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Diastolic Dysfunction in Type 2 Diabetes and its Correlation with Retinopathy and Nephropathy

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Abstract: ***Introduction: The prevalence of diabetes mellitus is on rising trend in developing countries like India. This burden of diabetes brings it with the potential for a catastrophic increase in the prevalence of renal, ophthalmic and cardiovascular complications. Objectives: This study is to assess the diastolic dysfunction in type 2 diabetic patients using Doppler 2D echocardiography and also to find out the correlation between diastolic dysfunction and microvascular complications (nephropathy and retinopathy). Methods: A cross sectional observational study was conducted in GCS HOSPITAL, Ahmedabad over a period of 6 months from July 2021 to December 2021 in type 2 diabetes mellitus patients. A total of 50 cases were observed in this study on both indoor and outdoor basis. All patients were taken for 2D echocardiography to assess diastolic dysfunction on the basis of E/A and E/E' ratio. Fundus examination and urine microalbumin has been done to detect retinopathy and nephropathy respectively. Results: There was a significant correlation between age, duration of type 2 diabetes mellitus, diastolic dysfunction, diabetic nephropathy and retinopathy. In this study, risk of diastolic dysfunction increases with age and duration of diabetes mellitus. Incidence of retinopathy (p value 0.0004) and nephropathy (p value-0.0002) are more in patients with diastolic dysfunction compared to patients not having diastolic dysfunction. Conclusion: Results of the present study reveals that there is significant evidence to support the conclusion that diabetic individuals with diastolic dysfunction having higher risk of developing microvascular complications such as nephropathy and retinopathy.***

Keywords: Diabetes Mellitus, Diastolic Dysfunction, Nephropathy, Retinopathy

1. Introduction

The incidence of Diabetes Mellitus (DM) is increasing worldwide and is one of the major public health challenges of the 21st century. According to the International Diabetes Federation (IDF) estimates, prevalence of diabetes in the population is predicted to rise as mentioned below in Table 1(in millions):[1]

Table 1: Predicted prevalence of Diabetes Mellitus

Year	2021	2030	2045
World	537	643	783
India	74	92	124

The detrimental effects of uncontrolled hyperglycemia are classified into macrovascular complications like coronary artery diseases, peripheral arterial diseases, stroke and microvascular complications like nephropathy, retinopathy and neuropathy.[2] It is importantfor physicians to understand the relationship between DM and its complications as the prevalence of DM is increasing day by day.

The metabolic dysregulations associated with DM causes secondary pathophysiological changes in multiple organ systems. These lead to long-term chronic complications which account for majority of the morbidity and mortality attributed to the disease. Thus, an early diagnosis can help to prevent or delay the development of these complications.[3]

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of >5000 individuals with Type 2 DM for >10 years. The UKPDS demonstrated that each percentage point reduction in HbA1c was associated with a 35% reduction in microvascular complications. Improved glycemic control also reduced the cardiovascular complication event rate in the follow up period of >10 years.[4]

The Action to Control Cardiovascular risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled evaluation (ADVANCE) trials also found that improved glycemic control reduced microvascular complications.[5,6]

In the past decade, patients with signs and symptoms of heart failure despite a near normal left ventricular systolic function have received growing attention, for which the term LV diastolic heart failure or heart failure with preserved ejection fraction (HFpEF) has been introduced. Unlike left ventricular systolic dysfunction (LVSD), left ventricular diastolic dysfunction (LVDD) is often underdiagnosed in diabetes. LVDD is itself associated with poor prognosis and can progress to LVSD[7,8] and is thought to predate the onset of LVSD in patients with diabetes. The presence of T2DM is also associated with worse clinical status and higher all-cause and cardiovascular (CV) mortality in both reduced and preserved ejection fraction HF.

Diabetic Nephropathy is the leading cause of chronic kidney disease, ESRD and CKD requiring renal replacement therapy. Patients with diabetes who are at increased risk of Diabetic Kidney Disease (DKD) include those with poor glycemic control, longer duration of diabetes, hypertension, retinopathy, raised proteinuria levels, non-White race, family history of hypertension, and cardiovascular diseases (CVDs).[9]

Prospective and epidemiologic studies have found that microalbuminuria is predictive independently of traditional risk factors for all-cause and cardiovascular mortality and CVD events in groups of patients with diabetes or hypertension and in the general population. The pathophysiological mechanism underlying the association between albumin excretion and CVD is not fully defined. One hypothesis is that microalbuminuria may be a marker of CVD risk because it reflects subclinical vascular damage in the kidneys and other vascular beds. It may also indicate systemic endothelial dysfunction that predisposes to future cardiovascular events. Based on this theory, periodic screening for microalbuminuria could allow early identification of vascular disease and help to stratify overall cardiovascular risk especially in patients with risk factors such as hypertension or diabetes.

