



A PROSPECTIVE LONGITUDINAL STUDY TO ASSESS LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND ITS ASSOCIATION WITH NT-proBNP IN PATIENTS WITH PREDIABETES

Endocrinology

**Dr. Ramesh
Krishnan**

DrNB Neurology, Department of Medicine and Endocrinology, Indraprastha Apollo Hospital, New Delhi.

ABSTRACT

Introduction: We aim to assess incidence of Left Ventricular Diastolic Dysfunction [LVDD] in patients with prediabetes, and to correlate incidence of LV Diastolic Dysfunction in patients with NT-proBNP. **Material And Methods:** It was Prospective Observational, For the margin of error at 10% and confidence level of study at 95%, a minimum of 53 patients in the 18-60 years of age are required to study Left Ventricular Diastolic Dysfunction in Patients with Prediabetes. Out of 53 cases of prediabetes LVDD was present among 11 (20.8%) cases. All studied patients were of age between 18-60 years. Most of the subjects were between 51-60 years of age. Diastolic dysfunction was prevalent in 9.1% of patients in age group of 31-40 years, 9.1% of patients with age group 41-50 years. Among the age group of 51-60 years diastolic dysfunction was most prevalent (81.8%). Mean age of the population with LVDD and without LVDD was 53.18 ± 6.40 years and 43.76 ± 10.34 years respectively. The mean age was significantly higher in patients with LVDD compared to patients without LVDD (p value = 0.035). NT-proBNP levels were more than two-fold elevated in patients with LVDD when compared with patients without diastolic dysfunction (p value = 0.025). **Conclusion:** Left ventricular diastolic dysfunction is moderately prevalent among patients with prediabetes. In the present study the prevalence of LVDD among prediabetic patients with normal blood pressure, having impaired fasting glucose and/or impaired glucose tolerance with no coronary or structural heart disease history was found to be 20.8%. In this study, it was identified that diastolic dysfunction detected with Doppler echocardiography has a strong relation to insulin resistance.

KEYWORDS

Prediabetes, Left Ventricular Diastolic Dysfunction, impaired glucose tolerance, Insulin resistance.

INTRODUCTION

Prediabetes is defined According to ADA as - Impaired fasting glucose (IFG) between 100-125 mg/dl or Impaired glucose tolerance (IGT) a plasma glucose level obtained 2 hours after a 75-g oral glucose challenge > 140 mg/dl but < 200 mg/dl or Haemoglobin A1c level of 5.7%-6.4%.^[1-3]

Prediabetes is predicted to affect 14 % of the population in India, according to the National Urban Diabetes Survey.[5]

Prediabetes Diagnostic Criteria According To Health Authorities.[6]

Diagnostic criteria	WHO	ADA	NICE
HbA1c	Not recommended for diagnosis	5.7-6.4%	6- 6.4%
2 Hour OGTT	140-200 mg/dl	140-200 mg/dl	140-200 mg/dl
Fasting plasma glucose	110-125 mg/dl	100-125mg/dl	110-125mg/dl

ADA American Diabetes Association, NICE – National institute Of health And care, OGTT- oral glucose tolerance test, WHO- World Health Organisation.

Since few studies are available in this regard in India so the present study was carried out to investigate the incidence of LV diastolic function in patients with prediabetes using tissue Doppler Echocardiography (TDE) and its correlation with HbA1c %, BMI, WR Ratio, HOMA- IR.

Aims And Objective

Aim:

To assess incidence of Left Ventricular Diastolic Dysfunction [LVDD] in patients with prediabetes.

Primary Objectives:

To correlate incidence of LV Diastolic Dysfunction in patients with prediabetes with with with NT- proBNP

MATERIALS AND METHODS

Study Type: Prospective Observational Study

Study Area: Department of Medicine and Endocrinology, Indraprastha Apollo Hospital, New Delhi.

Study Period: September 2019 to December 2020.

Study Design: Single center study in the Department of Medicine and Endocrinology, Indraprastha Apollo Hospital, New Delhi from

September 2019 to December 2020.

