ORIGINAL ARTICLE

A Comparative Study of Diastolic Dysfunction by Echocardiography among Diabetic and Non-diabetic Subjects

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Abstract:

Background: Cardiovascular Disease (CVD) is the most significant prognostic factor in individuals with Type 2 Diabetes (T2D). The myocardial damage in diabetic subjects affects diastolic function before the systolic function. *Aim and Objectives:* To compare the diastolic dysfunction and its parameters (E/A ratio, E/e' ratio) by transthoracic echocardiography among diabetic and non-diabetic patient and to find relation between diastolic dysfunction and HbA1c. *Material and Methods:* This was a prospective, observational and case control study. Diabetes Mellitus (DM) was labeled if Fasting Blood Sugar (FBS) ⩾ 126 mg/dL or HbA1c ⩾ 6.5%. Standardized Transthoracic Echocardiographic (TTE) examination was performed (American Society of Echocardiography). Left Ventricular Diastolic Dysfunction (LVDD) was labeled if 3 or more of these variables are abnormal: "Septal e <7 cm/sec, Lateral e <10 cm/sec), E/e ratio >14, LA volume index >34 mL/m^2, Peak TR velocity >2.8 m/sec." *Results:* A total of 50 subjects with Type 2 Diabetes Mellitus (T2DM) cases and 50 healthy age and gender matched controls were included in this study. The peak early trans-mitral filling wave velocity (E) in diabetic population was low in diabetes subjects [41 ± 12 cm/s vs 48 ± 8.5 cm/s]. Mean of E/A ratio in the Study Group was significantly lower as compared to the Control Group ('p' = 0.02). The E/e' ratio was significantly higher in diabetic group (16.5 ± 2.7 vs 14.13 ± 1.92) compared to Control Group. T2DM group had lower E/A ratio, deceleration time, e' compared to the controls and higher E/e' ('p' < 0.02). Total 21 (42%) subjects among diabetes mellitus had diastolic dysfunction [Grade I: 19 (38%) and Grade-II: 2 (4%)]. Total 2 (4%) subjects among control had diastolic dysfunction [Grade I: 2(4%)] ('p' < 0.00001). Age, Body Mass Index (BMI), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Left Ventricular Ejection Fraction (LVEF), duration of DM and HbA1c had negative correlation with parameters of diastolic dysfunction [E (cm/s),E/A, e', E'sr] and positive correlation with A, TR jet, Left Atrial Volume index (LAVi) and E/E'sr ratio. *Conclusion:* Present study highlighted the burden of diastolic dysfunction (42%) among the asymptomatic diabetic subjects with predominance of Grade I diastolic dysfunction. Age, BMI, blood pressure, duration of DM, HbA1c had negative correlation with parameters of diastolic dysfunction [E (cm/s),E/A, e', E'sr] and positive correlation with TR jet, LAVi, E/E'sr ratio.

Keywords: Diastolic Dysfunction, Transthoracic-echocardiography, Diabetes Mellitus, E/e' ratio, E/A ratio

Introduction:

The undoubted bidirectional relationship between Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease acts as a vicious circle, and the latter is an important complication in the former. T2DM is a diverse disorder described by variable degrees of insulin resistance, impaired insulin secretion and increased glucose production. This metabolic dysregulation related with secondary pathophysiologic changes in organ system resulting in complications which account for the morbidity

and mortality. An early diagnosis can be of great help to prevent or delay the development of these complications. The association between coronary heart disease and T2DM is wellknown. The recent confirmation suggests that diabetics may develop Heart Failure (HF) in absence of Coronary Artery Disease (CAD).Clinical and pathological studies have shown that abnormalities of Left Ventricular (LV) function, cardiomegaly and failure may occur without CAD, conceivably due to microangiopathy independent of atherosclerosis. Framingham heart study have shown an increased incidence of HF in patients with diabetes without CAD and hypertension. The diastolic dysfunction is more prevalent in diabetic than systolic dysfunction and develop without CAD. Early diagnosis of diastolic dysfunction will likely to make management well and eludes progression of cardiac dysfunction. Subclinical LV diastolic dysfunction in T2DM is a common finding and represents an early sign of diabetic cardiomyopathy. There is scarcity of data in Indian contest with regards to diastolic dysfunction in normotensive subjects with T2DM. This study was conducted to compare the diastolic dysfunction by transthoracic echocardiogram, using new criteria among asymptomatic T2DM and non-diabetic subjects [1-5].

Material and Methods:

To compare the diastolic dysfunction and its parameters (E/A ratio, E/e' ratio) by transthoracic echocardiography among diabetic and non-diabetic patient and to find relation between diastolic dysfunction and HbA1c. *Study Setting:* This study was conducted in Krishna Institute of Medical Sciences and Krishna Hospital, Department of Medicine and Cardiology over period of one year (1stApril 2018- 31stMarch 2019). The Institutional Ethics Committee (IEC) approval was taken. The Informed and written consent were taken from patients before enrolment for the study. *Study Design:* This was a prospective, observational and case control study. *Sample Size:* A total of 50 subjects with T2DMwere studied. A total of 50 healthy subjects will be included as the Control Group. *Inclusion Criteria:* All consecutive diabetic patients between ⩾ 18 to ⩽ 60 yr age group and apparently healthy individuals with age and gender matched as control. *Exclusion Criteria:* Patients with, hypertension, Ischemic Heart Disease (IHD), COPD, renal dysfunction, hepatic dysfunction, Thyroid dysfunction, anaemia, LV systolic dysfunction and age < 20 > 60 were excluded from this study. All enrolled subjects underwent medical history, physical examination and biochemical investigations. Diagnosis of diabetes mellitus: Fasting Blood Sugar (FBS) ⩾ 126 mg/dL (7.0 mmol/ L) or 2-h blood sugar ⩾ 200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) or HbA1c ⩾ 6.5% or Classic diabetes symptoms + random plasma glucose ⩾ 200 mg/dL (11.1 mmol/L) [6]. Body Mass Index (BMI) was calculated as: weight (kg) ÷ [height (m)]^2. Standardized Transthoracic Echocardiographic (TTE) examination and Doppler study: All examinations were obtained using General Electric company (GE) Vivid E-95 ultrasound machine (Chicago, Illinois United States) with 5 MHz probe and performed according to the recommendations of American Society of Echocardiography. Subjects were examined using standard Parasternal Long Axis (PLAX), Short Axis (PSAX) and Apical Two (A-2-CH view) and Four Chambers views (A-4-CH view). Conventional techniques (two-Dimensional-2D, M-mode echocardiography,

