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Diastolic Dysfunction in Diabetic Microangiopathies–Harbinger for Heart Failure

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Original Research Article

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Abstract: Heart failure is a life threatening problem in Diabetic population particularly with microangiopathies even in the absence of coronary artery disease. Early identification of diastolic dysfunction shall prevent heart failure in this vulnerable group. The aim is to determine the prevalence of diastolic dysfunction in type 2 diabetes mellitus patients and to correlate the association of diastolic dysfunction with diabetic microangiopathies. This cross sectional study was conducted in 120 type 2 diabetic patients who attended cardiology OPD in Government Stanley Medical College for 6 months. Echocardiography was performed to assess left ventricular diastolic function. Urine microalbumin was measured by Immunoturbidimetry method and Fundoscopic examination for retina. More than 50% of the diabetic population has diastolic dysfunction. Diastolic dysfunction directly correlates with duration of diabetes particularly after 5 years, elevated BMI and diabetic microangiopathies like retinopathy & nephropathy. The overall prevalence of retinopathy in our study was 51.6% and that of nephropathy was 66.67%. Out of 62 patients with retinopathy, 52(83.8%) had diastolic dysfunction. The proportion of patients with diastolic dysfunction was higher for proliferative retinopathy. Among 80 patients with nephropathy, 64 of them had diastolic dysfunction accounting for 80%.
Keywords: ADA (American Diabetes Association), BMI (Body Mass Index), DM (Diabetes Mellitus). LVEF (Left ventricular Diastolic Dysfunction), (NPDR) Non Proliferative Diabetic Retinopathy and PDR (Proliferative Diabetic Retinopathy).

INTRODUCTION

The incidence of diabetes mellitus (DM) is found to be increasing worldwide and its epidemic proportions are rapidly increasing. Many studies have reported that there is increase in incidence of myocardial dysfunction in diabetic subjects even in the absence of ischemic, valvular and hypertensive heart disease [1]. Studies have reported a raised prevalence of asymptomatic diastolic dysfunction among subjects with DM [2]. The evidence indicates that myocardial damage in diabetic subjects initially affects the diastolic function followed by systolic function. The complications of Diabetes can be classified as microvascular such as retinopathy, nephropathy and neuropathy and macrovascular complications such as coronary artery disease and peripheral vascular disease. The influence of diabetic complications on diastolic dysfunction has been investigated in several studies [3]. Abnormalities have been observed particularly in diabetic patients with severe microvascular complications like nephropathy, retinopathy as evidenced by marked proteinuria and proliferative retinopathy respectively.

AIM & OBJECTIVES

To determine the prevalence of diastolic dysfunction in Type 2 diabetes mellitus patients and to correlate the association of diastolic dysfunction with diabetic microangiopathies

MATERIALS & METHODS

This cross sectional study was conducted after obtaining approval from Ethical committee in 120 type 2 diabetic patients who attended cardiology OPD in Government Stanley Medical College for 6 months.

Inclusion criteria

All Asymptomatic type 2 diabetes subjects aged more than 30 years. Diabetes was diagnosed using ADA (American Diabetes Association) criteria.

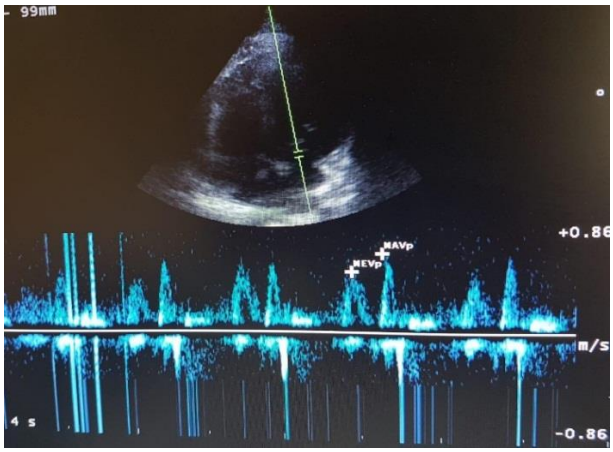
Exclusion criteria

Type 2 diabetes subjects with hypertension, kidney disease, coronary artery disease, heart failure, systolic dysfunction by echocardiogram, peripheral neuropathy and Type 1 diabetes patients.