Sample size:

For the margin of error at 10% and confidence level of study at 95%, a minimum of 53 patients in the 18-60 years of age are required to study Left Ventricular Diastolic Dysfunction in Patients with Prediabetes.

Formula for calculating the sample size $n = z^2 \times p(1-p) / e^2$

where, n is sample size, z is the z score, e is the margin of error, p is the population proportion

$$n = (1.96 * 1.96) \times (0.167 * (1 - 0.167)) / (0.1 * 0.1) = 53$$

Study Sample:

Patients diagnosed with Prediabetes (clinically and Laboratory diagnosis confirmed) within the age group of 18-60 years were included. These patients were then screened under the light of inclusion and exclusion criteria before recruiting them into the study population.

Inclusion Criteria:

Prediabetic patients within age group of 18-60 years, with normal blood pressure, having impaired fasting glucose and/or impaired glucose tolerance with no coronary or structural heart disease history attending the OPD IAH, were included in this study.

Exclusion Criteria:

- History of coronary artery disease [Unstable Angina, Myocardial Infarction, CABG].
- Chronic kidney disease
- Chronic obstructive lung disease
- Patients who were pregnant/ Planning to conceive.

Data Collection:

The data was collected in the proforma as attached in the annexure. Personal interview and review was done to acquire the relevant information from the patient or the relatives. Lab values of the test performed were taken from the hospital facility. Blood samples were drawn from the patients after obtaining consent for using the data obtained for this study.

Methodology:

The present study was conducted after obtaining clearance and approval from the Institutional Ethics Committee Indraprastha Apollo Hospital, New Delhi. This study was conducted in the Department of Medicine and Endocrinology and it was a Prospective Observational Study. The study was conducted during the period September 2019 to December 2020. The current randomized clinical trial was performed on 53 Prediabetic patients within age group of 18-60 years, with

normal blood pressure, having impaired fasting glucose and/or impaired glucose tolerance with no coronary or structural heart disease history.

LVDD was considered to be present if any of the following findings were seen on echocardiography previously described as follows:
 E/A ratio <0.75 or >1.5
 DT <150 or >220 ms

A pre designed semi-structural proforma was used for each of the prediabetic patients, which included

- A brief clinical information including particulars of the patient, chief complaints, family, past history etc.
- Proper general physical examination and systemic examination, including BMI and WH Ratio.
- Prediabetics diagnostic criteria
- All groups were subjected to full medical history and clinical examination, including blood pressure (BP), BMI, systemic examination and biochemical and echocardiographic studies.

Investigations:

haemoglobin, total white cell count, erythrocyte sedimentation rate, platelet count, Bleeding time, clotting time, routine urine analysis, Fasting blood glucose, and NTpro-BNP , 2D echocardiograms was performed in all patients.

Diabetes was diagnosed according to the American Diabetes Association (ADA) criteria. Blood was drawn after fasting for 8 h. A fasting blood sugar (FBG) level below 100 mg/dl or glycosylated haemoglobin (Hb A1c) <5.7% is considered normal. A FBG level between 100 and 126 mg/dl or Hb A1c 5.7–6.5% confirms the presence of prediabetes and FBG more than 126 mg/dl or HbA1c >6.5% confirms the presence of diabetes in two separate occasions.

In the 2D Echo evaluation of patients with diabetes, a short axis and long axis view of the heart were obtained with the patient in left lateral recumbent position. Anapical 4 chamber view of the heart was also seen. This was done to rule out any subclinical valvular heart disease and pericardial disease, especially constrictive pericarditis. In the short axis view with the cursor aligned just distal to the tips of mitral valve, an M-mode Echo was obtained to take the various dimensions such as LV dimensions in diastole and systole, septal, and posterior wall thickness.

Next, a color flow evaluation was performed to detect any subtle regurgitant lesion from an apical chamber view, and pulsed Doppler cursor is aligned parallel to the stream of inflow of blood from left atrium to left ventricle. A site was chosen along the cursor for sampling the mitral velocity profile such that the sample volume was taken just internal to the tips of mitral leaflets. A pulsed wave Doppler tracing was obtained, and the following parameters are measured.

