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Research Article

PREVALENCE OF LEFT VENTRICULAR DIASTOLIC DYSFUNCTION IN TYPE 2 DIABETES MELLITUS AND ITS ASSOCIATION WITH HBA1C

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ABSTRACT

Objective: Diabetes mellitus (DM) progressively increased in incidence over the previous years in India and throughout the world, with India contributing to a major portion of the global encumbrance. The present study has been aimed to assess left ventricular diastolic dysfunction (LVDD) in diabetic person and to evaluate the correlation of diastolic dysfunction with glycosylated hemoglobin level (HbA1c).

Methods: This prospective, cross-sectional, and observational study has been performed for 1 year from September 2018 to August 2019 at Srirama Chandra Bhanja Medical College and Hospital, Cuttack, Odisha. Seventy patients of Type 2 DM have been enrolled in the present study. The primary objective of the present study is to evaluate the incidence of LVDD in cases with Type 2 DM without any prior cardiac. Complications and to study the correlation of LVDD with glycosylated hemoglobin. Glycosylated hemoglobin has been estimated by ion exchange resin method. 2D Doppler echocardiography was used to diagnose LVDD.

Results: A large proportion or 48.6% of the diabetics in the study were diagnosed with LVDD of Grade I severity. Data revealed that increased levels of glycated hemoglobin caused the severity of LVDD to worsen. With HbA1c levels between 0 and 8.9%, 67.4% had Grade I LVDD, with HbA1c levels between 9 and 10.9%, majority or 76.9% had Grade II dysfunction and similarly with HbA1c between 11 and 18%, 90.9% of patients had Grade III LVDD. This correlation was found to be statistically significant ($p<0.00001$).

Conclusion: Higher values of fasting plasma glucose, PPPG, and HbA1c were associated with higher incidence of LVDD. Thus, optimal glycemic control may lower the risk of having early diastolic dysfunction and its progression. This has been perceived with cases with Type 2 DM who may may remain asymptomatic despite having significant LVDD.

Keywords: Diabetes mellitus, Left ventricular diastolic dysfunction, Fasting plasma glucose, PPPG, Glycosylated hemoglobin level, Glycemic control, Myocardial disorder.

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INTRODUCTION

Diabetes mellitus (DM) and associated complications seem difficulties and associated problems seems to be progressively increasing over the previous quarter period in India and throughout the world, with India contributing to a major part of the global burden [1,2]. Diabetes presently affects more than 62 millions of Indian population that is found to be more than 7.2% of the overall population [3]. Approximately 4 million Indians are reported to have died because of DM each year [4]. Cardiovascular system is one of the most commonly affected organ systems in DM. The presence of myocardial disorder and congestive cardiac disease in people with DM, in the lack of overt clinical coronary artery disorder, valvular disease, and other conventional cardiovascular threat aspects, namely, hypertension is called diabetic cardiomyopathy. The earliest and also the most common hemodynamic derangement of diabetic cardiomyopathy is left ventricular diastolic dysfunction (LVDD), therefore strengthening the significance of initial investigation of ventricular functioning in such persons.

LVDD may develop even when the patient is asymptomatic. Therefore, its early detection by echocardiography may help in early management and better clinical outcome. However, there is no uniform consensus regarding the role of routine echocardiography in asymptomatic diabetic individuals to assess left ventricular function. Correlation of glycosylated hemoglobin level (HbA1c) with the left ventricular diastolic function will help determine whether glycemic control is related with minor threat of the left ventricular dysfunction. With this background, the study has been commenced to assess LVDD in diabetic person and to evaluate the correlation of diastolic dysfunction with HbA1c.

METHODS

This prospective, cross-sectional, and observational study has been performed for 1 year from September 2018 to August 2019 at Srirama Chandra Bhanja Medical College and Hospital, Cuttack, Odisha. The objectives of the present study were to evaluate the incidence of LVDD in cases with Type 2 DM without any prior cardiac complications and to study the correlation of left ventricular diastolic dysfunction with age, glycaemic control and HbA1c levels. Patients of Type 2 DM aged above the age of 30 presenting to our Department, satisfying the inclusion and exclusion criteria were included in the study. Individuals with prior diagnosis of type 2 DM or those with symptoms of diabetes with random blood glucose concentration ≥11.1 mmol/L (200 mg/dL) or fasting plasma glucose (FPG) ≥7.0 mmol/L (126 mg/dL) or HbA1c ≥6.5% or 2-h plasma glucose (PPPG) ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test, were included in the present study. Classic symptoms of DM are polyuria, polydipsia, and weight loss. Random is termed as without considering the time since the last meal and fasting should be considered as no caloric consumption for at least 8 h. HbA1c was measured in a laboratory by technique permitted by the National Glycohemoglobin standardization program and associated to the reference assay of the diabetes control and complications test. Cases with previous history of hypertension, coronary artery disease, valvular heart disease, thyroid dysfunction, cardiomyopathy, chronic kidney disease, chronic obstructive pulmonary disease, and chronic alcoholism have been excluded from the study.

