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Role of NT-proBNP in Detection of Left Ventricular Diastolic Dysfunction in Asymptomatic Type 2 Diabetes Patients with Preserved Ejection Fraction: A Cross-sectional Study

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Abstract

Background: Left ventricular diastolic dysfunction (LVDD) represents the first stage of diabetic cardiomyopathy and is initially subclinical. Early diagnosis enables earlier treatment and stops further progression of the disease. Tissue Doppler Imaging (TDI) is a new diagnostic modality with high sensitivity and specificity to know ventricular diastolic function. N-terminal pro brain natriuretic peptide (NT-proBNP) is a cardiac neurohormone that can be used to identify the changes in ventricular diastolic function. We aimed to estimate the concentration of NT-proBNP and correlate its value with TDI for LVDD in asymptomatic type 2 Diabetes Mellitus.

Methods: In this comparative cross-sectional study, we enrolled 100 asymptomatic type 2 diabetic patients and 100 healthy people aged 30-60 years. In both groups, NT-proBNP levels were measured and the presence of LVDD was determined by TDI. The primary outcome parameter was the level of NT-proBNP in diabetics and healthy people. The secondary outcome parameter was the correlation of NT-proBNP level with various grades of LVDD.

Results: In patients with LVDD, NT-proBNP levels [median (IQR)] were 123 (102,194) pg/ml in diabetics and 72 (67, 77) pg/ml in the control group. In patients without LVDD, NT-proBNP levels [median (IQR)] were 69 (59, 76) pg/ml in diabetics and 57 (49, 63) pg/ml in the control group. The level of NT-proBNP was significantly higher in those with LVDD ($p < 0.001$). NT-proBNP concentration significantly increased as grades of LVDD increased.

Conclusion: NT-proBNP is a good marker for detection of preclinical LVDD in patients with uncontrolled diabetes prone to develop cardiovascular complications.

Keywords: Left ventricular diastolic dysfunction (LVDD), NT-proBNP, Tissue Doppler Imaging (TDI)

Declarations

Ethics approval and consent to participate: Ethical approval obtained from the Institutional Review Committee, B. P. Koirala Institute of Health Sciences (Ref No. Acd/376/071/072). Written informed consent taken from each participant before enrollment.
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Diabetics have a greater risk of cardiovascular morbidity particularly congestive heart failure compared to non-diabetics [1]. Left ventricular diastolic dysfunction (LVDD) is a frequent finding in type 2 Diabetes Mellitus (DM) without symptoms and signs of heart disease. It may represent the first stage of diabetic cardiomyopathy; thus, an early examination of the diastolic ventricular function is important in patients with DM [2]. Early diagnosis of LVDD enables the initiation of effective treatment to stop the progress of the disease and delay the development of symptomatic heart failure.

Tissue Doppler Imaging (TDI) is a new Doppler ultrasound modality that records regional systolic and diastolic velocities within the myocardium. The combination of the mitral annulus and mitral inflow velocities has been shown to provide better estimates of left ventricular filling pressures than other methods [3]. Though TDI in combination with transmitral Doppler accurately determines the presence and severity of diastolic dysfunction, it is expensive, not available in many hospitals, and requires an expertise.

N-terminal pro brain natriuretic peptide (NT-proBNP) is the precursor of brain natriuretic peptide (BNP), which has a longer half-life [4]. Abnormal diastolic filling pressure, the key functional abnormality in diastolic dysfunction or heart failure, leads to a release of cardiac neurohormones including natriuretic peptides [5]. Because NT-proBNP has a longer half-life compared to BNP its plasma level and perhaps diagnostic resolution for detecting diastolic dysfunction could be higher [6]. Hence, in this study, we aimed to evaluate the potential of NT-proBNP as a reliable biochemical marker in detecting LVDD in asymptomatic type 2 DM patients with preserved ejection fraction and to correlate NT-proBNP level with an established non-invasive method (TDI).

