

ECHOCARDIOGRAPHIC EVALUATION OF DIASTOLIC DYSFUNCTION IN ASYMPTOMATIC TYPE 2 DIABETES MELLITUS PATIENTS

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ABSTRACT: INTRODUCTION:As per the latest edition of International Diabetes Federation (IDF) Diabetes Atlas, diabetes mellitus currently affects approximately 371 million people worldwide, and majority (90%-95%) have type 2 diabetes mellitus, which is considered a metabolic cum vascular disease. The morbidity and mortality due to type 2 DM is due to its micro and macrovascular complications which affect nearly every organ system in the body – particularly heart. There is a marked increase in incidence of congestive heart failure, coronary artery disease in diabetic patients. The relative risk of developing heart failure is 3.8 in diabetic men and 5.5 in diabetic women, when compared with non-diabetic individuals. Despite similar left ventricular systolic dysfunction, patients with diabetes have more pronounced heart failure symptoms, use more diuretics, and have an adverse prognosis compared with those without diabetes; one putative explanation for these discrepancies is diastolic dysfunction of the left ventricle in diabetes mellitus. Left ventricular diastolic dysfunction thus represent the first stage of diabetic cardiomyopathy preceding changes in systolic function. The diastolic abnormalities are present in diabetic patients without overt diabetic complications of cardiovascular system, reinforcing the importance of early examination of ventricular function in individuals with diabetes mellitus. **MATERIALS AND METHODS:** This was a cross sectional study, conducted over a period of one year from August 2012 to August 2013. 50 patients with type 2 DM who had no symptoms of cardiovascular disease with normal BP and normal ECG were enrolled. Informed consent was obtained from the patients and they underwent a thorough physical examination, supported by laboratory investigations. A Doppler 2D echo was done in each patient and a calculation of LV ejection fraction, LA dimension, E velocity, A velocity and E/A ratio were done. E/A ratio of < 1 with increased LA size and normal ejection fraction of > 60% was used as echo diagnostic criteria for LV diastolic dysfunction. **RESULTS:** Our study consisted of 50 patients with type 2 DM, 30(60%) were females and 20(40%) males. Majority of patients were in the age group of 40 – 70 years. Diastolic dysfunction was present in 24(48%) patients out of whom 8 were males and 16 females. The maximum number of patients with LV diastolic dysfunction was in age group 50 – 59 years. There was a linear increase in prevalence of diastolic dysfunction with increasing age, increased duration of diabetes mellitus and increasing HbA1c levels. There was also significant correlation between LV diastolic dysfunction (LVDD) and microangiopathy. Out of 13 patients who had diabetic retinopathy, 8 patients had LVDD and out of 11 patients with microalbuminuria, 9 patients had LVDD. **CONCLUSION:** LV diastolic dysfunction is an early manifestation of diabetic cardiomyopathy. Its prevalence correlates with duration of diabetes, HbA1c values and presence of microangiopathy. LVDD contributes significantly to morbidity of congestive heart failure in diabetic patients. Echocardiography is a very useful noninvasive tool in detecting LVDD in asymptomatic type 2 DM patients.

KEY WORDS: Type 2 diabetes mellitus, LV diastolic dysfunction, Echocardiography.

INTRODUCTION: Diabetes mellitus is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications. Diabetes care is complex and requires multifactorial risk reduction strategies beyond glycemic control. Its incidence is increasing rapidly, and by 2030, this number is estimated to almost double¹. The greatest increase in prevalence is, however, expected to occur in Asia and Africa.²

India has more diabetics than any other country in the world, according to the International Diabetes Foundation. The disease affects more than 50 million Indians - 7.1% of the nation's adults - and kills about 1 million Indians a year. The average age on onset is 42.5 years.³

Diabetes and Heart: The existence of a diabetic cardiomyopathy was first proposed by Rubler et al⁴ in 1972 on the basis of postmortem findings. In 1974, Framingham study showed that heart failure was more common in diabetes due to diabetic cardiomyopathy. The Framingham Study, which involved 5209 patients followed up for 18 years, demonstrated that patients with diabetes had a greater likelihood of developing clinical heart failure. The relative risk of developing heart failure was 3.8 in diabetic men and 5.5 in diabetic women compared with nondiabetic patients. The study also revealed a marked increase in congestive heart failure, coronary artery disease and myocardial Infarction in diabetic patients.⁴