The present study has been performed in agreement of Declaration of Helsinki and Good clinical practices (ICH). Written knowledgeable

consent has been collected from all participants before enrolling them into the research. Ethical approval has been obtained from the Institutional ethics committee of S.C.B.M.C.H (ECR/84/Inst/OR/2013/13351 dated October 14, 2019) before the commencement of the study. Strict confidentiality was maintained throughout the study procedure.

All the study participants have been examined for thorough history, detailed clinical inspection, and supported by appropriate examinations. Glycosylated hemoglobin has been estimated by ion exchange resin method. 2D Doppler echocardiography was used to diagnose LVDD. Peak early mitral transmitted filling velocity during each diastole (E) and peak transmitral atrial filling velocity during late diastole (A) was measured and the LVDD were classified into various severity stages accordingly (Fig. 1).

Statistical analysis

Data have been evaluated using SPSS version 16.0 and Microsoft Excel 2016. Descriptive statistics has been performed for complete data and appropriate examinations of comparison were applied. Categorical variables were investigated with the Chi-square test and Fisher's exact test. Continuous variables were analyzed using the Independent t-test. $p<0.05$ was considered statistically significant.

RESULTS

Seventy patients of Type 2 DM have been enrolled in the present study. There seems male preponderance and majority of the study subjects were aged in their sixth decade of life. A large proportion or 48.6% of the diabetics in the study were diagnosed with LVDD of Grade I severity (Table 1).

The second objective of the study is to assess any possible correlation between LVDD and different demographic and clinical indicators such as age, glycemic control, and HbA_1c levels. The study findings suggest that the prevalence of LVDD was significantly linked to age (p=0.00), FPG (p=0.004), PPPG (p<0.001), and HbA1c (p=0.04). There was no significant association of LVDD with gender, serum cholesterol, and serum triglyceride (p>0.05; Table 2).

A further analysis revealed that the increased levels of glycated hemoglobin caused the severity of LVDD to worsen (Fig. 2). With HbA1c levels between 0 and 8.9%, 67.4% had Grade I LVDD, with HbA1c levels between 9 and 10.9%, majority or 76.9% had Grade II dysfunction and similarly with HbA1c between 11 and 18%, 90.9% of patients had Grade III LVDD. This correlation was found to be statistically significant (p<0.00001; Chi-square test).

It was observed that there was a significant decline in the average 'E' value in cases with LVDD than those who did not have diastolic dysfunction (p=0.006). A significant rise in the average 'A' value was also seen in those with LVDD than those without diastolic dysfunction (p=0.007). E/A ratio significantly declined in cases with LVDD (p=0.012). However, there was no statistically significant difference in the deceleration time between cases with and without diastolic dysfunction (Table 3).

Analysis of treatment with grades of LVDD showed that higher grades of severity, that is, LVDD Grade II and III were detected in patients on insulin. Diabetics on oral anti-diabetic agents had low grade or Grade I LVDD (p=0.001, Table 4). In addition, it was observed that patients on insulin had a higher probability than those taking OAD (odds ratio=2.8) of having higher grades of LVDD.

DISCUSSION

DM is one of the most common disorders worldwide and has acquired epidemic proportions. Globally and nationally, diabetes and its complications have become the most important contemporary and challenging health problem. In patients with T2DM, cardiovascular disorder characteristically develops 14.6 years previously [5], with larger severity than in persons without DM [1]. In addition, persons with Type 2 DM are twofold as probable to have cardiovascular disorder as compared to individuals without diabetes independent of age, smoking status, body mass index and systolic blood pressure [6], and DM has been connected with a more than doubled threat of demise from vascular reasons [7].

