



Evaluation of Left Ventricular Diastolic Dysfunction in Asymptomatic Normotensive Patients with Type-2 Diabetes Mellitus

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ABSTRACT

Introduction: Diabetes mellitus (DM) is known to affect cardiovascular system adversely. Various studies reported left ventricular diastolic dysfunction (LVDD) as an early sign of cardiac involvement in asymptomatic patients with type-2 DM, diagnosed using Color Doppler echocardiography. With this background, the study was conducted with an aim to study the prevalence of LVDD in normotensive asymptomatic type-2 DM patients and association with various risk factors.

Methodology: The cross-sectional study was carried out among the type 2 DM patients who visited our hospital for regular follow-up. 100 patients of type 2 DM were enrolled and patients without the history of hypertension, Heart diseases, renal dysfunction were recruited on a convenient basis. Demographic data such as age, sex, history, duration, treatment of DM, Investigations like Fasting and Postprandial blood sugar levels, Serum Creatinine, Fasting lipid profile, HbA1c, and also ECG, 2D echocardiography, and Treadmill test were carried out. Data were entered in MS Excel spread sheet and analysed with the help of SPSS software packages and Open Epi. Chi-square test was used for the comparison of qualitative data.

Results: LVDD was present in 64 (64%) among 100 patients. A strong association of LVDD with Duration of Diabetes and HbA1c ($p < 0.001$) was observed but there was no correlation with age, sex, Type of Treatment, total cholesterol, triglycerides, high-density lipoprotein.

Conclusion: Duration of diabetes and the level of HbA1c were found to have a strong association with LVDD. It is recommended that all patients with long term and uncontrolled type 2 DM should be screened for LVDD.

Keywords: LVDD, Duration of diabetes, HbA1c, Total cholesterol, Triglycerides, Diabetic cardiomyopathy.

Introduction

Diabetes mellitus, with the history of past 2500 years, is characterised by the state of chronic hyperglycemia and disturbance in carbohydrate, fat and protein metabolism. It is associated with

an absolute or relative deficiency of insulin secretion and/or insulin action, which is modulated by various factors like genetic, HLA and environmental factors which affect vascular system and lead to micro and macroangiopathy.

Various studies had reported important differences in the types and frequency of DM and its complications among various countries as well as ethnic and cultural groups ^{[1],[2]}. In the Current Scenario, DM has become a leading cause of premature death, disability and high health care costs.

As per WHO estimates, the burden of DM all over the world would be more than 500 million in the 21st century and by the end of 2025, India will have the largest number of diabetic patients in the world and one out of 5 diabetic patients in the world will be an Indian. India is on the way of the “Diabetic capital of the world” with 5.72 crores patients with DM by 2025. Various studies have reported that Indians are genetically more susceptible to Diabetes mellitus compared to other races. Various studies using Doppler echocardiography have confirmed the findings of abnormal diastolic function as an early indicator of cardiac involvement in asymptomatic patients with Type 1 or Type 2 diabetes mellitus ^[3].

It has been found that diabetics are more at risk of developing congestive heart failure in the absence of coronary heart diseases, hypertension or any known structural heart disease which termed as ‘Diabetic Cardiomyopathy’. It has been suggested that microangiopathic lesions of the myocardium, altered composition and fibrosis of myocardium interstitium and accumulation of lipids in myocardial cells are involved in the pathogenesis of diabetic cardiomyopathy ^{[4],[5],[6]}.

With this background, this study was aimed to identify the diastolic dysfunction in normotensive asymptomatic type 2 diabetes mellitus patients and to study an association between diastolic dysfunction with age, sex, duration of diabetes, type of therapy, HbA1c level and dyslipidemia.

Material and Methods

A cross-sectional study was carried out and 100 patients were enrolled with a convenient consecutive sampling. The study was done from March 2013 to August 2014 at a city based secondary care government hospital situated in

western India. 100 Patients with type 2 DM between the age groups 30-80 years attending medical OPD for a regular follow-up were recruited for the study after proper written informed consent as per inclusion criteria. Participant enrollment criteria to select type 2 DM participants were on the basis of American Diabetic Association (ADA) definition. According to ADA definition, fasting plasma glucose (FPG) ≥ 126 mg/dL, where Fasting is defined as no caloric intake for ≥ 8 hours or 2-hr plasma glucose (PG) ≥ 200 mg/dL during OGTT (75-g), using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water or HbA1C $\geq 6.5\%$. Individual with any acute complications of diabetes like diabetic ketoacidosis and non-ketotic hyperosmolar coma, hypertension, history of Myocardial infarction, unstable angina, stable angina, coronary artery disease, Rheumatic Heart disease, ischemic heart disease, Renal dysfunction were excluded from the study. The research protocol was approved by the ethical committee of the institution. Informed consent was taken from all study participants.