Pulsed-wave (PW) Doppler wave and Tissue Doppler Imaging (TDI) were used. Enrolled patients underwent echocardiographic measurements in the left decubitus position by one well-experienced cardiologist and was blind to patients' clinical information. (Figs.1 and 2)

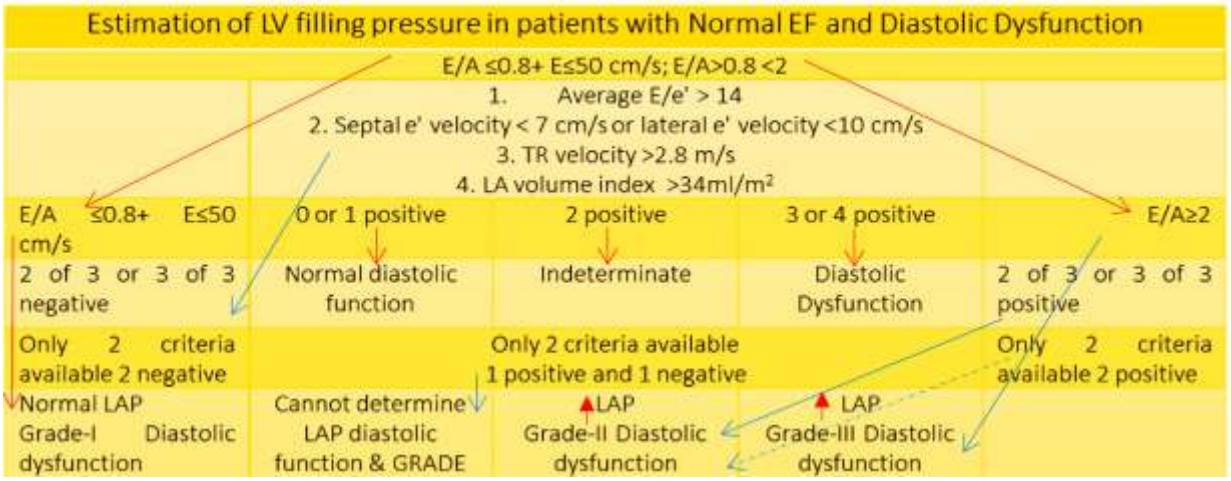

Fig. 1: Algorithm of Diastolic Dysfunction by 2-Dimensional Echocardiography and Doppler Study

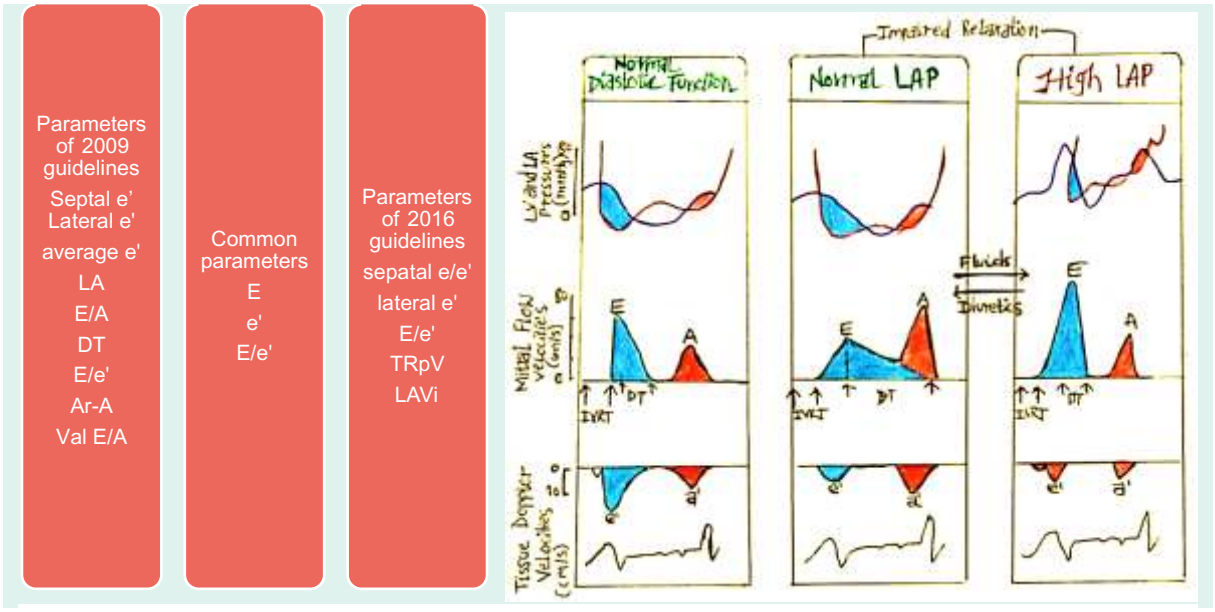

Fig. 2: Parameters of 2009 and 2016 Guidelines for LVDD and Relation of Mitral Inflow and TDI

Abbreviations: A: peak A wave velocity; Ar-A: difference between duration of A wave flow reversal and duration of the mitral A wave; E: peak E wave velocity; e': early diastolic annular velocity e' (septal, lateral, and average); E/A: E/A ratio; E/e': ration between E velocity and mitral annular e' velocity; LA left atrium; LAVi: left atrial volume index; DT: deceleration time of E wave; Val E/A: change in E/A with Valsalva maneuver; TRpV: peak velocity of tricuspid regurgitation

Diastolic Dysfunction:

Definition of LV diastolic dysfunction was indicated if 3 or more of these variables were abnormal: "Septal e <7 cm/sec, Lateral e <10 cm/sec), E/e ratio >14, LA volume index >34 mL/m^2, Peak TR velocity >2.8 m/sec." Diastolic dysfunction was divided into three grades (Grade I: impaired LV relaxation, Grade II: pseudonormal filling pattern and Grade III: restrictive filling pattern). Diastolic function was evaluated with conventional Doppler recordings and early (e') and late (a') myocardial velocities. The ratio between early transmitral filling (E) and the corresponding myocardial tissue velocity (e') served as an index of LV filling pressure [7] (Figs. 1 and 2).