In the present study, 15 (21.4%) had normal diastolic function while the rest 55 (78.6%) had Grade I, II, or III diastolic dysfunction. Mean age among cases with LVDD seems to be 58.04±10.048 years while the mean age in those without LVDD was 46.33±8.8 years. The observed

Parameter	Normal	Stage I Mild diastolic dysfunction	Stage II Moderate diastolic dysfunction	Stage III Severe diastolic dysfunction	Stage IV Severe diastolic dysfunction
E/A Ratio	1-1.5	<1	1.0-1.5	≥1.5	> 1.5
E/A with Valsalva	Both E and A decrease, ratio unchanged	Both E and A decrease, ratio unchanged	E decreases, A increases; ratio reverses	Ratio decreases	No response
Deceleration time (ms)	>140	>140	>140	< 140	< 140

Fig. 1: Staging of LVDD (E=peak early mitral transmitted filling velocity during each diastole; A=peak transmitral atrial filling velocity during late diastole)

Table 1: Baseline characteristics among the participants

Parameter	Frequency (%) (n=70)
Age distribution (in years)	
31–40	6 (8.6)
41–50	19 (27.1)
51–60	27 (38.6)
61–70	10 (14.3)
>71	8 (11.4)
Gender distribution	
Male	37 (52.9)
Female	33 (47.1)
LVDD	
Positive	55 (78.6)
Negative	15 (21.4)
Severity of LVDD	
Normal	15 (21.4)
Grade I	34 (48.6)
Grade II	11 (15.7)
Grade III	10 (14.3)
FPG (mg/dL)	
0–199	39 (55.7)
200–299	28 (40.0)
≥300	3 (4.3)
PPPG (mg/dL)	
0–250	28 (40.0)
251–350	28 (40.0)
>350	14 (20.0)
Serum cholesterol (mg/dL)	
0–199	57 (81.4)
≥200	13 (18.6)
Serum triglyceride (mg/dL)	
0–149	53 (75.7)
≥150	17 (24.3)
HbA1c levels (%)	
0–8.9	46 (65.7)
9.0–10.9	13 (18.6)
11–18	11 (15.7)

FPG: Fasting plasma glucose

result is comparable to the study performed by Srinivasa *et al.* [8] where the mean age of cases with LVDD was 52.68±5.69 years while that of population without LVDD was 46.38±5.15 years and the relationship between age and LVDD was observed to be statistically significant. There was a significant association between FPG levels and LVDD. Thus, it is evident that higher FPG values are related with greater prevalence of LVDD. Another study conducted by Kumar *et al.* [9] had reported the similar results, mean FPG with LVDD was 192.05±29.82 mg/dL and that of cases without LVDD was 173.67±27.71 mg/dL and the association was found significant. Similar were the conclusions with PPPG.

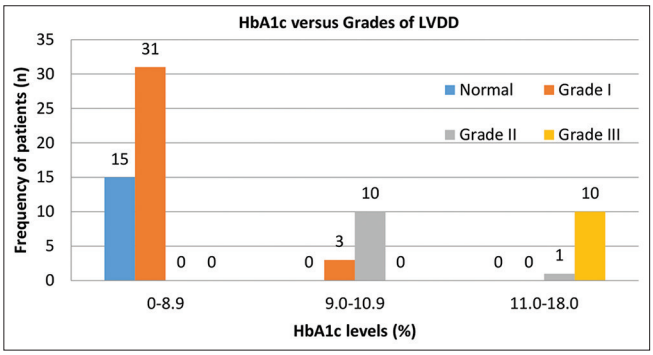

Fig. 2: Relation between glycated hemoglobin and different grades of LVDD

Table 2: Prevalence of LVDD among the participants

Parameters	LVDD		p-value
	Positive (n=55)	Negative (n=15)	
Age distribution			
31–40	2	4	
41–50	11	8	0.00#
51–60	25	2	
61–70	9	1	
>71	8	0	
Gender distribution			
Male	29	8	0.967*
Female	26	7	
FPG (mg/dL)			
0–199	25	14	
200–299	27	1	0.004*
≥300	3	0	
PPPG (mg/dL)			
0–250	15	13	
251–350	26	2	<0.001*
>350	14	0	
Sr cholesterol (mg/dL)			
0–199	44	13	0.556*
≥200	11	2	
Sr triglyceride (mg/dL)			
0–149	41	12	0.662*
≥150	14	3	
HbA1c levels (%)			
0–8.9	31	15	
9.0–10.9	13	0	0.04*
11–18	11	0	

FPG: Fasting plasma glucose

In the present investigation, we observed no statistically significant association among serum cholesterol and LVDD. This was contrary to the findings of Singhal *et al.* [10] where among cases, in those with total cholesterol <200 mg/dL and more than 200 mg/dL, 25(51.02%), and 7(63.63%) showed LVDD respectively, while in control group, in those with total cholesterol <200 mg/dL and more than 200 mg/dL, 0% and 2 (40%) showed LVDD respectively (p<0.012). Similarly, there was no statistically significant relation between serum triglycerides and LVDD. This was contrary to the findings of Singhal *et al.* [10] where among cases, in patients with serum triglyceride <150 mg/dL and >150 mg/dL, 25 (50%) and 7 (70%) had LVDD whereas among control group, in patients with serum triglyceride <150 mg/dL and >150 mg/dL, 0% and 2 (40%) of the patients had LVDD, respectively (p<0.012).