- Early diastolic flow velocity (E) cm/s
- Late diastolic flow velocity (A) cm/s
- E/A ratio
- IVRT (ms)
- Deceleration time (ms).

Statistical Analysis:

Data was checked for accuracy and completeness then coded and entered into (Statistical Package for the Social Sciences) version 19.0 for analysis. The results presented in frequency tables, cross tabulations and figures. Categorical data are presented as frequency with percentages. Continuous data with normal distribution are presented as mean with standard deviation. Chi-square or Fisher Exact test has been used to find the significance of study parameters on categorical scale between two groups. *p*-values <0.05 were considered significant.

Data Collection:

The data was collected in the proforma as attached in the annexure. Personal interview and review was done to acquire the relevant information from the patient or the relatives. Lab values of the test performed will be taken from the hospital facility.

Blood samples was drawn from the patients after obtaining consent for using the data obtained for this study.

DISCUSSION

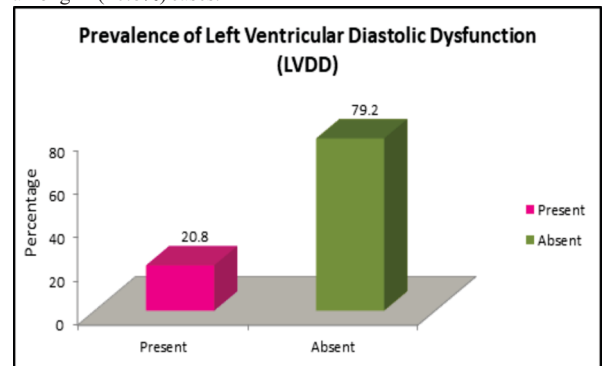
Although many studies have been performed about DM and left

ventricular dysfunction, studies associated with prediabetes, prediabetes subgroups and insulin resistance are insufficient. Hence the present study was aimed to assess the incidence of Left Ventricular Diastolic Dysfunction (LVDD) in patients with Prediabetes and to correlate incidence of LV Diastolic Dysfunction in patients with prediabetes with NT-proBNP. The present study was conducted in the Department of Medicine and Endocrinology and it was a prospective observational study. The current randomized clinical trial was performed on 53 Prediabetic patients within age group of 18-60 years, with normal blood pressure, having impaired fasting glucose and/or impaired glucose tolerance with no coronary or structural heart disease history.

In this study, we assessed the incidence of LVDD, a precursor of diabetic cardiomyopathy and its correlation with biochemical NT-proBNP in 53 prediabetic normotensive patients between the age of 18 to 60 years. LVDD was found in 20.8% of patients in this study.

LVDD	Frequency	Percentage
Present	11	20.8
Absent	42	79.2
Total	53	100.0

[Table 1] A total of 53 patients with prediabetes were enrolled in the present study. Out of 53 cases of prediabetes LVDD was present among 11 (20.8%) cases.



Sirkeci et al in their study investigated diastolic function in patients with prediabetes. They also reported the similar prevalence of LVDD in their study. They found diastolic dysfunction was detected in 10 (20%) out of the 50 patients.^[5]

Boyer et al stated that prevalence of LVDD in asymptomatic normotensive patient with Type 2 DM is high. Diastolic dysfunction was found in 43 of 57 patients (75%) when all of the above echocardiographic techniques were used. TDI detected diastolic dysfunction more often (63%) than any other echocardiographic approach.^[6]

Mishra et al in their case control study of 71 patients with Type 2 DM found that asymptomatic patients with diabetes have reduced diastolic function as compared with the patient without Type 2 DM. LV diastolic abnormalities correlated with the duration of diabetes.^[7]