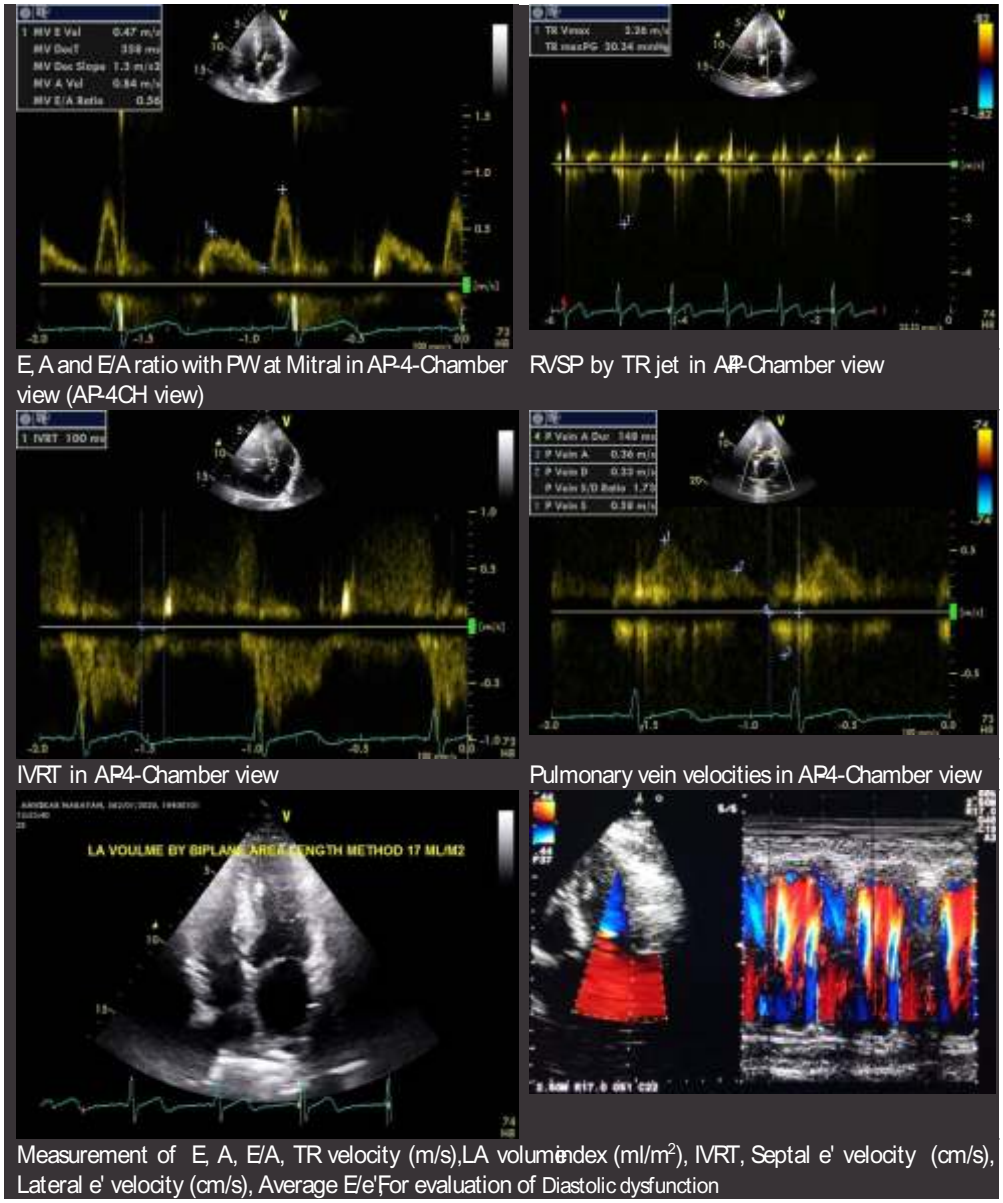

Fig. 3: Two-D-Echocardiography, Doppler (PW), M-mode and TR jet (CW)

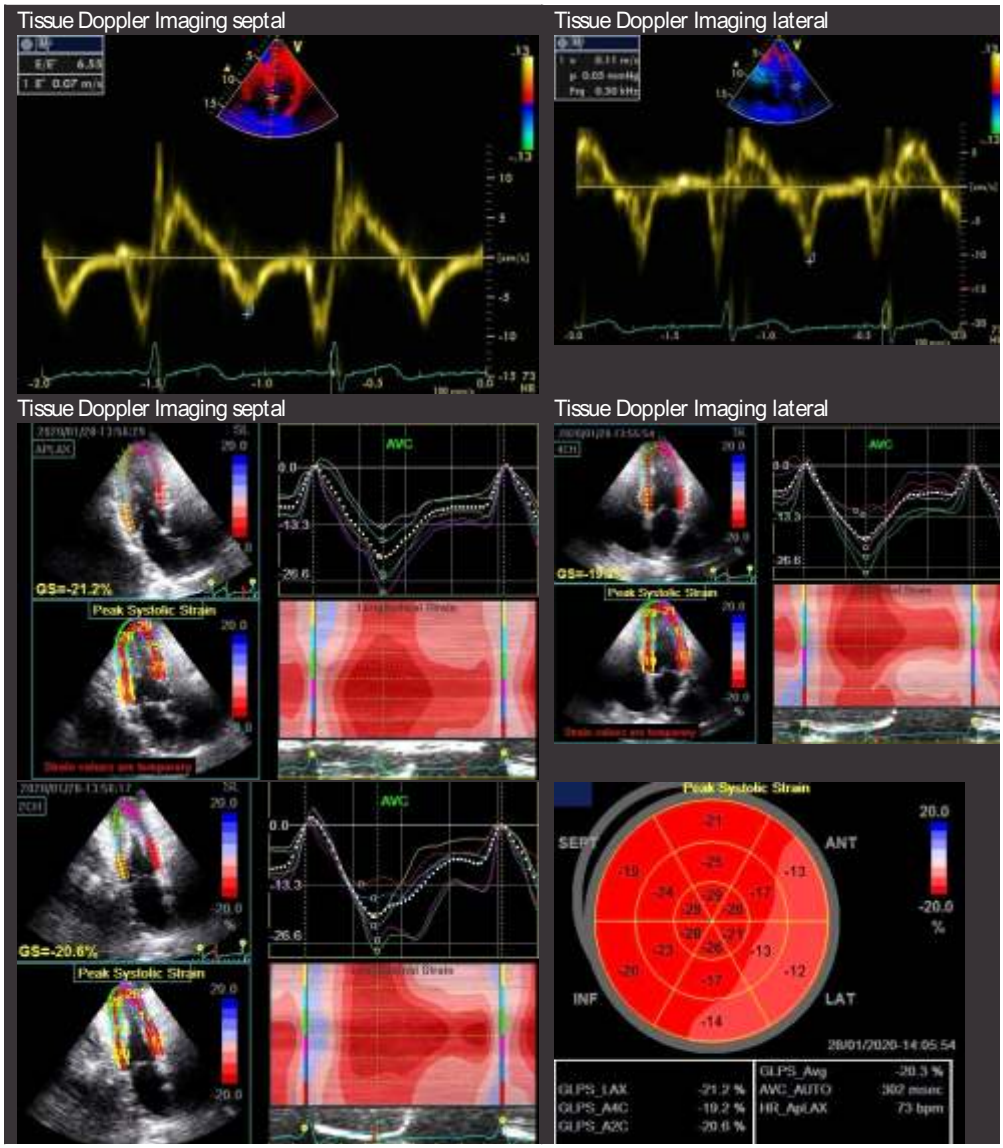

Fig. 4: Parameters of Diastolic Function by TDI, Speckle Tracking and Diastolic Strain Rate

