

# Diabetes Mellitus Type II: Correlation between HBA1C Level and Left Ventricular Diastolic Dysfunction.

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## ABSTRACT

**Background:** Diabetes is a metabolic disease which affects various organs of the body like heart, eye, kidney, skin and peripheral nerves. Diabetic cardiomyopathy is defined as the appearance of the symptoms of Congestive heart failure in diabetic patient in the absence of hypertension and any structural or congenital heart disease. The aim of the study is to find the relation between type 2 diabetes mellitus and cardiomyopathy, highlighting the variation in incidence according to age, sex and severity on basis of Doppler echocardiographic diagnosis. **Methods:** The prospective study was conducted for the duration of one year on 100 newly diagnosed Type 2 Diabetes patients aged between 30-60 years. Doppler echocardiography and HbA1c level of the patients was done. The study was conducted on the basis of grading of diastolic dysfunction on echocardiography. Quantitative data was analysed with the help of 't' test and qualitative data with the Chi-Square and Fisher Exact Test. Statistical significance was taken as  $P < 0.05$ . **Results:** In this study, 39% of the newly diagnosed type 2 diabetes mellitus patients developed diabetic cardiomyopathy. In females, the disease was statistically absent in more patients (35) as compared to males (26) ( $<0.05$ ). The commonest age group affected by grade 1 disease was 41-50 years. The incidence of grade 2 disease was more in age group 51-60 years. The grade 1 diabetic cardiomyopathy was statistically more common in males as compared to females ( $<0.05$ ). The grade 2 diabetic cardiomyopathy was more common in females, but was statistically insignificant. Patients with HbA1c  $<8$  have 16% chances to get LVDD with significant P value of 0.02. Patients with HbA1c between 8 to 10 have 30% chances to get LVDD with significant P value of 0.01. **Conclusion:** Diabetic cardiomyopathy is an important complication of type 2 diabetes mellitus patient. HbA1c level and Doppler echocardiography plays an important role in estimating the prevalence and severity of diabetic cardiomyopathy.

**Keywords:** Cardiomyopathy, Diabetes mellitus type 2, HbA1c level, Left ventricular diastolic dysfunction.

## INTRODUCTION

The incidence of diabetes mellitus (DM) is increasing rapidly in both developed and developing countries and is now being considered as an epidemic. On other hand, the early and late complications of diabetes have become a challenge globally. Recent comparative studies suggest that Indians are more susceptible to diabetes and its incidence is increasing at a remarkable rate. It has been found that about 19.4 million Indians are affected by this deadly disease. This figure will rise to 57.2 million by 2025.<sup>[1-3]</sup>

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Diabetes is a metabolic disease which affects various organs of the body like heart, eye, kidney, skin and

peripheral nerves. The prevalence of type 2 DM is increasing at a faster rate as compared to type I due to reduced physical activities and increased intake of fast food.<sup>[2]</sup>

The first case of diabetic cardiomyopathy was reported in 1972 by Rubler. It is defined as the appearance of the symptoms of Congestive heart failure in diabetic patient in the absence of hypertension and any structural or congenital heart disease.<sup>[4]</sup>

The pathogenesis of diabetic cardiomyopathy is still not clear. Some studies suggest that increased blood glucose level promotes the formation of free radicals and glycation of end products which affects the contractility of heart. As a result, myocardial fibrosis occurs.<sup>[5]</sup> Some scientists believe that activation of PPAR alpha receptors causes mitochondrial uncoupling of oxidative phosphorylation resulting in the dysfunction of cardiac rhythm.<sup>[6]</sup> According to another theory, in diabetic patient there is increased level of protein kinase C which causes reduction in the nitric oxide level, thus producing free radicles. All these changes result in the abnormality in the

functioning of the cardiac endothelium.<sup>[7]</sup> Various other factors are also reported like in diabetes there is reduction in the production of Vascular Endothelial Growth Factor causing cardiac ischemia. The alteration in the functioning of Renin Angiotensin and Aldosterone Mechanism stimulates formation of myofibroblast leading to myocardial fibrosis.<sup>[8]</sup>