METHODS

This comparative cross-sectional study was conducted in the Division of Cardiology, Department of Internal Medicine at B. P. Koirala Institute of Health Sciences from January 2014 to January 2015, after approval from the Institutional Review Committee. After getting informed written consent from all study participants, asymptomatic type 2 DM patients visiting the diabetic clinic were enrolled as the patient group, and non-diabetic and apparently healthy individuals visiting the outpatient clinic were enrolled as the control group. Age limit of 30 to 60 years was another eligibility criterion. The minimum sample size calculated was 65 in each group; the calculation was based on the prevalence of diastolic dysfunction in asymptomatic type 2 DM reported as 64% in a previous study and considering 95% confidence interval and 80% power [7]. We enrolled 100 patients to compensate for dropout cases and shift from normality in the data distribution.

Exclusion criteria were patients with constrictive pericarditis, cardiac tamponade, valvular heart disease, hypertrophic cardiomyopathy, arrhythmias, left ventricular ejection fraction (LVEF) < 50%, regional wall movement abnormalities, and poor acoustic window. Those with a history suggestive of coronary artery disease, hypertension, kidney disease, chronic pulmonary disease or thyroid disorders were also excluded.

All consenting diabetic patients and controls underwent two-dimensional (2D), M-Mode, color flow, pulsed wave Doppler, and tissue Doppler transthoracic echocardiography using X5-1 xMatrix probe by Philips iE33 echocardiography machine. Echocardiograms were obtained at rest in the left lateral decubitus or supine position using the standard parasternal and apical views by the same person in line with the guidelines of the American Echocardiography Society [5]. Systolic dysfunction was defined as LVEF < 50%. Patients and controls with systolic dysfunction were excluded from the study and those without systolic dysfunction underwent LV diastolic function assessment by conventional Doppler and TDI. Both the septal (medial) and lateral sites early (e') diastolic velocities were recorded for three consecutive cardiac cycles at a sweep speed of 100 mm/s and the mean lateral and medial sites velocity was obtained. It was combined with the E-wave velocity to get the medial and lateral E/e' ratio and the average of the two was calculated to estimate LV filling pressures. Grading of diastolic dysfunction was done as per the American Echocardiography Society [5].

After a resting period of 20 minutes, 5 ml of blood was drawn in Ethylenediamine tetraacetic acid tubes from the antecubital vein for NT-proBNP measurement. After centrifugation at 1500 rpm for 5 minutes, plasma was taken for NT-proBNP measurement immediately or was kept at -20°C if a delay was anticipated. NT-proBNP was measured by the Vidas machine using the enzyme-linked fluorescent assay technique. Other relevant investigations like fasting blood glucose (FBG) and 2 hour postprandial blood glucose (PPBG), Hemoglobin A1c (HbA1c), renal function tests, lipid profile,

resting electrocardiogram, and echocardiography were also done.

The study group and the control group were selected on a prospective sequential basis; the cardiologists doing echocardiography and biochemists doing laboratory investigations were unaware of the control or the study groups.

For descriptive statistics percentage, mean, standard deviation, median (IQR) was calculated. For inferential statistics, the chi-square test, independent t-test, and the Mann-Whitney U test were used as applicable to determine the significant differences between groups and other related variables. A p-value of < 0.05 was considered significant. The Pearson correlation coefficient was determined to see the correlation between the required variables.

RESULTS

Out of a large population of patients attending the out-patient and diabetic clinic, 110 asymptomatic type 2 diabetics were considered for echocardiography. Ten diabetics were excluded as five patients had regional wall motion abnormalities, three had a poor cardio echo window and two had valvular heart disease. Similarly, 100 non-diabetic healthy individuals were included as the control for comparison.