1. Ejection fraction (EF %) (Using Teichholz method).
2. E point (m/sec): Early diastolic velocities of mitral inflow (pulse wave Doppler) (Fig. 3).
3. Septal and lateral e point by tissue Doppler (m/sec): Early diastolic myocardial velocity, derived from tissue Doppler imaging (TDI) (Fig. 4).
4. E/e ratio: Ratio of early diastolic velocities of mitral inflow (PW-derived) and myocardial movement (TDI-derived) taken as left ventricular filling pressure.
5. Left atrial (LA) volume index (mL/BSA): In apical four and two-chamber views.

6. Peak tricuspid regurgitation (TR) velocity (m/sec). Systolic dysfunction was defined if LV Ejection fraction <50%.
7. The E/E'sr ratio was assessed using Two-dimensional (2D) speckle tracking echo-cardiography (STE) (Fig. 4).
8. 2D STE for left ventricular (LV) early global diastolic strain rate (E'sr)
9. Global diastolic strain rate (E/E'sr) Ratio of Early Mitral Inflow Velocity (E) to the Global Diastolic Strain Rate (E'sr)
10. Transmitral color Doppler M-mode flow propagation velocity (Vp). Vp is measured as the slope of the first aliasing velocity during early filling (E wave); a normal Vp is >55 cm/s (Fig. 3).

Statistical Analysis:

Data was entered in to MS Excel sheet and analyzed for mean, percentage, standard deviation, chi square test, by using SPSS-21 (Statistical Package for the Social Sciences) for Windows (SPSS, Chicago, IL) [trial version]. Chi-Square tests were applied to study quantitative data, and '*p*' value < 0.05 was considered statistically significant.

Results:

A total of 50 subjects with T2DM(cases) and 50 healthy age and gender matched controls were included in this case-control prospective study. In Study Group, there were 26 (52%) males and 24 (48%) females. In Control Group there were 25 (50%) males and 25 (50%) females. The mean age of cases was 53±11 years and 49±10 years in Control Group. Mean of BMI in case group was higher (27.5 ± 3.2) kg/m2 as compared to 21.4 ± 6.2, seen in Control Group. The systolic BP seen in study population was 126 ± 10.3 mmHg while in control population was 121 ± 9.5 mmHg. Different parameters were used to assess LVDD including the ratio between Early (E) and Late (A) ventricular filling velocity at the mitral valve (E/A ratio), E-wave Deceleration Time (DT)and the ratio of mitral early diastolic inflow velocity to mitral early annular lengthening velocity (E/é ratio). The peak early trans-mitral filling wave velocity (E) in diabetic population was 41 ± 12 cm/s while in control population was 48 ± 8.5 cm/s. the 'A' was 62 ± 17 cm/s and 36 ± 7.9 cm/s in case and control groups respectively. The early diastolic velocity of lateral mitral annulus (e') was 8.5 ± 2.13 cm/s in cases, while in controls it was 9.2 ± 1.92 cm/s. The E/e' ratio was higher in diabetic group (16.5 ± 2.7) as compared to control group 14.13 ± 1.92. Mean of TR jet velocity in diabetic age group (2.57 ± 0.75) was higher in comparison with the control group (0.85 ± 0.32) (Table 1).

Table 1: Mean and S.D. of Variables of the Study Population

Variable	Case (n=50)	Control (n=50)	Variable	Case (n=50)	Control (n=50)
Male	26	25	Female	24	25
Age (years)	53 ± 11	49 ± 10	e' (cm/s)	8.5 ± 2.13	9.2 ± 1.92
BMI (Kg/m2)	27.5 ± 3.2	21.4 ± 6.2	E/e' (TDI)	16.5 ± 2.7	14.13 ± 1.92
SBP (mm Hg)	126 ± 10.3	121 ± 9.5	e' septal	9.2 ± 1.92	9.7 ± 1.71
DBP (mm Hg)	70 ± 6.5	71 ± 5.7	e' lateral	9.7 ± 1.86	9.9 ± 1.83
Duration of DM (Y)	4.7 ± 2.1	-	TR jet (m/s)	2.57 ± 0.75	0.85 ± 0.32
HbA1c (%)	7.8 ± 2.01	-	LAVI (ml/m^2)	29.5 ± 12.2	21.5 ± 4.71
E (cm/s)	41 ± 12	48 ± 8.5	E'sr (1/s)	1.13±0.56	1.6±0.46
A (cm/s)	62 ± 17	36 ± 7.9	E/E'sr ratio	61. 3 ± 15. 7	39.15 ±7.4
E/A ratio (PW)	0.9 ± 0.15	1.2 ± 0.23	LVMI (g/m^2)	166 6 ± 45. 3	123±27.5
DT (ms)	183±43.22	197.7±37.7	LVEF (%)	50.5 ± 8.7	57 ± 3.2
VP (cm/s)	29.71±18.91	51.31±7.91			

[*NPDR: non-proliferative diabetic retinopathy E: peak early transmitral filling wave velocity; e': early diastolic velocity of lateral mitral annulus; E'sr: global diastolic strain rate LAVI: LA volume index, LVMI: left ventricular mass index, DT: Deceleration time (ms), VP: Propagation velocity*]

