hyperaldosteronism, were excluded. Plasma levels of NT-ProBNP for each class of NYHA, and LVEF were assessed. Type II diabetes was diagnosed according to WHO[18]. Kidney function was normal, and none of the patients had any nephropathy either by report or by creatinine /cystatin C values. No subjects were under new or

additional drug treatment with digitalis or nitrates. Data were analyzed statistically and findings evaluated with 95% confidence limit (CL). Mean comparison T-test and one way analysis variance (ANOVA) was used. NT-proBNP for each functional class (NYHA I-IV) and LVEF in patients with heart failure were compared. NT-proBNP was analyzed using a competitive enzyme immunosorbent assay designed to measure the immunoreactive NT-proBNP (BM Hitachi 902). The cutoff value for LVD was set to 350 pmol/l[19]. Plasma cystatin C was measured by a fully automated particle-enhanced turbidimetric assay on undiluted samples[20-22] using a Behring analyzer.

Statistics: Statistical studies were performed. Significance of differences was tested by 't'–test.

RESULTS

Relation of body mass index, and blood pressure etc., were for each factor individually analyzed in the patients, with NT-proBNP as the dependent variable and each of the factors used as independent variables. Table 1-2. Patients with diabetes had a higher median value of NT-proBNP than without diabetes. The proportion of individuals with a NT-proBNP value above the cutoff value (350 pmol/l) was significantly higher among the diabetic patients than in the control group. Distribution of NT-proBNP values in the patient (n=75) and control (n=25) cohorts. Table 1-4. A multiple logistic regression analysis model taking sex, age, pulse, BMI, cystatin C, and systolic and diastolic blood pressure into account was used. Systolic blood pressure (SBP), pulse, BMI, and cystatin C were all independently influencing the risk of diabetes. NT-proBNP values showed no correlation to HbA_{1c}, age, or SBP in the patients with diabetes. However, high blood pressure has been implicated as being a confounder to NT-proBNP values. The trend of change for NT-proBNP to age was estimated in a linear regression with NT-proBNP as a dependent variable and age as independent.

CONCLUSION

BNP has been shown to be elevated in early left ventricular systolic as well as in diastolic dysfunction[22]. An increase in BNP might also be dependent on a downregulation of the receptor population, as has been suggested for patients with nephropathy[23]. This should not be the case for NT-proBNP, which is solely eliminated through glomerular filtration. In our study, the NT-proBNP level was shown to be significantly elevated in the patients with diabetes. Patients with diabetes had a higher BMI, heart rate, and systolic and diastolic blood pressure than the control subjects. In the Rotterdam study, systolic dysfunction was reported in 4% of the population aged 55–95 years. However, 60% of these were asymptomatic[24]. Diastolic abnormality, as defined by the European Study Group on Diastolic Heart Failure, is much more prevalent, 11.1%, according to a substudy of the MONICA project. However, it differed between different age-groups, with 2.8% in those aged 25–35 years and 15.8% in subjects >65 years of age[25]. In previous studies, BNP has been shown to be an early determinant of both diastolic and systolic dysfunction. In animal models, BNP gene expression has been shown to reflect ventricular and atrial pressures[26]. In that study, even the animals with a mild compensated heart failure had elevated BNP levels. Thus, the NT-proBNP measurement, in addition to being an estimation of the combined diastolic and systolic performance, might be a more sensitive measurement of ventricular disturbances than the echocardiographical examination. This might explain why, in our material, 25% of the nondiabetic subjects had elevated levels of NT-proBNP. Table -3.

Despite this suggested sensitivity for ventricular dysfunction with elevated levels among 25% of control subjects, the patients with diabetes had significantly higher levels of NT-proBNP. The previously defined cutoff for our assay of 350 pmol/l might either be too sensitive or the true prevalence might be as high as depicted[27-34]. Echocardiographical characterization of healthy control subjects with mildly elevated NT-proBNP levels is acceptable. Several pathophysiological mechanisms might explain why an early deterioration of left ventricular function could overrun the age effect on NT-proBNP in the patients with diabetes. Hearts from patients with diabetes have increased collagen content, as have been verified in autopsy studies[5]. In the diabetic heart, proposing a functional explanation to the impaired relaxation in the myocardium[34-38]. These effects could be so strong that they would overrun the age effect in the diabetic group. Our data reveals that the patients with diabetes show no relation between NT-proBNP levels and their age. NT-proBNP serve as sensitive marker of LVD[39], but the levels are influenced by the rate of synthesis and respective clearance rate. The NT-proBNP is cleared solely by glomerular filtration. Because the glomerular filtration rate is easily controlled for, e.g., by cystatin C, and receptor clearance rate cannot be estimated by today's methods, a paired screening with NT-proBNP and cystatin C might be a preferred screening model in patients with diabetes. Blood lipids of traditional risk value differed between groups as expected, with diabetic patients having higher triglycerides and lower HDL cholesterol than control subjects. In conclusion, our data suggest that the secretion of NT-proBNP, if paired with an estimation of glomerular filtration rate, is increased in patients with type-2 diabetes compared with control subjects. The measurement of NT-proBNP paired with cystatin C might be a simple screening tool to identify patients with diabetes at risk for ventricular dysfunction requiring further examinations with echocardiography. The raised NT-proBNP concentration in a hypertensive population reflects LVSD, but does not add any further clinical information about LVH. The test thus remains a useful aid for the detection of LVSD even in hypertensive patients. However, it could be used as a screening tool to separate patients with diabetes eligible for an echocardiographical examination. However, this is a very early study that needs confirmation in larger-scale studies.