After obtaining written informed consent, detailed clinical history regarding age, sex, family history, history of diabetes in which duration and treatment of diabetes and if other complications of diabetes, ischemic heart disease, rheumatic heart disease, hypertension, smoking, alcoholism of all patients was recorded. Complete physical examination including vitals and anthropometric measurements were carried out on the pre designed semi-structured questionnaire. Blood investigation like Fasting and Postprandial blood sugar levels (oxidase & peroxidase method), Serum Creatinine (Modified Jaffe’s reaction, Initial rate assay), Fasting lipid profile (MERCKS ELECTRA PRO-M Automated Analyser), HbA1C (CATION EXCHANGE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY, CYSTEINE D-10 from bioered, USA). Estimated average glucose was calculated by the following equation: eAG (mg/dl) = $28.7 * (A1C - 46.7)$, Urine examination, ECG, Treadmill test,

2D echocardiography, M-mode with colour Doppler, Tissue Doppler using ultrasound machine (Philips HDI 5000) with 2.5 to 5 % MHz probes. All recordings were done with patients in supine and left lateral position. The transducer was placed in left parasternal, apical and subcostal areas of the chest and the parasternal long axis and short axis were taken to record various dimensions and measurements. At least three recordings with their mean were taken. Diastolic function of the left ventricle was assessed by evaluating the mitral inflow velocity curves (MIVC) by Echo- Doppler techniques. Mitral 'E' velocity (Peak velocity of early mitral flow), Mitral 'A' velocity (Peak velocity of late mitral flow), Mitral E/A ratio (normal 1-2), Isovolumic relaxation time (IVRT) (normal 60-100 msec), Deceleration time (DT) (normal 150-200 msec), Tissue Doppler E' velocity (normal ≥ 10 cm/s) were used to assess LVDD. The primary outcome was to study the association of LVDD with type 2 DM. The secondary outcome was to study the association of LVDD with individual parameters of patients like age, sex, duration of diabetes, type of treatment, HbA1C, lipid profile. The statistical analysis was done by using 16.0 version of statistical software SPSS. Chi-square test was used for comparison of qualitative data. The $p < 0.05$ was considered significant. All these tests were routinely carried out among the Diabetic patients and there was no financial burden on patients and all expenditure was incurred by the researchers.

Results

The Cross-sectional study was carried out among 100 participants and they were enrolled by a consecutive convenient sampling technique. The mean age of cases was 53.60 ± 10.30 year (32 – 78 years), out of which 56% were male and 44% were female. Out of the total, maximum numbers of participants were suffering from diabetes for less than 5 years (n=44) followed by 5-10 years (n=32) and more than 10 years (n=22). The majority of our participants were taking OHA (n=40), followed by Insulin (n=32) and Insulin + OHA (n=

28). Greater numbers of our participants were having LA size between 3.1 cm to 4 cm. The cholesterol level of less than 200 mg/dl was found in the majority of patients (n=69) followed by 22 participants having S. cholesterol level between 200-239 mg/dl. The serum HDL level of less than 40 mg/dl was found in 52% of participants, followed by 38% having S. HDL level between 40 to 60 mg/dl and 10% having more than 60 mg/dl (Table-1). Table 2 shows the sex wise distribution of participants. Maximum numbers of participants belong to the group of 50 to 59 years. According to sex distribution, maximum numbers of males and females belong to the same age group of 50 to 59 years.

The association between various risk factors and occurrence of diastolic dysfunction in diabetic patients has been depicted in Table 3. HbA1c level, LA size and the duration of diabetes were significantly associated with diastolic dysfunction as p-value was less than 0.05. Whereas, serum HDL level, line of treatment and S. triglyceride level were not associated significantly with the occurrence of diastolic dysfunction as p-value was more than 0.05

Out of 64 cases with LVDD, 16 had TG less than 150 mg/dl against 26 and 22 having 150-199 mg/dl and 200 – 499 mg/dl TG respectively. This correlation was statistically not significant ($p=0.171$). 32 cases among LVDD were having HDL less than 40 mg/dl, whereas 24 and 08 having HDL of 40-60 mg/dl and more than 60 mg/dl respectively. This was statistically not significant ($p=0.925$). (Table 3) Out of 64 cases with LVDD, 47 were having cholesterol of < 200 mg/dl with 12 and 05 were having cholesterol of 200 – 239 mg/dl and more than 240 mg/dl respectively. This association was also statistically not significant ($p=0.441$). We had also compared the association of LVDD with gender and type of treatment. Out of 64 cases with LVDD, 35 were male and 29 were female. There was no association between LVDD and gender ($p=0.724$). Out of 64 cases with LVDD, 20, 24 and 20 participants were taking insulin, oral

hypoglycemic agents(OHA) and insulin + OHA respectively. There was no association between LVDD and type of treatment (p=0.613). (Table 3)