The mean of DT was lower in Study Group (183 ± 43.22ms) as compared to control group (197.7 ± 37.7). Velocity Propagation (VP) was 29.71 ± 18.91 cm/s in cases and 51.31 ± 7.91 cm/s in controls. The global diastolic strain (E'sr) was 1.13 ± 0.56 in diabetic cases as compared to 1.6 ± 0.46 in controls. The E/E'sr ratio was 61.3 ± 15.7 in cases and 39.15 ± 7.4 in controls. Both LA and LV volume index was significantly higher in cases in comparison with controls. LAVI was 29.5 ± 12.2 ml/m² and 21.5 ± 4.71 ml/m² respectively. LVMI was 166 ± 45.3 in cases and 123 ± 27.5 in controls. The Ejection Fraction (EF) was 50.5 ± 8.7 % in diabetics while it was 57 ± 3.2 % in controls. The T2DM group had lower E/A ratio (0.9 ± 0.15 vs. 1.2 ± 0.23, $p < 0.01$), deceleration time (183 ± 43.22 vs 197.7 ± 37.7, $p < 0.05$), e' (8.5 ± 2.13 vs. 9.2 ± 1.92 cm/s, $p = 0.05$) as compared to the controls and higher E/e' (16.5 ± 2.7vs. 14.13 ± 1.92, $p < 0.02$). The mean duration of T2DM was 4.7 ± 2.1 years. Out of 50 cases, 9 (18%) had non proliferative diabetic retinopathy and 11 (22%) patients had peripheral neuropathy. Of total 9 patients with NPDR 8 (88.88%) patients had diastolic dysfunction. Of 11 patients with 9 (81.81%) had peripheral neuropathy. Diabetic

microvascular complication was associated with presence of diastolic dysfunction in absence of macro vascular complication (Table 1).

A total of 21 (42%) subjects among diabetes mellitus had diastolic dysfunction [Grade I diastolic dysfunction: 19 (38%) and Grade-II diastolic dysfunction: 2 (4%)]. Total 2 (4%) subjects among control had diastolic dysfunction [Grade I diastolic dysfunction: 2 (4%)]. (Chi-square: 20.384, p-value is < 0.00001). Age, BMI, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Left Ventricular Ejection Fraction (LVEF), duration of DM, HbA1c had negative correlation with parameters of diastolic dysfunction [E (cm/s),E/A, e', E'sr] and positive correlation with A, TR jet, LAVI, E/E'sr ratio in subjects with T2DM (Fig. 5). Correlation of various parameters of diastolic dysfunction with variables of control population, revealed negative correlation between and E/e' and increasing age and BMI (Table 2).

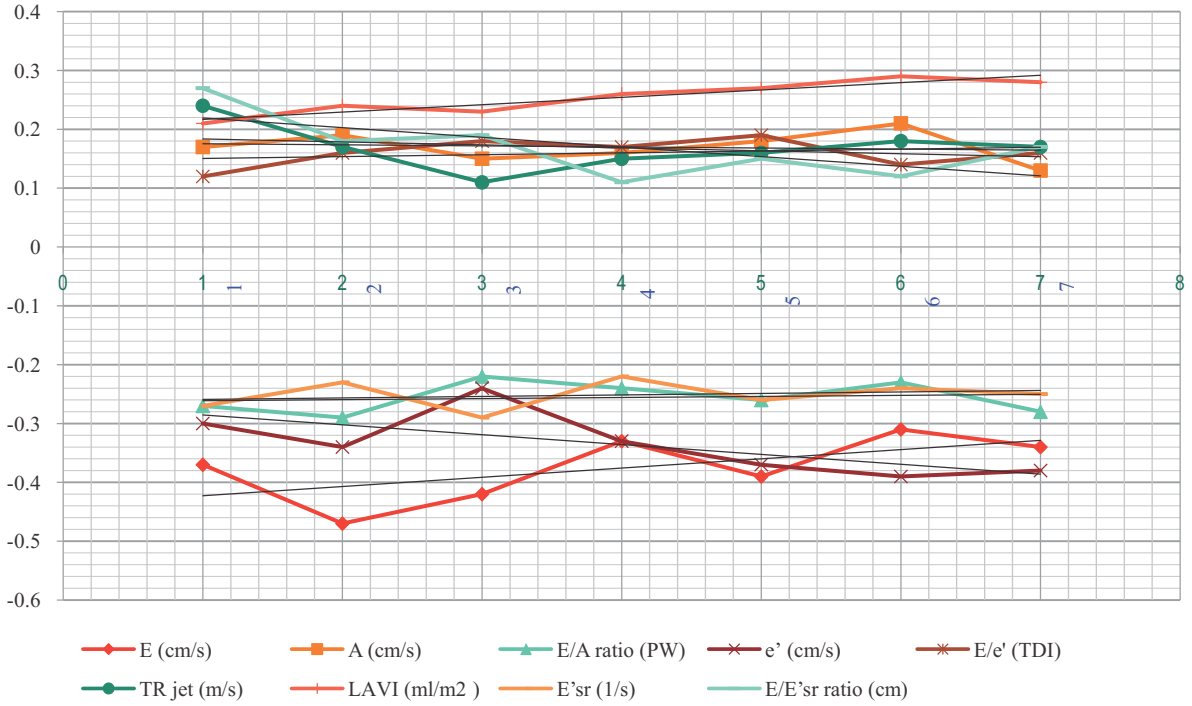

Fig. 5: Correlation of Various Parameters of Diastolic Dysfunction with Variables of Case Population

Table 2: Relation of Parameters of Diastolic Dysfunction with Variables of Control Population

Variable	E (cm/s)	A (cm/s)	E/A ratio	e' (cm/s)	E/e' (TDI)	TR jet (m/s)	LAVI ml/m^2	E'sr (1/s)	E/E'sr
Age (years)	-0.12	0.45	0.32	-0.13	-0.12	0.13	0.14	-0.12	0.12
BMI (Kg/m^2)	-0.26	0.13	0.24	-0.20	-0.11	0.16	0.10	-0.17	0.14
SBP (mm Hg)	-0.32	0.11	0.18	-0.14	0.08	0.09	0.13	-0.16	0.17
DBP (mm Hg)	-0.21	0.12	0.16	-0.23	0.14	0.12	0.19	-0.14	0.13
LVEF (%)	-0.27	0.10	0.19	-0.27	0.12	0.17	0.20	-0.18	0.16

Discussion:

