Diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function

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ABSTRACT

Background: The incidence of heart failure in diabetic subjects is high even in the absence of hypertension and coronary artery disease. **Aims:** The purpose of this study was to study the incidence of diastolic dysfunction in diabetic subjects and its relation to age, duration of diabetes mellitus (DM), Glycosylated hemoglobin (HbA1c) levels, obesity indices and diabetic microangiopathies. **Settings and Design:** This was a case control prospective study conducted at the teaching hospital during a one year period. **Materials and Methods:** A total of 127 subjects (case) with type 2 diabetes of more than five years duration were studied. Total 100 healthy subjects were included as the control group. Echocardiography was performed to assess left ventricular diastolic function. **Results:** Out of the total 127 subjects, 69 (54.33%) from the case group had diastolic dysfunction, and 11% amongst 100 in the control group population showed the diastolic dysfunction ($P < 0.001$). Patients with a longer duration of DM (of 11 to 15 years) had a higher prevalence of diastolic dysfunction ($P < 0.02$). Subjects with high waist circumference and high waist to hip ratio had statistically significant diastolic dysfunction with 'P' =0.001 and 'P' = < 0.02 respectively. Subjects with HbA1c > 7.5% had a higher prevalence of diastolic dysfunction than subjects with HbA1c < 7.5% ($P < 0.02$). Diastolic dysfunction was present in majority of the subjects with autonomic neuropathy and retinopathy. **Conclusions:** Present study reveals high incidence of diastolic dysfunction in asymptomatic diabetic; subjects and, this finding was correlated with the duration of diabetes, HbA1c levels, obesity indices and diabetic microangiopathies. We conclude that early diagnosis and institution of treatment will reduce morbidity and improve the outcomes, and prevent future heart failure.

Key words: Diastolic dysfunction, diabetes mellitus, echocardiography, heart failure

INTRODUCTION

The incidence of diabetes mellitus (DM) is increasing worldwide and rapidly assuming epidemic proportions. Over the last three decades, a number of epidemiological, clinical and autopsy studies have proposed the presence of diabetic heart disease as a distinct clinical entity. Diastolic heart failure (HF) is also referred to as HF, with preserved left ventricular systolic function. Many studies have reported that the incidence of heart failure in diabetic subjects is high even in the absence of hypertension and coronary artery disease. Studies have reported a high prevalence of pre-clinical diastolic dysfunction among subjects with DM.[1] The evidence indicates that myocardial damage in diabetic subjects affects diastolic function before the systolic function. The pathogenesis of this left ventricular (LV) dysfunction in diabetic subjects is not clearly understood.

Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease, and many mechanisms,

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such as microvascular disease, autonomic dysfunction, metabolic disorders, and interstitial fibrosis, have been suggested as causative factors.[2] However, the exact etio-pathogenesis of diabetic cardiomyopathy still remains unclear. 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 type 2DM, even in the asymptomatic subjects. Thus, this prospective case control study was conducted with the aim of determining the prevalence of asymptomatic LV diastolic dysfunction in type 2 diabetes subjects, and its relation to age, duration of DM, HbA1c, obesity indices and other diabetic complications such as microangiopathies.

MATERIALS AND METHODS

The objectives of our study

- To determine the incidence of LV diastolic dysfunction in asymptomatic type 2 DM patients and to compare it with normal subjects;
- and, to quantify the relation of LV diastolic dysfunction with age, duration of DM, HbA1c, obesity indices and other diabetic complications such as microangiopathies.

For the study, we hypothesized that the diastolic dysfunction, [as assessed by the mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') (E/e') ratio], worsens with age, duration of DM, HbA1c and obesity indices. A total of 127 normotensive subjects (case), with type 2 DM of more than five years duration with no clinical evidence of cardiac disease were studied. A total 100 apparently healthy subjects with age and sex matched were included as the control group. This case-control study was designed to determine the prevalence of asymptomatic left ventricular diastolic dysfunction in type 2 DM subjects and its relation to patient's age, duration of DM, control of diabetes as determined by HbA1c levels, biochemical profile and obesity indices. This was a case -control prospective, observational study conducted out at the Krishna Institute of Medical Sciences, Karad, over a period of one year period from January 2009 to December 2009. This study was approved by the ethical committee of Krishna Institute of Medical Sciences University Karad.

Inclusion criteria for case population

All type 2 DM with patients with duration > 5 years with normal left ventricular systolic function (LVEF: ≥ 50%).

Exclusion criteria for case population

- Subjects with evidence of coronary artery disease - CAD [excluded by history of angina, chest pain, Electrocardiogram (ECG) changes and abnormal Treadmill test (TMT) results];
- subjects with evidence of valvular disease;
- hypertensive patients, antihypertensive agents and/or angiotensin-converting enzyme (ACE) inhibitors, with evidence of left ventricular hypertrophy on echocardiography;
- and, subjects with poor transthoracic echo window.

