

## Diastolic Dysfunction in Asymptomatic Type 2 Diabetic Patients Having Preserved Systolic Function

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### ABSTRACT

**Objective:** To determine frequency of diastolic dysfunction in asymptomatic type 2 diabetic patients by employing two-dimensional (2D) echocardiography as a measurement method.

**Study Design:** It was an Analytical Cross-sectional study.

**Place and Duration of Study:** Rawalpindi Institute of Cardiology, Rawalpindi Pakistan, from Jul 2021 to Nov 2021

**Methodology:** Patients, already diagnosed as diabetics for more than 5 years and on dietary control or on medications, presenting to the outpatient department of the hospital were enrolled. They were subjected to a 2D echocardiography in left lateral position. We excluded patients with valvular heart disease, ischemia, congestive heart failure, cardiomyopathy of any aetiology, renal failure, pulmonary illness, anemia, hemoglobinopathies, prior myocardial infarctions in any region, smokers, and hypertension. Diastolic dysfunction was evaluated as per the guidelines of American society of Echocardiography.

**Results:** Overall (n=150) patients were calculated with reference to 11% prevalence of LVDD by sample size calculator, being the part of study who were fulfilling the inclusion criteria. There were 102(68.0%) male and 48(32.0%) female patients; mean age was 45.02±6.07 years. Mean duration of diabetes mellitus in years was 6.93±2.53 with ranges from 5 to 16 years. Patients on oral hypoglycemic were 121(80.7%), on insulin were 5(3.3%), on dietary control were 12(8%) and on mixed treatment were 12(8%). There were 58 (38.7%) patients who had diastolic dysfunction present on echocardiogram. Effect modifiers of duration of diabetes ( $p=0.2$ ) did not show significant association; however, Age ( $p=0.001$ ) and Gender ( $p=0.038$ ) significantly associated with Diastolic Dysfunction.

**Conclusions:** One of the simple and noninvasive approaches to diagnose diastolic dysfunction is doing 2D echocardiography which can identify large percentage of diabetic subjects having pre-clinical diastolic dysfunction. Thus, by on time detection we can initiate treatment and retard the progression of diastolic dysfunction.

**Keywords:** 2D echocardiography, Diastolic dysfunction, Type 2 diabetes mellitus.

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### INTRODUCTION

Diabetes mellitus (DM), which is regarded as a major risk factor, aggravates heart disease, including coronary artery disease and hypertension. In addition to these pathologies, there is evidence that it can cause heart failure even when left ventricle systolic function is normal.<sup>1</sup> According to various studies, diabetics are more prone than non-diabetics to have heart failure.<sup>2</sup> Further research suggests that the frequency of heart failure in people with type-2 diabetes is nearly 2.5 times greater than that in non-diabetic persons.<sup>3</sup>

A condition known as heart failure with preserved ejection fraction (HFPEF) or left ventricular diastolic heart failure (LVDHF) is diagnosed in patients who present with symptoms indicative of heart failure while having almost normal left ventricular (LV) systolic function. A significant relationship has

been found between heart failure with normal ejection fraction (HFNEF) and type-2 diabetes mellitus (T2DM). According to research, diabetics are 30–40 percent more likely than the general population to have HFNEF.<sup>4</sup>

Pre-clinical diastolic dysfunction is a condition in which individuals acquire diastolic dysfunction even if they are not experiencing any symptoms. In diabetics, damage to the myocardium appears to impact diastolic function before systolic function.<sup>5</sup> Diabetic cardiomyopathy's aetiology is still being investigated. There have been several hypotheses put out as to why diabetic cardiomyopathy could arise. Also, there are alterations in metabolic function and insulin resistance in the tissues; microvascular dysfunction; RAS malfunction; myocardial fibrosis; and autonomic dysfunction.<sup>6</sup>

Diastolic heart failure is characterised by the presence of clinical signs and symptoms of heart failure, the preservation of left ventricular ejection fraction (LVEF), and the presence of diastolic dysfunction on

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echocardiogram.<sup>7</sup> Diastolic dysfunction is thought to develop in diabetic cardiomyopathy before clinical examinations reveal any signs of pathological changes. The worsening of the situation is accompanied by an increase in filling pressure and a decrease in left ventricular compliance.<sup>8</sup>

A link between diabetes and diastolic dysfunction has been shown by several studies. According to a research by Paul Poirier *et al.* Diastolic function in diabetics who had no clinical signs of heart illness was shown to be impaired even when systolic function remained within acceptable limits.<sup>9</sup> Using echocardiography, Boonman *et al.*, found that 47 percent of older individuals with type-2 diabetes had diastolic dysfunction.<sup>10</sup>

This study was performed to assess the frequency of left ventricular dysfunction in type-2 diabetes (persons who do not have symptoms of heart failure), in order to detect these individuals early, before they advance to end stage diastolic heart failure.

