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A Study of Left Ventricular Diastolic Dysfunction as an Early Predictor of Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Diabetes Mellitus (DM) is a disease with multi-system complications. Left ventricular diastolic dysfunction (LVDD) is an early stage of diabetic cardiomyopathy that can develop to heart failure. It has no clinical symptoms and can be easily diagnosed with echocardiography.

Objectives: The study aims to evaluate the LVDD in Type-2 DM with no symptoms of cardiovascular disease and its association with glycaemic control(HbA1c), DM duration, and microangiopathy.

Methods: The cross-sectional hospital-based study included 100 asymptomatic patients with type2 DM without evidence of cardiovascular involvement were studied. LVDD was evaluated by doppler

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echocardiography, which included E/A ratio, assessed in relation with age, sex, duration of diabetes and HbA1c level.

Results:LVDD was present in 57 %of the type 2 DM patientswith males accounting for the majority of cases (63.2%). Diastolic dysfunction was more common in patients on oral hypoglycaemic agents (78%), insulin (2%) and/or both (19%).There was a linear progression of diastolic dysfunction with the increase age group (P = 0.001).LVDD was significantly associated with uncontrolled diabetes as measured by HbA1c levels with higher number patients among HbA1c >8.5 (71.9%; P = 0.001) and a longer duration of DM with highest among 6 -10 years (38.6%; P = 0.001)

Conclusion: Overall, the prevalence of diastolic dysfunction was 57% in asymptomatic type 2 DM subjects. Our study indicates that myocardial damage in patients with diabetes affect diastole function before systolic function in asymptomatic diabetes patients.Doppler Echocardiography identifies large percentage of diabetes subjects before abnormalities are detected with clinical examination and ECG.

Keywords: diabetes mellitus; diastolic dysfunction; echocardiography; glycosylated haemoglobin; heart failure

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia.[1] According to the Diabetes Atlas 2017, the India's diabetes population is currently about 72.9 million people and is expected to grow to 134.3 million by 2045 unless immediate preventive measures are adopted.[2]Although the prevalence of microvascular complications of diabetes like retinopathy and nephropathy are lower in Indians, premature coronary artery disease is considerably greatercompared to other ethnic groups.[3] However, heart failure was more common in diabetes due to diabetic cardiomyopathy.[4] The Framingham heart study revealed a marked increase in congestive heart failure, coronary artery disease, and myocardial Infarction in diabetic patients.[4]

Left ventricular diastolic dysfunction (LVDD) isan initial preclinical sign of diabetic cardiomyopathy priorto changes in systolic function.[5] The diastolic abnormalities in diabetic patients without diabetic complications of cardiovascular system, is the earliest and specific functional abnormality in diabetic cardiomyopathy and can affect patients who are free of macrovascular complications and newly diagnosed DM or even in those with a disease duration of less than a year.[6]Hence, earlier detection of diastolic dysfunction in diabetic patients could assist to prevent or considerably postpone the onset of CHF.

Doppler recordings of transmitral and pulmonary venous flow velocities have traditionally been used to assess LVDD and filling pressure.[7]E/e' (the early passive transmitral inflow velocity [E]) to pulsed tissue doppler velocity of the septal mitral annulus during passive filling [e'] ratio has appeared to independently predict the heart failure and mortality.[8,9] in DM. Several previous research investigationshave shown that the patients with DM have LVDD[10–12]; however, there is dearth in Indian literature. Therefore, this study was conducted to evaluate the Left ventricular diastolic dysfunction in Type-2 DM who have no symptoms of cardiovascular disease and its association with glycaemic control, duration, microangiopathy.

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Materials and Methods

Study design and settings

Patients with a history of type 2 diabetes who visited our tertiary care center's Department of Medicine between November 2016 and September 2018 were enrolled in the prospective cross-sectional hospital-based study. Simple random sampling technique was applied to include the study patients.Patients aged >18 years of diabetes mellitus (either on treatment or newlydiagnosed) were included.Patients with type 2DM with other cardiac diseases (valvular heart disease, congestive heart failure, ischemic heart disease, cardiomyopathy, hypertension) and neuro-psychiatric disorder were excluded. Institutional ethical committee was sought before the including the patients in the study. Informed consent was taken from the patients prior to their enrolment.All the included patients were evaluated for the LVDD.

Evaluations

All the patients underwent clinicaland relevant laboratory investigationssuch as ECG, FBS, PPBS, urea, creatinine, glycosylated haemoglobin (HbA1c), urine albumin, fasting lipid profile. Fundus examination and echocardiography were also performed.For each patient, a Doppler Echocardiographywas performed, and three to four cardiac cycles were analysed to determine the optimal phase for a better outcome. Doppler study was used to examine the following indices: E-peak velocity of early mitral flow, A-peak velocity of late mitral flow, and E/A ratio. Ejection fraction was also determined in all the patients.The data was recorded using a pre-tested proforma.

Statistical analysis

SPSS 18.0, and R ver.3.2.2 were used for the analysis of the data. Continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in number (%). Student t test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups, Nonparametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small. Significance is assessed at 5 % level of significance.