Detailed medical history was collected from each eligible subject; and, they underwent physical examination and biochemical investigations. After a 12-hour fast, a venous blood sample was collected and sent to the biochemistry laboratory for estimation of the following: plasma glucose level; glycatedHbA1c; total serum cholesterol (TC); High-density lipoprotein (HDL) cholesterol; Low density lipoprotein (LDL) cholesterol; Very low density lipoprotein (VLDL); and, serum triglyceride levels (TG). ECG was done in all subjects. Physical examination included routine general examination, systemic examination and anthropometric evaluation including height (meter), hip circumference in centimetre (HC), waist circumference in centimetre (WC) and weight in kilogram.

Echocardiography

All the subjects were underwent resting transthoracic 2-dimensional echocardiography and Doppler imaging, to assess left ventricular diastolic function. Echocardiographer was not aware of this study to avoid bias in the interpretation. A transthoracic 2-dimentionsional echocardiogram (TTE) with pulsed Doppler evaluation of transmitral inflow and Tissue Doppler Imaging (TDI) and 2D echocardiography was performed to minimize the errors in assessing the diastolic dysfunction. Echocardiography was performed by harmonic imaging mode by Acuson-Siemens-X 300 echocardiography machine (5-1 MHz multi-frequency probe) according to the standard protocol. Pulsed-wave Doppler (PWD)-derived transmitral inflow velocities was obtained in the apical 4-chamber view, with the sample volume placed at the mitral valve leaflet tips.[3] Measurements included the transmitral early diastolic rapid filling (E-wave) and atrial contraction late filling (A-wave) velocities to calculate E/A ratio, isovolumteric relaxation time (IVRT) and deceleration time (DT). For tissue Doppler imaging, the mitral annulus velocity was obtained with a 2 mm sample volume placed at the

lateral side and septal side of the mitral annulus. Diastolic dysfunction was labelled according to the standard guidelines. Left ventricular overall ejection fraction (systolic function) was calculated by modified Simpson's method; and, LVEF ≥ 50% was considered as normal.[3,4] All echocardiographic measurements were averaged over three consecutive cardiac cycles, measured by a single investigator blinded to all other variables [Figure 1].

Diagnostic criteria

- Dyslipidemia: was defined if TC ≥ 200 mg/dL; LDL cholesterol ≥ 130 mg/dL; HDL cholesterol 40 mg/dL; and, TG ≥ 150 mg/dL.[5]
- Obesity indices: Cut-off for high Body Mass Index (BMI) was ≥ 25 for females and ≥ 27 for males. Cut-off for high waist to hip ratio (WHR) was ≥ 0.9 for males, and ≥ 0.8 for females. Cut-off for high WC was > 85 cm for females and > 90 cm for males.[6]
- Diabetes mellitus (DM): If a subject is a known diabetic on treatment, or with any fasting blood sugar level (F-BSL) ≥ 126 mg/dL.[6]
- Retinopathy: Microangiopathy was assessed by fundoscopy (direct ophthalmoscopy). The ophthalmologist doing fundoscopy was unaware of this study. Fundoscopic examination was done after dilating the pupil with tropicamide (1%). Retinopathy status was labeled as follow:
  - no evidence of diabetic retinopathy;
  - background diabetic retinopathy, defined as presence of one or more microaneurysms, punctate or striate intraretinal hemorrhages, and hard exudates;
  - preproliferative diabetic retinopathy defined as soft exudates, venous beading, and intraretinal microvascular abnormalities;
  - proliferative diabetic retinopathy characterized by neovascularization on or within one disk diameter of the disk in extent. After these initial evaluations were completed, 127 diabetic subjects were enrolled into the study protocol. Hundred apparently healthy individuals, matched for age and sex served as control group.[7]
- Autonomic neuropathy: Autonomic function was evaluated by unmasking the sympathetic dysfunction by the blood pressure (BP) response to standing. A fall in systolic BP on erect position of < 10 mmHg was defined as normal and > 30 mmHg as abnormal.[7]
- Diastolic dysfunction: LV diastolic dysfunction was considered to be present if any of the following findings were seen, as previously described:[3,4]
  - E/A ratio < 1 or > 2
  - DT < 150 or > 220 ms,
  - IVRT < 60 or > 100 ms, or
  - E/e' ratio > 15

