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# Does the Duration of DM & HbA1c Levels Influence the Onset of Diastolic Dysfunction?

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**Abstract**

Diabetes Mellitus is a serious, chronic disease which is characterized by insufficient production of insulin by the pancreas. Myocardial infarction, stroke, nephropathy, peripheral vascular disease, retinopathy, peripheral & autonomic neuropathy resulting in premature death are some of the serious complications associated with diabetes mellitus. Evidence gathered from earlier data shows that there is a high prevalence of diastolic dysfunction among subjects with DM than in nondiabetic patients, even without clinical evidence of coronary artery disease. The objective of our study was to observe the prevalence of diastolic dysfunction in asymptomatic type 2 diabetes mellitus patients. We included 100 subjects with a diagnosis of type 2 DM and 100 age and gender matched controls. Diastolic function was assessed using trans-thoracic echocardiography. Our study showed that the risk of diastolic dysfunction was significantly higher among the patients with longer duration of DM. Similarly patients with higher HbA1c were more likely to suffer from diastolic dysfunction than patients with lower HbA1c levels. Early detection of diastolic dysfunction in diabetic subjects is warranted to prevent left ventricular dysfunction.

**Keywords:** Diabetes; Diastolic Dysfunction; Echocardiography; Left Ventricular Dysfunction; HbA1c.

## Introduction

Diabetes Mellitus is a serious, chronic disease which is characterized by insufficient production of insulin by the pancreas as per the body's demand or the inability of the body to effectively use the insulin it produces [1]. The global incidence and prevalence of diabetes type 2 are increasing perpetually leading to an abrupt rise in complications like myocardial infarction, stroke, nephropathy, leg amputation, retinopathy, peripheral & autonomic neuropathy resulting in premature death. Diabetes during pregnancy can also be fatal leading to increased risk of fetal death and many other complications [2]. According to WHO, it was estimated that in 1980, 108 million adults were suffering from diabetes which has gradually increased to 422 million adults in 2014. Prevalence (age-standardized) of diabetes has risen from 4.7% to 8.5% in the adult population since 1980, faster in low- and middle-income countries than in high-income countries [3]. Globally 30 million people were affected by diabetes in 1985, the figure marked up to 194 million people in 2003 and it is estimated that this figure will escalate to almost 592 million by 2035 [4,5]. A number of studies have reported a high prevalence of pre-clinical diastolic dysfunction among subjects with DM than in nondiabetic patients, even without clinical evidence of coronary artery disease [6]. Diastolic heart failure mortality ranges from 5-8% annually, when compared with patients with systolic heart failure which is 10-15% , suggesting that diastolic function gets affected by myocardial damage before the systolic function [7,8]. Changes in ventricular diastolic properties leading to decreased stroke volume are

the key factor leading to diabetic cardiomyopathy in diabetic patients. Gradually with the course of the disease, the early diastolic relaxation is impaired causing decreased myocardial contraction. Hence early prognostic measures should be taken in type 2 diabetes patients to prevent diabetic heart failure [9].

The aim of our study was to observe the prevalence of diastolic dysfunction in asymptomatic type 2 diabetes mellitus patients. We also assessed the relationship of diastolic dysfunction with the duration of diabetes mellitus and HbA1c level.

## Methodology

This study was an observational, analytical study that was conducted in the Department of Cardiology, SRM Medical College Hospital & Research Centre, Kattankulathur, Chennai, Tamil Nadu, from August 2015 to December 2016 (17 months).

### *Inclusion and Exclusion Criteria*

Patients with type 2 diabetes mellitus without any known cardiovascular disease were included in the study. Healthy subjects were included as controls. Patients with clinical features of heart failure, history of hypertension, evidence of ischemic heart disease (from suggestive history, ECG, evidence of regional wall motion abnormality on echocardiography), history of valvular heart disease, left ventricular systolic dysfunction (LVEF <50%), evidence of left ventricular hypertrophy on echocardiography, poor trans-thoracic echo window and whose estimated glomerular filtration rate (eGFR, ml/min per 1.73 m2) < 60 were excluded from the study.

