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Assessment of Diastolic Dysfunction in Normotensive Asymptomatic Type II Diabetes Mellitus and Correlation with Pulmonary Artery Pressure

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ABSTRACT

Aim: To estimate the prevalence of Diastolic Dysfunction in normotensive asymptomatic type 2 diabetes mellitus and determining its correlation with increased pulmonary artery pressure (PAP).

Methods: Retrospective and cross-sectional study with data obtained from Sevasadan Lifeline Super Speciality hospitals between 10/1/2020 to 31/3/2020. A total of 111 patients' records were retrieved. This study included inpatients of type 2 DM of all age groups and patients with cardiac diseases were excluded from the study. For each patient, clinical profile like age, gender, BMI, HbA1C, duration of diabetes, treatment of type 2 DM, Grades of diastolic dysfunction and PAP etc were studied. In this study pulmonary pressure was measured by acceleration time and then PAP was determined by using equation PAP=90-AT×0.62.

Results: Out of 111 subjects with type -2 DM, 63 (56.76%) were males and 48 (43.24%) were females. Mean age at the time of diagnosis was 46.53±10.35 years. Overall prevalence of diastolic dysfunction was 85.59%. Grade 1 LVDD was the most common (41.44%) in the present study. Statistically significant association was seen between pulmonary artery pressure and the prevalence of diastolic dysfunction

Conclusion: Overall prevalence of diastolic dysfunction was 85.59%. Grade 1 LVDD was the most common (41.44%). Statistically significant association was seen between pulmonary artery pressure and the prevalence of diastolic dysfunction ($p \leq 0.0001$, 0.64807) showing that prevalence of diastolic dysfunction is dependent on the increased pulmonary arterial pressure.

Keywords: Normotensive, Type 2 diabetes mellitus, Diastolic dysfunction and pulmonary artery pressure.

INTRODUCTION

Diabetes mellitus (DM) is the global epidemic, affecting not only developed countries but also posing a tremendous burden in developing countries. [1] Globally, DM prevalence rate is about 463 million in 2019, representing 9.3% of the global adult population. This figure is expected to increase to 578 million (10.2%) in 2030 and by 2045, almost 700 million (10.9%) people will have diabetes in the world. [2] According to the statistical estimates of the Indian Council of Medical Research-Indian Diabetes (ICMR-INDIAB) Study, around 62.4 million people were diagnosed with DM in India. The majority (>90%) of them have Type 2 DM. [3] Diabetes mellitus is considered as a major risk factor for the development of diastolic dysfunction. Recent studies have demonstrated that the incidence of diastolic dysfunction in diabetic patients is about 30-75%. [4] Diastolic dysfunction is defined as a disturbance in ventricular relaxation, distensibility or filling regardless of normal

or reduced ejection fraction (EF), which results in development of diastolic heart failure (DHF). [5] A number of epidemiological and clinical arguments suggest that diastolic abnormalities may contribute to the high morbidity and mortality among patients with diabetes. [6]

Numerous studies have shown an increased incidence of congestive heart failure in patients with diabetes irrespective of coronary heart disease and hypertension. [7] The evidence suggests that myocardial damage in diabetic patients affects diastolic function before the systolic function. The pathogenesis of this left ventricular (LV) dysfunction in diabetic patients is not clearly understood. [8] Left ventricular diastolic dysfunction (LVDD) represents the first stage of diabetic cardiomyopathy preceding changes in systolic function, reinforcing the importance of early evaluation of ventricular function in individuals with diabetes. [9] The diastolic abnormalities are present in diabetic patients in absence of diabetic complications of cardiovascular system. [10] Previously, several studies have determined the prevalence of LV diastolic dysfunction in patients with type 2 diabetes mellitus free of cardiovascular disease. However, there is no published data regarding the prevalence of diastolic dysfunction in normotensive asymptomatic type 2 DM and correlation with increased pulmonary artery pressure. Hence, the current study is intended to evaluate the prevalence of diastolic dysfunction in normotensive asymptomatic type 2 DM patients and its correlation with pulmonary artery pressure.