Patients with signs and symptoms of heart failure with preserved left ventricular systolic function i.e., ejection fraction of 60 % are said to have diastolic heart failure (DHF). Diabetes mellitus is one of the major risk factors for DHF. The mortality rates among the patients with diastolic heart failure ranges from 5-8 % annually as compared with 10-15% among patients with systolic heart failure. In Framingham heart study, it was shown that patients with diabetes mellitus carry an increased risk for coronary heart disease. Framingham data suggests that hyperglycemia as such is an independent risk factor.^{4,5}

The leading cause of LV systolic dysfunction and congestive heart failure in developed countries is coronary heart disease (CHD), with a prevalence in the recent multicenter heart failure trials of 66%. Thus, ischemic heart disease often contributes to the manifestation of heart failure, and the progression of heart failure in many cases may be a reflection of progression of CHD. This indicates that the prevention and treatment of heart failure in many patients should include use of established primary and secondary prevention guidelines, including control of blood pressure, use of statins and aspirin, smoking cessation, and implementation of ACEI therapy in persons with diabetes and cardiovascular riskfactors.⁶

Despite similar left ventricular systolic dysfunction, patients with diabetes have more pronounced heart failure symptoms, use more diuretics, and have an adverse prognosis compared with those without diabetes; one putative explanation for these discrepancies is diastolic dysfunction of the left ventricle in diabetes mellitus.⁷ Left ventricular diastolic dysfunction thus represent the first stage of diabetic cardiomyopathy preceding changes in systolic function, reinforcing the importance of early examination of ventricular function in individuals with diabetes.^{8,9}

The diastolic abnormalities are present in diabetic patients without overt diabetic complications of cardiovascular system, ¹⁰ it is the earliest and specific functional abnormality in diabetic cardiomyopathy and can affect patients who are free of macrovascular complications, even

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in newly diagnosed diabetes mellitus patients or in those with a disease duration of less than 1 year.¹¹

Diastole encompasses the time period during which the myocardium loses its ability to generate force and shorten and returns to an unstressed length and force ¹². By extension, diastolic dysfunction occurs when these processes are prolonged, slowed, or incomplete. Moreover, if diastolic function is truly normal, it must remain normal both at rest and during the stress of a variable heart rate, stroke volume, end-diastolic volume, and blood pressure.

Diastolic dysfunction refers to a condition in which abnormalities in mechanical function are present during diastole. The causes of diastolic dysfunction may be subdivided into a decrease in passive myocardial diastolic compliance, and an impairment in active LV relaxation. Abnormalities in diastolic function may occur in the presence or absence of a clinical syndrome of heart failure and with normal or abnormal systolic function. Therefore, whereas diastolic dysfunction describes an abnormal mechanical property, diastolic heart failure describes a clinical syndrome⁸.

MATERIALS AND METHODS: This was a cross sectional study conducted at Victoria Hospital and Bowring and Lady Curzon Hospital, both of which are affiliated to Bangalore Medical College and Research Institute, Bangalore, over a period of one year between August 2012 to August 2013.

Inclusion criteria: The study comprised of a total of 50 cases type 2 diabetes mellitus, which clinically had no symptoms of cardiovascular disease and normal blood pressure of < 130/80 mmHg, with normal ECG.

Exclusion criteria: All patients with type 2 diabetes mellitus with overt cardiac diseases like Ischemic and hypertensive heart disease congestive heart failure, valvular heart disease, and cardiomyopathy were excluded from the study.

Informed consent was obtained from the subjects. Patients underwent thorough clinical examination supported by relevant investigations.

The patients underwent the following investigations.

- a. ECG.
- b. FBS, PPBS.
- c. Urea, creatinine.
- d. Glycosylated haemoglobin (HbA1c).
- e. Urine albumin.
- f. Fasting Lipid profile.
- g. Fundus examination.
- h. Echocardiography.
- i. Doppler Echo was done in each patient and 3-4 cardiac cycles were analysed to get best phase for better outcome of results. Ejection fraction was calculated in all patients.

In Doppler study following values were evaluated.

- a. E-peak velocity of early mitral flow
- b. A- peak velocity of late mitral flow
- c. E/A ratio
- d. Left atrial size

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Reduction in E velocity increase over A velocity with E/A ratio of <1 and increase in left atrial (LA) size were considered as the evidence of left ventricular diastolic dysfunction (DD).