The mean E value in patients with LVDD was 84±21.36 cm/s and those without diastolic dysfunction had mean E value of 103.16±29.26 cm/s. The reduction in mean E value in patients with LVDD than those without diastolic dysfunction was significant. This was similar to the results obtained by Patil and Burji [11] study, where it was observed the mean E value in those with LVDD was 61±0.15 cm/s and that in subjects without LVDD was 82±11 cm/s and the difference was significant. Likewise, the increase in A value in those with LVDD (96.67±30.4 cm/s) than those without diastolic dysfunction (73.9±17.36 cm/s) was significant. The study by Patil and Burji [11] also had similar result with significant increase in mean A value (88±19 cm/s) in those with LVDD than those without LVDD (mean A=60±15 cm/s). There was a substantial reduction of E/A ratio in cases with left ventricular diastolic disorder. The findings were similar to earlier studies by Patil and Burji [11] and Hasan *et al.* [12] which also demonstrated substantial decrease of E/A ratio in those with LVDD.

The findings of the present study suggest that patients with lower HbA1c levels have no or grade I LVDD while patients with higher HbA1c levels have either Grade II or III LVDD. This association among HbA1c levels and LVDD is found to be statistically significant. It was also seen that individuals with higher HbA1c levels (11–18) have 6 times higher risk (odds ratio=5.9) of having higher grades of LVDD (II or III). Comparable observations have been obtained in the research done by Srinivasa *et al.* [8] where the mean HbA1c of cases with LVDD was 7.95±1.09 and of subjects without LVDD was 7.21±1.22 and the correlation was found significant. The study by Singhal *et al.* [10] also showed that maximum cases showed HbA1c >7.5% (68.3%); among cases, in patients with HbA1c<7.5% and > 7.5%, 1 (5.26%) and 31 (75.60%) had LVDD respectively whereas among control group, withHbA1c <7.5% and >7.5%, 2(6.7%) and 0% had LVDD, respectively (p<0.001).

Analysis of treatment with insulin and OAD and grades of LVDD revealed that majority patients on insulin had either Grade II or III LVDD. This was a statistically significant finding. Estimation of odds ratio showed that patients on insulin had 3 times higher risk of having higher grades of LVDD (odds ratio=2.8). However, DM duration effects

Table 3: LV filling patterns

LV filling patterns	Min. value	Max. value	Average values (mean±SD)			p-value#
			Overall	LVDD positive	LVDD negative	
E (cm/s)	42	160	88.2±24.4	84±21.4	103.16±29.3	0.006
A (cm/s)	41	162	91.8±29.6	96.67±30.4	73.9±17.4	0.007
E/A	0.16	3.6	1.1±0.5	0.97±0.6	1.36±0.1	0.012
DT (ms)	90	258	173.4±39.5	172.2±42.2	177.87±28.1	0.627

A=peak transmitral atrial filling velocity during late diastole, DT=deceleration time); #independent t-test, (E=peak early mitral transmitted filling velocity during each diastole

Table 4: Occurrence of LVDD w.r.t treatment received

Treatment	Grade of LVDD		p-value
	I	II and III	
Insulin	11 (35.5)	20 (64.5)	0.001*
Oral anti-diabetic drug	19 (100)	0	

*Chi-square test

and degree of glycemic control on such findings cannot be ruled out and could be confounding variables. Contrary to such result, study by Patil and Burji [11] showed that correlation of treatment profile (insulin and OAD) with diastolic dysfunction was not significant. Limitations of our study comprise a lesser study population and cross sectional type of the study which did not allow follow-up of the patients.

CONCLUSION

Higher values of FPG, PPPG, and HbA1c were associated with higher incidence of LVDD. Thus, optimal glycemic control may lower the risk of having early diastolic dysfunction and its progression. This has been observed in individuals with Type 2 DM who may remain asymptomatic LVDD, it could be a good predictor of cardiovascular involvement in DM. Early detection and treatment of such patients may retard further deterioration and improve quality of life, thus reinforcing the importance of periodic screening of asymptomatic diabetics for ventricular dysfunction by echocardiography. However, further prospective studies with more number of patients are required to reach a definite consensus.

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AUTHOR CONTRIBUTION

All the authors equally contributed to this manuscript writing process.

CONFLICTS OF INTEREST

Nil.

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