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ORIGINAL RESEARCH ARTICLE

Left Ventricular diastolic dysfunction in type-2 diabetes mellitus patients with no overt cardiac symptoms or signs by color flow Doppler study and its correlation with microvascular complications: A cross-sectional study

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Abstract:

Introduction: Diabetes mellitus is a group of metabolic disorders resulting in hyperglycemia with disturbances in carbohydrate, fat, and protein metabolism. Hyperglycemia when present for a long period of time leads to a host of metabolic abnormalities and also results in end organ damage. Diastolic dysfunction is an early sign of diabetic heart muscle disease preceding the systolic and diastolic damage. Only a few studies have been conducted in central India to establish this prevalence and association in diabetic patients

Aim: The aim of study was to assess left ventricular diastolic dysfunction in diabetic patients and its correlation with microvascular complications**.**

Material and Method:

In this cross-sectional study, 150 normotensive patients with type 2 diabetes mellitus and no clinical evidence of cardiovascular disease were enrolled by simple random selection. The sample size was calculated by standard formula with a confidence interval of 95% and an error margin of less than 5%. A semi-structured pro forma was used to record the demographic profiles with full medication history. Left ventricular diastolic dysfunction was assessed by electrocardiographic & Echocardiographic studies. Microangiopathies were assessed by fundoscopy and blood & urine renal profile. Autonomic function was evaluated by standing blood pressure and heart rate response to the valsalva maneuver.

Statistical Analysis: Data obtained by various methods was analyzed statistically using

1. SPSS 20
2. Chi-square test

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

Result: The present study showed that 85 out of 150 types 2 diabetic patients had diastolic dysfunction, out of which 80 had Grade I diastolic dysfunction and, 5 of them had Grade II diastolic dysfunction. The proportions of patients with diastolic dysfunction were higher for retinopathy, nephropathy, and neuropathy.

Conclusion: The study concluded that asymptomatic normotensive patients of type 2 diabetes mellitus have heart failure with preserved ejection fraction (HFpEF). Left ventricular diastolic abnormalities were correlated with diabetic microangiopathies like retinopathy, nephropathy, and neuropathy. Type 2 diabetes mellitus is the strongest independent correlate of left ventricular diastolic dysfunction and microangiopathies.

Keywords: Echocardiography, heart failure with a preserved ejection fraction, microangiopathy.

1. INTRODUCTION

The incidence of diabetes mellitus (DM) is increasing worldwide rapidly. Over the last decades, studies have proposed the presence of diabetic heart disease as a distinct clinical entity. Diastolic heart failure is also referred to as heart failure with preserved ejection fraction (HFpEF). Many studies have reported that the incidence of heart failure(54.33%) in diabetic subjects is high even in the absence of hypertension and coronary artery disease.[1-4] Studies have reported a high prevalence of diastolic dysfunction among subjects with type-2 diabetes mellitus(DM).[5]

The evidence suggests that diastolic dysfunction precedes systolic dysfunction in diabetics. The pathogenesis of this left ventricular (LV) diastolic dysfunction in diabetics is not known.[6]

Diastolic dysfunction is an early sign of diabetic heart muscle disease preceding systolic damage. Diastolic dysfunction is independently associated with increased all-cause mortality as well as cardiovascular mortality in a population-based sample of middle-aged and elderly adults.[7]

The American College of Cardiology and the American Heart Association suggest that diabetes mellitus is considered one of the major risk factors for heart failure because it is of great importance to the advance of heart dysfunction.[8]

One of the key markers of diastolic dysfunction severity is increased left atrial (LA) volume with or without LV inflation pressure. Fibrosis and remodeling underlying LA dysfunction in heart failure with preserved ejection fraction(HFpEF) patients.[9]

This study aimed to determine the prevalence of LV diastolic dysfunction in Indian patients with type 2 diabetes mellitus with no overt cardiac symptoms or signs by color flow Doppler study and correlation with microvascular complications. . Previous studies suggested that left ventricular diastolic dysfunction is common in individuals with type 2 diabetes mellitus. Hence it is important that regular monitoring and screening for the progression of cardiac dysfunction is done along with appropriate therapeutic risk mitigation measures, given the long-term prognostic implications of LVDD.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

2. MATERIALS AND METHODS

This cross-sectional study was conducted in Sanjay Gandhi Memorial hospital associated with Shyam Shah medical college, Rewa from April 2021 to March 2022 after clearance from Medical College Ethical Committee [IEC No. 430].

150 normotensive type 2 diabetes mellitus patients with no clinical evidence of cardiovascular disease were enrolled by simple random selection. The sample size was calculated by standard formula with a confidence interval of 95% and an error margin of less than 5%.The calculated sample size was 385. The study was designed during the COVID-19 pandemic, which resulted in a relatively small sample size. There could also be confounders posed by COVID-19 in the selection of the patients with patients who were actively shielding not having visited the hospital, total of 150 cases enrolled for this study.