Methods

2D echocardiography was performed by Esoate mylab 5 according to the standard protocol. Diastolic dysfunction was labelled according to the standard guidelines. Left ventricular overall ejection fraction (systolic function) was calculated by modified Simpson's method; and, LVEF ≥ 50% was considered as normal [4]. Mid-stream urine was examined for microalbuminuria, Urine microalbumin was measured by Immunoturbidimetry method. Fundoscopic examination for retina. Body mass index was calculated.

Body mass index (BMI) = $\frac{\text{Weight of the patient (in kg)}}{(\text{height})^2 \text{ (in m}^2)}$



Diagnostic criteria

- Diabetes mellitus (DM): If a subject is a known diabetic on treatment[5]
- Diabetic retinopathy if present was identified and classified non proliferative retinopathy (NPDR) and proliferative retinopathy (PDR).
- Diastolic dysfunction: LV diastolic dysfunction was considered to be present if any of the following findings were seen, as previously described• E/A ratio < 1 or > 2 • Deceleration Time < 150 or > 220 ms,

STATISTICAL ANALYSIS

Data were analysed by SPSS software 16 versions and chi square test.

RESULTS

Table-1: Baseline characteristics of patients in this study

	Grade I dd	Grade II dd	Normal diastolic function
Age distribution			
30-39(n= 30)	6	0	24
40-49(n= 28)	14	0	14
50-59 (n= 36)	22	2	12
>60 (n= 26)	22	2	2
Sex distribution			
Male(n=68)	32	4	32
Female(n=52)	32	0	20
Duration(years)			
0-4(n=46)	10	0	36
5-9(n=40)	26	2	12
>10(n=34)	28	2	4
BMI			
<25(n=30)	8	0	22
25 – 29.9 (n= 70)	46	0	24
>30 (n=20)	10	4	6
Retinopathy(n=62)			
Non proliferative(n52)	38	4	10
Proliferative(n10)	10	0	0
Nephropathy(n=80)			
Micro(n=68)	50	2	16
Macro(n=12)	10	2	0

Out of 120 patients enrolled in the study, 68 were male patients and 52 were female patients. Only patients above the age of 30 years were included in the study. Maximum number of patients was in the age group 50 -59 years (36 patients). 26 patients were above the age of 60 years. The mean age in our study was 49.3±10.4. Most patients (70 patients out of 120) had a BMI value between 25 and 29.9 kg/m^2. 20 patients were obese (BMI > 30 kg/m^2. The mean BMI value in our study was 26.58±2.78. Among the 120 patients, 62 patients (51.67%) had retinopathy of which 52 of them had non proliferative retinopathy and 10 patients had proliferative retinopathy. Out of the 62 patients with retinopathy, 32 patients had diabetes for 10 years or more. The prevalence of retinopathy` was very low when the duration of diabetes was less than 5 years.80 patients out of 120 had evidence of nephropathy in the form of proteinuria. Microalbuminuria is present in 68 patients and overt nephropathy (macroalbuminuria) is present in 12 patients. The prevalence of nephropathy was considerably higher when the duration of diabetes was more than 5 years.

The overall prevalence of retinopathy in our study was 51.6% and that of nephropathy was 66.67%. The above mentioned patients had isolated diastolic dysfunction. Patients having associated systolic dysfunction were excluded from the study population. None of these patients had clinical evidence for heart failure.

The mean E/A ratio in our study were 1.047±0.356. In patients with diastolic dysfunction the E/A ratio was much lower (0.7701±0.09) than patients with normal function (1.326±0.24) (p<0.001**).

Diastolic dysfunction and retinopathy

Out of 62 patients with retinopathy, 52(83.8%) had diastolic dysfunction. The proportion of patients with diastolic dysfunction was higher for proliferative retinopathy. All 5 patients with proliferative retinopathy had diastolic dysfunction.