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Table -1 NT-ProBNP levels in CHF patients based on NYHA functional class:[n=75]

NYHA class	N	NT-ProBNP Mean(pgl/ml)	Standard Deviation	Confidence limit	One way ANOVA
I	15	165.4	43.8	12.3 – 321.0	
II	18	205.4	89.5	124.2 -298.5	F=8.984;Df=3
III	19	487.5	52.9	351.7- 596.4	P<0.001
IV	23	698.4	82.5	445.6 – 897.3	

Table 2- General Characteristics of Patients : Age, Sex, Hypertension, Diabetes Mellitus-II, Heart Failure and Ischemic Heart Disease etc.

	Biological Indexes [N=100 subjects]	Diabetic type-II [n=75]	Nondiabetic[n=25] Control	*P*-value
1	Age years	53±8.5	52±9	t= -2.1 df=79; p<0.03
2	Sex (% Women)	54.6	66	t=-0.78 df=77 p<0.034
3	BMI (kg/m^2)	28 (25–37.2)	31.5±3.6 (23–38.9)	P<0.0002
4	Hypertension	133 (67%)	171 (47%)	t=1.0; df= 79 p=0.03
5	Fasting glucose (mmol/L)	8.1 (7.1–9.7)	5.3 (5–5.7)	<0.0001
6	HbA1C (%)	6.9 (6.1–9.4)	5.6 (5.2–5.7)	<0.0001
7	Creatinine clearance (mL/min)	64 (53–97)	89 (77–113)	0.0002
8	Plasma troponin (g/L)	20 (6–41)	20 (5–41)	0.37
9	CK-MB (UI/L)	136 (63–341)	114 (47–265)	0.59
10	HDL-cholesterol (mmol/L)	1.08±0.36	1.16±0.38	0.0181
11	LDL-cholesterol (mmol/L)	2.99±0.92	3.01±1.02	0.90
12	Triglycerides (mmol/L)	1.49 (0.87–1.82)	1.27 (0.83–1.62)	0.0157
13	Glomerular Filtration Rate (ml/min)	68.4±29.5	97.5±24.5	t=-1.3,p<0.01
14	Cystatin C (g/l)	1.08 (0.9- 1.19)	1.089 (1.00- 1.28)	<0.0036
15	Systolic BP (mmHg)	138.6±14.9	135.8±18.9	
16	Diastolic BP (mmHg)	75.5±15.4	74.8±9.4	
17	Urinary Protein mg/24h)	542.5±147.2***	174.35±69.8	0.01

Table- 3. Clinical Characteristics of the hypertensive patients with LVSD

Characteristics	Control [n=25]	CVD D [n=20]	CVDND [n=19]	(DM+LVH) [n= 18]	(DM+LVH+CKD) [n=11]	CKD +DM [n=7]
Age years	52±9	53±8.5	53±11	52±11	58±7	51±9
BMI (kg/m^2)	31.5±3.6	27.8±5.2	31.4±4.5	27.8±4.7	29.9±5.2	32.4±4.2
GFR (ml/min)	97.5±24.5	78.4±21.6**	58.2±28.5**	68.4±29.5	66.8±26.7	54.8±31.2*
Systolic BP (mmHg)	135.8±18.9	138.6±14.9	136.8±19.5	139.7±18.2	132.3±25.6	135±31.7
Diastolic BP (mmHg)	74.8±9.4	75.5±15.4	81.4±14.6	83.4±7.8	82.9±6.7	83.4±8.6
Urinary Protein mg/24h)	174.35±69.8	542.5±147.2***	647.9±112.6	547.6±285**	532.8±387.4**	1912±1154*
NT-proBNP (pg/ml)	175.9±104.3	498.56±245.7	783.9±457.8	989.3±574.8	1421.5±563.2	1001.4±687

CVDD-Diabetes with Cardiovascular Disease; **CVDND**- Cardiovascular Disease Non Diabetes; **LVH**- Left Ventricular Hypertrophy; **CKD**- Chronic kidney Disease, **DM** –Diabetes Mellitus-II.

Table -4. NT- Pro BNP levels in CHF patients based on LVEF [n=75]

NT-ProBNP LVEF%	N	Mean(pg/ml)	Standard Deviation	Confidence limit	One way ANOVA
40- 49 %	26	2287	768	153.3-374.7	
29 – 39%	24	4785	415	3784 - 6715	F=4.614; df=2 P<.0013
≤28 %	25	5324	457.8	3584 - 6994	

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