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Echocardiographic evaluation of asymptomatic left ventricular diastolic dysfunction in type 2 diabetes mellitus

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Abstract: *Background:* Diabetes is a chronic metabolic disorder and is a fast growing global epidemic with widespread physical, mental, social and economical consequences. The first stage of diabetic cardiomyopathy is represented by left ventricular diastolic dysfunction (LVDD) with preserved systolic function in an asymptomatic individual. *Objectives:* To determine the prevalence of asymptomatic LVDD in type 2 diabetes mellitus (DM) patients and to study the relationship between LVDD and age, duration of diabetes and glycemic control. *Methods:* This was a prospective case control and observational hospital-based study conducted on 200 subjects, 100 cases of type 2 DM aged 35-65 years with duration of diabetes more than 5 years and 100 age- and sex-matched controls without diabetes. Transthoracic 2D echocardiography (ECHO) was performed on all the subjects to detect the presence of LVDD. The data was compiled and tabulated to explore the association between DM and its various components with LVDD. Chi square test was used to test the significance of association. *Results:* LVDD was more prevalent in the study group patients as compared to controls (74% versus 18%). Presence of LVDD showed positive correlation with duration of diabetes, glycosylated hemoglobin (HbA1C) and presence of albuminuria, and negative correlation with estimated glomerular filtration rate (eGFR). *Conclusions:* LVDD is quite prevalent in type 2 DM as compared to general population and is a marker of evolving heart disease among diabetics. Presence of LVDD in diabetics increases with duration of disease, poor glycemic control, presence of albuminuria and worsening of GFR. Early diagnosis and treatment of LVDD in diabetic patients may reduce cardiovascular morbidity by preventing future development of heart failure in these patients.

Keywords: Left ventricular diastolic dysfunction, echocardiography, type 2 diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a worldwide health problem, afflicting millions in both developed and developing countries [1]. Its incidence is increasing worldwide and rapidly assuming epidemic proportions. India leads the world with highest number of diabetic subjects earning the dubious distinction of being the "diabetes capital of the world" [2].

Cardiovascular disease is a major cause of morbidity and mortality in patients with DM. Numerous mechanism such as microvascular disease, autonomic dysfunction, metabolic disorders and interstitial fibrosis, have been suggested as causative factor of diabetic cardiovascular disease [2-3]. The first stage of diabetic cardiomyopathy is represented by left ventricular diastolic dysfunction (LVDD) with preserved systolic function in an asymptomatic patient [4-8]. Diastolic dysfunction can affect diabetic patients who are free of macrovascular complications, even in those with disease duration of less than 1 year or those who are recently detected to have DM [9-10]. LVDD precedes changes in systolic function thus reinforcing the importance of early examination of ventricular function in individuals with diabetes. Left Ventricular mass in diabetic patients may also increase with HBA1c level [11-12]. The possible contribution of hyperinsulinemia and hyperglycemia to left ventricular mass have been suggested in normotensive diabetic patients [13]. Left ventricular hypertrophy further contributes to LVDD in DM.

Diastolic heart failure (DHF) is a well recognized entity and accounts for approximately half of the patients with a heart

failure symptom [14]. Patients with diastolic dysfunction have impaired quality of life because of deterioration in exercise capacity that limits the activity of daily living [15-16]. Due to widespread implications of presence of LVDD in DM, this study was undertaken to detect prevalence of LVDD in asymptomatic type 2 diabetic patients in comparison with general population and to assess association between LVDD and duration of DM, glycemic control and diabetic complications.

Material and Methods

It was a prospective case control observational study conducted in the department of Medicine of a tertiary care teaching hospital. A total of 200 subjects were included, 100 cases of type 2 DM aged 35-65 years with duration of diabetes more than 5 years and 100 age- and sex-matched healthy controls without diabetes. Permission was sought from the institutional ethics committee and written informed consent was taken from each subject before enrolling him/her for the study.

Inclusion criteria: Both males and females in the age group of 35-65 years having type 2 DM (according to American Diabetes Association criteria) with duration of diabetes more than 5 years and normal left ventricular systolic function (left ventricular ejection fraction, LVEF>55%).