If two or more of the following echocardiographic abnormalities are seen, LV diastolic dysfunction was considered to be present: E/A ratio of 1 or greater than 2, Deceleration Time (DT) of 150 or greater than 220 ms, IVRT of 60 or greater than 100 ms, or E/e' ratio greater than 15,  $e' = 0.11m/se$ . E=peak transmitral modal velocity at the leading end of the spectral waveform in early diastole. A is the peak trans-mitral modal velocity in late diastole at the leading edge of the spectral waveform, DT is the time interval between the commencement of the E wave and the end of the E wave at zero baseline, and IVRT is the time interval between the aortic and mitral valve closures.

E/e' ratio=mitral E velocity divided by mitral annular e' velocity, where e'=mean of medial and lateral mitral annular velocities measured using tissue Doppler imaging (TDI). Patients already diagnosed as diabetics for more than 5 years and on dietary control or on medications are labeled as TYPE 2 Diabetics

## METHODOLOGY

Following permission by the Institutional Ethical Review Board (IERB Letter# RIC/RERC/06/21), the cross-sectional study was carried out utilising a non-probability purposive sampling approach.

**Sample Size:** With reference to 11% prevalence of LVDD (11), sample size calculated was (n=150) by WHO calculator.

**Inclusion Criteria:** Patients regardless of gender, aged 25 to 55 years, who had a documented history type-2

diabetes mellitus for more than 5 years were included in study.

**Exclusion Criteria:** Patients with valvular heart disease, ischemia, congestive heart failure, cardiomyopathy of any etiology, renal failure, pulmonary illness, anaemia, hemoglobinopathies, prior myocardial infarctions in any region, smokers, and hypertension were excluded.

The patients presenting to the outpatient department of the hospital were subjected to a 2D echocardiography in the left lateral position. The chambers were measured in accordance with the guidelines of the American Society of Echocardiography. Mitral inflow velocities were measured using a sample volume in the apical four chamber view. The transmitral E wave, A wave, E wave deceleration time (DT), and E/A ratio were all determined. Isovolumic relaxation time (IVRT) was also measured from the apical 5 chamber view while the mitral and aortic flows were simultaneously recorded. By activating the TDI feature, Tissue Doppler Imaging (TDI) was conducted. To quantify diastolic dysfunction, two velocities were measured at the Mitral annulus: peak early diastolic velocity (Em) and peak late diastolic velocity (Am).

Two distinct locations on the mitral annulus, lateral and septal, were chosen using an apical 4-chamber view. The mean results from the two locations mentioned above were utilised to evaluate global diastolic left ventricular function. The normal cut-off values for Doppler echocardiography and Tissue Doppler Imaging ventricular diastolic dysfunction were established as adopted by the American Society of Echocardiography. The left ventricular ejection fraction (LVEF) was estimated using a modified Simpson's technique, with LVEF greater than 50% deemed normal. To prevent the effects of circadian rhythm on diastolic function, measurements were done during midday.

## Data Analysis

Data was analyzed in SPSS version 23. The variables were age, sex, diastolic dysfunction duration of diabetes mellitus, Ejection fraction, Mitral inflow velocities, Isovolumic relaxation time and Mitral-E wave deceleration time on Doppler Echocardiography and the Mean diastolic mitral annular velocities on TDI. Means and standard deviations were calculated for quantitative variable while frequency and percentage were calculated for qualitative variables. Chi-square test was used to compare effect modifier like age stratification with diastolic dysfunction.

## RESULTS

Data was entered and analyzed in SPSS version 23. Total 150 patients were included in the study according to the inclusion criteria of the study.

Mean age (years) was  $45.02 \pm 6.07$  with ranges from 35 to 55 years. There were 102(68.0%) male and 48 (32.0%) female patients in the study. Mean duration of diabetes mellitus in years was  $6.93 \pm 2.53$  with ranges from 5 to 16 years. Patients on oral hypoglycemic were 121(80.7%), on insulin were 5(3.3%), on dietary control were 12(8%) and on mixed treatment were 12(8%) as shown in Table-I.