METHODOLOGY

This was a retrospective and cross-sectional study. For the study, we hypothesized that diastolic dysfunction, [as assessed by the mitral peak velocity of early filling (E) to early diastolic mitral annular velocity (e') (E/e') ratio], worsens with increased pulmonary artery pressure. The data for this retrospective study was obtained from Sevasadan Lifeline Super Speciality Hospitals between 10/1/2020 to 31/3/2020. The study comprised a total of 111 normotensive, asymptomatic type 2 DM subjects with no clinical evidence of cardiac disease were studied. This study included both male and female inpatients of all age groups. All patients with cardiac diseases like valvular heart disease, ischemic heart disease, hypertension, LV reduced EF (Ejection fraction) and other cardiac symptoms were excluded from the study. Data collection comprised factors thought to be associated with diastolic dysfunction as suggested by previous studies. [11] For each patient, the following information were collected: age, gender, BMI, HbA1C, duration of diabetes, treatment given for management of type 2 DM, Diabetic complications, Grades of diastolic dysfunction and pulmonary artery pressure. During the study period pulmonary pressure was measured by acceleration time and then pulmonary artery pressure was determined by using equation PAP=90-AT×,62.

Statistical Analysis:

Statistical analysis was done by estimating the prevalence rate of diastolic dysfunction and correlating with pulmonary artery pressure. All the statistical analysis was done using the software STATA. All characteristics were summarized descriptively. For continuous variables, data were represented using means ± SD. For categorical data, the number and percentage were used in the data summaries. Relationship between two variables was done using Pearson correlation test. The Correlation coefficient value ranges from -1 to +1, the negative value represents that the parameters are inversely proportional to each other and the positive value represents that the parameters are directly proportional to each other. The extent to which this correlation coefficient can show a significance was given in terms of p-value. P value of <0.05 was taken as statistically significant and the data was represented in the form of tables.

RESULTS

A total of 111 normotensive subjects, with type 2 diabetes mellitus were included in this retrospective and cross-sectional study. Out of 111 subjects with type -2 DM, 63 (56.76 %) were males and 48 (43.24 %) were females. All studied patients were of age between 21-75 years. Mean age of the population at the time diagnosis was 46.53±10.35 years. Table 1 shows demographic characteristics of subjects. As shown in Table 1, mean BMI was 26.33 kg/m^2 and the mean HbA1C in our study was observed to be 8.53 mmol/mol.

The median duration of diabetes for the study subjects was 5 years ranging from 1 to 22 years. Out of total 111 subjects with type-2 DM, Majority (63.06 %) of the patients (70) were treated with oral hypoglycaemic drugs (OHD) followed by insulin (21, 18.92 %) and diet control (20, 18.02%). Table 2 represents summary statistics of diabetes related parameters. Various diabetes related complications were noticed during the study period. Among all observed complications, diabetic nephropathy (DN) was the most common (10, 9.01 %) followed by both diabetic nephropathy and diabetic retinopathy (DR) (8.11 %), both diabetic retinopathy and peripheral neuropathy (PN) (7.21%), Diabetic Retinopathy (6.31%) and Diabetic Retinopathy and Peripheral Artery Disease (PAD) (4.50%) respectively.

Table 1: Summary of patients Demographics

PARAMETER	VALUE
Age (Years)	
N	111
Mean	46.53
Standard deviation	10.35
Median	46.00
Minimum	21.00
Maximum	75.00
Gender N (%)	
Male	63 (56.76 %)
Female	48 (43.24 %)
BMI (kg/m^2)	
N	111
Mean	26.33
Standard deviation	2.52
Median	26.00
Minimum	21.00
Maximum	34.00
HbA1C (mmol/mol)	
N	111
Mean	8.53
Standard deviation	1.08
Median	8.50
Minimum	6.60
Maximum	11.60

Table 2: Summary statistics of Diabetes Related Parameters

PARAMETER	VALUE
Duration of Diabetes (Years)	
N	111
Mean	6.16
Standard deviation	4.23
Median	5.00
Minimum	1.00
Maximum	22.00
Treatment Given N (%)	
Diet Control	20 (18.02 %)
Oral Hypoglycaemic Drugs (OHD)	70 (63.06 %)
Insulin	21 (18.92 %)
Other Complications N (%)	
Cerebrovascular Accident (CVA)	1 (0.90 %)
Diabetic Nephropathy (DN)	10 (9.01 %)
Diabetic Retinopathy (DR)	7 (6.31 %)
Peripheral Neuropathy (PN)	4 (3.60 %)
Cerebrovascular Accident (CVA), Diabetic Retinopathy (DR)	2 (1.80 %)
Diabetic Nephropathy (DN), Peripheral Neuropathy (PN)	3 (2.70 %)
Diabetic Nephropathy (DN), Diabetic Retinopathy (DR)	9 (8.11 %)
Diabetic Nephropathy (DN), Peripheral Artery Disease (PAD)	3 (2.70 %)
Diabetic Nephropathy (DN), Diabetic Retinopathy (DR), Peripheral Neuropathy (PN)	5 (4.50 %)
Diabetic Retinopathy (DR), Peripheral Artery Disease (PAD)	5 (4.50 %)
Diabetic Retinopathy (DR), Peripheral Neuropathy (PN)	8 (7.21 %)
Peripheral Neuropathy (PN), Cerebrovascular Accident (CVA)	1 (0.90 %)
Peripheral Neuropathy (PN), Peripheral Artery Disease (PAD)	1 (0.90 %)