DM is characterized by hyperglycemia, insulin resistance and metabolic dysregulation leading to diastolic and systolic dysfunction. Changes in metabolic signaling pathways, mediators and effectors contribute to the pathogenesis of cardiac dysfunction in DM called Diabetic Cardiomyopathy (DC). Echocardiographic studies report on the association between DM and the presence of cardiac hypertrophy and myocardial stiffness that lead to diastolic dysfunction. LV Diastolic Dysfunction (LVDD) is a well-established and early echocardiographic characteristic of diabetic cardiomyopathy [8]. According to the DD2016, evaluation of LVDD is mainly based on six indices: E wave, E/A ratio, septal or lateral e′, average E/e′, LAVI: left atrial volume indexed, TRpV: Tricuspid Regurgitation peak Velocity (TRpV) and left ventricular filling pressure. LVFP and LAP are often used interchangeably to designate elevated filling pressure. The different grades of LVDD as stated by the latest recommendations are similar to the previous classification (Grade I, Grade II, Grade III). The algorithmic association for grading has changed, namely for evaluation of LVFP, making diagnosis and grading of LVDD more practical and simpler to implement in daily practice [7]. Early cardiovascular manifestations in diabetes is high on international research and prevention agenda given that cardiovascular events are the leading cause of death for diabetic patients. The undeniable bidirectional relation between T2DM and cardiovascular disease acts as a vicious circle [3]. The prevalence of diastolic dysfunction is on the rise and higher than systolic dysfunction [9]. In diabetic patients, cardiomyopathy is an important cause of HF, but its pathophysiology has not been completely understood thus far. Myocardial hypertrophy and diastolic dysfunction have been considered the hallmarks of DC. Increased intrinsic cardiomyocyte stiffness is probably the most important contributor to myocardial stiffness. Antidiabetic drugs, Nitric Oxide (NO) stimulating agents, anti-inflammatory agents, and Sodium–Glucose co-Transporter-2 (SGLT2) inhibitors are emerging as potential treatment options for DC [10]. LVDD in asymptomatic patients with diabetes mellitus may represent the early stage of diabetic cardiomyopathy and have a preserved left ventricular systolic function [11]. Although, IHD is the major cause of death in diabetic patients, DCM is increasingly recognized as a clinically relevant entity. DC is common in diabetic asymptomatic patients; it is frequently underdiagnosed in its primary stages [12]. So, far very few population-based studies have been carried out in India, to demonstrate the prevalence of diastolic dysfunction in diabetic subjects in the Indian patients. The objective of our study was to determine whether there is any association between diastolic dysfunction and T2DM, even in the asymptomatic subjects. Our results were compared with various studies (Table 3).

Echocardiographic Parameters of Diastolic Dysfunction:

In the present prospective case-control study 50 T2DM cases and 50 healthy controls were studied for diastolic dysfunction by transthoracic-echocardiography. The mean peak early trans-mitral filling wave velocity (E), early diastolic velocity of lateral mitral annulus (e'), and E/A ratio was low in and mean of E/e' ratio and TR jet velocity were higher in subjects with T2DM.

Similarly, Ofstad *et al.* (2015) quoted T2DM group had diastolic dysfunction with lower E/A ratio, DT, e' and a' compared to the controls, and higher E/e' with, more advanced subclinical impairment of diastolic function in T2DM [5]. Sanfilippo *et al.* reported among the tissue Doppler imaging-derived variables e' and E/e' seem most reliable with acceptable limitations for diagnosis and grading of LVDD [13].Similarly in the present study the T2DM group had lower E/A ratio (0.9 ± 0.15 vs. 1.2 ± 0.23, $p < 0.01$), deceleration time (183±43.22 vs 197.7±37.7, $p < 0.05$), e' (8.5 ± 2.13 vs. 9.2 ± 1.92 cm/s, $p < 0.05$) and higher E/e' (16.5 ± 2.7 vs. 14.13 ± 1.92, $p < 0.02$) compared to the controls. The latest recommendations for assessment of left ventricular diastolic function are mainly based on six parameters: E wave, E/A ratio, septal or lateral e′, average E/e′, left atrial volume indexed, and peak tricuspid regurgitation velocity [14]. Fontes-Carvalho *et al.* (2015) quoted that the individuals with no MS, to patients with MS and no diabetes, to patients with diabetes, there was a progressive decrease in E' velocity, higher E/E' ($p < 0.0001$) and more diastolic dysfunction. HOMA-IR score and metabolic syndrome were independently associated with LVDD [15]. Kozakova *et al.* (2017) reported 35.2% T2DM patients had e' velocity lower than that expected for age with one-third of T2DM patients had subclinical LV diastolic dysfunction [16]. Suran *et al.* (2016) quoted reduced mean mitral septal and lateral E' velocities compared to healthy controls ($p < 0.001$) and mean ratios E/E' were significantly higher in diabetics [17]. Yap *et al.* (2019) HF and preserved EF (HFpEF; EF ⩾ 50%), the prevalence of T2DM were 45.0%, respectively ('p'=0.003). In HFpEF with T2DM was associated with higher mitral E/e' ratio [18].

Diabetic Microvascular Complication:

In present study, a total of 8 out of 9 (88.88%) patients with diabetic retinopathy and 9 out of 11 (81.81%) with diabetic peripheral neuropathy had diastolic dysfunction. Chung *et al.* (2017) observed that, among the diastolic function parameters, patients with diabetic retinopathy exhibited higher E/E′ ratios than patients without DR ($p = 0.022$) [19]. During the 3-year follow-up study by Bergerot, (2018) observed that, prevalence of diastolic dysfunction increased from 49% to 67% ($P = 0.001$). Age, retinopathy, and increase in blood pressure over time are associated with an increased risk of diastolic function deterioration in T2DM patients, these findings are comparable with present study [20]. Microvascular complications are common among patients with DM. HF with preserved Ejection Fraction (HFpEF) in patients with DM may be a manifestation of microvascular disease compared with HFrEF [21]. Mishra *et al.* (2008) quoted that, the asymptomatic diabetic patients have reduced left ventricular systolic and diastolic function as compared with healthy subjects. Left ventricular systolic and diastolic abnormalities were correlated with the duration of diabetes and with diabetic microangiopathies, like retinopathy and neuropathy. DM is the strongest independent correlate of left ventricular diastolic dysfunction [22]. DR may not only represent microvascular long-term complications in patients with diabetes but may also be associated with more advanced form of diastolic dysfunction [19]. Sharavanan *et al.* (2016) found that the association between glycosylated hemoglobin and diastolic dysfunction in diabetic patients was statistically significant. ($p = 0.001$) [23].