**Table-I: Baseline and Clinical Characteristics of the diabetic patients and outcomes of the study(n=150)**

| Variables                    | Mean $\pm$ SD/n(%) |
|------------------------------|--------------------|
| Age in years                 | 45.02 $\pm$ 6.07   |
| <b>Gender</b>                |                    |
| Male                         | 102(68%)           |
| Females                      | 48(32%)            |
| Duration of DM(years)        | 6.93 $\pm$ 2.53    |
| <b>Types of Treatment</b>    |                    |
| Oral hypoglycemic            | 121(80.7%)         |
| Mixed                        | 12(8%)             |
| Dietary control              | 12(8%)             |
| Insulin                      | 5(3.3%)            |
| <b>Diastolic Dysfunction</b> |                    |
| Present                      | 58(38.7%)          |
| Absent                       | 92(61.3%)          |

The outcome of the study was the frequency of diastolic dysfunction in type-2 diabetic patients. There were 58(38.7%) patients who had diastolic dysfunction present on echocardiogram. There were 1(1.8%) 21 (36.21%) and 36(2.08%) patients having age between 25-35, 36-45 and 46-55 years respectively who have diastolic dysfunction. There were 34(58.62%) male and 24(41.38%) female patients who had diastolic dysfunction. There was statistically significant association between gender stratification and diastolic dysfunction ( $p$ -value 0.038).

There were 47(81.03%) patients having diastolic dysfunction in group 5-10 years. Similarly, there were 9(15.52%) patients having diastolic dysfunction who had diabetes between 11-14 years and 2(3.45%) patients having diastolic dysfunction in group having diabetes for more than 14 years. Taking into account duration of diabetes mellitus with diastolic dysfunction no statistically significant association was observed ( $p$ -value 0.200), as shown in Table-II.

## DISCUSSION

The number of persons suffering with diabetes mellitus (DM) is increasing at an alarming rate

throughout the world. Numerous studies performed over the last three decades have revealed that diabetic heart disease is a distinct clinical entity from other types of heart disease. According to study, diabetics' diastolic function deteriorates first, followed by their systolic function. Diabetic ventricular dysfunction can be caused by a variety of factors, although the actual reason is currently unknown.<sup>12</sup>

**Table-II: Frequency of Diastolic Dysfunction and its association with Different Effect Modifiers**

|                               | Diastolic Dysfunction | Number of patients (n) | %      | $p$ -value |
|-------------------------------|-----------------------|------------------------|--------|------------|
| <b>Age Groups (in years)</b>  |                       |                        |        |            |
| 25-35                         | Present               | 1                      | 1.8%   | 0.001      |
|                               | Absent                | 4                      | 4.35%  |            |
| 36-45                         | Present               | 21                     | 36.21% |            |
|                               | Absent                | 60                     | 65.22% |            |
| 46-55                         | Present               | 36                     | 2.08%  |            |
|                               | Absent                | 28                     | 30.43% |            |
| <b>Gender</b>                 |                       |                        |        |            |
| Male                          | Present               | 34                     | 58.62% | 0.038      |
|                               | Absent                | 68                     | 73.91% |            |
| Female                        | Present               | 24                     | 41.38% |            |
|                               | Absent                | 24                     | 26.09% |            |
| <b>Duration of DM (years)</b> |                       |                        |        |            |
| 5-10                          | Present               | 47                     | 81.03% | 0.2        |
|                               | Absent                | 82                     | 89.13% |            |
| 11-14                         | Present               | 9                      | 15.52% |            |
|                               | Absent                | 6                      | 6.52%  |            |
| >14                           | Present               | 2                      | 3.45%  |            |
|                               | Absent                | 4                      | 4.34%  |            |

The prevalence of diastolic dysfunction in diabetic patients varies widely, ranging from 21 percent to 75 percent. In a study based exclusively on the most recent recommendations of the European Association of Echocardiography and the American Society of Echocardiography, the prevalence of diastolic dysfunction was estimated to be 47 percent.<sup>13</sup> According to the findings of the study, diastolic dysfunction was observed in 38 percent of diabetic individuals. Diabetes has a far more adverse effect on Asians compared to Europeans and this effect is generalized in the form of global cardiac dysfunction including diastolic dysfunction. Hyperglycemia has a stronger negative impact on the LV function of South Asians. The accumulation of advanced glycation end products in the myocardial and aorta and increased oxidative stress, altered energy metabolism, and accelerated fibrosis that are all linked to long-term hyperglycemia may have a negative impact on the left ventricle's function.

In the Framingham Heart study, female diastolic dysfunction patients outnumbered male diastolic dys-

function patients. After menopause, women's hormones begin to shift. Studies in both clinical and basic science have connected postmenopausal diastolic dysfunction to activation of the RAAS, which is linked to the loss of ovarian estrogens. An abnormal nitric oxide synthase (NOS) pathway contributes to the development of female-specific diastolic heart disease as a result of elevated tissue ANG II and low estrogen levels. In addition, females have tendency for developing arterial stiffness, left ventricular hypertrophy and have comparatively smaller Left ventricular chamber size all precursor of diastolic dysfunction.<sup>14</sup>

