Plasma B-Type Natriuretic Peptide (BNP) As a Marker of Left Ventricular Diastolic Dysfunction in Diabetic Patients

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Abstract

The first stage of diabetic cardiomyopathy is represented by left ventricular diastolic dysfunction (LVDD) with preserved systolic function, in an asymptomatic patient. B-type Natriuretic Peptide (BNP) is a cardiac neurohormone predominantly released from the cardiac ventricles in response to left ventricular volume expansion and pressure overload. The diagnostic role of BNP for detecting LVDD in asymptomatic diabetic patients is still debated and this study was undertaken to find out this relationship of plasma BNP level with LVDD in asymptomatic diabetic patients. First 100 patients who had type 2 diabetes for more than 5 years and had no known cardiac disease other than LVDD (grade-1 & 2), admitted in BIRDEM Hospital were recruited. Plasma BNP was measured by fluorescence polarization immunoassay (FPIA) method using AXSYM auto analyzer. Two-dimensional, M-mode, spectral, and color flow Doppler echocardiograms was repeated on the same day of blood collection for plasma BNP measurement. After processing of all available data, statistical analysis of their significance was done with the help of computer based SPSS (Statistical Program for Social Science) program. Male female distribution of the study participants was 46% and 54% respectively. Mean plasma BNP level in all participants was 150 pg/ml. In male and female participants the values were 168 and 135 pg/ml respectively. The distribution did not show any significant association ($p=0.491$). Of the 100 study participants 89% had E/A ratio < 1. Distribution of participants with abnormal E/A and E/e did not show any significant association ($p=0.955$ and 0.844 respectively). Study participants with varying level of plasma BNP level were analyzed in terms of E/A and E/e ratio. Distribution of participants between BNP Groups and E/A and E/e groups did not show statistically significant association ($p=0.529$). We concluded that plasma BNP has no relation with LVDD (grade-1 and 2) in patients with type 2 diabetes mellitus (T2DM) who had no known cardiac disease.

Introduction

Diabetic patients are increasing in Bangladesh. It is estimated that the diabetic patients will almost be doubled globally (2.8% vs 4.4%) by 2030.[1] In Bangladesh, the overall prevalence of type 2 DM (T2DM) in urban population is 11.2%.[2] An increased prevalence of diabetes (6.8%) in rural population was also reported.[3]

Great majority of the diabetic patients (80%) die of macrovascular complications, including coronary artery disease (CAD), stroke, and peripheral vascular disease (PVD).[4] Cardiac involvement in diabetes covers a wide spectrum, ranging from asymptomatic silent ischemia to clinically evident heart failure.[5] The first stage of diabetic cardiomyopathy is represented by

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left ventricular diastolic dysfunction (LVDD) with preserved systolic function, in an asymptomatic pattern.[5-8] The global prevalence of diastolic dysfunction largely ranges from 30% to 75%, depending on the defined echocardiographic parameters.[6,9-12] No data is available in Bangladesh. In India, the overall prevalence of LVDD in asymptomatic type 2 DM subjects is 54%.[10]

B-type Natriuretic Peptide (BNP) is a cardiac neurohormone predominantly released from the cardiac ventricular wall in response to left ventricular volume expansion and pressure overload.[13-17] Initial studies demonstrated that BNP levels were highly correlated with increasing symptoms of congestive heart failure (CHF).[18-23] BNP was also demonstrated to be a good diagnostic and prognostic marker in diabetic patients with heart failure, systolic dysfunction, silent myocardial ischemia and vascular complications.[24-27] In general, the following cut off values of BNP may be employed for diagnosing patients with CHF: <100 pg/mL indicates CHF is unlikely, if the level is 100-400 pg/mL clinical judgment need to be used, and >400 pg/mL indicates CHF is likely.[28,29]

The diagnostic role of natriuretic peptides for detecting LVDD in asymptomatic diabetic patients is still debated.[26,30-33] However, a single study in Bangladesh showed that raised plasma BNP level may indicate LVDD.[34] Probably the reason of this association is the presence of high risk group of ischemic heart diseases (IHD) in their study population. Hence, this study was undertaken to find out the relationship of plasma BNP level with LVDD in patients with type 2 DM without any known cardiac disease.