Clinically, the patient develops no symptoms in early phase. Later, myocardial diastolic dysfunction occurs followed by systolic dysfunction. This results in development of features of congestive heart failure like weakness, dyspnea, cough, pedal oedema and effort intolerance.<sup>[9]</sup>

Doppler Echocardiography is considered as an important tool in the diagnosis of left ventricular diastolic dysfunction. It plays an important tool in detecting the structural and functional abnormality of heart. The variables commonly measured are early ventricular filling (E), late ventricular filling wave (A) and E/A ratio, Isovolumetric Relaxation Time (IVRT), Deceleration Time (DT), velocity at the mitral annulus level during early ventricular filling (e').<sup>[5]</sup>

The aim of the study is to find the relation between type 2 diabetes and cardiomyopathy, highlighting the variation in incidence according to age and sex. The study also evaluates the incidence of severity of disease in both the genders and its relation with HbA1c level.

## MATERIALS AND METHODS

The prospective study was conducted in the Department of General Medicine for the duration of one year. A total of 100 patients aged between 30-60 years were included in this study, out of which 50 were males and 50 were females. All these patients were newly diagnosed cases of type II diabetes mellitus. Institutional ethical clearance was taken and written consent was taken from the patients. The aim of the study was to establish the relation between HBA1C levels and severity of left ventricular diastolic dysfunction in newly diagnosed diabetes mellitus. The diagnosis of diabetes mellitus was made on the basis of four criteria given by American Diabetes Association 1) Fasting blood sugar (FBS)  $\geq 126$  mg/dl, 2) Two hours plasma glucose (PPBS)  $\geq 200$  mg/dl during an Oral Glucose tolerance test, 3) Random blood sugar level  $\geq 200$  mg/dl with symptoms like polyuria, polydipsia, polyphagia and significant weight loss, 4) HbA1C  $> 6.5\%$ . The left ventricular diastolic dysfunction is defined as the decrease in the ratio E/A  $< 1$  where 'E' stands for peak velocity of early mitral flow and 'A' stands for peak velocity of late mitral flow, along with rise in size of Left Atrial (LA) with preserved ejection.

### Inclusion Criteria

1. Newly diagnosed Type 2 diabetes mellitus patients.

2. Absence of any cardiovascular symptoms.
3. Blood pressure of  $< 130/80$  mmHg.
4. Absence of any abnormality in ECG.

### Exclusion Criteria

1. Old diagnosed diabetic patients on drugs.
2. Presence of any cardiovascular heart disease clinically.
3. Blood pressure  $> 130/80$  mmHg.
4. Renal failure.
5. Thyroid dysfunction.

Hundred patients fulfilling all the criteria were selected for the study and detailed history was taken followed by the basic investigations (FBS, PPBS, Glycosylated haemoglobin (HbA1c), Urea, Creatinine, Fasting lipid profile, Urine routine, ECG). In each patient 3-4 cycles of Doppler Echo was done and following parameters were noted:

1. E-peak velocity of early mitral flow.
2. A-peak velocity of late mitral flow.
3. E/A ratio
4. Isovolumetric Relaxation Time (IVRT).
5. Deceleration time (DT).

The study was conducted on the basis of grading of diastolic dysfunction on echocardiography.<sup>[10]</sup>

**Grade I:** Reversal of E/A ratio, IVRT  $> 100$  ms, DT  $> 240$  ms

**Grade II:** E/A ratio return to range of 0.8 to 1.5, IVRT  $< 90$  ms, DT  $< 160$  ms.

**Grade III:** E/A ratio  $> 2$ , IVRT  $< 80$  ms, DT  $< 160$  ms.

**Grade IV:** No reversibility of diastolic abnormalities on Valsalva manoeuvre, E/A ratio  $> 2$ .

All data was collected in terms of mean values and percentages. Suitable statistical tests were applied for comparing two variables. Quantitative data was analysed with the help of 't' test and qualitative data with the Chi-Square and Fisher Exact Test. Statistical significance was taken as  $P < 0.05$ .

