ORIGINAL ARTICLE

# Diastolic Dysfunction in Type 2 Diabetes Mellitus without Cardiovascular Abnormality

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## ABSTRACT

*Aim: The purpose of the study was to investigate the prevalence of diastolic dysfunction in patients with type II diabetes mellitus without overt cardiovascular disease, and to investigate whether its presence is associated with age, sex, onset of diabetes, glycemic control and obesity.*

*Patient and methods: We studied 30 patients with type 2 diabetes; 11 were men and 19 were women; their ages ranged from 40 – 65 years; all patients had no evidence of hypertension, coronary artery disease, congestive heart failure, anatomical disease of heart, arrhythmia; and myocardiac ischemia at maximal treadmill exercise test. Diastolic dysfunction was evaluated using Doppler echocardiography.*

*Results: Diastolic dysfunction was found in 22 subjects (73.3%) of whom 21 (70%) had abnormal relaxation and one (3.3%) had a pseudonormal pattern of ventricular filling. Systolic function was normal in all subjects, and there was no correlation between diastolic dysfunction and age, sex, onset of diabetes, glycemic control and obesity.*

*Conclusion: Diastolic dysfunction is much more common than previously reported. The high prevalence of this phenomenon population suggests the importance of screening for diastolic dysfunction among such high-risk patients.*



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## INTRODUCTION

Diabetes mellitus patients could suffer various complications, including microvascular as well as macrovascular conditions. In the field of cardiology, in addition to coronary conditions, cardiomyopathy is a separate entity that is important to undergo further scrutiny among patients with diabetes mellitus.

Diastolic dysfunction in the left ventricle is an initial manifestation of cardiomyopathy. Studies abroad report a high rate of diastolic dysfunction (20-60%) among diabetes mellitus patients without prior history of hypertension and other cardiovascular abnormality. [1,2,3]

The pathogenesis of diabetic cardiomyopathy is different from artherosclerotic cardiovascular abnormality. [4,5,6] There is an accumulation of PAS (Periodic Acid Schiff) – positive glycoprotein material in patients with diabetic cardiomyopathy. There is also fibrosis and increased collagenous tissue, causing myocardiac hypertrophy and hyperplasia that causes systolic myocardiac contractile dysfunction as well as diastolic dysfunction.[7]

Diastolic function pertains to an increase in intracardiac pressure that occurs when the heart is filled with blood. Diastolic dysfunction pertains to increased resistance for ventricular filling, thus increasing intracardiac pressure.[8]

On echocardiography, diastolic dysfunction is made up of abnormal, pseudonormal, and restrictive relaxation. The degree of diastolic dysfunction is classified into 4 grades as follows:

- Grade 1 : abnormal relaxation
- Grade 2 : pseudonormal relaxation
- Grade 3 : restrictive (reversibel) relaxation
- Grade 4 : restrictive (irreversibel) relaxation

## METHOD

Thirty patients with type 2 diabetes mellitus who attended the Metabolic-Endocrinology Out-Patient Clinic at Cipto Mangunkusumo Hospital were selected consecutively. There were 11 males and 19 females. Type 2 diabetes was established based on the 1998 national consensus for the management of diabetes mellitus. Screening was conducted to eliminate hypertension and cardiovascular abnormality using sphygmomanometry, electrocardiography (ECG), treadmill test, and echocardiography. Blood sugar control was obtained from HbA1c levels. Obesity was determined using body mass index (BMI). The first onest of diabetes was during the initial diagnosis. The age was determined during the study.

Electrocardiography (ECG) was performed using a Fukuda 2000 instrument, treadmill test with Bruce method, and echocardiography with Apogee CX 200, all conducted at the division of Cardiology of Cipto Mangunkusumo Hospital. HbA1c levels were determined using a variant instrument with high pressure liquid chromatography at the Prodia Laboratory. The age was based on the patient's national ID card.

Body mass index is weight (kg) divided by a square of body height (m2). Diastolic dysfunction gradation was determined using an echodoppler according to the Nishimura criteria.

### Statistical Analysis

The data was analyzed using on a computer the SPSS for windows 10 program. Descriptive data were presented as text, tables, and figures for analysis. The significance level was alpha=0.05. The following statistical tests were used: univariant analysis to determine the mean average and standard deviation, while the Fisher's exact test was used for bivariant analysis to determine the correlation between 2 variables, diastolic dysfunction, as the dependent variable, and various independent variables. Numeric data that followed the normal (bell) curve distribution was analyzed using the T test, while those that were not normally distributed were analyzed using Mann-Whitney test.