INCLUSION CRITERIA:

- Patients diagnosed with type 2 diabetes mellitus [10]

Patients attending SGMH Hospital as outpatients and inpatients from April 2021 to March 2022.

Newly diagnosed patients were also included in the study.[10] The age group of 30 to 70 years was used to avoid overlap of type 1 and other forms of diabetes mellitus.

EXCLUSION CRITERIA:-

- Myocardial infarction by history and resting electrocardiogram (ECG)
- Patients with evidence of coronary artery disease [excluded by the history of angina, chest pain, Electrocardiogram (ECG) changes, and abnormal Treadmill test (TMT) results]
- Patients with hypertension, thyroid disorder, respiratory or renal diseases
- Pregnant women
- Type 1 Diabetes mellitus patients
- Significant alcoholic patient
- Patients with evidence of underlying heart diseases with normal systolic ejection fraction.

A semi-structured pro forma was used to record the demographic profiles with full medication history. Left ventricular diastolic dysfunction was assessed by electrocardiographic & Echocardiographic studies. Microangiopathies were assessed by fundoscopy and blood & urine renal profile. Autonomic function was evaluated by standing blood pressure and heart rate response to the valsalva maneuver.

ASSESSMENT OF DIASTOLIC DYSFUNCTION:

All the patients enrolled in the study underwent Echocardiography. Transthoracic echocardiography was done to assess the ventricular dimensions, presence of regional wall motion abnormalities, and left ventricular ejection fraction. The parasternal long-axis and short-axis views were utilized. The ejection fraction was obtained using Simpson's approach.[11]

Doppler echocardiography was done using the apical four-chamber view. The transmitral velocities were obtained by positioning the sample volume at the level of the tips

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

of mitral leaflets. The early mitral inflow velocity (E) and late inflow velocity (A) were obtained and the E/A ratio was calculated.

The E/A ratio of less than 1 was considered grade 1 diastolic dysfunction. When the E/A ratio was more than 1, additional parameters like the velocity propagation and E wave deceleration time were considered to differentiate Grade II diastolic dysfunction from a normal pattern.[12]

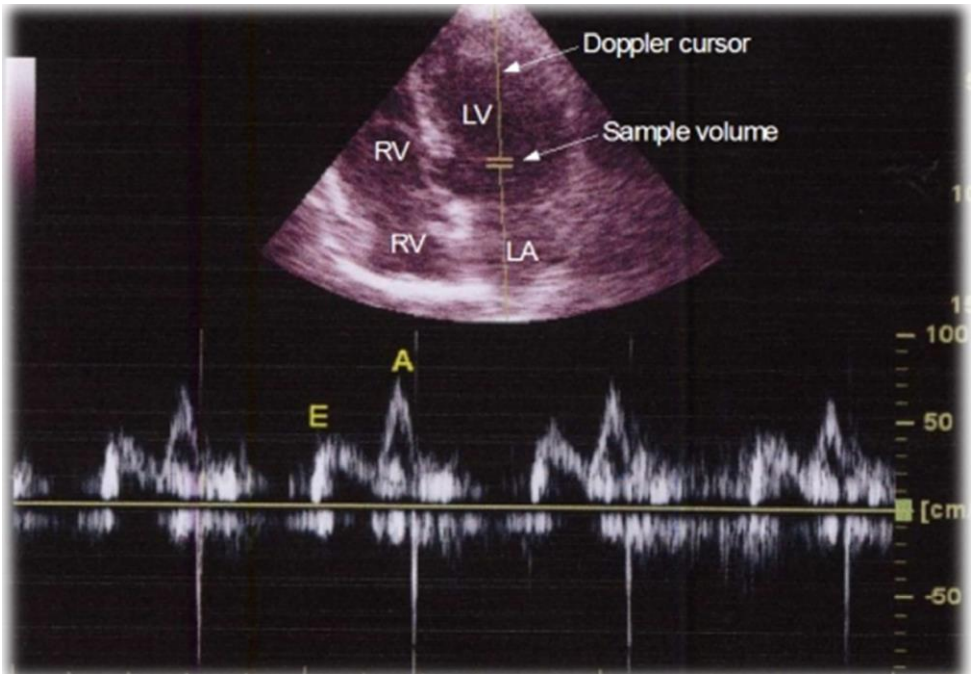

Figure 1- Doppler ECHO: Measurement of E velocity and A velocity

Left Ventricular Diastolic Function

Mitral inflow was assessed with pulsed-wave Doppler done with the transducer in the apical 4-chamber view, with the Doppler beam aligned perpendicular to the plane of the mitral annulus along with color M-mode Doppler echocardiography was done. Tissue Doppler was used at the septal and lateral mitral annulus to measure the mitral plane movement. LV filling was divided into 4 distinct filling patterns, according to a combination of mitral inflow, tissue Doppler measurements of the mitral plane movement, and mitral inflow assessed with color M-mode.[13]