The age of patients (mean ± SD) was similar ($p = 0.98$) in patients with type 2 DM (47.1 ± 7.7 years) and the control group (47.1 ± 7.1 years). Similarly, the BMI (mean ± SD) of diabetic patients (21.55 ± 1.66 kg/m2) and control patients (21.60 ± 1.69 kg/m2) was similar ($p = 0.83$). The systolic blood pressure (mean ± SD) was 124.8 ± 7.0 mmHg in diabetics and 124.4 ± 7.6 mmHg in the control group ($p = 0.70$). Diastolic blood pressure was 77.5 ± 6.7 mmHg in diabetics and was 76.7 ± 7.0 mmHg in the control group ($p = 0.41$).

Fifty-seven patients with DM had diastolic dysfunction, while only 16 in the control group had diastolic dysfunction ($p < 0.001$). The levels of LDL-cholesterol, FBG, PPBG, HbA1c, and NT-proBNP were significantly higher in the diabetic group than the control group (**Table 1**). No significant differences were found in total cholesterol, HDL-cholesterol, triglyceride, and serum creatinine between the groups.

The LVEF was comparable between the study

Table 1: Comparison of biochemical characteristics between diabetics and healthy people and between individuals with and without LVDD. Values are expressed as mean ± SD or median (IQR)

Biochemical characteristics	Diabetic patients (n=100)	Healthy People (n=100)	*p*-value
TC (mg/dl)	189.04 ± 42.78	181.09 ± 38.36	0.17
HDLC (mg/dl)	45.93 ± 7.67	45.95 ± 7.62	0.98
TG (mg/dl)	127.26 ± 38.19	124.58 ± 26.13	0.61
LDLC (mg/dl)	149.10 ± 40	138.25 ± 37.41	0.05
FBG (mg/dl)	147.97 ± 35.79	76.25 ± 15.01	**< 0.001**
PPBG (mg/dl)	230.54 ± 51.81	143.65 ± 34.91	**< 0.001**
HbA1c (%)	7.6 ± 1.37	5.37 ± 0.52	**< 0.001**
NT-proBNP (pg/ml)*	91 (69, 134)	62 (53, 66)	**< 0.001**
Serum creatinine (mg/dl)	0.82 ± 0.26	0.81 ± 0.21	0.58
	LVDD present (n=57)	LVDD absent (n=43)	*p*-value
TC (mg/dl)	189.05 ± 46.42	189.02 ± 37.95	0.99
HDLC (mg/dl)	46.51 ± 8.33	45.16 ± 6.70	0.39
TG (mg/dl)	127.44 ± 40.09	127.02 ± 35.99	0.96
LDLC (mg/dl)	144.53 ± 44.90	155.16 ± 31.88	0.19
FBG (mg/dl)	166.47 ± 35	123.44 ± 17.49	**< 0.001**
PPBG (mg/dl)	242 ± 62.33	215.35 ± 27.07	**0.01**
HbA1c (%)	8.46 ± 1.09	6.44 ± 0.66	**< 0.001**
NT-proBNP (pg/ml)*	123 (102,194)	69 (59,76)	**< 0.001**

TC: Total cholesterol; HDLC: high-density lipoprotein cholesterol; TG: triglyceride; LDLC: low-density lipoprotein cholesterol; FBG: fasting blood glucose; PPBG: postprandial blood glucose; HbA1c: hemoglobin A1c; NT-proBNP: N-terminal pro brain natriuretic peptide
*median (IQR)

groups. The rest of the echocardiographic and tissue Doppler variables (e' septum, E/A, e' lateral, E/e' septum. E/e' lateral) showed a statistically significant difference between the groups.

The age (mean ± SD) of participants with LVDD was 50.5 ± 5.9 years in the diabetes group and 48.3 ± 5.5 years in the control group (p = 0.19). Out of 57 patients with diastolic dysfunction, 29 (51%) were male and 28 (49%) were female. Among 16 individuals with diastolic dysfunction in the control group, 8 were male and 8 were female. The distribution of sex among the patients with diastolic dysfunction was comparable between the two study groups (p = 0.95). The BMI (mean ± SD) of patients with diastolic dysfunction was 22.17 ± 1.34 kg/m2 in the diabetic group and 21.78 ± 1.16 kg/m2 in the control group (p = 0.29).