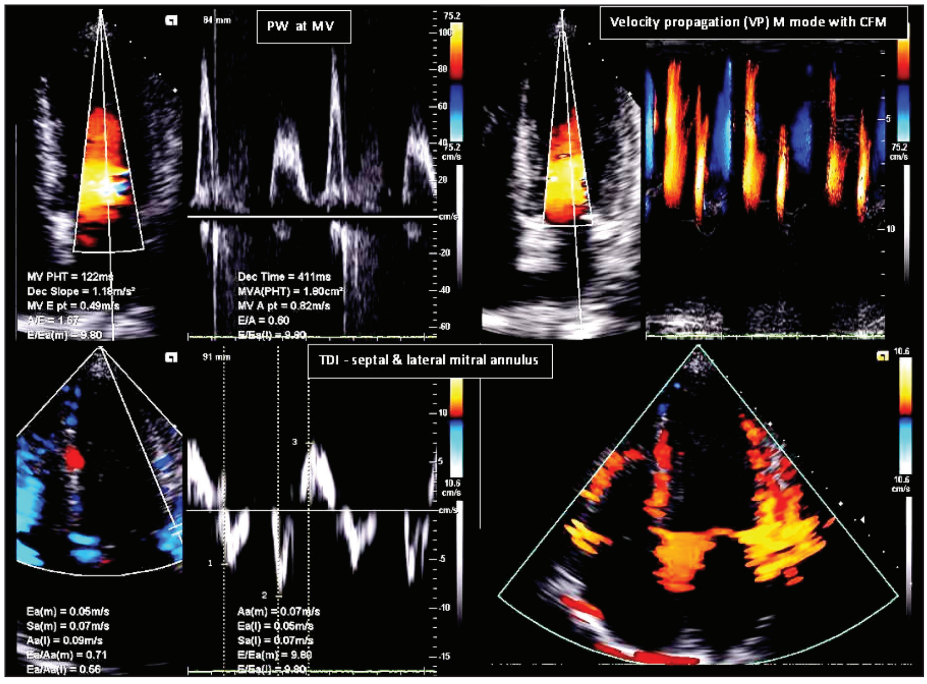

Figure 1: Two dimensional transthoracic echocardiographic evaluation of diastolic dysfunction by pulse wave Doppler (PW) at mitral valve, velocity propagation (VP) by colour 'M' mode and tissue Doppler imaging (TDI) at septal and lateral mitral annulus

Statistical analysis

Data was analysed for mean, percentage, standard deviation, chi square test, multiple correlation and multivariate analysis, by using SPSS-10 (Statistical Package for the Social Sciences) for Windows (SPSS, Chicago, IL). Variables that were not normally distributed were reciprocally transformed for analysis. The't'-test and Chi-Square tests were applied to study quantitative and qualitative data, respectively with '*P*' value < 0.05 was considered statistically significant. Correlation of various factors was determined using r^2 and multiple linear regression analysis. Correlation (*r*) findings were describes as follows: $r = 0.8$ (high correlation coefficient); $r = 0.4–0.7$ (moderate correlation); and, $r = 0.3$ and above (low correlation coefficient).

RESULTS

A total 127 subjects with type-2 diabetes mellitus (cases) and 100 healthy age and sex matched controls were included in this case-control prospective study. Out of 127 subjects with type -2 DM, 69 (54.93 %) were male and 58 (46.66%) were female. Total 56 (54%) male and 44 (46%) female were control healthy subjects. Mean standard deviation of biochemical, anthropometric indices and echocardiographic parameters were obtained [Table 1]. Mean of BMI in the case group was significantly higher as compared to the control group ('*P*' < 0.05). Mean of WC in the case group was significantly higher as compared to the control group ('*P*' = 0.02). Mean of WHR in the case group was significantly higher as compared to the control group ('*P*' < 0.02). Mean of TC in case group was high compared to control group. Mean of TG in the case group was significantly higher as compared to control group ('*P*' =0.032). Mean of LDL- cholesterol in the case group was higher as compared to the control group. Mean of HDL- cholesterol in the case group was significantly lower as compared to the control group ('*P*' < 0.05). Mean of BSL in the case group was significantly higher as compared to the control group ('*P*' = 0.01). Mean of E/A ratio in the case group was significantly lower as compared to the control group ('*P*' = 0.02). Mean of E/e' ratio in the case group was significantly higher as compared to the control group ('*P*' < 0.001). Total 69 (54.33%) subjects from the case group had diastolic dysfunction; and, 11 (11%) amongst control group had the diastolic dysfunction. Diastolic dysfunction in type -2 DM subjects was significantly higher as compared to the control group ('*P*' < 0.001) with odds ratio of 2.18 [Table 1].