Diabetic Retinopathy can also be used to predict CVD-related death in individuals with type 2 diabetes. Several studies conducted in patients with type 2 diabetes have revealed that the presence of DR is associated with an excess risk of heart failure or cardiovascular mortality. Furthermore, a reduced eGFR was also noted in patients with diabetes compared to patients without diabetes, as well as in patients with DR compared to patients with diabetic and non-diabetic retinopathy

2. Aims and Objectives

1) To estimate the prevalence and grade of Diastolic dysfunction in type 2 diabetic patients using Doppler echocardiography.
2) To find out the correlation between diastolic dysfunction and microvascular complications. (Nephropathy and Retinopathy).

3. Materials and Methods

Study design: Cross sectional study.

Study subjects: All type 2 diabetic subjects who attended the outpatient and inpatient wards of medicine department in GCS Hospital who satisfied the inclusion criteria were included in the study.

Sample size: 50

Study period: 6 months (July 2021 – December 2021)

Inclusion criteria:

- Known case of type 2 diabetes mellitus.
- Newly diagnosed type 2 diabetes mellitus patients.
- Age group >30 years was used to avoid overlap of type 1 and other forms of diabetes mellitus.

Exclusion criteria:

- Pregnant women.
- Hypertensive patients.
- Known coronary artery disease patients.
- Patients with valvular heart diseases and arrhythmias.
- Patients with any concurrent illnesses like chronic liver disease and hypothyroidism.
- Patients with Chronic kidney disease on maintenance haemodialysis.
- Patients with Acute illnesses like Fever, UTI, Congestive heart failure, etc.

4. Methodology

After informed consent, 50 number of patients who fulfilled the inclusion criteria were included in this study. A pre-formed questionnaire was used to collect the clinical data including age, gender, past history, family history, drug history and personal history. Clinical examination, routine and relevant investigations were carried out for all patients. Patient's height and weight were measured to calculate the BMI. It was calculated as weight in kilograms divided by height in square meters (kg/m^2).

Diagnosis of Diabetes Mellitus was made according to ADA criteria 2021[2] or patients who were known diabetic taking insulin or oral antidiabetic agents. Patients were subject to laboratory investigations like complete blood count, renal function test, fasting blood sugar level, postprandial blood sugar level, HbA1c level, fasting lipid profile.

Ophthalmoscopic evaluation was done in all patients using the direct and indirect ophthalmoscope. Diabetic retinopathy if present was identified and classified as Non-Proliferative Retinopathy (NPDR), Proliferative Retinopathy (PDR) and Clinically Significant Macular Edema (CSME).

Diabetic nephropathy was assessed in the patient by measuring the renal parameters (blood urea and serum creatinine). Urine routine and cultures were done to exclude a urinary tract infection. Albuminuria was assessed in all patients in a spot urine sample using photometric techniques by the method of fully automated immune-turbidometry. Normal urine albumin excretion is less than 10. Urine albumin excretion rate of 30 to 300 and more than 300 mg/day correspond to microalbuminuria and macroalbuminuria respectively.

2D echocardiography was done to assess the ventricular dimensions, presence of regional wall motion abnormalities and left ventricular ejection fraction. The ejection fraction was obtained using Simpson's approach. Doppler echocardiography was done and using the apical four chamber view. The early mitral inflow velocity (E) and late inflow velocity (A) was obtained and E/A ratio was calculated.

E/A ratio of less than 1 was considered grade 1 diastolic dysfunction. When E/A ratio was more than 1, additional parameters like the velocity propagation, E wave deceleration time were considered to differentiate Grade II diastolic dysfunction from a normal pattern. The velocity propagation of the early mitral inflow was assessed using a colour M mode Echocardiography.

Statistical analysis:
Data entry and statistical analysis were done using Microsoft excel 2019 and SPSS version 26.0. Categorical variables were expressed as numbers and percentages. All continuous data was expressed as mean standard deviation. Chi-square test was used to assess the association among different categorical variables and unpaired t test was used to assess the association among continuous variables. Correlation was performed to find out the relation between different continuous variables. For all statistical analyses $p<0.05$ was considered statistically significant at a confidence level of 95%.