Patients with and without LVDD had significantly higher concentration of NT-proBNP than in the control group with or without LVDD (p < 0.001) (**Table 2**). The duration of time since the diagnosis of diabetes was significantly less (p < 0.001) in patients without diastolic dysfunction (1.67 ± 0.79 years) as compared to patients with diastolic dysfunction (4.18 ± 1.65 years). The level of total cholesterol, HDL cholesterol, triglyceride, and LDL cholesterol did not vary between patients with normal LVDD and patients with LVDD (**Table 1**). Patients with LVDD had a significantly higher level of FBG, PPBG, HbA1c, and NT-proBNP than patients without LVDD.

Table 2: NT-proBNP in study group with and without LVDD

Group	NT-proBNP (pg/ml)*		*p*-value
	Patient	Control	
With LVDD	123 (102, 194)	72 (67, 77)	< 0.001
Without LVDD	69 (59, 76)	57 (49, 63)	< 0.001

**median (IQR)*

Patients without LVDD and E/e´ of ≤ 8 had a median (IQR) NT-proBNP level of 69 (59, 76) pg/ml. NT-proBNP level (median (IQR) in patients with grade I LVDD and E/e´ of ≤ 8 was 120 (96, 146) pg/ml, in patients with grade II LVDD and E/e´ of 9 to 15 was 221 (134, 221) pg/ml and in patients with grade III LVDD and E/e´ of > 15 was 587 (333, 629) pg/ml (Table 3). The difference in the NT-proBNP concentration between and among the different grades of LVDD and without LVDD was statistically significant (p < 0.001).

Table 3: NT-proBNP in patients according to LVDD (**n** = 100)

Diastolic function	NT-proBNP (pg/ml)*
Normal (n = 43)	69 (59, 76)
Grade I diastolic dysfunction (n = 44)	120 (96, 146)
Grade II diastolic dysfunction (n = 9)	221 (134, 221)
Grade III diastolic dysfunction (n = 4)	587 (333, 629)

**median (IQR)*

The NT-proBNP level and E/ e´ average had a significantly positive correlation (p < 0.001) (**Table 4**). In patients without LVDD, NT-proBNP level was negatively correlated with an early diastolic velocity at the annulus (e´ septum and e´ lateral) and positively correlated with E/ e´ but was not statistically significant.

DISCUSSION

This comparative cross-sectional study demonstrates that pre-clinical diastolic dysfunction is common in patients with type 2 DM. We found that asymptomatic diastolic dysfunction is not uncommon in type 2 DM, even in the absence of hypertension and heart disease. While 57% of patients with type 2 DM had LVDD, only 16% of non-diabetic healthy controls had diastolic dysfunction. This finding was comparable to other studies where 47 to 64% of asymptomatic patients with type 2 DM had LVDD [8, 9].

In this study, FBG, PPBG, and HbA1c level in diabetic patients with LVDD were significantly higher than in diabetic patients without LVDD. Our finding is similar to other reports in which poor glycemic control was correlated with the echocardiographic findings of diastolic dysfunction [10-12]. Similarly, diastolic dysfunction has been reported to be more frequent in poorly controlled diabetic patients and its severity has been positively correlated with HbA1c level [13]. Another study showed that HbA1c level was significantly high-

Table 4: Correlation between NT-proBNP, e´ septum, and e´ lateral in patients with LVDD (n = 57)

Variables	Pearson correlation coefficient (r)	*p*-value
NT-proBNP and e´ septum	-0.14	0.15
NT-proBNP and e´ lateral	-0.47	**< 0.001**
NT-proBNP and E/ e´ average	0.77	**< 0.001**

er in type 2 diabetic patients with LVDD than those without LVDD [14]. These findings are attributed to the influence of hyperglycemia on heart metabolism which leads to the accumulation of advanced glycation end products in the myocardium and interstitium. Advanced glycation of sarcoplasmic/endoplasmic reticulum Ca2+-ATPase2a has been shown to lead to a decrease in its activity and a prolongation of cardiac relaxation [15].