Subjects were chosen randomly from the OPD of Department of Cardiology, SRM Medical College Hospital, and Research Centre, Kattankulathur, Chennai. Detailed medical history of each study subject was collected. Presence of ischemic heart disease (IHD) was assessed by the history of anginal chest pain, past history of IHD, ECG changes, and presence of regional wall motion abnormality in Echocardiography.

The study was approved by Institutional Ethics Committee. Informed consent was obtained. Those who did give consent underwent following investigations like Fasting blood glucose, Serum urea, and Creatinine, Glycosylated hemoglobin (HbA1c), 2-dimensional echocardiography with Doppler imaging, to assess left the ventricular diastolic function.

A resting trans-thoracic 2-dimensional echocardiogram (TTE) with Doppler evaluation of trans-mitral inflow and Tissue Doppler Imaging (TDI) was performed to assess left the ventricular diastolic function. Echocardiography was performed by Siemens action cv70 echocardiography machine according to the standard protocol. Doppler-derived trans-mitral inflow velocities were obtained in the apical 4-chamber view, with the sample volume placed at the mitral valve leaflet tips. Measurements included the trans-mitral early diastolic rapid filling (E-wave) and atrial contraction late filling (A-wave) velocities to calculate E/A ratio, isovolumteric relaxation time (IVRT) and deceleration time (DT). For tissue Doppler imaging, the mitral annulus velocity was obtained with sample volume placed at the lateral side and septal side of the mitral annulus. Diastolic dysfunction was labeled according to the standard guidelines.

### *Statistical Analysis*

Statistical analysis was performed using SPSS. V.16.0. Chi-Square Test was used to test the association of different study variables with the study groups. A t-test was used to compare the means and Z-test was used to test the significant difference between two proportions. Odds ratio (OR) with 95% Confidence Interval (CI) was calculated to measure the different risk factor. The significance level was set at 0.05 and confidence intervals were at 95 percent level.

## Results

The total number of subjects enrolled in the study was 200 (100 subjects were diabetic and 100 subjects were nondiabetic). The baseline characteristics of patients like age, gender, BMI, fasting blood glucose, HbA1c (%), mode of treatment was observed. No significant difference was found in the baseline characteristics of the patients between the diabetic and nondiabetic group groups (Table 1).

The patients were evaluated with 2-dimensional echocardiography with Doppler imaging. Parameters like E/A Ratio, E/A Ratio with Valsalva, IVRT, E/e' Ratio and DT were observed. E/A Ratio was significantly lower in diabetic patients than in nondiabetic patients (p=0.001). Even after measuring E/A Ratio with Valsalva, it remained significantly lower in diabetic patients (p=0.0001). Isovolumetric relaxation time (IVRT), deceleration time (DT) and E/e' ratio were significantly higher (p= 0.0001) in

diabetic patients when compared with nondiabetic patients (Table 2).

The risk of diastolic dysfunction was significantly higher (p=0.0001) among the patients whose mean duration of DM (8.93 ± 4.02) was 8 years than patients with mean duration of DM (5.59 ± 3.95.) of two years (Figure 1a). Patients with a greater percentage of HbA1c (8.03±1.49 ; p value = 0.001) were likely to suffer from diastolic dysfunction than patients with lower HbA1c levels (7.06±1.12) (Figure 1b).