5. Results

Table 1: Presence of Diastolic dysfunction based on various clinical and laboratory characteristics

Variable		Diastolic Dysfunction		N (total 50)	% With Diastolic Dysfunction	SD (95% CI)	Chi Square	P value
		Present (N=27)	Absent (N=23)					
Age (years) (mean=49.36)	30-39	3	9	12	25%	±0.05	10.4733	0.014
	40-49	6	7	13	46.15%	±0.923		
	50-59	8	6	14	57.14%	±1.14		
	>60	10	1	11	90.91%	±1.81		
Gender	M	15	13	28	53.57%	±1.07	0.047	0.820
	F	12	10	22	54.54%	±1.09		
Duration of Diabetes(years) (mean=6.28)	0-4	4	15	19	21.05%	±0.42	15.212	0.0004
	5-9	10	6	16	62.50%	±1.25		
	>=10	13	2	15	86.67%	±1.73		
BMI (mean)		27.33	25.78	26.62	-	-	-	0.57
HbA1c (mean)		10.40	10.33	10.372	-	-	-	0.89
Retinopathy	Absent	5	18	23	21.73%	±0.43	15.638	0.0004
	NPDR	17	5	22	77.27%	±1.54		
	PDR	5	0	5	100%	±2		
Nephropathy	Albuminuria Absent	2	15	17	11.7%	±0.23	17.036	0.0002
	Microalbuminuria	19	8	27	70.3%	±1.46		
	Macroalbuminuria	6	0	6	100%	±2		

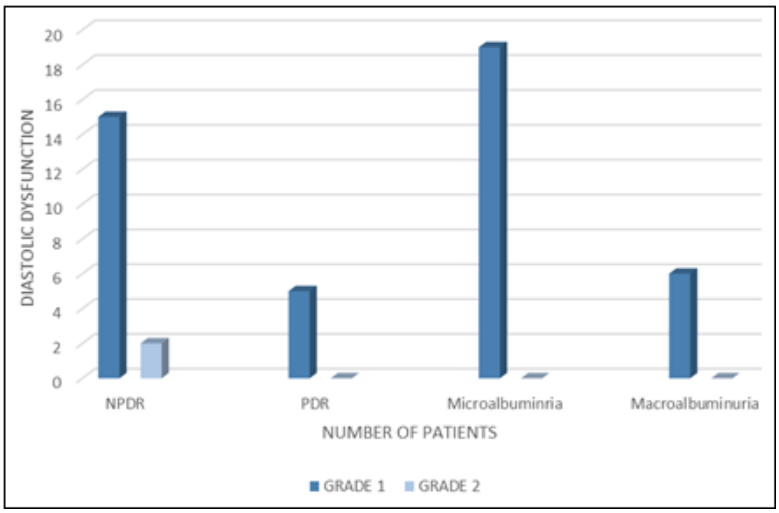

Figure 1: Relation of Diastolic Dysfunction with grade of microvascular complications