Results

A total of 100 patients with type 2 DM were studied. Mean age of the patients was 52.11±9.98 years with a male dominance (63%). The study group's average age of diabetes onset was 44.45 years, with an average duration of 7.7 years.Three-fourths (78%) of the patients were on Oral hypoglycaemic agents and 54% of them used them on regular basis. Table 1 list other baseline characteristics of the study cohort.

Table 1: Baseline demographics, clinical, and biochemical investigations of the study population

Variables	**N = 100**
Age (years)	52.11±9.98
Gender	
Female	37 (37%)
Male	63 (63%)
Duration of DM (years)	7.72±5.94
BMI (Kg/m2)	26.14±2.34
Age of onset (years)	44.45±7.20
Treatment of OHA	
NA	1 (1%)
Oral hypoglycaemic agents	78 (78%)
Insulin	2 (2%)

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Both	19 (19%)
Treatment	
NA	3 (3%)
Regular	54 (54%)
Irregular	43 (43%)
Blood pressure	
Systolic (mmHg)	120.82±6.46
Diastolic (mmHg)	77.62±4.58
FBS	199.13±66.89
PPBS	276.29±78.63
HbA1c%	9.08±1.84
Urine Albumin	
Nil	78 (78%)
Traces	13 (13%)
1+	6 (6%)
2+	3 (3%)
Urine sugar	
Nil	65 (65%)
0.50	3 (3%)
1.50	2 (2%)
1%	5 (5%)
2%	25 (25%)
Blood Urea (mg/dl)	31.74±12.97
Serum Creatinine (mg/dl)	0.90±0.32
Total Cholesterol (mg/dl)	202.90±26.62

Data are expressed in N (%) and mean ± SD

Clinically, none of the diabetic patients showed cardiovascular system abnormalities, just one had peripheral neuropathy, and 10% had diabetic retinopathy. In84% of the patients had EV max values between 50 and 100, while 90% had AV max values between 50 to 100. More than half of the patients had E/A ratio < 0.8 and 72% EF between 60 to 70% in (Table 2).All the patients' ECGs were within normal limits.

Table 2:Baseline Cardiovascular Characteristics of the study population

Variables	N = 100 (%)
CVS examination	
NAD	100 (100%)
Abnormal	0 (0.00)
Peripheral neuropathy	
No	99 (99%)
Yes	1 (1.00%)
Fundus	
NAD	90 (90%)
Diabetic retinopathy	10 (10%)
EV Max	

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<50	13 (13%)
50-100	84 (84%)
>100	3 (3%)
AV Max	
<50	0 (0)
50-100	90 (90%)
>100	10 (10%)
E/e Ratio	
<0.8	57 (74%)
>0.8	43 (22%)
EF%	
<60	25 (25%)
60-70	72 (72%)
>70	3 (3%)

CVS, Cardiovascular system; NAD, no abnormality detected; EF, Ejection fraction; E/e' (the early passive transmitral inflow velocity [E]) to pulsed tissue doppler velocity of the septal mitral annulus during passive filling [e'] ratio.

Table 3 shows association between clinical variables and the incidence of LVDD in DM patients. Diastolic dysfunction of the left ventricle was found in57% of the study population. Out of 57 LVDD patients, most of them were in the age range of 51-60 years old (22%; *P* = 0.001) with a male predominance (63.2%; *P* = 0.970). The majority of LVDD patients (38.6%; *P* = 0.001) had DM for 6-10 years and had HbA1c >8.5 (71.9 percent; *P* = 0.001) and 95% of LVDD patients had no abnormalities on fundus examination (*P* = 0.18).

Table 3: Association of clinical variables with incidence of LVDD in DM patients

Variables	**LVDD (N = 100)**		**P-value**
	No (n = 43)	**Yes (n = 57)**	
Age			
30 – 40	11 (25.6%)	4 (7%)	0.001
41 – 50	16 (37.2%)	13 (13%)	
51 – 60	14 (32.6%)	22 (22%)	
61 – 70	1 (2.3%)	17 (17%)	
> 70	1 (2.3%)	1 (1%)	
Gender			
Female	16 (37.2%)	21 (36.8%)	0.970
Male	27 (62. 8%)	36 (63.2%)	
Duration of DM			
0 – 5	33 (77.1%)	13 (22.9%)	0.001
6 – 10	6 (14%)	22 (38.6%)	
11 – 15	3 (37.2%)	12 (21.1%)	
16 – 20	0 (0)	7 (12.3%)	
> 20	1 (1%)	3(5.3%)	
HbA1c			
<6.5	1 (%)	0 (0)	0.001

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6.5 – 8.5	29 (67.4%)	16 (28.1%)	
> 8.5	13 (30.2%)	41 (71.9%)	
Fundus			
NAD	41 (95.4%)	49 (95.4%)	0.18
DR	2 (4.6%)	8 (4.6%)	

NAD, no abnormality detected; DR, diabetic retinopathy

Discussion

Due to cardio-metabolic consequences of diabetes, a thorough assessment of cardiovascular function in diabetic patients is critical, and some changes can be noticed even in individuals with gestational diabetes.[13] Diabetes changes the structure and function of the heart even if there is no atherosclerotic disease.[13] Doppler echocardiography is a noninvasive diagnostic technique that delivers accurate information on diastolic and systolic function at various stages.[13]Hence, in our study, E/e′ ratio, a robust predictor of severe cardiovascular events in patients with type 2 diabetes, was used to quantify LVDD. A total of 100 asymptomatic type 2 diabetic patients were studied for the incidence of LVDD and its association to age, gender, duration of DM, HbA1C, and microagiopathy, and it was found that age, duration of DM, HbA1C are the significant contributing factors.The prevalence (57%) of LVDD was almost comparable to other studies, which ranged from 54% to 68%.[12,14,15] While the prevalence of LVDD was to be higher in older group patients',particularly those above the age of 50.