Echocardiographic Grades of Diastolic Dysfunction:

In present study total of 21 out of 50 (42%) subjects among diabetes mellitus had diastolic dysfunction (predominantly Grade I diastolic dysfunction). Compared to control diabetic patients had statistically significant diastolic dysfunction ('p' < 0.0001). Similarly, Chaudhary *et al.* (2015) reported incidence of LVDD of 41% with. Grade 1 LVDD was most common and HbA1c and age, were found to be strong indicators of LVDD in newly diagnosed cases of T2DM [24]. Maiello *et al.* (2017) reported high prevalence of LVDD in asymptomatic diabetic postmenopausal women (23.3%) [25]. Milwidsky *et al.* (2015) LVDD was more prevalent among patients with IFG and DM than in euglycemic individuals (27, 30 and 15%, respectively; p < 0.001). IFG was independently associated with a significant increase in the LVDD [26]. Zheng C *et al.* (2019) quoted LVDD in 34.39% with abdominal obesity, hypertension, and elevated blood glucose were the contributors for LVDD [27]. Bouthoorn *et al.*(2018) in their review article of 28 studies quoted that the LVDD 48% and 35% affecting both the gender equally [28]. Ashour *et al.* (2018) a care control cross sectional study quoted LVDD is more prevalent in diabetic patients comparing with control group (62.3% versus 12.8%, p<0.05) correlated independently with increasing age, duration of the disease and HbA1c level [11].

Park *et al.*(2017) quoted that the 15% developed incident T2D with had greater LV mass index, worse and higher prevalence of LV diastolic dysfunction (34.6 vs. 54.2%), compared with those who did not develop T2DM ('p' < 0.001) [29]. Zakriaa *et al.* (2017) quoted 80% patients have diastolic dysfunction in patients with diabetes mellitus [30]. Sharavanan *et al.* (2016) reported that the more than half of the diabetic patients were detected to have diastolic dysfunction [23].

Correlation of Echocardiographic Parameters of LVDD with Variables of Study Population:

Age, BMI, SBP, DBP, LVEF, duration of DM, HbA1c had negative correlation with parameters of diastolic dysfunction [E (cm/s),E/A, e', E'sr] and positive correlation with TR jet, LAVI, E/e' ratio in present study. Similarly, Seo *et al.* (2017) observed that the BMI was independently associated with higher A, lower E', and higher E/E'. The risk of diastolic dysfunction was significantly higher among overweight [p = 0.001] and obese participants (p <0.001) compared to normal-weight participants. Obesity and overweight independently predicted diastolic dysfunction [31]. Abhay Kumar *et al.* (2015) reported mean HbA1c level of LVDD group was found higher as compared to those without LVDD. LVDD was very common at the time of diagnosis of T2DM even in normotensive patients. HbA1C and age, were found to be strong indicators of LVDD in newly diagnosed cases of T2DM [24]. Patil *et al.* (2012) reported prevalence of DD in 64% of the diabetic patients and associated with increasing HbA1c levels, longer duration of diabetes and increasing age [32]. Kozakova *et al.* (2017) One-third of T2DM patients with preserved LV ejection fraction had sign of subclinical LV diastolic dysfunction. HbA1c levels were positively associated with early

diastolic velocity e′ [16]. Inoue *et al.* (2016) reported that E/e' was significantly correlated with age ($p<0.001$), sex ($p<0.001$), duration of diabetes ($p=0.002$), systolic blood pressure ($p=0.017$). Hyperinsulinemia and sulfonylurea use may be important in the development of LVDD in patients with T2DM [33].

Speckle tracking echocardiography:

The global diastolic strain (E'sr) was 1.13 ± 0.56 in diabetic cases as compared to 1.6 ± 0.46 in controls in present study. The E/E'sr ratio was 61.3 ± 15.7 in cases and 39.15 ± 7.4 in controls. Both LA and LV volume index was significantly higher in cases in comparison with controls. Loncarevic *et al.* (2016) DM patients impaired LV relaxation LVDD was21% detected by conventional and speckle tracking echocardiography even in asymptomatic patients, whereas moderate or severe diastolic dysfunction was estimated at 7% [14]. Kishi *et al* (2017) quoted that the early DM group had less favorable early diastolic strain rate [Ell_SRe] ($p < 0.05$) than the NGT group. High IR was associated with worse Ell, E', and Ell_SRe. Cumulative exposure to DM beginning in early adulthood adversely impacts LV remodeling and function at middle age [34].

The co-occurrence of T2DM and HF, either with reduced (HFrEF) or HFpEF, is frequent (30–40%). SGLT2 inhibitors, empagliflozin and canagliflozin, have shown a significant reduction in HF hospitalization in patients with at risk of CV disease [35]. In patients with T2DM, 6 months liraglutide treatment was associated with a significant improvement in diastolic function [36]. Patients with T2DM and elevated urinary Albumin: Creatinine Ratio (ACR) with persistent microalbuminuria have markers of diffuse cardiac fibrosis including elevated extracellular volume fraction and diastolic dysfunction, which may in part be reversible by renin–angiotensin– aldosterone blockade. Increased risk in these patients may be mediated by subclinical changes in tissue structure and function [37]. In young adults with T2DM, diabetes duration and aortic distensibility were associated with diastolic dysfunction [38]. The updated algorithm for LVDD is more effective in predicting adverse cardiovascular events in patients with established LVDD. The elevated values of the index E/e' can point to early diastolic impairment, foretelling diabetic cardiomyopathy [3]. Diabetes mellitus frequently coexists with HF. In HFpEF and HFrEF, T2DM is associated with smaller left ventricular volumes, higher mitral E/e' ratio, poorer quality of life, and worse outcomes, with several differences noted between HF phenotypes [18]. The stepwise approach in evaluation of LV diastolic function is essential in any patients with dyspnea on exertion or HF. LV filling pressures is usually synonymous with Pulmonary Capillary Wedge Pressure (PCWP), mean Left Atrial Pressure (LAP), mean LV diastolic pressure, and LV End-Diastolic Pressure (LVEDP) [39].Sodium glucose cotransport-2 inhibitors reduce the risk of HF and glucagon-like peptide-1 receptor agonists lower thrombotic events, but for optimum benefit, they will require to be used in conjunction with lifestyle interventions, which may actually modify the underlying pathophysiological process of T2DM development [40]. Canagliflozin appears to significantly improve left ventricular diastolic function [41]. Pioglitazone improves whole-body and myocardial insulin sensitivity, LV diastolic function and systolic function in T2DM.

Improved myocardial insulin sensitivity and diastolic function are strongly correlated [42]. Changes in diastolic function are already present before the onset of diabetes, being mainly associated with the state of insulin resistance. BMI levels and HbA1c levels were significantly associated with LVDD in the patients with T2DM [43].