Relation of diastolic dysfunction with various dependent variables in type 2 diabetes subjects

Out of 89 subjects with HbA1c < 7.5%, 39 (42.82%) had diastolic dysfunction; and, out of 38 subjects with HbA1c > 7.5%, 31 (81.57%) had diastolic dysfunction. Subjects with HBA1c > 7.5% had more prevalence of

Table 1: Mean and standard deviation of numerical parameters of the patients in the study

Variables	Case population		Control population		'P' value
	Male (n=69)	Female (n=58)	Male (n=56)	Female (n=44)	
Age (years)	51 ± 9	49 ± 10	± 49 ± 7	48 ± 8	NS
Duration of diabetes (years)	11 ± 5	10 ± 4	-	-	-
Body mass index (Kg/m²)	27.6 ± 2.2	26 ± 2.5	23.5 ± 1.6	23.7 ± 1.3	< 0.05
Waist circumference (WC - cm)	92 ± 8	78 ± 7	77 ± 3.9	74 ± 6	0.02
Waist to hip ratio (WHR)	0.92 ± 0.17	0.84 ± 0.19	0.75 ± 0.19	0.75 ± 0.15	< 0.02
Total cholesterol	213 ± 24.4	223 ± 25	147 ± 8.7	135 ± 15	NS
Triglyceride	208 ± 25.7	198 ± 23.5	135 ± 7.9	129 ± 9	0.032
LDL- cholesterol	134 ± 13	145 ± 10	96 ± 13	106 ± 7.8	NS
HDL- cholesterol	39 ± 16	38.5 ± 13	49.5 ± 7.8	43 ± 5.7	< 0.05
Blood sugar level	145 ± 16.7	139 ± 23.5	85 ± 7.8	85 ± 5.0	0.01
HbA1c (%)	8.3 ± 1.91	8.1 ± 1.3	-	-	-
E/A ratio (PW)	0.79 ± 0.13	0.81 ± 0.11	1.21 ± 0.22	1.19 ± 0.11	0.02
E/e' ratio (TDI)	18.6 ± 3.5	18.3 ± 3.2	8.8 ± 1.24	8.67 ± 2.16	< 0.001
IVRT (ms)	79 ± 9	81 ± 7	95 ± 14.8	97 ± 16	NS
DT (ms)	168 ± 23	172 ± 19	159 ± 23.8	139 ± 11	< 0.002
EF (%)	54 ± 3	55 ± 2	62 ± 3	49 ± 3	NS
Diastolic dysfunction	39 (56.52%)	30 (51.72%)	6 (10.71%)	5 (11.36%)	< 0.001

LDL = Low density lipoprotein; HDL = High density lipoprotein; HbA1c = glycosylated haemoglobin; E = early diastolic (E-wave: cm/s) velocity; A = atrial (A-wave: cm/s) velocity; E/e' ratio = mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') ratio; IVRT = isovolemetric relaxation time; DT = deceleration time; EF = Ejection fraction; PW = Pulse Wave Doppler; TDI = tissue Doppler imaging; NS = not significant

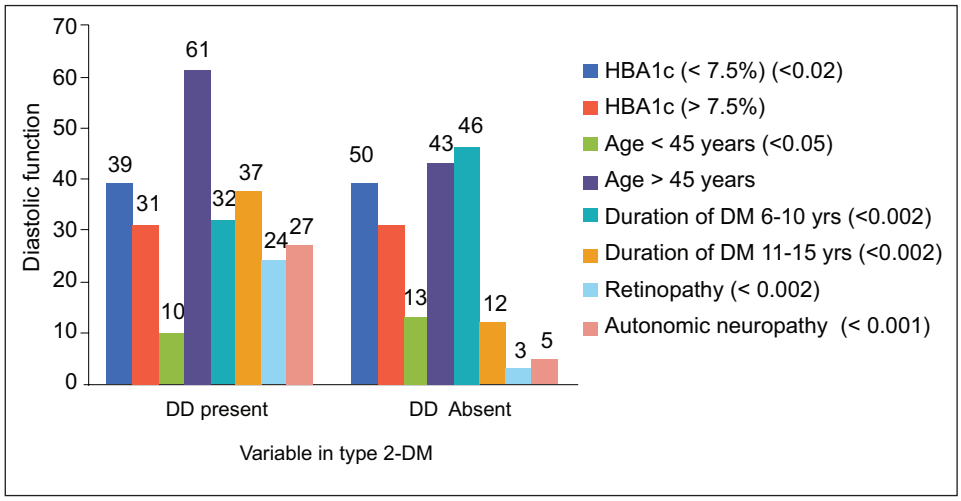

Figure 2: Relation of diastolic dysfunction with various dependent variables in type 2 DM