## RESULTS

The study took place from October to December 2001. There were 30 people as sample. Complete details of the samples can be found in the Table for General Characteristics as follows (see Table 1).

**Table 1. General Characteristics (n=30)**

| | Sum (N) | Mean average | SB | % | Min | Max | med |
|---|---|---|---|---|---|---|---|
| *Male* | *11* | - | - | *37* | | | |
| *Female* | *19* | - | - | *63* | | | |
| *Age (years)* | - | *51.5* | *6.5* | - | | | |
| *BMI (kg/m²)* | - | *24.86* | *3.09* | - | | | |
| *HbA1c (%)* | - | *8.58* | *1.75* | - | | | |
| *TD Systolic (mmHg)* | - | *121.33* | *8.60* | - | | | |
| *TD Diastolic (mmHg)* | - | *78* | *4.07* | - | | | |
| *Ejection Frac (%)* | - | *75.47* | *8.39* | - | | | |
| *Onset of DM (years)** | | | | | *1* | *16* | *7.53* |

* *presented in the form of median*

### The Prevalence of Diastolic Dysfunction

All of the 30 patients with type 2 diabetes mellitus that participated in the study had a satisfactory systolic function (within normal limits) with a mean ejection fraction of 75.47 ± 8.39 %, while 73.3 % (22 patients) had a diastolic dysfunction and the remaining 26.7 % (8 patients) had a normal diastolic function.

Out of the group with diastolic dysfunction (22 patients), 70% (21 patients) had an abnormal relaxation and 3.3% (1 person) had a pseudonormal relaxation, while no patient was found with the restrictive form (see figures 1 and 2).

The statistical calculations between diastolic dysfunction and the independent variables could be found in Table 2a).

**Table 2a. The Correlation Between Diastolic Dysfunction and Various Independent Variables.**

| | Dysfunction (+) n=22 | Diastolic (-) n=8 | Statistical test | P |
|---|---|---|---|---|
| *Age (years)* | *52.40 ± 5.6* | *49 ± 8.49* | *t-test* | *0.217* |
| *BMI (kg/m2)* | *24.63 ± 3.02* | *25.48 ± 3.39* | *t-test* | *0.52* |
| *Onset of DM *(years)* | *7 (1-16)* | *7 (3-15)* | *Mann - Whitney* | *0.96* |
| *HbA1c (%)* | *8.59 ± 1.85* | *8.56 ± 1.57* | *t-test* | *0.97* |

**: presented in the form of median*

Based on the Fisher's exact test, the correlation between diastolic dysfunction in type 2 diabetes mellitus without cardiovascular abnormality and sex was not significant.

There was no significant correlation between diastolic dysfunction in type 2 diabetes mellitus without cardiovascular abnormality and the duration of disease (diabetes mellitus) according to the Mann-Whitney statistical test. Based on the Fisher's exact test, the correlation for the group with an onset of over 5 years or the group with an onset of 5 years or less (see Table 2b) was not significant.

**Table 2b. The Correlation Between Diastolic Dysfunction and Various Independent Variables.**

| | Dysfunction (+) n=22 | Diastolic (-) n=8 | Total | Statistical test | P |
|---|---|---|---|---|---|
| Male | 8 | 3 | 11 | | |
| Female | 14 | 5 | 19 | Fisher | 0.637 |
| Onset > 5 years | 14 | 6 | 20 | | |
| ≤ 5 years | 8 | 2 | 10 | Fisher | 0.451 |
| HbA1c > 7 mg/dL | 18 | 6 | 24 | | |
| ≤ 7 mg/dL | 4 | 2 | 6 | Fisher | 0.519 |
| BMI > 25 kg/m$^2$ | 11 | 5 | 16 | | |
| ≤ 25 kg/m$^2$ | 11 | 3 | 14 | Fisher | 0.426 |

According to the independent t-test, there was no significant correlation between diastolic dysfunction in type 2 diabetes mellitus without cardiovascular abnormality and age.

The correlation between diastolic dysfunction in type 2 diabetes mellitus without cardiovascular abnormality and HbA1c according to the independent T test was not significant. The correlation between diastolic dysfunction in type 2 diabetes mellitus without cardiovascular abnormality and HbA1c levels of more than 7mg/dL or HbA1c ? 7mg/dL using the Fisher's exact test was also found to be not significant.

The correlation between diastolic dysfunction in type 2 diabetes mellitus without cardiovascular abnormality and body mass index was not significant according to independent T test. Based on the Fisher's exact test for body mass indexes (BMI) of over 25 kg/m$^2$ and BMI ? 25 kg/m$^2$ there was also no significant correlation.