Statistical analysis was done by estimating the prevalence rate of diastolic dysfunction and co-relating with the with glycemetic control.

RESULTS: Our study consisted of 50 patients with type 2 DM, among whom 30(60%) were females and 20 (40%) males. Most of the subjects were in 40-70 years age group (Table 1, Table2).

| Gender | Total | Diastolic Dysfunction | | Percentage | |
|---------|-------|-----------------------|--------|------------|--------|
| | | Present | Absent | Present | Absent |
| Males | 20 | 8 | 12 | 40% | 60% |
| Females | 30 | 16 | 14 | 53% | 47% |

Table 1: Correlation between gender and diastolic dysfunction

Diastolic dysfunction was present in 24 (48%) of the cases among them, 8 were males, 16 were females. Though statistically not significant, diastolic dysfunction was more prevalent in females.

Out of 24(48%) with Diastolic dysfunction maximum prevalence was found in 50-59 years age group. 8(57.14%) patients out of 14 in this group had diastolic dysfunction. In patients in the age group 60-69 years 6(50%) patients of 12 had diastolic dysfunction. Among the age group of 50 – 59 years and 60 – 69 years, diastolic dysfunction was almost comparable. There was a linear increase in the prevalence of diastolic dysfunction with the increasing age.

| Age wise distribution | No of cases | | | Percentage | Diastolic dysfunction | |
|-----------------------|-------------|--------|-------|------------|-----------------------|--------|
| | Male | Female | Total | | Present | Absent |
| 30-39 | 2 | 5 | 7 | 14 | 1 | 6 |
| 40-49 | 5 | 7 | 12 | 24 | 4 | 8 |
| 50-59 | 4 | 10 | 14 | 28 | 8 | 6 |
| 60-69 | 7 | 5 | 12 | 24 | 6 | 6 |
| 70-above | 2 | 3 | 5 | 10 | 5 | 0 |
| Total | 20 | 30 | 50 | 100 | 24 | 26 |

Table 2: Age wise distribution and correlation with diastolic dysfunction

Comparing with duration of diabetes, we had 21(42%) patients with less than 5 year duration of diabetes and 20(40%) patients with 5-10 years duration of diabetes. Statistically it was significant as we had higher percentage of patients with diastolic dysfunction as duration of diabetes increased (table 3, Fig 1).

| Duration in year | No of cases | | | Percentage | Diastolic dysfunction | |
|------------------|-------------|--------|-------|------------|-----------------------|--------|
| | Male | Female | Total | | Present | Absent |
| 0-5 | 6 | 15 | 21 | 42 | 7 | 14 |
| 6-10 | 10 | 10 | 20 | 40 | 10 | 10 |
| 11-15 | 3 | 4 | 7 | 14 | 5 | 2 |
| >15 | 1 | 1 | 2 | 2 | 2 | 0 |
| Total | 20 | 30 | 50 | 100 | 24 | 26 |

Table 3: Duration of diabetes and correlation with diastolic dysfunction

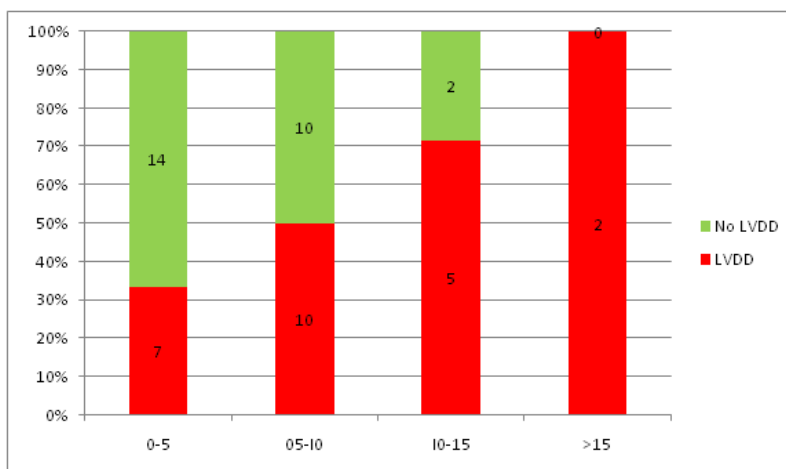


Fig. 1: Correlation between duration of diabetes diastolic dysfunction

Patients receiving OHAs were more 32 (64%) compared to 11 (22%) patients who were on insulin. And 7(14%) patients were on both insulin and OHAs(Table 4).