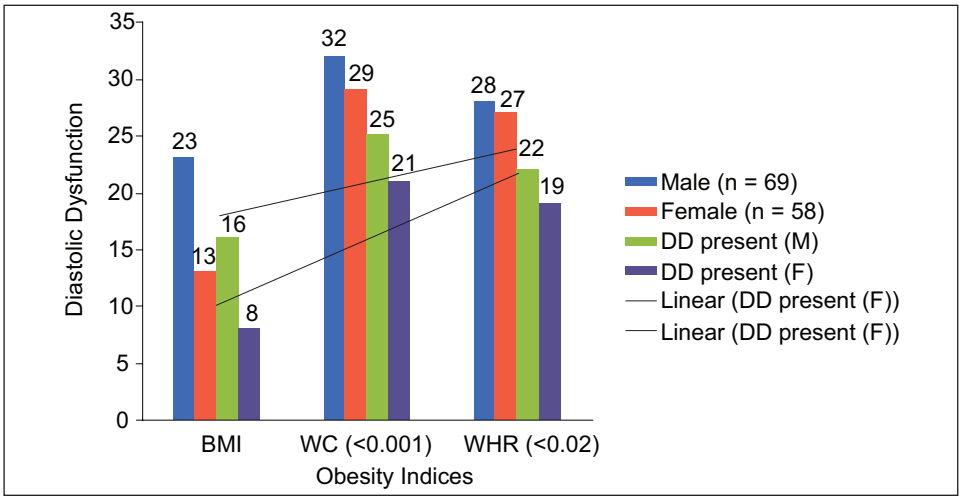

Figure 3: Relation of diastolic dysfunction with obesity indices in type 2 DM

diastolic dysfunction, than subjects with HBA1c < 7.5% (‘*P*’ < 0.02). Out of 23 subjects with age < 45 years, 10 (43.47%) had diastolic dysfunction; and, out of 104 subjects with age > 45 years, 61 (58.65%) had diastolic dysfunction. Diastolic dysfunction was significantly high in patients with age > 45 years, compared to age < 45 years (‘*P*’ < 0.05). Total 78 (61.41%) subjects were with the duration of diabetes between 6-10 years, and 49 (38.58%) were between 11-15 years. Out of 78 (61.41%) subjects with duration of diabetes between 6-10 years, 32 (41.02%) had diastolic dysfunction. Out of 49 (38.58%) subjects with duration of diabetes between 11-15 years, 37 (75.51%) had diastolic dysfunction. Comparing duration of diabetes of 6 to 10 years and 11 to 15 years with diastolic dysfunction, patients with 11 to 15 years duration of diabetes had more prevalence of diastolic dysfunction (‘*P*’ < 0.02). Total 27 (21.25%) subjects had retinopathy, of which 24 (88.88%) had diastolic dysfunction (‘*P*’ < 0.002). Out of 32 (25.19%) subjects with postural hypotension, 27 (84.37%) had diastolic dysfunction (‘*P*’ = 0.001) [Table 2 and Figure 2].

Relation of diastolic dysfunction with obesity indices

Total 23 (33.33%) male and 13 (24.41%) female patients had high BMI; and, out of them 16 (69.56%) male and 8 (61.53%) female had diastolic dysfunction. Total 32 (46.37%) male and 29 (50%) female patients had high WC; and, out of them, 25 (78.12%) male and 21 (72.41%) female patients had diastolic dysfunction (‘*P*’ =0.001). Total 28 (40.57%) male and 27 (46.55%) female patients had high WHR; and, out of them, 22 (78.57%) male and 19 (81.48%) female had diastolic dysfunction (‘*P*’ = < 0.02). Subjects with high WC and high WHR had statistically significant diastolic dysfunction [Table 3 and Figure 3].

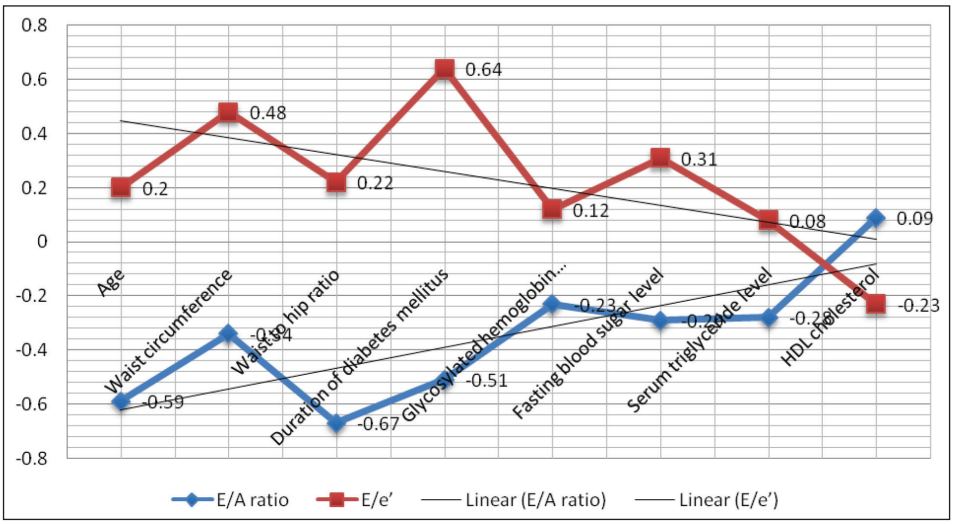

Figure 4: Correlation of parameters of diastolic dysfunction with biochemical profile and obesity indices in type 2 DM

Table 2: Relation of diastolic dysfunction with various dependent variables in type 2 diabetes mellitus subjects in the study