**Table 1:** Baseline Characteristics of diabetic and non diabetic patients

| Characteristics | Diabetic (N=100) | Non diabetic (N=100) | P-value |
|---|---|---|---|
| Age (in years) | 51.92±8.20 | 50.05±6.96 | >0.05 |
| Gender (%) | 56 | 52 | >0.05 |
| BMI (kg/m²) | 24.15±2.07 | 23.74±1.68 | >0.05 |
| HbA1c | 7.63±1.43 | 5.11±0.34 | <0.01 |

**Table 2:** Echocardiographic Parameters of Diabetic and Non diabetic patients

| Echo Parameters | Diabetic | Non Diabetic | P value |
|---|---|---|---|
| E/A Ratio | 1.06±0.38 | 1.22±0.26 | 0.001 |
| E/A Ratio with Valsalva | 0.91±0.33 | 1.13±0.25 | 0.0001 |
| DT (ms) | 222.44±37.63 | 199.92±27.95 | 0.0001 |
| IVRT (ms) | 95.2±14.7 | 86.2±12.14 | 0.0001 |
| E/e' Ratio | 7.49±2.50 | 6.46±1.09 | 0.0001 |

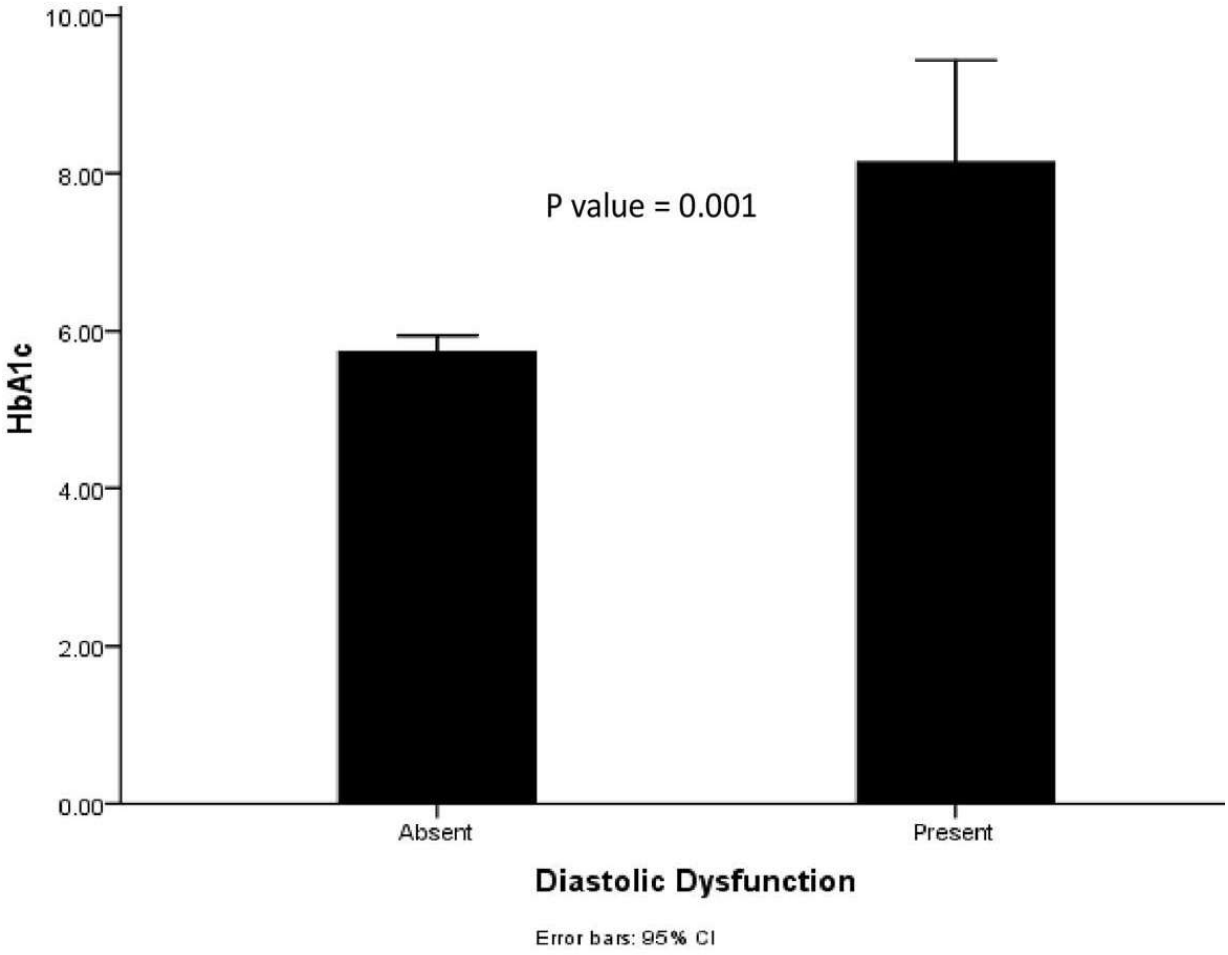


**Fig. 1a:** Risk of diastolic dysfunction and mean duration of DM

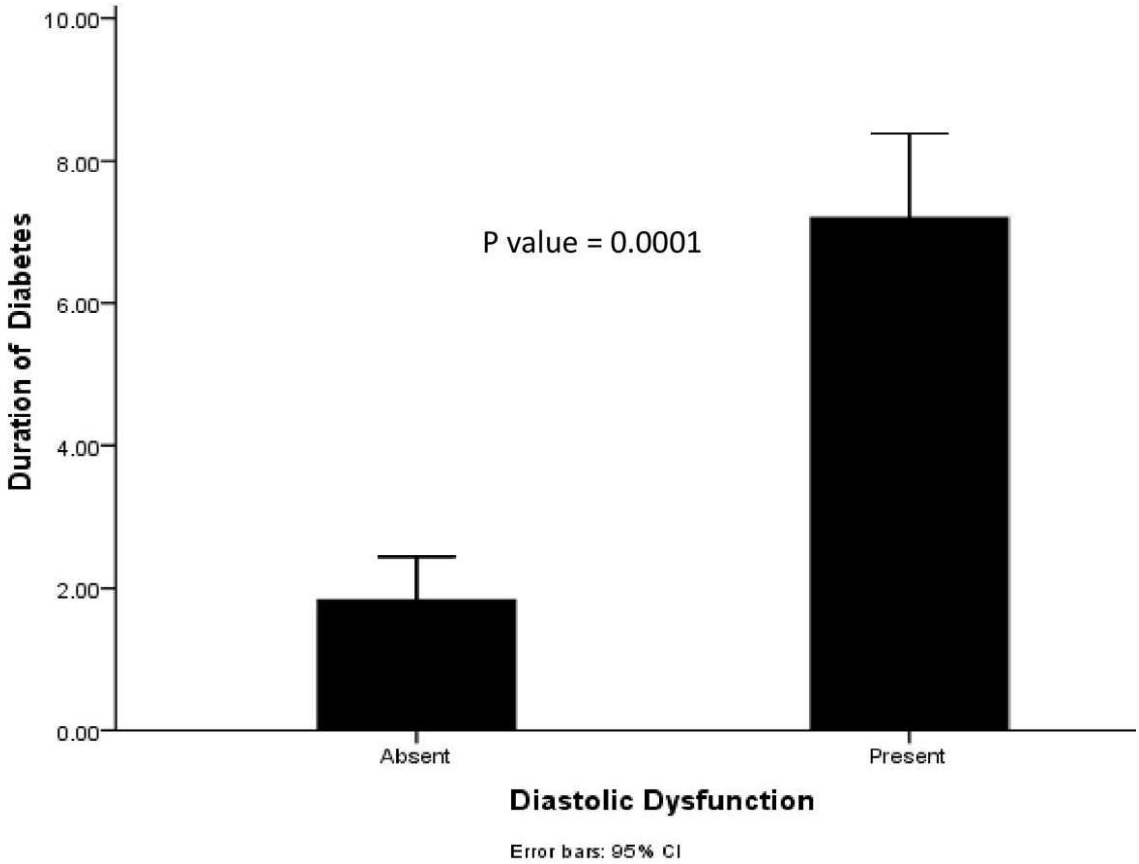


**Fig. 1b:** HbA1c levels & Risk of diastolic dysfunction

## Discussion

Our study showed that diastolic dysfunction has a higher prevalence in patients with diabetes mellitus than in the control group. A prospective study was conducted in Maharashtra, for 1 year. The main objective of the study was to study the incidence of diastolic dysfunction in diabetic subjects and its association with age, duration of diabetes mellitus (DM), Glycosylated hemoglobin (HbA1c) levels, obesity indices and diabetic micro angiopathy. 127 study subjects with Type 2 diabetes and 100 controls were enrolled in the study. After studying the subjects for five years it was observed that 69 (54.33%) subjects from the case group had diastolic dysfunction, whereas in the control group only 11% showed the diastolic dysfunction ($P < 0.02$) [10].