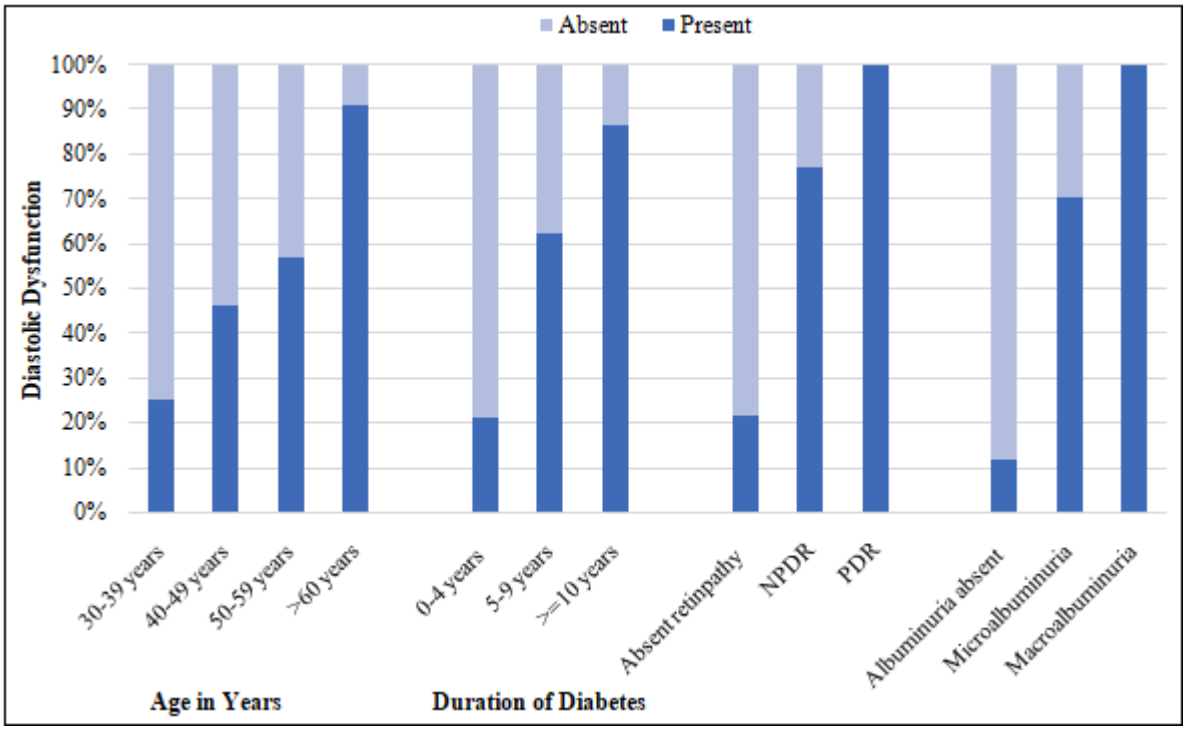

Figure 2 : Relation of diastolic dysfunction with various dependent variables in type 2 DM

6. Results

Diastolic dysfunction in diabetes:
Out of 50 type 2 diabetic patients taken in our study; 27 patients (54%) had diastolic dysfunction out of which 25 patients (92.59%) had Type 1 diastolic dysfunction and 2 patients (7.40%) had Type 2 diastolic dysfunction.

Diastolic dysfunction and age:
In our study 3 patients (25%) in the age group of 30- 39; 6 patients (46.15 %) in the age group of 40-49; 8 patients (57.15 %) in the age group of 50-59; and 10 patients (90.91 %) in the age group of > 60 had diastolic dysfunction. As mentioned in Table 1; the chi square value was 10.47 and p value was 0.014 which was statistically significant.

Diastolic dysfunction and gender:
Twelve females out of 22 (54.54%) had diastolic dysfunction whereas fifteen males out of 28 (53.57%) had diastolic dysfunction. As mentioned in Table 1; the chi square value was 0.047 with the p value being 0.820 which was statistically insignificant.

Diastolic dysfunction and duration of diabetes:
Considering duration of diabetes and diastolic dysfunction; 4 patients (21.05 %) had the duration of diabetes between 0-4 years; 10 (62.5%) with the duration between 5-9 years; 13 (86.67%) with the duration between more than or equal to 10 years. The chi square value was calculated as 15.212 and p value being 0.0004 which was statistically significant.

Diastolic dysfunction and glycemic control:
Patients who had diastolic dysfunction had a mean HbA1c level of 10.40 whereas the patients without diastolic dysfunction had 10.33 mean HbA1c level. The p value being 0.89 by unpaired t test which was statistically insignificant.

Diastolic dysfunction and BMI:
Patients with diastolic dysfunction had a mean BMI of 27.33 whereas the ones without diastolic dysfunction had a mean BMI of 25.78. Applying unpaired t test; the p value was 0.89 which was statistically insignificant.

Diastolic dysfunction and retinopathy:
In our study out of 27 patients having diastolic dysfunction; only 5 (18.51%) patients did not have evidence of diabetic retinopathy; whereas 17 (62.96 %) had non proliferative diabetic retinopathy and 5 (18.51%) patients had proliferative diabetic retinopathy. Out of 22 patients with NPDR ;17 (77.27%) had diastolic dysfunction and 5 patients with PDR all 5 (100%) had diastolic dysfunction. Chi square value being 15.638 and p value 0.0004 thereby proving statistical significance.

Diastolic dysfunction and nephropathy:
Out of 27 diabetic patients having diastolic dysfunction; 2 (7.4%) did not have any albuminuria; 19 patients (70.37%) had microalbuminuria and 6 patients (22.22%) had macroalbuminuria. Out of 27 patients with microalbuminuria; 19 patients (70.3%) had diastolic dysfunction and out of 6 patients with macroalbuminuria all 6 patients (100%) had diastolic dysfunction. The chi square value being 17.036 with the p value being 0.0002 making the findings statistically significant.