Subjects and Methods

Study design

A total 100 adult patients with type 2 diabetes mellitus (T2DM) with duration of diabetes more than five years and diagnosed case of diastolic dysfunction without coronary artery disease (CAD) and congestive heart failure (CHF) were recruited. As the patients with diastolic dysfunction of grade-3 & 4 are symptomatic, they were excluded from our study. CAD and CHF were excluded according to history, physical findings, ECG and chest radiography (CXR). Any patients with ambiguous clinical features or borderline abnormal ECG & CXR for CAD and CHF were excluded.

Blood sample for measurement of BNP was collected in EDTA tube. Plasma was separated after 30 min following centrifugation at 3000 rpm for 10 minutes. Plasma BNP was measured by Fluorescence Polarization ImmunoAssay (FPIA) method using AXSYM auto analyzer. Two-dimensional, M-mode, spectral, and color flow Doppler echocardiograms was reviewed on the same day of blood collection for plasma BNP measurement. Two-dimensional imaging examinations were performed in parasternal long- and short axis views and apical four chamber view. Pulsed Doppler spectral recordings were obtained at the tips of the mitral leaflets. Doppler echocardiography is an effective method to establish the presence of abnormalities in diastolic function. Diastolic function can be classified by using a combination of Doppler criteria including mitral inflow and tissue Doppler imaging (TDI). Diastolic heart dysfunction is graded by severity from Grade 1 to Grade 4. A number of diastolic parameters have been used for such grading. Pressure gradient across mitral valve is termed as E (first rapid filling phase) & A (last rapid filling phase). In normal subjects E/A ratio is >1.0. Early diastolic dysfunction shows E/A ratio <1.0. In grade 2 diastolic dysfunction, however, mitral flow shows "normal" pattern (= pseudonormal) which is detected by TDI where corresponding E/e ratio is ≥10 where "e" is the velocity of early diastolic mitral annulus motion.[35-38]

Statistical analysis

After processing of all available data, statistical analysis of their significance was done. Obtained data were expressed in frequency, percentage, mean and standard deviation as applicable. Continuous variables were expressed as mean ± SD. Comparison between groups was done by the Student's t-test where appropriate for continuous variables. Categorical data were analyzed by Chi-square test. The whole analyses was done with the help of computer based SPSS (Statistical Program for Social Science) program. P-value of <0.05 was considered as significant.

Results

A total 100 subjects of LVDD grade 1 & 2 were recruited in the study. Male female distribution of the study subjects was 46% and 54% respectively. Mean (±SD) of the target variables were within 95% confidence interval (CI).

Table-1: *Plasma BNP level in subjects with different grade of LVDD*

LVDD	BNP value (pg/ml)		
	Mean	**SD**	**Range**
Grade-1	137	127	10-593
Grade-2	117	91	31-384
t/p value	*0.763/0.448*		

Data were expressed as mean±SD and range.
LVDD = Left Ventricular Diastolic Dysfunction.
BNP = B-type Natriuretic Peptide.

Mean plasma BNP in all subjects was 150pg/ml. In male and female subjects the value was 168 and 135 pg/ml respectively. Considering the nature of distribution of the variables median value for all subjects in either gender was calculated which were 93.6 pg/ml, 108 pg/ml and 89.8 pg/ml respectively.

Abnormal relaxation (grade 1 diastolic dysfunction) was present in 89% (Male 41 and Female 48 out of total 89) and pseudonormal (grade-2) diastolic dysfunction in 11% (Male 5 and Female 6 out of total 11) cases. This distribution did not show any significant association (p=0.969).