## DISCUSSION

There have been no previous studies on diastolic dysfunction in patients with type 2 diabetes mellitus in Indonesia. Studies abroad more frequently report studies on type I rather than type 2 diabetes mellitus.

Out of the 30 patients that met the inclusion criteria, more were female (63%) than male (37%). In the 22 samples with diastolic dysfunction, more were also female (63.6%) than male (36.6%). There are no references on the frequency distribution according to sex of diabetes mellitus patients with diastolic dysfunction. The Framingham Heart Study only reported more female than male diabetes mellitus patients suffer from a heart abnormality, while Lee et al did not report a significant difference in the incidence of diastolic dysfunction among male and female diabetes mellitus patients.[10]

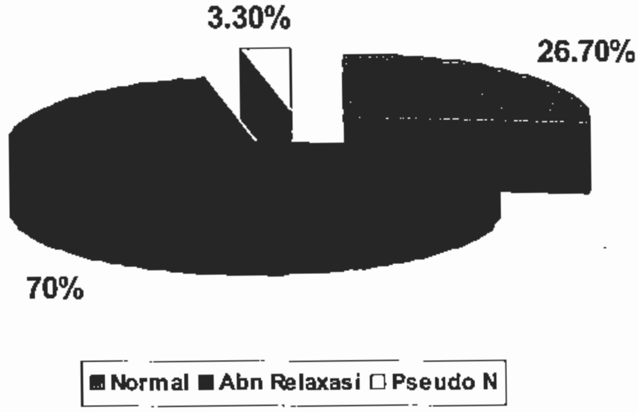


*Figure 1. The Prevalence Rate of Diastolic Dysfunction Normal, Abnormal Relaxation, Pseudo-normal*

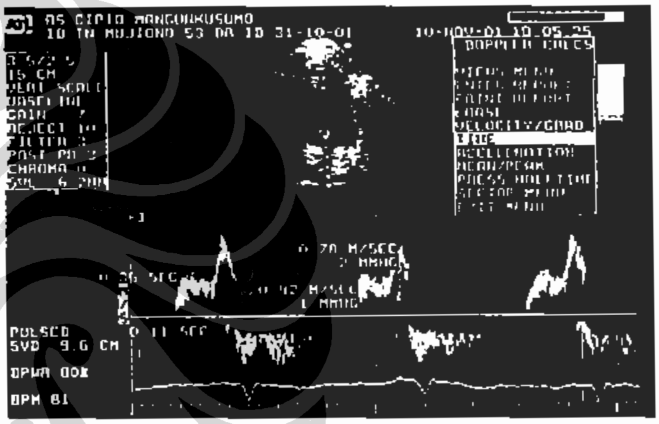

*Figure 2. Diastolic Dysfunction Demonstrated Using Echo-doppler.*

The oldest patient in this study was 65 years. We limited the age since advaced age physiologically produces diastolic dysfunction due to cardiomyohypertrophy.[11]

In this study of 30 samples, a large number of diabetes mellitus patients who were originally found without cardiovascular disease were identified with diastolic dysfunction (73.3%). This study found a higher prevalence rate than previous studies that reported diastolic dysfunction in patients with diabetes mellitus without previous cardiovascular abnormality, which found a frequency of 20-60% of all samples. [1,2,3,12]

The form of diastolic dysfunction in this study was mostly abnormal relaxation, which is a mild type, which can be understood since the sample was selected from out-patients from the Metabolic-Endocrinology out-patient clinic who did not have clinical cardiovascular abnomality.

The mean HbA1c level (8.58 ±1.75) in this study reflected a poor glycemic control condition in 3 months. Theoretically, poor glycemic control influences the incidence of diastolic dysfunction, but this was not significantly identified in this study. This may have been due to the lack of a clear parameter to determine long term glycemic control. Stratton et al in the UKPDS reported that patients with type 2 diabetes mellitus with a high risk of diabetic complication had a strong correlation with hyperglycemia. Each reduction in HbA1c level reduces the risk of complication, with the lowest risk among those with HbA1c levels around normal, of less than 6%.[13]

The average onset of diabetes mellitus in this study was 7.53 ± 4.22 years. References state that the appearance of diabetic complications is in line with the duration of the disease (diabetes mellitus), where earlier onset would allow a higher frequency of complications. Shapiro et al reported a significant correlation between the history of diabetes mellitus and microvascular complication index in 50 patients with type 1 diabetes mellitus, with an average onset of 10 ± 9 years.14 This study did not find a significant correlation between the duration of diabetes mellitus and diastolic dysfunction.