| Type of Treatment | Total | Diastolic Dysfunction | |
|-------------------|-----------|-----------------------|-----------|
| | | Present | Absent |
| OHA | 32 | 14 | 18 |
| Insulin | 11 | 6 | 5 |
| Both | 7 | 4 | 3 |
| Total | 50 | 24 | 26 |

Table 4: Correlation between type of treatment and diastolic dysfunction

25(50%) subjects had HbA1c >8 %which indicated poor glycemic control (Table 5). Prevalence of diastolic dysfunction increased gradually with the rise in HbA1c levels and it was statistically significant as shown in (Table 5 Fig 2). Diastolic dysfunction was present in 6 patients out of 24with HbA1c between <8%. 18(75%)patients of 24 who had diastolic dysfunction had HbA1c >8. In patients with HbA1c >10 % out of 7 patients 6 had diastolic dysfunction.

| HbA1C level | Total | Diastolic Dysfunction | |
|--------------|-----------|-----------------------|-----------|
| | | Present | Absent |
| 6.4-7 | 4 | 1 | 3 |
| 7.1-8 | 21 | 5 | 16 |
| 8.1-10 | 18 | 12 | 6 |
| >10 | 7 | 6 | 1 |
| Total | 50 | 24 | 26 |

Table 5: Correlation between HbA1C level and Diastolic Dysfunction

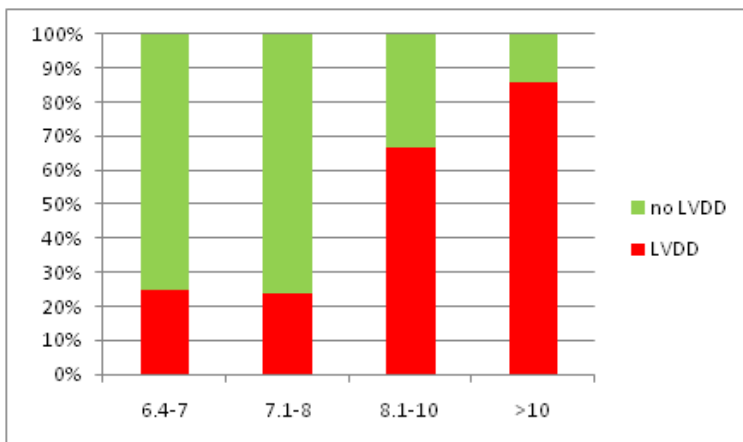


Fig. 2: Correlation between HbA1C level and Diastolic Dysfunction

There were significant changes in E, A and E/A ratio in patients who had diastolic dysfunction. Left atrial size was higher in patients who had diastolic dysfunction. The mean LA size was 2.711 ± 0.14 in patients who did not have diastolic dysfunction and it was 3.40 ± 0.25 in patients who had diastolic dysfunction.

There was a significant correlation with diastolic dysfunction and microangiopathy. Out of 13 patients who had diabetic retinopathy, 8 patients had diastolic dysfunction. Out of 11 patients who had microalbuminuria, 9 had diastolic dysfunction (table 6 and 7).

| | | Diabetic retinopathy | | |
|-----------------------|---------|----------------------|--------|-------|
| | | Present | Absent | Total |
| Diastolic Dysfunction | Present | 8 | 16 | 24 |
| | Absent | 5 | 21 | 26 |
| Total | | 13 | 37 | 50 |

Table 6: Correlation between diabetic retinopathy and Diastolic Dysfunction

| | | Microalbuminuria | | |
|-----------------------|---------|------------------|--------|-------|
| | | Present | Absent | Total |
| Diastolic Dysfunction | Present | 9 | 15 | 24 |
| | Absent | 2 | 24 | 26 |
| Total | | 11 | 39 | 50 |

Table 7: Correlation between microalbuminuria and Diastolic Dysfunction

DISCUSSION: Numerous studies have shown that impairment of the LV diastolic function may be detected in patients with diabetes. Diastolic LV abnormalities have been initially disclosed by cardiac catheterization. Regan et al ¹³ demonstrated in normotensive, diabetic patients without coronary artery disease and without clinical evidence of heart failure, increased left-ventricular end-diastolic pressure, a decreased left-ventricular end-diastolic volume with a normal ejection fraction. Paul Poirier et al ¹⁴ in 2001 evaluated 40 diabetic patients without clinical evidence of cardiac disease by

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Doppler Echocardiography and came to conclusion that diastolic function in diabetic patients was impaired even in patients with normal systolic function.