7. Discussion

Diastolic dysfunction in diabetes
As per our study, 54% of type 2 diabetes patients had diastolic dysfunction and 92.59% patients had Grade 1 diastolic dysfunction. In Chee KH *et al.* [10] 70.1% had left ventricular diastolic dysfunction and 90.5% had Grade 1/mild severity. A study by Chaudhary *et al.*[11] on normotensive newly diagnosed T2DM patients before

treatment initiation found an alarming 41.0% prevalence of LVDD, majority (87.8%) with Grade 1 dysfunction. Therefore, our study proves that there is an increased incidence of Diastolic dysfunction in Type 2 diabetic patients.

Diastolic dysfunction and age

As per our study, increasing age is a risk factor in diabetes for diastolic dysfunction. Almost 67% of patients with diastolic dysfunction were above the age of 50 years making it quite evident that with increasing age the risk for diastolic dysfunction increases. In V Suresh Kumar *et.al.*[3] 72.4% of patients above the age of 50 years documented Type 1 Diastolic dysfunction. The study done by Chee KH *et al* [10] showed that with every unit increase in age; the risk for LVDD increased by 1.05 [95% confidence interval (CI); p < 0.001].

Diastolic dysfunction and gender

Our study demonstrates that the female diabetic population has an increased prevelance (54.54%) of diastolic dysfunction as compared to the male diabetics (52.57%). However, this difference is not statistically significant to prove that females have an increased risk for developing diastolic dysfunction (P value – 0.82). In V Suresh Kumar *et.al.*[3] females had shown more prevalence of diastolic dysfunction (80%) in comparison to the males (57%). According to the study done by Yadava *et. al* [12] there was no significant association between diastolic dysfunction and gender. In a study done by Bouthoorn *et. al* [13], the prevelance of left ventricular diastolic dysfunction among type 2 diabetes patients is similarly high in men and women, while heart failure with preserved ejection fraction seems to be more common in women than men, at least in community people with type 2 diabetes.

Diastolic dysfunction and duration of diabetes

Mishra *et al.* [14] in their case control study of 71 subjects with type 2 DM found that asymptomatic diabetic patients have reduced LV systolic and diastolic function as compared with healthy subjects. LV systolic and diastolic abnormalities are correlated with the duration of diabetes and with diabetic microangiopathies, like retinopathy and neuropathy. Similar findings have been demonstrated in our study; corroborating that longer duration of diabetes increases the risk of diastolic dysfunction. In Dr.S.Ch. Bhaskar Dorapudi*et.al*[15] the mean duration of type 2 DM among cases with diastolic dysfunction was 8.84 years and among cases without diastolic dysfunction was 6.4 years. On unpaired t test, this difference was found to be statistically significant (P value <0.05). Thereby the study showed that more the duration of type2 DM, more is the risk of diastolic dysfunction. High statistical significance (p = 0.0004) was observed for the association between the duration of diabetes and diastolic dysfunction. In our study as well. Patients with more than 10 years of duration had an extremely high chance for developing diastolic dysfunction (86.67%).

Diastolic dysfunction and glycemic control

Hameedullah*et al.* [16]in their study population of 60 patients with type 2 DM found that there was a strong correlation between HbA1c level and diastolic indices. Diastolic dysfunction was more frequent in poorly controlled patients with diabetes, and its severity is correlated with glycemic control.

In Chaudhary *et al.* [11] the mean HbA1C of population with LVDD was found higher (7.67±0.90%) as compared to population without LVDD (7.24±0.64%). Correlation was found significant using unpaired t-test (p-value=0.0057). This signifies that higher the HbA1C at the time of diagnosis, higher will be the incidence of LVDD.

In our study out of total patients with diastolic dysfunction 40.74% had HbA1C level less than 10; whereas 59.25% had HbA1c level more than 10. This shows that there is a positive correlation between Hba1c levels and diastolic dysfunction.

This is a limitation in our study wherein the mean Hba1c level is 10.37 (N=50). Our study did not include patients with a wide range of HbA1c level and hence the association between HbA1c and diastolic dysfunction could not be established. Ours being a tertiary hospital majority of the patients presented with higher HbA1c levels. Moreover, only a single HbA1c level was taken into consideration in our study i.e., at a single point of time and serial values were not taken. All these factors are collectively responsible for the limitation of our study.