In this study, statistical assessment using the Fisher's exact test did not find a significant correlation between diastolic dysfunction and sex in type 2 diabetes mellitus without cardiovascular abnormality. Such findings is similar to that of the study by Lee et al.[10]

The group with diastolic dysfunction has an older mean age compared to the group without. Nevertheless, statistical analysis using t-test found the correlation between diastolic dysfunction and age to be insignificant. Poirer et al 3 reported that type 2 diabetes mellitus patients with normal diastolic blood pressure were generally younger than those without, with a mean age of 48±6 and 57±6 respectively, with a $p < 0.001$.

The references state that aging reduces the diastolic function due to reduced passive elasticity, myocardial relaxation, and heart compliance, causing a reduction in LV cavity size and pressure and a reduction in the rate of ventricular filling.[15,16,17]

The incidence of diastolic dysfunction correlated with age and heart failure due to diastolic dysfunction is also increased in line with age, as stated by Sagie A et al and Benjamin E et al.[18,19]

Statistical calculation using the Mann-Whitney test on the correlation between diastolic dysfunction and the onset of diabetes mellitus in this study was found to be insignificant. This finding had been reflected from a similar mean value among samples with diastolic dysfunction compared to those without. Theoretically, the longer the onset of diabetes mellitus, the greater the possibility of complications.

Shapiro [14] et al reported a significant correlation between the onset of diabetes mellitus and an abnormal isovolumic relaxation time among 50 patients with type 1 diabetes mellitus, with a mean of 10 ± 9 years, $p < 0.001$, as well as a correlation between microvascular complication index and the onset of diabetes mellitus. Raey DC,[15] who studied 157 patients with type 1 diabetes mellitus reported a strong correlation between the frequency of diastolic dysfunction and systolic dysfunction and the onset of diabetes mellitus, with a p of less than 0.001. The study by Poirer et al on type 2 diabetes mellitus achieved similar results as that conducted at Cipto Mangunkusumo Hospital. The difference in the results of the study conducted on type 1 and 2 diabetes mellitus poses the question on whether the mechanism underlying the complications is different for type 1 and type 2 diabetes mellitus.

The difference in the results in this finding may be caused by an uncertainty of the actual onset of diabetes mellitus. Sample calculations demonstrating an equivalent mean HbA1c levels among the groups with diastolic dysfunction and those with normal diastolic function with the possibility of no difference between the two groups was proven from an independent sample calculation with an insignificant result from the t-test for HbA1c.

Twenty-two patients were found with positive diastolic dysfunction, compared to the group with an HbA1c level of over 7, which is still larger than the group with an HbA1c level of less than 7, but the results were not significant according to Fisher's exact test.

UKPDS reported a correlation between a good blood sugar control in type 2 diabetes mellitus and a reduced complication for diabetes mellitus, while the Diabetic Control and Complication Trial (DCCT) Research Group on type 1 diabetes mellitus found that in a sample with unsatisfactory HbA1c levels (over 6 to 11%), there was a correlation between unsatisfactory blood sugar control and the progressiveness of microvascular complications after 6 years follow-up.[20] The difference in the results of this study may be due to an insufficient sample size.

The average BMI of the group with diastolic dysfunction and those with normal diastolic function was not much different, demonstrated to be insignificant based on a calculation of independent samples from the t-test diastolic dysfunction for BMI.

There were 22 patients with diastolic dysfunction, whose number of members with normal BMI was equivalent to those who were obese, with a insignificant correlation based on Fisher's exact test.

In this study, the correlation between diastolic dysfunction and the studied variable did not demonstrate a significant correlation with age, onset, and hyperglycemic control. This may be due to an inadequate number of samples that did not reflect the true condition of the population. It was difficult to achieve a satisfactory number of samples in the field due to a very selective inclusive criteria.

## CONCLUSION

This study found a 73.3% prevalence of diastolic dysfunction among patients with type 2 diabetes mellitus without cardiovascular abnormality. The most frequent type of diastolic dysfunction was abnormal relaxation, making up 70% of the sample (21 patients), while the remaining 3.3% (1 patient) had a pseudonormal relaxation. Doppler echocardiography was useful to detect early symptoms of diastolic dysfunction.

This study found no significant correlation between diastolic dysfunction and the study variables as follows: sex, age, HbA1c, onset of diabetes mellitus, and obesity.

This study alerts people that type 2 diabetes mellitus with no clinical cardiovascular abnormality may have diastolic dysfunction.

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