Table 1 Socio demographic profile (n-100)

Variables	Groups	No. (%)
Age in years	30 – 39	12(12.0%)
	40 – 49	20(20.0%)
	50 – 59	40(40.0%)
	60 – 69	22(22.0%)
	≥ 70	06(06.0%)
	Sex	Male
Female		44 (44.0%)
Duration of diabetes	0 – 5	44 (44%)
	6 – 10	32 (32%)
	11 – 15	22 (22%)
	Treatment	Insulin
Treatment	OHA	40(40%)
	Insulin + OHA	28(28%)
	HbA1c	< 6.5
6.5 – 7.4		32(32%)
7.5 – 8.5		16(16%)
LA size (cm)		2.1 – 3.0
LA size (cm)	3.1 – 4.0	50(55%)
	> 4.0	06(6%)
	S. Cholesterol	< 200
200 – 239		22(22%)
> 240		09(9%)
S. HDL	< 40	52(52%)
	40 – 60	38(38%)
	> 60	10(10%)

Table 1 depicts the socio demographic profile of the 100 participants at the time of enrollment.

Table 2 Age wise sex distribution (n-100)

Age in Years	Male (n = 56) No.(%)	Female (n= 44) No.(%)	Total (n=100) No. (%)
30 – 39	08(14.3%)	04(09.1%)	12(12.0%)
40 – 49	12(21.4%)	08(18.2%)	20(20.0%)
50 – 59	24(42.9%)	16(36.4%)	40(40.0%)
60 – 69	12(21.4%)	10(22.7%)	22(22.0%)
≥ 70	0	06(13.6%)	06(06.0%)

Table 2 shows the age and sex wise distribution of study participants.

Table 3 Univariate analysis to show the association of diastolic dysfunction to various risk factors

Variable name	Group	Diastolic dysfunction		P value
		Present	Absent	
Age (years)	30–39	05(41.7%)	07(58.3%)	0.133
	40–49	11(55.0%)	09(45.0%)	
	50–59	27(67.5%)	13(32.5%)	
	60–69	15(68.2%)	07(31.8%)	
	≥ 70	06(100.0%)	0(0%)	
Duration of Diabetes (years)	0 – 5	18(40.9%)	26(59.1%)	0.001
	6 – 10	26(81.3%)	06(18.8%)	
	11 – 15	18(81.8%)	04(18.2%)	
	> 15	02(100%)	0(0%)	
Line of treatment	Insulin	20(62.5%)	12(37.5%)	0.613
	OHA	24(60.0%)	16(40.0%)	
	Insulin + OHA	20(71.4%)	08(28.6%)	
Hb A1c level	< 6.5	0(0%)	0(0%)	0.001
	6.5–7.4	06(18.8%)	26(81.2%)	
	7.5–8.5	12(75.0%)	04(25.0%)	
	> 8.5	46(88.5%)	06(11.5%)	
LA size (cm)	2.1–3.0	18(40.9%)	26(59.1%)	0.001
	3.1–4.0	40(80%)	10(20%)	
	> 4.0	6(100%)	0(0%)	
HDL (mg)	< 40	32(61.5%)	20(38.5%)	0.925
	40–60	24(63.2%)	14(36.8%)	
	> 60	08(80.0%)	02(20.0%)	
Triglyceride (mg)	< 150	16(59.3%)	11(40.7%)	0.171
	150–199	26(76.5%)	08(23.5%)	
	200–499	22(56.4%)	17(43.6%)	
	≥ 500	16(59.3%)	11(40.7%)	

*P value less than 0.05 is considered as significant.

Table 3 depicts the association of various risk factors and the occurrence of diastolic dysfunction.

Discussion

Epidemiological data indicates a greater risk of cardiovascular morbidity and mortality particularly heart failure, in diabetic patients compared to non-diabetic patients. Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease and left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy. Several studies have shown the evidence of left ventricular systolic and diastolic dysfunction in asymptomatic, normotensive, type 2 diabetic patients. However, the exact causes and mechanisms remain unclear. Sanderson et al [7] and Shapiro et al [8] suggest that the impairment of diastolic function of the left ventricle, i.e. its filling abnormalities is far more common than systolic dysfunction. In the present study, an attempt has been made to evaluate left

ventricular function by M-mode 2-D echocardiography, colour Doppler studies and tissue Doppler in asymptomatic Type 2 diabetes patients and to determine the association of LVDD with age, sex, duration of diabetes, type of treatment, HbA1c, lipid profile, and LA size. 100 patients who were normotensive and diabetic were enrolled in this study and evaluated for the left ventricular diastolic dysfunction and association of various parameters with diastolic dysfunction.