In a study done by Poirier et al it was observed that out of 46 men, 28 subjects (60%) had left ventricular diastolic dysfunction, out of which 13 (28%) patients had a pseudo-normal pattern of ventricular filling and 15 (32%) had impaired relaxation. LVDD was much more common in patients suffering from diabetes mellitus independent of clinically detectable heart disease (paul et al). In a study where 55 subjects with Type 2 DM were compared with 66 age- and sex-matched healthy control subjects, a greater prevalence of diastolic abnormalities was observed among the diabetic subjects [11].

Our study exhibited the increasing risk of diastolic dysfunction in association with the duration of diabetes mellitus. In a study, 486 patients with diabetes mellitus were selected from Olmsted County, MN from the year 1996 to 2007 using an electronic coding system. The study revealed that the duration of diabetes ≥ 4 years was independently associated with LV diastolic dysfunction (E/e'>15) in multivariate logistic regression modeling after adjustment for age, gender, body mass index, prior coronary disease, prior hypertension and ejection fraction (OR=1.91, 95% CI=1.19–3.07; p=0.007). [12] Hyun et al in his study enrolled 65 subjects with type 2 diabetes (M : F = 45 : 20; mean age 51 [26 to 76] years; mean body mass index [BMI] 25.0±2.5 kg/m2) without hypertension, heart disease, or renal disease. Fifteen patients were diagnosed with diastolic

dysfunction when evaluated by Doppler echocardiography. After adjusting for age and sex, the results showed that duration of diabetes was longer (9.65 ± 1.48 vs. 4.71± 0.78 years; $P < 0.01$) in patients with LV diastolic dysfunction than in those without diastolic dysfunction [13].