Among 111 subjects, Diastolic dysfunction was found in 95 subjects (85.59 %) of which 46 (41.44 %) had impaired relaxation (Grade I), 45 (40.54%) had a pseudo normal filling pattern (Grade II), 4 subjects (3.60%) had reversible restrictive (Grade III) and none of the subjects had Fixed restrictive (Grade IV) as shown in Table 3. The average Pulmonary arterial pressure (PAP) in our study was found to be 29.40mmHg. In this study, we calculated the correlation co-efficient between Diastolic dysfunction and Pulmonary arterial pressure. As shown in Table 4, statistically significant association was seen between pulmonary artery pressure and the prevalence of diastolic dysfunction (Correlation Coefficient= 0.64807, $p \leq 0.0001$) showing that prevalence of diastolic dysfunction is dependent on the increased Pulmonary arterial pressure. Positive correlation was observed between Grade II and Grade III of diastolic dysfunction with pulmonary artery pressure. Negative correlation was observed between Grade I of diastolic dysfunction and increased PAP.

Table 3: Summary statistics of Diastolic Dysfunction and Pulmonary Arterial Pressure (PAP)

PARAMETER	VALUE
Diastolic Dysfunction N (%)	
Absent	16 (14.41 %)
Present	95 (85.59 %)
Impaired relaxation (Grade I)	46 (41.44 %)
Pseudonormal (Grade II)	45 (40.54 %)
Reversible restrictive (Grade III)	4 (3.60 %)
Fixed restrictive (Grade IV)	0 (0.00 %)
Pulmonary Arterial Pressure	
N	111
Mean	29.40
Standard deviation	5.84
Median	30.00
Minimum	17.00
Maximum	44.00

Table 4: Correlation Coefficients of Diastolic Dysfunction with Pulmonary Arterial Pressure (PAP)

Parameter	Correlation Coefficient with PAP	p - value
Diastolic Dysfunction	0.64807	< 0.0001
Impaired relaxation (Grade I)	-0.25858	0.0061
Pseudonormal (Grade II)	0.41382	< 0.0001
Reversible restrictive (Grade III)	0.38576	< 0.0001

DISCUSSION

The present study estimated the prevalence of diastolic dysfunction in normotensive asymptomatic type 2 diabetes mellitus and its correlation with increased pulmonary artery pressure. The baseline characteristics of the study participants showed average age as 46.53± 10.35 years at the time of presentation. Out of 111 subjects with type -2 DM, 63 (56.76 %) were males and 48 (43.24 %) were females. A study by Chaudhary et al., [12] observed that out of total 100 patients, 65(65%) males and the average age was 50.08 ± 6.32 years. Based on this study, we estimated that that males were more susceptible to diastolic dysfunction in comparison to the females. Previous studies hypothesized that the diastolic dysfunction worsens with age, duration of DM, HbA1c and obesity indices. [1] In our study, the mean BMI was 26.33 kg/m^2 and the mean HbA1C was observed to be 8.53 mmol/mol.