The present study reported that the majority of subjects 56 (56%) were male and 44 (44%) were females which were similar to the study conducted by Paul Poirier et al^[9] and Abdul Khaliq M.H. et al^[10]. In our study we found that the age was ranging from 32 - 78 years with an average age being 53.60 years and SD of 10.30. The majority of patients belong to 4th and 5th decade which is supported by Paul Poirier et al.^[9], Abdul Khaliq M.H. et al^[10]. The present study and the study conducted by Patil MB^[11] et el reported similar findings like 41% of cases of diastolic dysfunction belong to the age group of 30 - 39 years which is less as compared to 55.0%, 67.5%, 68.2% and 100.0% of cases who are of age 40 – 49yrs, 50 – 59yrs, 60 – 69yrs and \geq 70yrs respectively. Diastolic dysfunction is present in 62% of male cases which is comparable with 65.9% of female cases and similar findings were reported by Patil MB et al^[11], and also by the strong heart study by Devereux and colleagues in 2000^[12].

In this study, we found that the 40% cases who had Diastolic dysfunction had diabetes from 0 – 5 yrs which is significantly less as compared to 81%, 81% and 100.0% of cases who had diabetes from 6 – 10yrs, 11 – 15yrs and > 15yrs respectively. This finding is supported by Paul Poirier et al^[9], and also by Patil MB^[11] and this result is comparable with those studies. The present study and the study conducted by Patil MB et el^[11] reported around 18% of cases who had HbA1c level 6.5 – 7.4% which was significantly less as compared to 75.0% and 88% of cases who had HbA1c 7.5 – 8.5% and > 8.5% respectively. Diastolic dysfunction was present in 41% of cases

who had LA size 2.1 – 3.0 cm which is significantly less as compared to 80.0% and 100.0% of cases who had LA size 3.1 – 4.0cm and > 4.0 cm respectively. The similar findings were reported by Paul Poirier et al^[9], and Patil MB et al^[12]. However, the past studies were done using complex left atrial volume index which shows that the left atrial volume index is better associated with the degree of diastolic dysfunction but calculation for the left atrial volume index^[13] is quite difficult so more studies should be conducted by using this simple variable of LA size. 100.0% of cases with LA size 3.1 – 4.0 cm and > 4.0 cm had Diastolic dysfunction Grade I which is significantly more as compared to 89% of the cases with LA size 2.1 – 3.0 cm. Two patients have left atrial size of 2.1 to 3 cm having grade II diastolic dysfunction while none of the patients with LA size of >3 cm has grade II diastolic dysfunction. 71.4% of cases who has diastolic dysfunction are on Insulin + OHA treatment which is more as compared to 62.5% and 60.0% of cases who has line of treatment as Insulin and OHA respectively. A similar type of result was obtained by Patil MB et al^[12], and findings are comparable with that study. In present study level of cholesterol, HDL, and LDL were not correlated with diastolic dysfunction which is comparable with previous study conducted by Paul Poirier et al^[9]. The Grading of diastolic dysfunction was also not correlated with cholesterol, HDL, LDL.

Conclusion

Diastolic dysfunction is more prevalent in western Indian population. Diastolic dysfunction is found to be associated with duration of diabetes. It indicates as the duration of diabetes increases; patients are more prone to have diastolic dysfunction. Grading of diastolic dysfunction is also not affected by the treatment of diabetes. Diastolic dysfunction is also statistically significantly associated with HbA1c level which indicates that diastolic dysfunction is common in patients whose diabetes is not well controlled.

Diastolic dysfunction is also statistically significantly associated with the size of LA, which denotes that we can take LA size as a marker of Diastolic dysfunction. However, more studies should be conducted to establish relationship between these two parameters. Diastolic dysfunction is not associated with age, sex, and dyslipidemia. Grading of diastolic dysfunction is not affected by any of the study parameters. Routine screening for LVDD in patients with type 2 DM can be helpful to estimate the magnitude of cardiovascular abnormalities and helps us in early detection and prompt intervention of LVDD, so as to design the holistic strategies of management.

Recommendation

Our study recommends that a diabetic person should undergo 2D echo cardiography at proper intervals so that the early changes of diastolic dysfunction and changes in LA size can be identified before a person has symptomatic diastolic or systolic heart failure.

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