A significant association of glycemic status with diastolic dysfunction was seen in our study. Similar results were observed in a study done by Hameedullah et al. The study was conducted at Peshawar from March to September 2007. Sixty normotensive type 2 diabetic patients, 20 well controlled, 20 moderately controlled and 20 poorly controlled (Group-3) diabetic patients were enrolled in the study. A significant association was observed between HbA1c level and diastolic indices ($p < 0.05$). Recurrent diastolic dysfunction was maximum in poorly controlled diabetic patients [14].

*Limitations of the Study*

As this was a cross-sectional study done for shorter patients, we were unable to evaluate the correlation between the progression of diabetes with diastolic dysfunction across a longer time period. The Diastolic dysfunction can be assessed with more refined tools such as cardiac MRI or stress echocardiography or invasive cardiac catheterization.

However since the study was being done in a population of patients within a limited time frame, logistic issues pre-empted us from using these methods. Further cardiac catheterization is an invasive procedure and cannot be used in a noncardiac population with no reasonable indication.

## Conclusion

Our study validates the fact the fact that even in diabetic patients without any history of cardiovascular events, diastolic dysfunction is present. The duration of diabetes also appeared to have a significant role in the degree of diastolic dysfunction. It is essential that clinicians treating diabetes refer patients for detection of early diastolic dysfunction so that appropriate preventive measures are taken before the onset of left ventricular dysfunction.

*Conflict of Interest*

We declare that we do not have any conflict of interest.

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