Exclusion criteria: Subjects with age<35 or >65 years, evidence of coronary artery disease, hypertension, valvular heart disease, cor pulmonale, portal hypertension, volume overload due to any cause, LVEF<55%, left ventricular hypertrophy and pericardial effusion were excluded from the study.

All recruited subjects underwent detailed history, clinical examination and necessary investigations like complete blood count, liver function tests, renal function tests, serum electrolytes, urine complete examination, electrocardiography (ECG), chest X ray and echocardiography (ECHO). eGFR was calculated using Cockcroft-Gault Equation: eGFR=(140-age) x body weight / 72 x S.creatinine. Transthoracic 2D ECHO with pulse doppler evaluation of transmitral inflow, tissue doppler imaging and M mode ECHO was performed to minimize the errors in assessing the diastolic dysfunction. ECHO was performed by harmonic imaging mode by Alpha prosound 6-aloka echocardiogram and doppler machine (multi frequency probe) according to the standard protocol. Pulsed wave doppler (PWD)-derived transmitral inflow velocities were obtained in the apical 4-chamber view with the sample volume placed at the mitral valve leaflet tips. Measurement included the transmitral early diastolic (E wave) and atrial (A-wave) velocities to calculate E/A ratio. For tissue doppler imaging, the mitral annulus velocity was obtained with a 2 mm sample volume placed at the septal side of the mitral annulus. Diastolic dysfunction was detected according to the following criteria [17-18}:

- E/A RATIO<1 or >2
- DT<150 or >220 ms
- IVRT<60or >100 ms
- E/e'<15
- E'/A'<1.0

The data was compiled and tabulated to explore the association between DM and its various components with LVDD. Chi square test was used to test the significance of association.

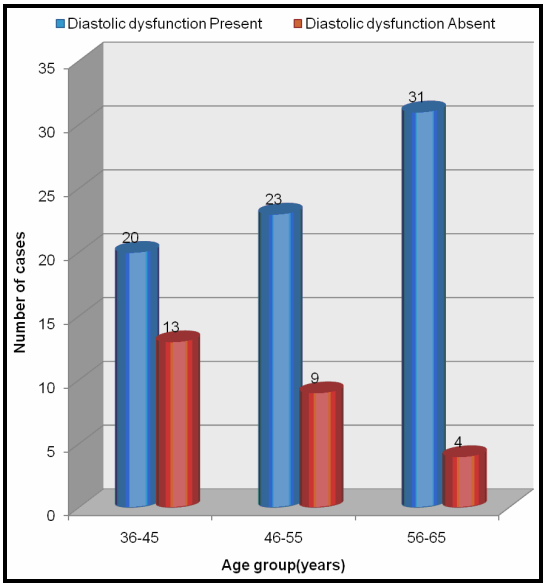
Results

Cases were divided into three age groups: 33 patients belonged to the age group of 36-45 years, 32 and 35 patients were in the 46-55 years and 56-65 years age groups respectively. Among controls, 33, 35 and 32 persons belonged to the age groups of 36-45 years, 46-55 years and 56-65 years respectively. Both cases and controls had 50 males and 50 females each. In the case group patients, 74 (74%) were found to have LVDD while only 18 (18%) of controls had LVDD. Among 74 patients having LVDD, 40 were females and 34 were males, however this finding was statistically insignificant (p=0.171). Among 18 controls having LVDD, 9 were males and 9 were females.

Prevalence of LVDD increased with advancing age among cases as well as controls. In the case group, LVDD was present in 20 patients (60.60%) out of 33 in the age group of 36-45 years, in 23 (71.90%) out of 32 patients in 46-55 years age group and in 31(88.60%) out of 35 patients in 56-65

years age group. It was statistically significant (p=0.03) (Figure 1). Among controls, LVDD was present in 1(3.10%) out of 33 in 36-45 years age group, in 3(8.60%) out of 35 in 46-55 years age group and 14(43.80%) out of 32 in 56-65 years age group. It was also statistically significant (p=0.001).