## RESULTS

The study was conducted on 100 patients (50 males and 50 females) to evaluate the age and sex distribution of the patient. The severity of the disease was also studied in both the genders and different age groups. The mean age of the incidence of disease was 44.28 years and 45.61 years in males and females respectively, but the difference in both the genders was statistically insignificant ( $> 0.05$ ) [Table 1].

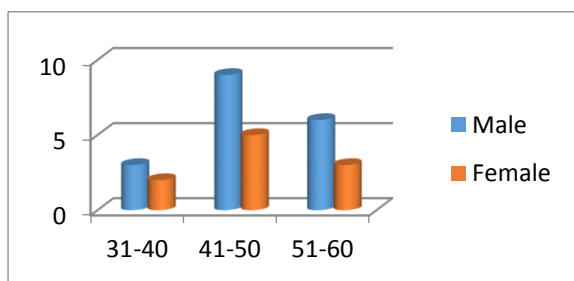
**Table 1: Mean age (years) of disease in both the genders.**

Left Ventricular Diastolic Dysfunction (LVDD)	Males (years)	Females (years)	P value
Present	44.28	45.61	$> 0.05$
Absent	42.89	43.83	$> 0.05$

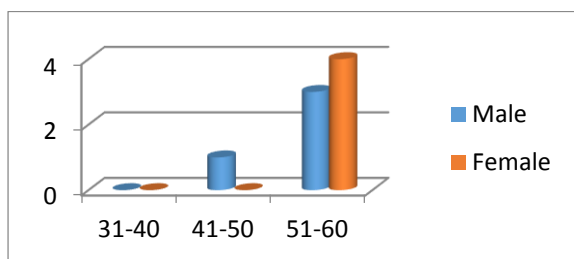
**Table 2: Sex distribution of Left ventricular diastolic dysfunction (LVDD).**

Grade of LVDD	Males (n)	Females (n)	P value
1	18	10	<0.05*
2	4	4	>0.05
3	2	1	>0.05
4	0	0	-
Absent	26	35	<0.05*

On the basis of various parameters of Doppler echocardiography, the patients were divided into four categories. In females, the disease was statistically absent in more patients (35) as compared to males (26) (<0.05). The grade 1 diabetic cardiomyopathy was statistically more common in males as compared to females (<0.05). No patient of grade 4 diabetic cardiomyopathy was found in study sample [Table 2].



**Figure 1: Incidence of grade 1 LVDD in different age groups.**



**Figure 2: Incidence of grade 2 LVDD in different age groups.**

The incidence of grade 1 diabetic cardiomyopathy was higher in males as compared to females. The commonest age group affected by grade 1 disease was 41-50 years in both the genders [Figure 1]. The incidence of grade 2 diabetic cardiomyopathy was less as compared to grade 1 [Table 2]. In both the genders the incidence of grade 2 disease was more in age group 51-60 years. In this age group females were more commonly affected than males, but it was statistically insignificant [Figure 2].

Patients with HbA1c <8 have 16% chances to get LVDD with significant P value of 0.02. Patients with HbA1c between 8 to 10 have 30% chances to get LVDD with significant P value of 0.01 [Table 3].