Numerous studies in humans have explored the association of diabetes with histopathological abnormalities of myocardium. Alterations in intramyocardial coronary arteries, similar to those seen in other organs of diabetic patients have been reported. Endothelial proliferation and subendothelial hyaline thickening with PAS-positive material in the vessel wall have been described in some but not all patients with or without overt congestive heart failure¹⁵ Capillary basement membrane thickening and capillary microaneurysms have also been observed in hearts of diabetics^{16,17}. Zoneraich et al¹⁸ who conducted their study in young normotensive type 1 diabetics, found small vessel disease in 72% of diabetic patients, while it was present in only 12% of non-diabetic subjects.

Interstitial accumulations of advanced-glycated end products (AGEs), which include collagen, elastin and other connective tissue proteins, as well as fibrosis in the myocardium, have been reported in biopsy or post-mortem studies of human diabetic hearts^{13,19}. The mechanism of collagen accumulation in the diabetic myocardium seems to be due to impaired degradation rather than enhanced synthesis²⁰. The interstitial abnormalities could explain an increase in end-diastolic stiffness as well as LV mass and contribute to the diastolic dysfunction¹³. In the less advanced forms of tissue abnormality, the interstitial changes seem to predominate for some time and are associated with preserved cell morphology that is consistent with normal systolic function. As a potential diagnostic tool, it has been suggested that collagen accumulation in the extracellular matrix of the heart is responsible for abnormal acoustic properties of the myocardium in diabetic patients.

In our study most of the patients had duration of diabetes less than 10 years. This was because, as the duration of diabetes increased, other associated co-morbid diseases like hypertension, IHD, would also appear and hence could not be included in our study. So the patients with duration of diabetes more than 15 years and above age of 70 years were less. When the treatment profile was evaluated most of the patients were on OHAS / OHAS with insulin, most of the subjects had poor glycemic control, reasons are multifactorial Viz., poor compliance of the patient with reference to treatment, lifestyle modifications, inadequate doses, poor regular checkup.

Left ventricular diastolic dysfunction (LVDD) was found in 24(48%) of our patients. This prevalence of diastolic dysfunction was almost comparable with other studies as shown in (Table 8).

| Studies | Percentage |
|----------------------------------|------------|
| Paul Poirier et al ¹⁴ | 60 |
| Faden G et al ²¹ | 64 |
| Markuszewski et al ²² | 43 |
| Patil C et al ²³ | 54.33 |
| Present study | 48 |

Table 8: Comparison of diastolic dysfunction with other studies

Genderwise comparison of LVDD showed 53 % female subjects had diastolic dysfunction compared to 40 % of males. This could be due to hormonal changes that accompany after menopause. The prevalence of diastolic dysfunction increased with duration of diabetes. The previous studies also confirmed the above findings.

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Celentano et al ²⁵ studied 64 subjects with normal glucose tolerance (n = 25), with impaired glucose tolerance (n = 15) and with type 2 diabetes mellitus (n = 24) diagnosed by an oral glucose tolerance test according to the recommendations of the World Health Organization. They found early signs of diastolic dysfunction (assessed by E/A mitral flow ratio), not only in patients with diabetes but also in those with impaired glucose tolerance, independent of the confounding role of ischemia, body weight, and blood pressure.

CONCLUSION: The prevalence of left ventricular diastolic dysfunction in asymptomatic, normotensive patients with type 2 DM without significant coronary artery disease is much higher than previously suspected as evidenced by the results of this study and also of similar other studies. LV diastolic dysfunction correlated with duration of diabetes, HbA1c levels and microangiopathies, and it contributes significantly to the morbidity of congestive heart failure in diabetic patients. Echocardiography with measurements of diastolic functional parameters appears to be a sensitive noninvasive method for evaluating the manifestation and course of early diabetic cardiomyopathy. Early diagnosis and institution of treatment for LVDD in diabetic patients will reduce the morbidity and improve the outcomes by preventing future development of heart failure.

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