Patients can have diastolic dysfunction even if they have normal systolic dysfunction, which is in accordance with the findings of a prior study on 40 diabetic patients who were participants in the investigation. In such subsets, the left ventricle does not dilate and contracts appropriately; yet, the diastolic function of the heart is substantially impaired. Diastolic heart failure is characterized by an increase in diastolic stiffness (reduced compliance) in the left ventricle. This causes the left ventricle to be unable to effectively fill at normal diastolic pressures, which is one of the hallmark symptoms of the condition. This condition is characterized by a reduction in end-diastolic volume, an elevation in end-diastolic pressure, or both of these symptoms. Decreased left ventricular filling volume leads to lower stroke volume, which in turn leads to symptoms of limited output. Elevated left ventricular filling pressures, on the other hand, cause symptoms of pulmonary congestion in the patient. Therefore, heart failure symptoms, such as the left ventricle's inability to meet the demands of the skeletal muscle during exercise while maintaining appropriate filling pressures, may originate from predominantly diastolic processes and may be present in individuals with normal left ventricular systolic performance. Diabetes-induced cardiomyopathy has been associated with a number of functional and structural problems. An examination of the heart's histopathology in diabetic individuals revealed perivascular and interstitial fibrosis, myocardial hypertrophy, and endothelial proliferation in the coronary arteries of the small vessels. Vascular lesions of the small coronary arteries in patients with diabetes mellitus, which lower the coronary flow reserve and result in myocardial insufficiency, have also been reported in the literature. Myocardial ischemia happens as a result of this. Myocardial ischemia results in diastolic dysfunction and a reduction in left ventricular compliance. As a result, coronary resistance may be increased even further, resulting in an even greater

drop in coronary flow reserve. As a result, a vicious cycle is established and intensified.<sup>15</sup>

Study participants aged 46 to 55 were more likely to have diastolic dysfunction than those in the 51-55 age range. This is consistent with findings from Zaman *et al.* who reported that diastolic dysfunction was more common in this age group than those in the 51-55 age range (65.1 percent). The discovery of age-related alterations in diastolic performance in the absence of overt cardiovascular disease risk factors lends support to the concept that normal ageing itself results in declines in the measurements widely used to assess left ventricular diastolic function. This is further supported by the fact that normal early diastolic velocity falls at a sharp and linear drop with age in normal adults, from 16cm/s at the age of 20 years to 6cm/s at the age of 80 years. This decline occurs between the ages of 20 and 80 years. Every year, this decrease amounts to a loss of 0.16cm/s, which is equivalent to a loss of 1% of the value when it is first measured.<sup>16</sup>

In a study by Mishra *et al.* years of diabetes duration linked well with diastolic dysfunction, which is contradictory to the findings seen in our study that showed that majority of the patients belonged to year group from 5-10 years.<sup>17</sup> Similarly, in a research by Raev *et al.* diastolic dysfunction was seen in patients with diabetes who had only been diagnosed for six months.<sup>18</sup> These findings suggest that pre-clinical cardiomyopathy in diabetics may have a distinct etiology independent of duration of diabetes mellitus (DM). Microvascular complications including microangiopathy, dysfunction in the autonomic dysfunction, alteration in the normal functioning of cellular calcium transport and modifications in the myocardial metabolic system, and left ventricular dysfunction begin to emerge as a result of poor diabetic control, first in the form of left ventricular diastolic dysfunction and then as diabetes-related left ventricular diastolic problems that include a reversible component that can be avoided with aggressive treatment.<sup>19,20</sup> If left ventricular diastolic dysfunction is detected early and accurately in type-2 diabetes patients, it may have therapeutic implications.<sup>21</sup>

Because diastolic dysfunction can be detected in its very early stages with a simple non-invasive test such as echocardiography, this study stresses the importance of early diagnosis of diastolic dysfunction as part of preventive management in the treatment of diabetes. Because of the high prevalence of morbidity and mortality associated with heart disease in

diabetics, it is important to utilise a screening test such as echocardiography to identify diastolic dysfunction in diabetes patients.

### LIMITATIONS OF STUDY

Our study was a single centered study and had a small group of patients in each treatment, so whether these conclusions can be extrapolated on a larger group needs to be further investigated.

### CONCLUSION

Diastolic dysfunction is prevalent in type 2 diabetic people without a history of cardiovascular disease. Diastolic dysfunction should be detected and treated promptly, as the prognosis is poor in the late stages. Diastolic dysfunction can be detected with two-dimensional echocardiography, which can detect a significant proportion of diabetics with pre-clinical diastolic dysfunction. Finally, early detection enables us to initiate therapy and limit the progression of LV diastolic dysfunction.

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**Conflict of Interest:** None.

### Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

MWB: Manuscript writing, concept and editing

IZ: Concept, design, Proof read, Data collection

KK: Data collection, data interpretation and proof reading

ZM: Manuscript drafting, proof reading and critical review

MA: Manuscript drafting, data interpretation, Literature review

KA: Literature review, proof reading and editing

AS: Proof reading, formatting and critical review

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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