Table 3: Comparison of Various Studies with Present Study

Study and Author	Type of Study	Diastolic Dysfunction	Conclusion
Loncarevic *et al*. (2016) [14]	DM patients (n=210)	LVDD is estimated at 21% moderate or severe diastolic dysfunction is 7%	The latest recommendations for assessment of LVDD are simple
Kozakova *et al.* (2017) [16]	Case-control (n=125 T2DM patients) (n=101 healthy)	35.2% T2DM patients had e' velocity lower than expected (P < 0.0001).	1/3rd of T2DM patients with preserved LVEF had LVDD.
Milwidsky *et al*. (2015) [26]	Retrospective cross-sectional (n=2971)	Patients with IFG and DM had lower ratios of early (E) to late (A) trans-mitral flow (0.9 ± 0.3 & 0.9 ± 0.3 vs. 1.1 ± 0.4, p < 0.001).	LVDD: prevalent among patients with IFG and DM than in euglycemic (27, 30 and 15%, respectively; p < 0.001).
Chaudhary *et al.* (2015) [24]	Cross-sectional (n=100) 2 DM Age: 50.08 ± 6.32	LVDD was 41%. Grade 1 LVDD was most common	HbA1c and age, were indicators of LVDD in newly diagnosed cases of T2DM.
Patil *et al.* (2012) [32]	Cross-sectional hospital- based study (n=50)	Diastolic dysfunction was present 64%	DD increased with longer duration of diabetes. increase age HbA1c levels and uncontrolled DM
Zheng *et al.* (2019) [27]	Cross-sectional (n=1963)	LVDD:34.39%	abdominal obesity, hypertension, BSL were contributors to LVDD
Suran *et al.* (2016) [17]	Case control (n=51)	Reduced mean mitral septal and lateral E' velocities compared to healthy (p< 0.001); ratios E/E'sept, E/E'lat and E/E't were higher in DM	TDI is essential to detect subclinical diastolic deterioration of both ventricles.
Maiello *et al*. (2017) [25]	Cross-sectional (n=456)	LVDD was present in (23.3%)	high prevalence of LVDD in asymptomatic diabetic
Mishra *et al*. (2008) [22]	Case control DM (n=73) Control: 34	Asymptomatic diabetic patients have reduced left ventricular systolic and diastolic function as compared with healthy subjects	LV diastolic abnormalities are correlated with the duration of diabetes and microangiopathies (retinopathy and neuropathy)
Ofstad *et al*. (2015) [5]	T2DM case n=100 Non-diabetic controls n=100 58.4 ± 10.5 years	T2DM patients had more hypertrophy, lower E/A ratio, DT, e', a' and higher E/e' compared to the controls	Pseudo normalization and increased filling pressure in the T2DM group, whereas the controls had relaxation abnormalities

Continued...

Study and Author	Type of Study	Diastolic Dysfunction	Conclusion
Sharavanan *et al.* (2016) [23]	2 DM (n=120)	diastolic dysfunction: 66	HbA1c and LVDD in diabetic patients was significant (p=0.001).
Bouthoorn (2018) [28]	Review 28 studies (hosp n=2959; general n=2813)	Hospital population: 48% general population: 35%	Equal prevalence of DD among male and females (47%: 46%)
Zakriaa *et al*. (2017) [30]	55 patients with T2DM	DD: 80%, 1 diastolic dysfunction: 47%, 2 pseudonormal 7%	Diabetic cardiomyopathy is an important diabetes complication
Fontes-Carvalho *et al.* (2015) [15]	Population-based (EPIPorto) (n=1063) 61.2 ± 9.6 years	progressive decrease in E' velocity, higher E/e' ($p < 0.0001$) and more diastolic dysfunction among DM.	HOMA-IR score and metabolic syndrome were independently associated with LVDD.
Kishi *et al*. (2017) [34]	CARDIA (n=3,179)	DM subjects had Early diastolic strain rate [Ell_SRe] ($p < 0.05$)	DM beginning in early adulthood affect LV remodeling and function
Zuo *et al*. (2019) [43]	(n=925)	BMI were associated with LVDD in the patients with T2DM [P = 0.001]. LVDD: 72.22%	HbA1c has a detrimental impact on the myocardium with LVDD.
Tromp *et al*. (2019) [21]	601 (21.5%)	DM with microvascular complications were more likely to have HFpEF (P = 0.008).	HFpEF may be a clinical manifestation of microvascular disease in DM.
Bergerot (2018) [20]	3-year follow-up in a prospective cohort of 310 DM2	diastolic dysfunction increased from 49% to 67% (P = 0.001)	Age, retinopathy, and increase in blood pressure over time are associated with an increased risk
Ashour Kumar *et al.* (2018) [11]	Cross sectional (n=86 diabetics) (n=65 controls)	LVDD was prevalent in diabetic patients comparing with control group (62.3% vs 12.8%, $p<0.05$)	LVDD can occur in diabetic patients even in young. TDI, LA size and peak TR were sensitive indices of LVDD
Present study	Case-control (n=50 T2DM cases and n=50 controls)	E/e' ratio and TR jet velocity in DM group was significantly higher. T2DM group had lower E/A ratio (0.9 ± 0.15 vs. 1.2 ± 0.23, $P < 0.01$), e' (8.5 ± 2.13 vs. 9.2 ± 1.92 cm/s, 'P' = 0.05) compared to the controls and higher E/e' (16.5 ± 2.7vs. 14.13 ± 1.92, $P < 0.02$). Total 88.88% with retinopathy and 81.81% with peripheral neuropathy had LVDD	Total 42% subjects among DM had diastolic dysfunction [grade I LVDD (19/21). Age, BMI, SBP, DBP, LVEF, duration of DM, HbA1c had negative correlation with parameters of diastolic dysfunction [E (cm/s),E/A, e', E'sr] and positive correlation with TR jet, LAVI, E/e' ratio.

Conclusion:

Present study highlighted the burden of diastolic dysfunction among the asymptomatic diabetic subjects with majority of them had Grade I diastolic dysfunction. Age, BMI, blood pressure, duration of DM, HbA1c had negative correlation with parameters of diastolic dysfunction [E,E/A, e', E'sr] and positive correlation with TR jet, LAVI and E/e' ratio. E/e' ratio and TR jet velocity in DM group was significantly higher. Diastolic dysfunction was also significantly associated with diabetic microvascular complication in the form of diabetic retinopathy and peripheral neuropathy. Echocardiography is a simple non-invasive valued tool in detecting diastolic dysfunction in diabetics before they develop cardiac symptoms. Echocardiography should be done for even in asymptomatic diabetic patients to assess the cardiac function.

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