In subjects with Grade 1 LVDD (E/A ratio <1) plasma BNP was 137 (pg/ml) [SD-127; range-10-593]. In those with Grade 2 LVDD (E/e ratio ≥10) plasma BNP level was 117 (pg/ml) [SD-91; range-31-384]. Mean plasma BNP level between the LVDD groups did not show significant statistical difference (p=0.448; Table 1).

Of the total study subjects 53 had plasma BNP level below the cut-off and out of these 46 (51.7%) had grade

Table-2: *Distribution of study subjects on the basis of LVDD grade and plasma BNP cut-off level*

LVDD	BNP value (pg/ml)		
	<100 (n=53) N (%)	100-400 (n=39) N (%)	>400 (n=8) N (%)
Grade-1	46 (51.7)	35 (39.3)	8 (9.0)
Grade-2	7 (63.6)	4 (36.4)	—
	p=0.529		

Data were expressed as number (percent). Chi-square (Fisher Exact) test was performed.
LVDD = Left Ventricular Diastolic Dysfunction; BNP = B-type Natriuretic Peptide
Grade-1 LVDD = E/A ratio <1; Grade-2 LVDD = E/e ratio ≥10

1 LVDD and rest 7 (63.6%) had grade 2 LVDD function. Thirty nine subjects had plasma BNP level between 100-400 pg/ml and of these 35 (39.3%) had grade 1 LVDD and rest 4 (36.4%) had grade 2 LVDD function. Only 8 subjects (out of 100) had plasma BNP level above the cut off and all of them had grade 1 LVDD (Table 2). This distribution did not show statistical significant association (p=0.529).

Correlation analysis was performed between plasma BNP levels and variables of interest. Statistical significant association was lacking for any one of the target variables.

Discussion

This is for the first time plasma BNP was determined in a group of type 2 diabetes mellitus patients and explored its relationship with variables of interest. It is understood that plasma BNP secretion shows heterogenecity in respect to gender and age. Male and female distribution and their mean age were found to be matched in the study. Mean (±SD) plasma BNP level for all subjects was 150±187 which did not show statistical difference with that of male and female values. We analyzed our data between plasma BNP level (as mean, SD & range) with grade 1 & grade 2 LVDD but got no significant statistical association (p=0.448). However, as plasma BNP level is classified into three groups (i.e. <100 pg/ml as normal, 100-400 pg/ml as doubtful, and >400 pg/ml as confirmatory) for diagnostic purpose of cardiac illness, we also analyzed whether there is any association between these different values with the grading of LVDD (Table 2), but these were also found to be statistically insignificant (p=0.529). These findings demonstrated the absence of significant association in distribution of heart functional status on the basis of plasma BNP level. This is in contrast to the earlier report.[32] But that study included high risk group of IHD in their population which have been excluded in this study. However, debate still exists regarding plasma BNP as biochemical marker in the diagnosis of LVDD.[26, 28-31]

An important limitation of this study was the lack of coronary angiographic (CAG) evaluation of coronary arteries and therefore, the inability to correlate the echocardiographic findings with underlying coronary artery disease. Because diabetes is notoriously associated with silent myocardial ischemia in up to 10-20% cases,[39-41] asymptomatic patient with normal

ECG would not exclude true cardiac ischemia. However, CAG is an expensive and time-consuming investigation to rule out CAD and is not always used to detect ischemic heart disease. Another important limitation was relative small size of the study population which was mainly due to lack of sufficient fund and time.

However, our study had several strengths. First, this was for the first time in Bangladesh plasma BNP was determined in a group of type 2 diabetes mellitus patients who were asymptomatic for known cardiac disease and explored its relationship with variables of interest. Second, we used routine and clinically applicable echocardiographic methods to evaluate LV function. Third, the echocardiographic analysis of LV function was performed by a single technician who was blinded to the order of echocardiography studies.

In conclusion, the study revealed that the plasma BNP level had no relation with LVDD (grade 1 and 2) in patients with T2DM without any known cardiac disease.

Acknowledgement

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