In our patients with diastolic dysfunction, the mean duration of diabetes was 4 years, which was significantly longer than in patients with a normal diastolic function. A similar observation was noted in another study in which a history of type 2 DM ≥ 4 years was independently associated with the presence of LVDD and subsequent development of overt heart failure and increased mortality [16]. Similarly, the risk for developing diastolic dysfunction is reported to be increased as the duration of diabetes increased in 100 asymptomatic type 2 DM patients studied [17].

Routine processes such as medical history, physical examination, or electrocardiogram cannot differentiate between systolic and diastolic heart failure. Echocardiography is considered the cornerstone of the diagnostic evaluation in patients with suspected LVDD, but limited availability and high cost prohibit its use as a routine screening test in diabetic patients leading to a diagnostic delay. As many biochemical changes have a diagnostic value for the underlying disease, in recent days, the studies have concentrated on simple, easily available, and minimal biochemical testing for screening for subclinical cardiac dysfunction. In a study the levels of NT-proBNP were significantly higher in the LVDD diabetic group compared to the non LVDD diabetic group [18]. Similarly, NT-proBNP concentration was significantly higher in the poorly controlled type 2 DM patients with diastolic dysfunction compared to those with a normal left ventricular diastolic function [19, 20]. Similarly, in this study, diabetics with diastolic dysfunction had poorly controlled blood sugar as reflected by higher HbA1c levels compared to those with a normal diastolic function. The concentration of NT-proBNP was significantly higher in LVDD diabetics compared to diabetics with normal left ventricular diastolic function. Hence, NT-proBNP may be a marker playing role in the early diagnosis of LVDD in diabetics.

The NT-proBNP levels have been found to be associated with diastolic dysfunction. Hence, it can be used in the prediction of the left ventricular end-diastolic pressures [21, 22]. The E/e´ ratio that can be evaluated with TDI modality is a parameter predicting the ventricular filling pressure which increases in LVDD [23]. The E/e´ ratio > 15 is reported to have 86% specificity for the mean left ventricular filling pressure > 15 mmHg [24]. Normal filling pressures is also reported in 85% of the patients with E/e´ ratio < 8 and increased left ventricular filling pressure in all the patients with E/e´ > 15 [24]. In a study E/e´ ratio was associated with increased levels of BNP [25]. A linear correlation has been reported between NT-proBNP levels and grade of diastolic dysfunction, left atrial volume index and E/e´ ratio. Patients with E/e´ ratio > 15 had the highest NT-proBNP value [26, 27]. Similarly, in this study NT-proBNP level was significantly associated with a grade of LVDD or E/e´ ratio and had a significantly positive correlation with the E/e´ ratio. The concentrations of NT-proBNP were found to be significantly raised in different grades of LVDD with the highest level in grade III LVDD and had the lowest level in control without LVDD.

The major limitation of our study was the lack of invasive measurements to confirm elevated filling pressure; hence, further studies may be needed to directly compare the measured indices from the echocardiography and NT-proBNP levels with catheter measured left ventricular end-diastolic pressure.

CONCLUSION

NT-proBNP is a good marker for detecting preclinical LVDD in asymptomatic patients with uncontrolled diabetes who are prone to develop cardiovascular complications. Hence, it can be an easy and appropriate biochemical parameter to screen those with preclinical LVDD especially among patients with high HbA1c and long duration of diabetes. This investigation can be sent by the physician and those with high NT-proBNP levels can be ordered for echocardiography for a detailed evaluation of diastolic function. Those with diastolic dysfunction can be advised and counseled for better glycemic control to prevent the development of diabetic cardiomyopathy.

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