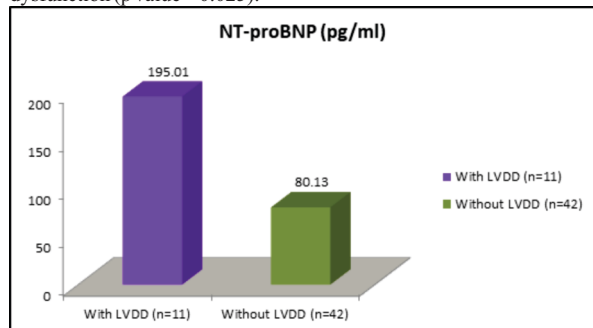
The prognostic importance of BNP and the N-terminal of pro (NT-pro)BNP has previously been investigated in patients with acute coronary syndromes and patients with HF, and both markers were shown to be strong predictors of mortality and morbidity.^[121] In particular, diastolic wall stress has been demonstrated to have a stronger correlation with NT-proBNP levels, as compared with systolic wall stress.^[122] Previous studies have suggested that the estimation of BNP values via a fast and reliable blood test may be accepted as a diagnostic tool for assessing asymptomatic diastolic dysfunction in patients with hypertrophic cardiomyopathy (HCM), diabetes and hypertension. Furthermore, as BNP has been demonstrated to be a highly useful, simple and noninvasive diagnostic biomarker, BNP levels may be used for the differential diagnosis of cardiac and pulmonary dyspnea in emergency departments to guide therapy. However, whether BNP levels are predictors of morbidity and mortality in patients with diastolic dysfunction is yet to be investigated.

In the present study NT-proBNP levels were more than two-fold elevated in patients with LVDD when compared with patients without diastolic dysfunction (*p* value = 0.025).

NT-proBNP (pg/ml)	With LVDD (n=11)		Without LVDD (n=42)	
	Mean	±SD	Mean	±SD
	195.01	±6.75	80.13	±13.81

Statistical Inference | p value: 0.025

[Table.2.] NT-proBNP levels were more than two-fold elevated in patients with LVDD when compared with patients without diastolic dysfunction (p value = 0.025).



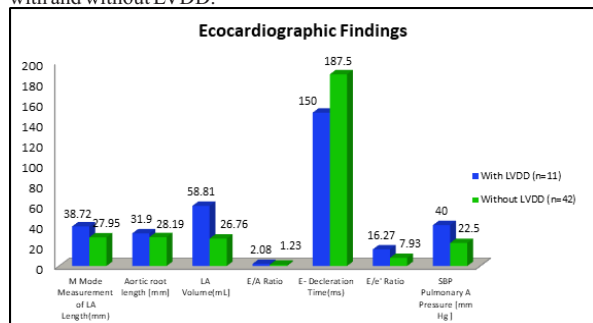
C. Tschöpe et al in their study investigated N-terminal pro-B type natriuretic peptide (NT-proBNP) as a possible non-invasive parameter to diagnose isolated diastolic dysfunction. In their study they reported NT-proBNP levels were four-fold elevated in patients with diastolic abnormalities when compared with control patients [189.54 pg/mL (86.16–308.27) vs. 51.89 pg/mL (29.9–69.7); p value=0.001].^[8]

Albertini and co-workers assessed BNP value in 91 consecutive patients with type 2 diabetes mellitus, finding that BNP level was significantly higher in patients with LVDD, especially in case of untreated hypertension (87 ± 20 vs 13 ± 2, p < 0.0001); anyway, comparing the mean value of patient with normal LV function with those ones with LVDD, independently from the anti-hypertensive treatment, BNP was significantly higher in the latter group (p < 0.001).^[9]

The main finding of the current study is that IR is associated with impaired left ventricular diastolic function. The E/A ratio exhibited a stepwise decrease from the control to the prediabetic to the IR groups, primarily a result of increased A-wave velocity. The isovolumic relaxation time was significantly longer in the IR group.