Variables	Diastolic dysfunction present	Diastolic dysfunction absent	Total (%)	'*P*' value
HBA1c (< 7.5%) (n = 89)	39 (42.82)	50	70.07	< 0.02
HBA1c (> 7.5%) (n = 38)	31 (81.57)	7	29.92	
Age < 45 years (n = 23)	10 (43.47)	13	18.11	< 0.05
Age > 45 years (n = 104)	61 (58.65)	43	81.88	
Duration of diabetes mellitus 6-10 years (n = 78)	32 (41.02)	46	61.41	< 0.002
Duration of diabetes mellitus 11- 15 years (n = 49)	37 (75.51)	12	38.58	
Retinopathy present (n = 27)	24 (88.88)	3	21.25	< 0.002
Autonomic neuropathy (postural hypotension) (n = 32)	27 (84.37)	5	25.19	< 0.001

Where, HbA1c = glycosylated haemoglobin, Figures given in parenthesis are in percentage

Table 3: Relation of diastolic dysfunction with obesity indices of the patients in the study

Obesity indices	Male (n = 69)	Female (n = 58)	Diastolic dysfunction present		'*P*' value
			Male	Female	
Body mass index (Kg/m^2)	23 (33.33)	13 (24.41)	16 (69.56)	8 (61.53)	NS
Waist circumference (cm)	32 (46.37)	29 (50)	25 (78.12)	21 (72.41)	< 0.001
Waist to hip ratio	28 (40.57)	27 (46.55)	22 (78.57)	19 (81.48)	< 0.02

NS = not significant, Figures given in parenthesis are in percentage

Correlation of echocardiography parameters of diastolic dysfunction with obesity indices, duration of diabetes mellitus and biochemical profile

Age was negatively correlated with E/A ratio (-0.59); and, positively with E/e' ratio (+0.2). WC was negatively correlated with E/A ratio (-0.34); and, positively with E/e' ratio (+0.48). WHR was negatively correlated with E/A ratio (-0.67); and, positively with E/e' ratio (+0.22). Duration of diabetes was negatively correlated with E/A ratio (-0.51); and, positively with E/e' ratio (+0.64). GlycatedHbA1c level was negatively correlated with E/A ratio (-0.23); and, positively with E/e' ratio (+0.12). Fasting BSL was negatively correlated with E/A ratio (-0.29); and, positively with E/e' ratio (+0.31). Serum TG level was negatively correlated with E/A ratio (-0.28); and, positively with E/e' ratio (+0.08). Serum HDL cholesterol levels were negatively correlated with E/e' ratio (-0.23); and, positively with E/A ratio (+0.09) [Table 4 and Figure 4]. By multivariate analysis of covariance (MACOVA) and Cox's proportional hazard regression analysis, (after adjustment for age, sex) it was determined that the diastolic dysfunction (measured by E/A ratio and E/e' ratio), was significantly associated with longer duration of DM, HbA1c, serum

Table 4: Correlation of parameters of diastolic dysfunction with biochemical profile and obesity indices of the patients in the study

Variables	Echocardiographic parameters of diastolic dysfunction	
	E/A ratio	E/e'
Age	-0.59	+0.20
Waist circumference	-0.34	+0.48
Waist to hip ratio	-0.67	+0.22
Duration of diabetes mellitus	-0.51	+0.64
Glycosylated hemoglobin (HbA1c)	-0.23	+0.12
Fasting blood sugar level	-0.29	+0.31
Serum triglyceride level	-0.28	+0.08
HDL cholesterol	+0.09	-0.23

HDL = High density lipoprotein

TG levels, WC and WHR, retinopathy and autonomic neuropathy ('*P*' < 0.002).

DISCUSSION

Our current findings demonstrate that pre-clinical diastolic dysfunction is common in patients with DM. Pre-clinical diastolic dysfunction has been broadly defined as diastolic dysfunction in patients with normal systolic function, and no symptoms of heart failure (HF). Present study reveals high burden of diastolic dysfunction in cohort of type 2 DM population. In the present prospective case control study, 127 subjects with type-2 DM as cases; and, 100 healthy subjects as controls, were included. Overall mean of obesity indices like BMI, WC and WHR were significantly higher in subjects with type 2 DM compared to the control group. Mean of fasting BSL, HbA1c, serum TC, serum TG and LDL cholesterol in case group was significantly higher as compared to the control group. The mean of HDL cholesterol was lower in the case group as compared to the control group. Total 69 (54.33%) subjects from the case group had diastolic dysfunction, and 11 (11%) amongst control group showed the diastolic dysfunction. Diastolic dysfunction in type -2 diabetes subjects was significantly higher as compared to the control group ('*P*'< 0.001). E/A ratio negatively correlated with age, WC, WHR, duration of DM, HbA1c level, fasting BSL, and serum TG levels; and, positively correlated with serum HDL- cholesterol. E/e' ratio positively correlated with age, WC, WHR, duration of DM, HbA1c level, fasting BSL, and serum TG levels; and, negatively correlated with serum HDL- cholesterol. Duration of diabetes mellitus of 11 to 15 years had more prevalence of diastolic dysfunction ('*P*' < 0.02). Subjects with high WC and high WHR had statistically significant diastolic dysfunction. Subjects with HBA1c > 7.5% had more prevalence of diastolic dysfunction than subjects with HBA1c < 7.5% ('*P*' < 0.02). Diastolic dysfunction was significantly high in patient with age > 45 years compared to age < 45 years ('*P*' < 0.05). Diastolic dysfunction was present in majority of the subjects with autonomic neuropathy and retinopathy [Figure 2].