Left Atrial Volume Index

Left atrial volume was approximated by the biplane area-length method, using measurements at the apical 4- and 2-chamber views at end-systole (maximum LA size). LA volume index was calculated as LA volume divided by the body surface area. LA volume index was considered moderate or severely increased if it was 32 mL/m2. [13]

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

Table 1: Schematic diagram of diastolic dysfunction(in echocardiography)[14]

Grade of diastolic dysfunction	Pathological abnormality	Echocardiographic parameters
Grade I	Impaired relaxation	E/A ratio < 1
Grade II	Impaired relaxation and compliance	E/A ratio>1 with increased left atrial pressures
Grade III	Restrictive filling(reversible)	E/A ratio > 2.5 and elevated ventricular filling pressures
Grade IV	Restrictive filling (irreversible)	Same as grade III with irreversible changes

STATISTICAL ANALYSIS:

Data were analyzed for mean, percentage, standard deviation, chi-square test, multiple correlation, and multivariate analysis, by using SPSS-10 (Statistical Package for the Social Sciences) for Windows (SPSS, Chicago, IL). Variables that were not normally distributed were reciprocally transformed for analysis. The Chi-Square test was applied to study quantitative and qualitative data with a '*P*' value < 0.05 considered statistically significant.

3. RESULTS

Prevalence of diastolic dysfunction

The present study showed that 85 out of 150 types 2 diabetic patients had diastolic dysfunction, out of which 80 had Grade I diastolic dysfunction and, 5 of them had Grade II diastolic dysfunction. Grade III and Grade IV diastolic dysfunction were not found in the present study.

The mean E/A ratio was 1.047±0.356. The E/A ratio was much lower (0.7701±0.09) in patients with diastolic dysfunction as compared to patients with normal function (1.326±0.24). The p-value was found less than 0.001 by the chi-square test, which was significant.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

Table2 : Diastolic dysfunction and microangiopathies

Diastolic dysfunction and Retinopathy						
S. No.		**Grade 1**		**Grade 2**		**% of patients of diastolic dysfunction**
1	Non-proliferative diabetic retinopathy (NPDR) (n=65)	51	78.46	5	7.69	86.15
2	proliferative diabetic retinopathy (PDR) (n=9)	9	100.0	-	-	100.0
TOTAL	74	60		5		
Diastolic Dysfunction and Nephropathy						
1	Microalbuminuria (n=85)	48	56.47	2	2.35	58.82
2	Macroalbuminuria(n=15)	12	80.0	3	20.0	100.0
TOTAL	100	60		5		
Diastolic Dysfunction and Neuropathy						
1	Autonomic(n=27)	20	74.07	5	18.51	92.58
2	Sensori-Motor(n=38)	31	81.57	3	7.89	89.46
TOTAL	65	51		8		

Table3 : Diastolic dysfunction and microangiopathies

Diastolic dysfunction and Retinopathy							
SN	**Retinopathy (n=74)**	**No. of patients (n=150)**				**Total No. of patients**	
		Normal Diastolic function		**Diastolic dysfunction**			
		No.	**%**	**No.**	**%**	**No.**	**%**
1	No Retinopathy	56	73.68	20	26.31	76	50.66
2	Retinopathy	9	12.16	65	87.83	74	49.33
	Total	65		85		150	
Diastolic dysfunction and Nephropathy							
SN	**Nephropathy (n=100)**	**No. of patients (n=150)**				**Total No. of patients**	
		Normal Diastolic function		**Diastolic dysfunction**			
		No.	**%**	**No.**	**%**	**No.**	**%**
1	No Nephropathy	45	90.00	5	10.00	50	33.33
2	Nephropathy	35	35.00	65	65.00	100	66.67
	Total	80		70		150	
Diastolic dysfunction and Neuropathy							
SN	**Neuropathy (n=65)**	**No. of patients (n=150)**				**Total No. of patients**	
		Normal Diastolic		**Diastolic**			

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

		function		dysfunction			
		No.	**%**	**No.**	**%**	**No.**	**%**
1	No Neuropathy	63	74.11	22	25.88	85	56.66
2	Neuropathy	6	9.23	59	90.76	65	43.33
	Total	69		81		150	

The chi-square test values for the above data: p value<0.001.

Out of 74 patients with retinopathy, 65 (87.83%) had diastolic dysfunction. The proportion of patients with diastolic dysfunction was higher for proliferative retinopathy. All 9 patients with proliferative retinopathy had diastolic dysfunction.