Median duration of diabetes for the study subjects was 5 years ranging from 1 to 22 years. Noh JH, et al., [4] in their study, of 65 type 2 diabetic patients, found that median duration of diabetes for the study subjects was 5 years. From et al., [13] in their study of 484 subjects between 1996 to 2007 year observed that a duration of diabetes ≥ 4 years was independently associated with LV diastolic dysfunction. Out of total 111 subjects with type-2 DM, Majority (63.06 %) of the patients (70) were treated with oral hypoglycaemic drugs (OHD) followed by insulin (21, 18.92 %) and diet control (20, 18.02%). A comparative study conducted by Suresh et al., [11] found that, among 50 diabetic patients, 16 were on oral hypoglycaemic agents, 6 were on insulin, and 28 were on insulin and oral hypoglycaemic agents. Oral Hypoglycaemic Agents were found to be most effective in the management of type 2 DM, which results reduced prevalence of diastolic dysfunction. Earlier study findings demonstrated that pre-clinical diastolic dysfunction is most common in patients with DM. Pre-clinical diastolic dysfunction has been broadly defined as diastolic dysfunction in patients with normal systolic function, and no symptoms of heart failure

(HF). [1] The influence of diabetic complications on LV diastolic dysfunction has been investigated in several studies. In the earlier studies, abnormalities have been observed especially in the population of diabetes with severe microvascular complications (marked proteinuria and proliferative retinopathy). [9] In our study, a total of 111 subjects with type-2 DM, diabetic nephropathy (DN) was the most common (10, 9.01 %) followed by both diabetic nephropathy and diabetic retinopathy (DR) (8.11 %), both diabetic retinopathy and peripheral neuropathy (PN) (7.21%), Diabetic Retinopathy (6.31%) and Diabetic Retinopathy and Peripheral Artery Disease (PAD) (4.50%) respectively.

Boyer et al., [14] stated that the prevalence of LV diastolic dysfunction in asymptomatic, normotensive patients with type 2 diabetes disease is high. Diastolic dysfunction was found in 75% subjects. Patil et al., [1] in their study, of 127 asymptomatic subjects found the prevalence of diastolic dysfunction in asymptomatic type 2 diabetics as 54.33%. [1] In our study, prevalence of diastolic dysfunction was 85.59 %. Among 95 diastolic patients, 46 (41.44 %) had impaired relaxation (Grade I), 45 (40.54%) had a pseudo normal filling pattern (Grade II), 4 subjects (3.60%) had reversible restrictive (Grade III) and none of the subjects had Fixed restrictive (Grade IV). We compared our results with various studies. Shreshta et al., [15] in 100 asymptomatic type 2 Diabetes Mellitus, LVDD was found in 71 subjects of whom 60 had impaired relaxation and 11 had a Pseudo normal pattern of ventricular filling detected by Doppler Echo which included Valsalva Maneuver. Mikael et al., [16] found that 121 patients (40%) had diastolic dysfunction, of which 67 patients (22%) had grade 1 diastolic dysfunction, 54 patients (18%) had grade 2 diastolic dysfunction, and no patients had grade 3 diastolic dysfunction. Chaudhary et al., [12] in 100 newly diagnosed normotensive, type 2 diabetic patients, LVDD was found in 41% of patients in this study with a predominance of Grade I LVDD (87.80%) evidenced by delayed relaxation time pattern in pulsed doppler echocardiography. No case of LV systolic dysfunction was found. Study demonstrated high incidence of diastolic dysfunction in normotensive and asymptomatic type 2 diabetics even at the time of diagnosis.

The average Pulmonary arterial pressure (PAP) in our study was found to be 29.40mmHg. In this study, we calculated the correlation co-efficient between Diastolic dysfunction and Pulmonary arterial pressure. Statistically significant association was seen between pulmonary artery pressure and the prevalence of diastolic dysfunction (Correlation Coefficient= 0.64807, $p \leq 0.0001$) showing that prevalence of diastolic dysfunction is dependent on the increased Pulmonary arterial pressure. Positive correlation was observed between Grade II and Grade III of diastolic dysfunction with pulmonary artery pressure. Negative correlation was observed between Grade I of diastolic dysfunction and increased PAP.

CONCLUSION

In the present study, overall prevalence of diastolic dysfunction was 85.59%. Diastolic dysfunction is very common at the time of diagnosis of type 2 DM even in normotensive patients independent of confounding effect of hypertension, valvular heart disease, ischemic heart disease, LV reduced EF and other cardiac symptoms. Diastolic abnormalities were correlated with the pulmonary artery pressure. Grade 1 LVDD was the most common (41.44 %). Statistically significant association was seen between pulmonary artery pressure and the prevalence of diastolic dysfunction (Correlation Coefficient= 0.64807, $p \leq 0.0001$) showing that prevalence of diastolic dysfunction is dependent on the increased Pulmonary arterial pressure. Positive correlation was observed between Grade II and Grade III of diastolic dysfunction with pulmonary artery pressure.

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