Table-2: Retinopathy and Diastolic Dysfunction

Retinopathy	No. of patients(n=120)		Total no. of patients
	Normal diastolic function	Diastolic dysfunction	
No retinopathy	42	16	58
Retinopathy	10	52	62

Chi square test values for the above data: p value=<0.001**

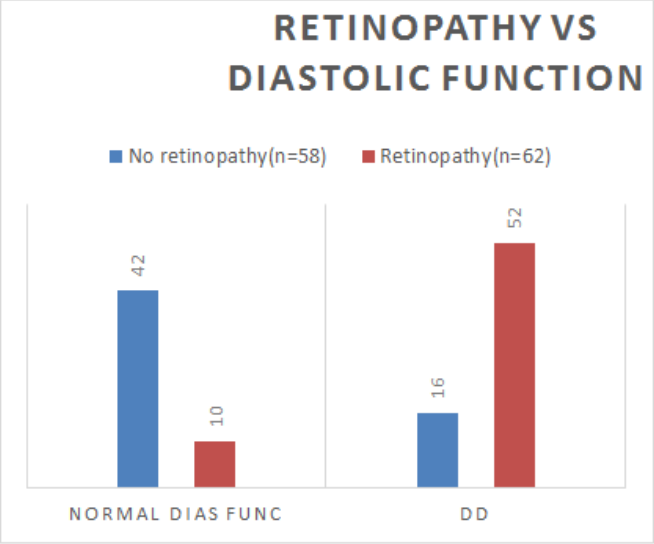


Table-3: Diastolic dysfunction and retinopathy

Retinopathy	No. of patients with diastolic dysfunction (n=52)		% of patients with diastolic dysfunction
	Grade I	Grade II	
Non proliferative retinopathy(n= 52)	38	4	80.8%
Proliferative retinopathy(n = 10)	10	0	100%
Total (n=62)	48	4	83.8%

Diastolic dysfunction and nephropathy

Among 80 patients with nephropathy, 64 of them had diastolic dysfunction accounting for 80%. The association with macro albuminuria was significantly higher with all 6 patients developing diastolic dysfunction.

Table-4: Diastolic dysfunction and retinopathy

Nephropathy	No. of patients (n=120)		Total no. of patients
	Normal diastolic function	Diastolic dysfunction	
No nephropathy	36	4	40
Nephropathy	16	64	80

Chi square test value: p <0.001**

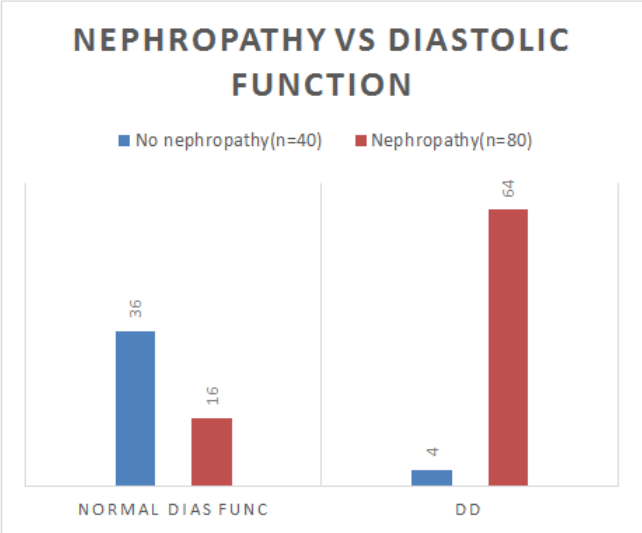


Fig-1

Table-5: Diastolic dysfunction and retinopathy

Nephropathy	No. of patients with diastolic dysfunction (n=64)		% of patients with diastolic dysfunction
	Grade I	Grade II	
Microalbuminuria (n= 68)	50	2	76.5%
Macroalbumuria (n = 12)	10	2	100%
Total (n=80)	60	4	80.0%