Fig-1: Diastolic dysfunction in different age groups in the study population



Sixty three patients in the case group had DM for 5-8 years. Out of these 63, 41 (65.10%) were found to have LVDD. Twenty nine patients had DM for 9-12 years, among whom 25 (86.20%) had LVDD. Patients with duration of DM >12 years were 8 in number and all (100%) had LVDD. Thus, prevalence of LVDD increased as the duration of DM increased (p=0.022) (Table 1)

Table-1: Distribution of diastolic dysfunction according to duration of diabetes

Duration of diabetes (Years)	Diastolic dysfunction		Total
	Present	Absent	
05-08	41 65.10%	22 34.90%	63 100.00%
09-12	25 86.20%	4 13.80%	29 100.00%
>12	8 100.00%	0 0.00%	8 100.00%
Total	74 74.00%	26 26.00%	100 100.00%

X^2 =7.662, df=2, p=0.022.Statistically significant.

Among cases, 33 patients had fasting blood sugar (FBS) <126 mg/dl. Of these, 19 (57.60%) were found to have LVDD. Remaining 67 patients had FBS >126 mg/dl; 55 (82.10%) of these had LVDD on ECHO. This was statistically significant (p=0.009). Out of 100 cases, 30 had HbA1c <6.5% and among these 30 patients, 16 (53.30%) had LVDD. Remaining 70 cases had HbA1c >6.5%. LVDD was detected in 58 of these 70 patients (i.e. in 82.90%). Thus, prevalence of LVDD increased with increase in HbA1c which was statistically significant (p=0.002) (Table 2).

Table-2: Distribution of diastolic dysfunction according to HbA1c levels in the study population

HbA1c	Diastolic dysfunction		Total
	Present	Absent	
<6.5%	16 53.30%	14 46.70%	30 100.00%
>6.5%	58 82.90%	12 17.10%	70 100.00%
Total	74 74.00%	26 26.00%	100 100.00%

X^2=9.514, df=1, p=0.002. Statistically significant.

Both cases and controls were tested for albuminuria. In the case group, 37 (37%) had albuminuria. Out of these 37 patients, 33 (89.2%) had LVDD. 41(65.1%) out of 63 patients without albuminuria had LVDD. This was statistically significant (p=0.008). Among the control group, 5 (5%) had albuminuria; 3 of these 5 patients (60%) had LVDD. Of 95 controls without albuminuria, LVDD was observed in only 15 (15.80%). This was also statistically significant (p=0.012).

eGFR was measured in all the cases using Cockcroft-Gault equation. Out of 100 patients in the study group, 37 (37%) had GFR>90 ml/min/1.73m^2 and 34 (34%) had GFR 60-89 ml/min/1.73m^2. Out of these 37 and 34 patients, 21 (56.80%) and 28 (82.40%) respectively had LVDD. 22 (22%) and 7 (7%) had GFR 30-59 ml/min/1.73m^2 and 15-29 ml/min/m^2 respectively and LVDD was observed in 18 (81.80%) out of these 22

patients and in all 7 (100%) patients having GFR between15-29 ml/min/m^2 respectively (Table 3). Table 4 compares the baseline characteristics between study and control groups.

Table-3: Distribution of diastolic dysfunction according to GFR in the study population

Stages of CKD	Diastolic dysfunction		Percentage
	Present	Absent	
>90 ml/min/1.73m^2 Stage 1	21 56.80%	16 43.20%	37 100%
60-89 ml/min/1.73m^2 Stage 2	28 82.40%	6 17.60%	34 100%
30-59 ml/min/1.73m^2 Stage 3	18 81.80%	4 18.20%	22 100%
15-29 ml/min/1.73m^2 Stage 4	7 100.00%	0 0.00%	7 100.00%
<15ml/min/1.73m^2 Stage 5	0 0.00%	0 0.00%	0 100.00%
Total	74 74.00%	26 26.00%	100% 100.00%

Table-4: Comparison of base line characteristics in the study and control population

Variables	Study Group		Control Group		t value	df	P value
	Mean	SD	Mean	SD			
Age	51.51	8.011	50.19	9.465	1.065	198	0.288
Duration of diabetes	8.01	2.963	-	-	-	-	-
FBS	155.17	42.277	92.83	10.784	14.288	198	0.000**
HbA1c	7.50	1.658	5.71	5.132	3.310	198	0.001*
GFR	78.03	27.866	89.43	22.575	3.178	198	0.002*
E/A	0.996	0.605	1.228	0.280	3.488	198	0.001*
e/a	0.954	0.295	1.259	0.230	8.145	198	0.000**
LV ejection fraction	60.91	5.057	60.68	5.813	0.298	198	0.766

*p<0.05; Significant; **p<0.001; Highly significant

Discussion

Epidemiological data indicates that there is a significant relationship between diabetes and cardiovascular disease. Diabetic cardiomyopathy has been proposed as an independent risk factor for cardiovascular disease and LVDD may represent the first stage of diabetic cardiomyopathy. Various studies have shown the evidence of LVDD in normotensive, type2 diabetic patients. However, the exact causes and mechanisms remain unclear [19].