We compared our results with various studies. Soldatos *et al.*[8] in their case control study of 55 individuals with type -2 DM found that Diastolic dysfunction, present in a significant proportion of population with Type 2 DM. Similarly, in the present study, 54.33% of subjects from the case group had diastolic dysfunction and 11 (11%) amongst control group had the diastolic dysfunction (*P* < 0.001). Sacre *et al.*[9] found that there was an independent association between global cardiac autonomic neuropathy (CAN) and left ventricular (LV) dysfunction in patients with type 2 DM. These findings are comparable to our study, where diastolic dysfunction was present in majority of the subjects with autonomic neuropathy documented by postural hypotension. Out of the 32 (25.19%) subjects with postural hypotension; 27 (84.37%) had diastolic dysfunction ('*P*'= 0.001). Van Heerebeek *et al.*[10] in their study of 36 type -2 DM patients stated that, the cardiomyocyte resting tension is more important when LVEF is normal. Excessive diastolic left ventricular stiffness is an important contributor to heart failure in subjects with DM. Diabetes is presumed to increase stiffness through myocardial deposition of collagen and advanced glycation end products. Similarly, in the present study, 54.33% of subjects from the case group had diastolic dysfunction with normal LVEF.

Masugata *et al.*[11] in their case control study of 77 normotensive patients found that, the cardiac diastolic dysfunction without LV systolic dysfunction in patients with well-controlled type 2 DM is related neither to hypertension nor LV hypertrophy, but rather to aging and the duration of type 2 DM. Similarly, in the present study, total 54.33% of subjects from case group without hypertension and CAD had diastolic dysfunction with normal LV systolic function. Annonu *et al.*[12] in their case control study of 66 subjects found that there was an inverse correlation between the duration of diabetes and E/A ratio (r = -0.4, '*P*' <.005). E/A ratio < 1 was associated with a higher prevalence of retinopathy (49% versus 20%, '*P*' =0.01) and abnormal blood pressure response to standing (29% versus 4%, '*P*' <.005). LV systolic and diastolic abnormalities are correlated with the duration of diabetes and with other diabetic microangiopathies, such as diabetic retinopathy and neuropathy. These results are comparable to the present study, where diastolic dysfunction was present in majority of the subjects with autonomic neuropathy and retinopathy with '*P*' = 0.001 and

0.002, respectively. Duration of diabetes mellitus of 11 to 15 years had more prevalence of diastolic dysfunction as compared to the 6 -10 years group (‘*P*’ < 0.02).

Mishra *et al.*[7] in their case control study of 71 subjects with type 2 DM found that asymptomatic diabetic patients have reduced LV systolic and diastolic function as compared with healthy subjects. LV systolic and diastolic abnormalities are correlated with the duration of diabetes and with diabetic microangiopathies, like retinopathy and neuropathy. These results are comparable with present study, where 54.33% of type -2 DM population had diastolic dysfunction and the DM was correlated to advancing age, increasing duration of DM, postural hypotension, retinopathy, high obesity indices, HbA1c >7.5% and dyslipidemia.

From *et al.*[2] in their study of 484 subjects between 1996 to 2007 year found that a duration of diabetes ≥ 4 years was independently associated with LV diastolic dysfunction (E/e’ >15) with odds ratio 1.91. Doppler imaging velocity of the medial mitral annulus during passive filling (E/e’) ratio in diabetic patients is associated with the subsequent development of HF and increased mortality. Similarly in our study, duration of diabetes 11-15 yrs had more prevalence of diastolic dysfunction as compared to the 6-10 year group (‘*P*’ < 0.02). Sohail *et al.*[13] in their study of 212 diabetic population found that 30.76% patients with type-2 DM had diastolic dysfunction. The LV diastolic dysfunction is much more prevalent in patients with type-2 diabetes mellitus and LV diastolic dysfunction is an early marker of diabetic cardiomyopathy. In our study, prevalence of type 2 DM was 54.33%. Exiara *et al.*[14] in their study of 114 subjects stated that the prevalence of LV diastolic dysfunction in normotensive, asymptomatic and well-controlled DM type 2 patients is high, and increases with age. A total of 63.2% patients had diastolic dysfunction in their study compared to our prevalence of 54.33%. Diamant *et al.*[15] 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*’ < 0.02). These findings are similar to our results. Bonito, *et al.*[16] stated that, an impairment of LV diastolic function occurs early in the natural history of type-2 DM, and is related to clinical evidence of microangiopathic complications. Aaron *et al.*[17] in 1,760 diabetic patients found that, 411 (23%) patients had diastolic dysfunction and diabetic patients with diastolic dysfunction had a significantly higher mortality rate compared with those without diastolic dysfunction. An increase in the TDI velocity of the medial mitral annulus during passive filling (E/e’) ratio in diabetic patients is associated with the subsequent development of HF. These findings are comparable with our study.