**Table 3: Correlation between HbA1c levels and LVDD.**

LVDD	Odds ratio	P value	Females Odds ratio (P value)	Males Odds ratio (p value)
HbA1c <8	0.16	0.02	1.1	0.31 (0.4)
HbA1c 8-10	0.3	0.01	0.17 (0.02)*	0.62 (0.5)
HbA1c >10	1	NA	1(NA)	1 (NA)

## DISCUSSION

In this study, males of age group 31 to 60 years were studied, in which 48% males and 30% females developed diabetic cardiomyopathy. In a similar study done by Perumal et al<sup>[11]</sup> found that patents with age between 31 to 50 have 28% chances to get LVDD with significant P value of 0.04. Patients with age between 31 to 40 have 45% chances to get LVDD without significant P value of 0.142. Chaudhary et al<sup>[8]</sup> in their study of 100 newly diagnosed type 2 diabetes subjects found that 41% of them developed diastolic dysfunction. These studies support our findings.

Kumar et al<sup>[12]</sup> in their study on diabetic patients concluded that age of the patients was very significantly associated with incidence of LVDD (p=0.0012), meaning that older the age at the time of diagnosis higher the incidence of LVDD. In this study, we found that incidence of grade 1 diabetic cardiomyopathy was commonest in age group 41-50 years in both the genders whereas grade 2 was more common in age group 51-60 years.

Many researchers<sup>[9-13]</sup> found a strong correlation between the development of diabetic cardiomyopathy and increased level of HbA1c. Mean of HbA1c (%) was found higher in group with LVDD (7.67±0.90) as compared to group without LVDD (7.24±0.64). This concludes that HbA1c is strongly associated with presence of LVDD (p=0.0057). Perumal et al<sup>[11]</sup> in his study found that patients with HbA1c between 6.5 to 8 have 17% chances to get LVDD with significant P value of 0.03. Patients with HbA1c between 8 to 10 have 35% chances to get LVDD with significant P value of 0.02. Patients with HbA1c 6.5 to 8 have double the chances when compared to HbA1c 6.5 to 8 with significant association statistically. Female patients with HbA1c 8 to 10 have 15% chances of having LVDD with significant association statistically (P value 0.02). Male patients with HbA1c between 6.5 to 8 have 36% chances to get LVDD without significant P value of 0.279.

Patil et al<sup>[13]</sup> in their study found that the patients with constantly increased mean fasting blood sugar have higher chances of developing LVDD as compared to patients with normal blood sugar levels.

Rubler et al<sup>[14]</sup> in their study suggested that the incidence of diabetic cardiomyopathy in type 2 diabetes patient was equal in both the genders. In contrast to this study, we found that 24 out of 50 males and 15 out of 50 females developed diabetic cardiomyopathy. Besides this the severity of the disease was also high in males.

Various invasive (Cardiac catheterization) and non-invasive (Echocardiography, Cardiac Doppler, Systolic Time Intervals (STI), Apex Cardiography (ACG), Gadolinium-enhanced cardiac MRI) techniques are used for evaluation of left ventricular function. But trans-mitral Doppler is considered as a very useful and cheaper method to diagnosis left ventricular diastolic dysfunction. LV diastolic dysfunction was considered to any one of the following findings. E/A ratio <1 or >2, DT <150 OR >220 ms, IVRT <60 OR >100 ms, E/e' ratio >15 (Ratio of mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e')).<sup>[15,16]</sup>

## CONCLUSION

- In this study, 39% of the newly diagnosed type 2 diabetes mellitus patients developed diabetic cardiomyopathy.
- The mean age of the incidence of disease was 44.28 years and 45.61 years in males and females respectively.
- In females, the disease was statistically absent in more patients (35) as compared to males (26) (<0.05).
- The severity of the disease increased with the advancing age.
- The commonest age group affected by grade 1 disease was 41-50 years.
- The incidence of grade 2 disease was more in age group 51-60 years.
- The grade 1 diabetic cardiomyopathy was statistically more common in males as compared to females (<0.05).
- The grade 2 diabetic cardiomyopathy was more common in females, but is statistically insignificant.
- Patients with HbA1c <8 have 16% chances to get LVDD with significant P value of 0.02.
- Patients with HbA1c between 8 to 10 have 30% chances to get LVDD with significant P value of 0.01.

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