Table-5: Prevalence of diastolic dysfunction in type 2 DM

Sl. No.	Study	Year	Prevalence of diastolic dysfunction	P value
1	Boyer et al [20]	2004	75%	P<0.02
2	Bajraktari et al [21]	2005	65.8%	P=0.001
3	Mishra et al [22]	2008	54.8%	P<0.001
4	Patil VC et al [2]	2011	54.33%	P<0.001

Prevalence of diastolic dysfunction in type 2 DM: In our study, 74% patients in the study group had LVDD while only 18% had diastolic dysfunction in the control group (p=0.0001). Similar results were obtained in previous studies (Table 5).

Relationship of diastolic dysfunction with age: Present study revealed positive correlation between LVDD and age among cases as well as controls. It was comparable to the study conducted by Londhe A et al wherein mean age of cases was 46.7 years and it was observed that between 50-59 years, prevalence of LVDD was about 57.14% and in cases of age 70 years and above, all had diastolic dysfunction (100%) [19].

Relationship of diastolic dysfunction with gender: In the case group, LVDD was more prevalent in females however, it was statistically insignificant. Nevertheless, similar finding was observed in studies by Patil MB et al [9] and Londhe A et al [19], wherein diastolic dysfunction had female predominance of 68.18% & 53% respectively.

Relationship of diastolic dysfunction to duration of diabetes: The present study found that as the duration of diabetes increased, prevalence of LVDD also increased with statistical significance. These results were comparable to those obtained by Annou AK et al [23] and Patil VC et al [2].

Relationship of diastolic dysfunction with fasting blood glucose levels and glycemic control: In this study, LVDD was more prevalent in patients with FBS >126 mg/dl and HbA1c >6.5%, thus revealing that LVDD increased as glycemic control worsened. Similar results were declared by Hammedullah et al who observed that there was a strong correlation between HbA1c levels and diastolic indices ($p < 0.05$) [24]. Patil VC et al showed that 81.57% of diastolic dysfunction was present in patients with HbA1c level>7.5% [2]. Londhe A et al also correlated diastolic dysfunction with poor glycemic control and noted that 72% of patients with HbA1c>8% had diastolic dysfunction [19].

Relationship of diastolic dysfunction with GFR: It was observed that with decrease in GFR, prevalence of diastolic dysfunction increased. This decline in GFR was seen with increasing age as study population excluded the patient already diagnosed to have chronic kidney disease. This correlation was also observed by Neprin et al [25] who postulated that this correlation between decline in GFR and left ventricular dysfunction was due to chronic activation of renin angiotensin aldosterone system (RAAS) which led to remodelling of left ventricle even before heart failure developed. Similar associations were observed by Martin et al who demonstrated that mild renal insufficiency resulted in early cardiac fibrosis and impaired diastolic dysfunction which progressed to more left ventricular remodeling and further to heart failure [26].

So, the present study revealed high prevalence of diastolic dysfunction in asymptomatic type 2 diabetics as compared to general population. LVDD had positive correlation with age, duration of diabetes, poor glycemic control, presence of albuminuria and declining GFR. Further research is essential to understand the pathophysiological mechanisms underlying the development of diastolic dysfunction in type 2 DM which can be targeted early on in the disease before frank diastolic heart failure sets in.

Conclusions

Left Ventricular Diastolic dysfunction which is a precursor for diabetic heart disease is strongly associated with diabetes. Moreover left ventricular diastolic dysfunction has direct co relation with duration of diabetes, HbA1c levels and poor glycemic control. This study highlights the importance of early detection and diagnosis of asymptomatic left ventricular diastolic dysfunction which can contribute significantly in prevention of heart failure in diabetic patients.

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