Echocardiographic Findings	With LVDD (n=11)	Without LVDD (n=42)	p Value
M Mode Measurement of LA Length(mm)	38.72 ±3.63	27.95 ±3.50	0.587
Aortic root length [mm]	31.90 ±1.70	28.19 ±1.56	0.317
LA Volume(mL)	58.81 ±5.54	26.76 ±3.36	0.006
E/A Ratio	2.08 ±0.43	1.23 ±0.18	<0.0001
E- Deceleration Time(ms)	150.00 ±21.44	187.50 ±5.38	<0.0001
E/e' Ratio	16.27 ±1.35	7.93 ±1.24	0.660
SBP Pulmonary A Pressure [mm Hg]	40.00 ±5.25	22.50 ±2.55	<0.0001

[Table 3] Comparison of echocardiographic findings among patients with LVDD and without LVDD is presented in. Above analysis we found LA length, aortic root length and E/e ratio was comparable among patients with and without diastolic dysfunction while the other variables like LA volume, E/A ratio, E-deceleration time, SBP pulmonary A pressure showed significant difference among patients with and without LVDD.



These findings suggest that there is a progressive impairment in left ventricular relaxation depending on the insulin sensitivity and increasing burden of IR on myocardial function. Our results are

consistent with that of a recently published study in patients without overt type 2 diabetes.^[10] In addition, the diastolic changes were associated with an unaltered geometric pattern and a no significant depressed systolic function in all groups. These different findings indicate that the functional changes are independent and precede the systolic and structural changes. Our observation is consistent with those of prior studies in the fields of obesity, metabolic syndrome and diabetes.^[12]

Above analysis we found LA length, aortic root length and E/e ratio was comparable among patients with and without diastolic dysfunction while the other variables like LA volume, E/A ratio, E-deceleration time, SBP pulmonary A pressure showed significant difference among patients with and without LVDD.

Diamantet al stated that early (E) acceleration peak, deceleration peak, peak filling rate, and E/A ratio, and all other indices of diastolic function, were significantly decreased in patients with recently diagnosed, well-controlled and uncomplicated type 2 diabetes compared with the controls (p value=< 0.02). These findings are similar to our results.^[13]

The Present Study Summarizes:

- The present study was conducted in the Department of Medicine and Endocrinology and it was a Prospective Observational Study. The study was conducted during the period September 2019 to December 2020.
- The current randomized clinical trial was performed on 53 Prediabetic patients within age group of 18-60 years, with normal blood pressure, having impaired fasting glucose and/or impaired glucose tolerance with no coronary or structural heart disease history.
- The present study aimed to assess the incidence of Left Ventricular Diastolic Dysfunction (LVDD) in patients with Prediabetes and to correlate incidence of LV Diastolic Dysfunction in patients with prediabetes and NT-proBNP.
- Out of 53 cases of prediabetes LVDD was present among 11 (20.8%) cases.
- All studied patients were of age between 18-60 years. Most of the subjects were between 51-60 years of age. Diastolic dysfunction was prevalent in 9.1% of patients in age group of 31 -40 years, 9.1% of patients with age group 41-50 years. Among the age group of 51-60 years diastolic dysfunction was most prevalent (81.8%). Mean age of the population with LVDD and without LVDD was 53.18 ± 6.40 years and 43.76 ± 10.34 years respectively. The mean age was significantly higher in patients with LVDD compared to patients without LVDD (p value=0.035).
- Out of 53 participants 32 (60.4%) were males and 21 (39.6%) were females. In terms of prevalence of LVDD we found males shown more prevalence of diastolic dysfunction (63.6%) in comparison to the females (36.4%).
- NT-proBNP levels were more than two-fold elevated in patients with LVDD when compared with patients without diastolic dysfunction (p value = 0.025).
- Above analysis we found LA length, aortic root length and E/e ratio was comparable among patients with and without diastolic dysfunction while the other variables like LA volume, E/A ratio, E-deceleration time, SBP pulmonary A pressure showed significant difference among patients with and without LVDD

At the end of our study, we come to the conclusion that:

- Left ventricular diastolic dysfunction is moderately prevalent among patients with prediabetes. In the present study the prevalence of LVDD among prediabetic patients with normal blood pressure, having impaired fasting glucose and/or impaired glucose tolerance with no coronary or structural heart disease history was found to be 20.8%.
- Therefore, it could be suggested that significance of detailed echocardiographic examination should be emphasized for patients with evident insulin resistance.

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