Diastolic dysfunction and BMI

Our study documented a positive correlation between the values of BMI and diastolic dysfunction in diabetic patients. Patients with diastolic dysfunction had a mean BMI of 27.33 whereas the ones without diastolic dysfunction had a mean BMI of 25.78. Obesity in diabetic patients is thus a risk factor for developing diastolic dysfunction. According to the study done by Yadava *et. al* [12], there was no significant association between diastolic dysfunction and dyslipidaemia, BMI, tobacco smoking, alcohol consumption, HbA1c and gender.

Diastolic dysfunction and retinopathy

In our study, 54% of patients showed evidence of retinopathy, the mean duration of diabetes in our study being 6.28 years. Out of total patients with NPDR; 77.27% had evidence of diastolic dysfunction whereas the ones with PDR 100% had diastolic dysfunction.

The association between retinopathy and diastolic dysfunction had a strong correlation in our study (p<0.0004). Patients with proliferative retinopathy had a stronger association.

In Patil *et. al* [17] 89% of patients with Diabetic retinopathy had Diastolic dysfunction with 'P' = 0.002 proving a statistical significance between the two.

In Annonu*et al.*, [18] diabetic retinopathy was present in 38% of patients with NIDDM. There was a significant correlation between diabetic retinopathy with diminished EF (P < .005), reversed E/A ratio (P < .05) and diminished EF deceleration slope (P < .005). This may be explained by the associated microvascular disease involving the coronary circulation with subsequent impairment of systolic and diastolic LV performance.

Diastolic dysfunction and nephropathy

In our study, 66% of the diabetic patients had nephropathy; out of which 81.9% patients had microalbuminuria. 70.3 % of patients with diastolic dysfunction had microalbuminuria in our study. 100% patients having macro albuminuria had diastolic dysfunction. The association between nephropathy and diastolic dysfunction is strong in our study ($p<0.0002$). The present study was in correlation with the studies by J. Miyazato *et al*[19] which showed increased prevalence of diastolic dysfunction indiabetics with nephropathy. In Jensen *et al*. [20] mean UACR of cases with diastolic dysfunction was 61.9 andwithout diastolic dysfunction was 24.1. On unpaired t test thisdifference was found to be statistically highly significant (P value<0.01) thereby proving that diabetic nephropathy has a significant association with diastolic dysfunction. Jiteshri*et. al* [21]also studied the association of microalbuminuria with left ventricular dysfunction in patients of Type 2 Diabetes Mellitus. The presence of microalbuminuria is associated with increased likelihood of LVDD in type 2 diabetes.

In recent times, several important studies like the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study, Prevention of Renal and Vascular End stage disease (PREVEND) study and Nord-Trøndelag Health Study (HUNT) have showed that, like diabetes, presence of microalbuminuria is predictive of CV events. Indeed, some studies have suggested that the presence of microalbuminuria increases the relative risk of adverse CV events similar to the presence of hypercholesterolemia.

8. Conclusion

As per our study performed on 50 patients with type 2 diabetes free of coronary artery disease and hypertension,

- Diastolic dysfunction is a common complication in individuals with type 2 diabetes. Out of Grade 1 and Grade 2; Grade 1 diastolic dysfunction is more frequently encountered. Diastolic dysfunction in our study was isolated and asymptomatic.
- Increasing age in diabetic patients is a risk factor for diastolic dysfunction. The risk is substantially increased above the age of 50 years.
- Our study did not document a statistical significance between gender and diastolic dysfunction in diabetics.
- Increased BMI in diabetic patients is also a risk factor for developing diastolic dysfunction.
- Duration of type 2 diabetes positively correlates with diastolic dysfunction. Longer the duration of diabetes, greater is the prevalence of diastolic dysfunction. Diastolic dysfunction is also associated with the levels of HbA1c. Higher the HbA1c level at the time of diagnosis more is the risk for developing diastolic dysfunction.
- Microvascular complications like retinopathy and nephropathy strongly correlate with diastolic dysfunction. This association is stronger in patients with PDR and macroalbuminuria.
- Our study recommends that screening for subclinical LVDD using Echocardiography should be done in patients with Type 2 DM especially having risk factors like advanced age, obesity, longer duration of diabetes and uncontrolled diabetes (Higher HbA1c).
- Type 2 diabetes patients with microalbuminuria and diabetic retinopathy should also be screened annually with Echocardiography for early detection of LVDD.
- Such screening measures constitute a part of mandatory early preventive strategies.

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