DISCUSSION

According to our study, 57 % of type 2 diabetes had diastolic dysfunction. In Khalil S I *et al.* about 58% of diabetic patients had diastolic dysfunction of which majority of them had Grade I diastolic dysfunction. In our study, increasing age is a risk factor in diabetes for diastolic dysfunction. With almost 70% patients above the age of 50 years had diastolic dysfunction, indicated that age is directly proportional to the prevalence of diastolic dysfunction. Srivastava *et al*. confirmed that increasing age has an independent influence for both myocardial dysfunction and diastolic dysfunction in type 2 diabetic patients. Khalil S I *et al*. also demonstrated that age is an important risk factor for diastolic dysfunction in type 2 diabetes [6]. In the study, prevalence of diastolic dysfunction in the age group 41-50 years were around 80% compared to 12.5% in the 21- 30 year age group. The mean age of the study group was 40.79± 7.65 years. R. Wachter *et al.* showed that the presence of diabetes mellitus has an influence on diastolic function in males but there was no difference in females between the diabetic and non-diabetic population. Non diabetic males showed a lower prevalence (58.9%) of impaired relaxation compared to those with diabetes (69.7%). The presence of coexisting coronary artery disease did not change the outcome. High statistical significance (p = 0.001**) was observed for the association between duration of diabetes and diastolic dysfunction

Data from Khalil S I *et al*. 2007 showed the prevalence of diastolic dysfunction increases with duration of diabetes. The study demonstrates a 100% prevalence of diastolic dysfunction when the duration of diabetes was more than 10 years. In our study, the prevalence was 88.3% in the duration of diabetes of more than 10 yrs[7].

Obesity as defined by BMI > 30 kg/m^2 was present in 16.6% of patients. Srivastava *et al*. 2006

showed that over 50 % of the study population was obese. Obesity in the above study was defined by value of BMI > 30 kg/m^2. Patients with a BMI > 30 kg/m^2 had a significant increase in cardiac dysfunction and diastolic dysfunction as per the study. Although, the prevalence of obesity was comparatively lower in our study, the risk of diastolic dysfunction in obese individuals had comparable results.

Diastolic dysfunction and nephropathy

It is known that 60% of patients with type 2 diabetics develop retinopathy at the end of 20 years. In our study, nearly 50% of patients showed evidence for retinopathy, the mean duration of diabetes in our study being 6.07 years. The association between retinopathy and diastolic dysfunction had strong correlation in our study ($p<0.001$**). Patients with proliferative retinopathy had a stronger association. Takenaka *et al*. demonstrated an association between retinopathy and type 2 diabetic patients free from coronary artery disease and hypertension. Annonu *et al*. [7] demonstrated that E/A ratio < 1 in 49 % of patients with retinopathy.

Diastolic dysfunction and nephropathy

The prevalence of nephropathy in our study was 66.6%, compared to other Indian data, which reported the prevalence of around 30%. End stage renal disease was not observed in our study because hypertensive patients were excluded from the study and most ESRD patients would have associated hypertension. However, the association between nephropathy and diastolic dysfunction is strong in our study ($p<0.001$**). Although various studies done in type 1diabetes suggest an association between albuminuria and diastolic dysfunction, study done in type 2 diabetes by Annonu *et al*. failed to demonstrate a significant association. The association of diastolic dysfunction with microvascular complications strongly suggests the possibility of a background microangiopathy. Since microalbuminuria is also marker of endothelial dysfunction, diastolic dysfunction indicates a widespread endothelial dysfunction. Zoneraich *et al*. demonstrated small vessel disease in 72% of diabetic patients. Microvascular changes include formation of microaneurysms and capillary membrane thickening. Depositions 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, have been reported in biopsy specimens of human diabetic hearts [8].

Hence, with the available supporting data from our study, the existence of diastolic dysfunction in diabetics, who are normotensive and free from coronary artery disease, is confirmed. More importantly diastolic dysfunction exists in isolated form and is asymptomatic [9]. The possible pathogenic mechanism for diastolic dysfunction has been proposed due to its strong association with microvascular complications. Newer modalities of diabetic treatment targeting the pathogenic mechanisms like aldose reductase inhibitors, PKC pathway inhibitors, ACE inhibitors can reverse diastolic dysfunction and improve cardiovascular mortality.

CONCLUSION

More than 50% of the diabetic population have diastolic dysfunction. Diastolic dysfunction directly correlates with duration of diabetes particulary after 5 years [10, 11], elevated BMI and diabetic microangiopathies – retinopathy and nephropathy. Therefore, Diastolic dysfunction may be a forerunner for an incipient heart failure in diabetic patients with longer duration, obesity and microangiopathies.

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