Of all 100 patients with nephropathy, 65 of them had diastolic dysfunction accounting for 65.0%. The correlation with macroalbuminuria was significantly higher with all 15 patients developing diastolic dysfunction. (Table-3)

Out of 65 patients with neuropathy, 59(90.76%) had diastolic dysfunction. The proportion of patients with diastolic dysfunction was higher for autonomic neuropathy.

4. DISCUSSION

Diastolic dysfunction in diabetes:

As per this study, the prevalence of left ventricular diastolic dysfunction was 56.66% in patients with type 2 diabetes mellitus.

In a study done by Yadava SK, the prevalence of diastolic dysfunction in type 2 diabetes mellitus was 47.8%.[15]

T.K.V. Sharavaran also showed a 55.0% prevalence of diastolic dysfunction in diabetic subjects.[16]

Diastolic dysfunction and Retinopathy:

In present study, out of 74 patients with retinopathy, 65 (87.83%) had diastolic dysfunction. The proportion of patients with left ventricular diastolic dysfunction was higher for proliferative retinopathy. All 9 patients with proliferative retinopathy had evidence of diastolic dysfunction.

The association between retinopathy and diastolic dysfunction was strongly correlated in our study (p<0.001). Patients with proliferative retinopathy had a stronger association.

Takenaka et al.showed an association between retinopathyandtype 2 diabetic patientswithout coronary artery disease and hypertension.[17]

Anonu et al. showed that in his 49% of patients with retinopathy, her E/A ratio was less than 1.[18]

Diastolic Dysfunction and Nephropathy:

Out of 100 patients with nephropathy, 65 (65%) had evidence of diastolic dysfunction. The prevalence of microalbuminuria in this study was 56.66%. The association with macroalbuminuria was significantly higher in all 15 patients who developed diastolic

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

dysfunction. However, in this study, the association between nephropathy and diastolic dysfunction was strong ($p< 0.001$).
A study done in type 2 diabetes by Annonu et al failed to demonstrate a significant association between albuminuria and type 2 diabetes mellitus patients.[18]

Diastolic Dysfunction and Neuropathy:

In this study, out of 65 patients with neuropathy, 59(90.76%) had diastolic dysfunction. The proportion of patients with diastolic dysfunction was higher for autonomic neuropathy.

Sacre *et al*., found that there was an independent association between global cardiac autonomic neuropathy (CAN) and left ventricular (LV) dysfunction in patients with type 2 DM.[19]

Patil VC et al., found that majority(84.37%) of diabetic patients with autonomic neuropathy had diastolic dysfunction.[20]

These findings are comparable to this study, where left ventricular diastolic dysfunction was present in the majority of the patients with autonomic neuropathy documented by postural hypotension. Out of the 27, patients with autonomic neuropathy; 25 (92.59%) had diastolic dysfunction.

The association between diastolic dysfunction and microvascular complications strongly suggests underlying microangiopathy. Diastolic dysfunction indicates widespread endothelial dysfunction, as microalbuminurias also a marker of endothelial dysfunction.
Zoneraich S etal showed that 72% of diabetic patients had small vessel disease.
Microvascular changes include microaneurysm formation and capillary membrane thickening.[21]

Deposition of advanced-glycated end products (AGEs), which include collagen, elastin, and other connective tissue proteins in the interstitial spaces, as well as fibrosis in the myocardium has been reported in biopsy specimens of human diabetic hearts.[22]

Thus, the data from this study confirm the evidence of diastolic dysfunction in normotensive diabetic patients without coronary artery diseases. More significantly, left ventricular diastolic dysfunction is an isolated form and asymptomatic.

LIMITATIONS

- The lack of a control group in this study was a major limitation to differentiate diastolic abnormalities between diabetic and non-diabetic populations.
- In the current study, we tried to exclude coronary artery diseases by non-invasive symptom-limited routine implementation test and wall motion evaluation by transthoracic echocardiography. Despite normal treadmill exercise and wall motion test and resting ECG, the applied tools do not exclude the presence of atherosclerosis.
- The sample size of the present study was small.
- All the assessments were done only once for the patients though, the valuation of the results was estimated accurately. However, assessment of LA function by Two-dimensional speckle tracking echocardiography (2DSTE) leads to some incorrect measurements.

ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

Author's Contribution:
SKS-Concept and design of the study prepared the first draft of the manuscript; **MT**-Interpreted the results; Reviewed the literature and manuscript preparation; **KSK & CDC**- Coordination, preparation, and revision of the manuscript, Statistical analysis, and interpretation; **MP & UPS**-Data Interpretation and review; **PG –** review of literature and manuscript revision.

Conflicting Interest – None
Source of funding– None

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ISSN: 0975-3583,0976-2833 VOL14, ISSUE2, 2023

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