Mean age of the present study was almost identical to other previous studies with the majority being males. Mean duration of diabetes was 7.72 ± 5.94 years. The majority of the individuals in this study had diabetes for less than 5 years and were between the ages of 51 and 60, which was consistent with prior studies[12,14,15].This was because as the duration of diabetes rose, other associated co-morbid conditions such as hypertension and IHD were more prevalent, which were removed from our analysis, resulting in a lower number of patients with diabetes for more than 15 years and above the age of 70.

In our study, 99% of the DM patients were on medication i.e., OHAs or insulin or on both. In a study conducted by Patil et al., diastolic dysfunction was present in 29/43 cases (67.44% of 43) who were solely on OHA and 2/3 cases who on subcutaneous insulin injections. While 4cases who were on both OHAs as well as insulin injections had diastolic dysfunction.[14]This resultindicates diastolic function is mostly affected in patients who were taking diabetic treatment. Furthermore, diastolic dysfunction was more prevalent in those who were on combined modalities of therapy i.e., both insulin and OHAs.

Ejection fraction being the most sensitive parameter for LV systolic function, the mean value was 62.37±4.24 and was in normal in all patients in our study. WhileE/e ratio being the most sensitive and specific predictor showed 57% of the DM patients had E/e ratio of < 0.8 as compared to 43%had > 0.8. This indicates that E/e ratio is a reliable predictor to forecast cardiovascular events. A study by Blomstrand et al., shown that patients with an *E*/*e′* ratio >15 are at three times higher risk of having myocardial infarction or stroke[9]or even might lead to heart failure.[8]

Previous studied demonstrated LVDD was found in patients who were free of cardiovascular disease and had diabetes for 5 years.[16]or 7 years.[17] Patil et al. studied 127 subjects who had type 2 diabetes for more than 5 years reported that diastolic dysfunction was more common in patients with DM for longer periods of time (11 to 15 years).[12]Hence, patients with DM from longer duration need to be cautiously monitored to detect the risk of diastolic dysfunction in future. Furthermore, the presence of LVDD was found to be independent of the DM patients' age and gender.[17] However, in our study, there was a linear progression of diastolic dysfunction with the increase age group. Another study by From *et al*. demonstrated that diastolic dysfunction was significantly associated with age, female gender, BMI, and diabetes duration.[8]

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In our study, the incidence of diastolic dysfunction increased gradually with the rise in HbA1c levels. Patil et al. study conducted in 50 normotensive diabetic patients reported diastolic dysfunction in just 3/16 patients with a HbA1c of <7 and in all the cases with HbA1c levels >10.[14] This indicates that uncontrolled diabetes or elevated HbA1c might indicates the risk of diastolic dysfunction in patients with DM and independent of the *E*/*e′* ratio. While in another study by Romano et al., reported no significant in HbA1c in patients with and without LVDD.[17] It was also reported that for every 1% increase in HbA1c is associated with 18% increase in the risk of cardiovascular events in patients with type 2 DM.[18]

We conclude that diabetics before they develop cardiac symptoms, patient need to be followed up on a regular basis to assess the cardiac function. Hence, early diagnosis and therapeutic interventions in DM might reduce the risk of heart disease progression and prevent the heart failure.There are some potential limitations to our research that should be mentioned. The research was carried out on the general population of India. As a result, these findings must be investigated in various racial and ethnic groups. Our study is not a Case-Control study, which would allow us to compare normal and diabetes participants more effectively. Due to a lack of resources, the homeostatic model assessment (HOMA) index for examining fasting insulin concentration was not calculated in our study. The HOMA index was found to be a significant predictor of diastolic dysfunction. Our study did not examine left atrial size, which is critical because left atrial size varies by gender and is lower in females than in males.

Conclusion

Overall,the prevalence of diastolic dysfunction was 57% in asymptomatic type 2 DM subjects. The findings in our study indicates that myocardial damage in patients with diabetes affect diastole function before systolic functionin asymptomatic diabetes patients. E/A ratio is significantly altered in diabetic patients with diastolic dysfunction, and it is associated with age, duration of diabetes, and glycemic control. Doppler Echocardiography is a valuable simple non-invasive method to detect LVDD which is more prevalent in diabetes which shows linear progression. It identifies large percentage of diabetes subjects before abnormalities are detected with clinical examination and ECG.

Acknowledgments

All the authors have contributed equally to the development of manuscript

Conflicts of interest

None

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