Boyer *et al.*[18] stated that the prevalence of LV diastolic dysfunction in asymptomatic, normotensive patients with type 2 diabetes disease is high. Diastolic dysfunction was found in 75% subjects. They also found that, TDI detected diastolic dysfunction more often than any other echocardiographic parameter. In our study, prevalence of diastolic dysfunction was 54.33%. Poulsen *et al.*[19] in their prospective observational study of 305 patients with type 2 DM found that, abnormal LV filling is closely associated with abnormal myocardial perfusion on myocardial perfusion scintigraphy. Takeda *et al.*[20] in their population of 544 consecutive Japanese DM patients with ejection fraction ≥ 50%, found that diastolic dysfunction (impaired relaxation) plays a crucial role in the induction of HF with normal systolic function in DM patients, regardless of the severity of DM and renal dysfunction. These findings are partially comparable with our study where diastolic dysfunction was more prevalent with HbA1c > 7.5.

Poanta *et al.*[21] in their study of 58 subjects found that, cardiac autonomic neuropathy was associated with LV diastolic dysfunction in patients with type 2 DM, but without clinical manifestation of the heart disease. Similarly Poirier *et al.*[22] stated that, diastolic dysfunction and CAN (cardiac autonomic neuropathy) are associated in patients with otherwise uncomplicated well-controlled type 2 DM. Hameedullah *et al.*[23] in their study population of 60 patients with type 2 DM found that there was strong correlation between HbA1c level and diastolic indices (‘*P*’ < 0.05). Diastolic dysfunction was more frequent in poorly controlled diabetic patients, and its severity is correlated with glycaemic control. Similarly in our study, HbA1c > 7.5 % had higher prevalence of diastolic dysfunction compared to HbA1c < 7.5%. C.M. Schannwell *et al.*[24] in their study population of 87 subjects concluded that even young subjects with diabetes mellitus suffer from a diastolic dysfunction, while systolic ventricular function is normal. From the above discussion and comparison of present study findings with various studies, we found that there was high prevalence of diastolic dysfunction in subjects with asymptomatic type 2 DM, and it was correlated with age, duration of diabetes, HbA1c, dyslipidemia, autonomic neuropathy, retinopathy and various obesity indices.

Our study demonstrates that the incidence of pre-clinical diastolic dysfunction is high in type 2 DM subjects. Furthermore, we found that there is a direct correlation between the duration of DM and diastolic dysfunction; and, that significant diastolic dysfunction occurs > 5 years after the onset of DM independent of coronary disease or hypertension. Therefore, future studies should be conducted to test the hypothesis that screening and aggressive management of diabetic patients with pre-clinical diastolic dysfunction may delay the progression to heart failure.

Study limitations

The study was conducted on Indian general population. Thus, these findings need to be examined in different racial and ethnic groups. Homeostatic model assessment (HOMA) index for investigating fasting insulin concentration is not calculated in the present study due to resources limitations. HOMA index is considered as an independent factor for diastolic dysfunction.

CONCLUSIONS

Overall prevalence of diastolic dysfunction was 54.33% in asymptomatic type 2 DM subjects in the present study. Asymptomatic type 2 DM had significantly high prevalence of diastolic dysfunction as compared to healthy subjects. LV diastolic abnormalities were correlated with the duration of diabetes and with diabetic microangiopathies, like retinopathy and autonomic neuropathy. In the present study, DM was the strongest independent factor for LV diastolic dysfunction. This study confirms that asymptomatic diastolic dysfunction is more prevalent in subjects with type 2-DM. There was a significant correlation of LV diastolic dysfunction with the duration of diabetes, glycatedHbA1c levels, obesity indices (WC and WHR), retinopathy, autonomic neuropathy and hypertriglyceridemia, as determined by multivariate analysis. We conclude that early diagnosis and institution of treatment for diastolic dysfunction in the form of ACE inhibitors, angiotensin II receptor blockers, aldosterone antagonists, diuretics etc. depending on clinical scenario, will reduce the morbidity and improve the outcome of diastolic HF. In order to improve the current poor prognosis in subjects with DM, the treatment of diastolic HF must be optimised. Subjects with DM type 2 should be screened for sub clinical diastolic dysfunction by echocardiography.

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