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Original Article

Asymptomatic left ventricular diastolic dysfunction in NIDDM; evaluation and association with glycemic control.

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Abstract

DM is an established risk factor for congestive cardiac failure, in which the diastolic function is impaired. The majority of these patients may be asymptomatic without signs of overt heart failure. The aim of this study was to determine asymptomatic Left Ventricular Diastolic Dysfuction (LVDD) in Non-Insulin Dependent Diabetes Mellitus (NIDDM) in association with glycemic control and to assess the risk factors for the development of diastolic dysfunction. This cross sectional study was conducted at the Tabba Heart Institute, Karachi from Dec, 2011 to Nov 2012, 101 asymptomatic patients with type 2 diabetes without evidence of cardio-respiratory illness were enrolled. LVDD was evaluated by Doppler echocardiography, which included the valsalva manoeuvre. A total of 101 patients, LVDD was found in 67 subjects (66.34%) of whom 52 (51.48%) had impaired relaxation and 15 (14.85%) had a pseudonormal pattern of ventricular filling. The potential risk factors for the development of LVDD in type 2 diabetics were (a) age ≥45 years was associated with an almost three times higher risk for LVDD, (b) females had almost two times a higher risk of LVDD as compared with men, and (c) Diabetic patients of more than two years' duration had a two times higher risk of LVDD. The study results also indicate that LVDD was significantly associated with increased age, longer duration of Diabetes and glycemic control (glycated HbA1c levels) and LVDD is found in diabetic patients before the onset of clinically detectable disease. The high prevalence of LVDD suggests that screening for LVDD should include procedures such as the valsalva manoeuvre.

Keywords

Non-Insulin Dependent Diabetes Mellitus (NIDDM), Left ventricular diastolic dysfunction (LVDD), Echocardiography (ECHO), Glycosylated Hemoglobin (HbA1c), Pakistani patients

Introduction

Diastolic heart failure is a clinical syndrome characterized by the symptoms and signs of heart failure, a preserved ejection fraction and abnormal diastolic function. (Grundy, 1999) Left ventricular diastolic function (LVDF) is affected earlier than systolic function in the development of congestive cardiac failure. (Zariach, 1980).

Diabetes mellitus (DM) is a chronic metabolic disorder causing both acute and chronic life-threatening complications (WHO, 2004; Wild S., 2004). Cardiovascular complications are increased and commonly associated with Diabetes, mainly ischemic cardiomyopathy and left ventricular (LV) dysfunction (Grundy, 1999).

The results of Framingham Heart study have shown that the incidence of congestive cardiac failure, in diabetic patients occurs irrespective of coronary artery disease or hypertension. (Kennel,1979). In overt heart failure, diastolic dysfunction often co-exists with systolic dysfunction as a consequence of ischemic heart disease, but the diastolic dysfunction is a frequent finding in type 2 diabetes mellitus without signs and symptoms of heart disease and is presumably due to diabetic cardiomyopathy. In DM patients, an early examination may help detect of left ventricular diastolic function, thereby allowing early intervention for a more favorable outcome. (Raev, 1999).

Pakistanis are an ethnic group having an inherent predilection to develop diabetes. Increase in life expectancy and major changes in diet, lifestyles and social development further contribute to the existing trends (Hameedullah, 2010). This study was done to understand the burden of left ventricular diastolic dysfunction (LVDD) in patients with type 2 diabetes and to assess the risk factors for the development of diastolic dysfunction in such patients.

A cross sectional study was conducted in Echocardiography unit, Department of Cardiology at Tabba Heart Institute, Karachi from Dec, 2011 to

Nov 2012 (1 year). The hospital ethical board committee (EC/IRB) ethically approved the study. In the study, 101 subjects, male or female, ages between 40 and 55, with type 2 diabetes (diagnosed in accordance with the criteria of the American Diabetes Association) were enrolled from the outpatient clinic and the diabetes clinic. The subject with type 1 diabetesm heart problems, Pneumonias, kidney insufficiency, hormonal therapy (estrogen/progesterone) and difficulties for acquiring an echocardiographic window were excluded from the study. Before enrolled, as per GCP guidelines, subject was signed informed consent for their voluntary participation in the study.

Diastolic dysfunction: LV diastolic dysfunction was considered to be present if any of the following findings were seen, as previously described: (Galdesisi, 2006, Ommen, 2000)

- E/A ratio < 1 or > 2
- DT < 140 or > 240 ms,
- IVRT < 70 or > 90 ms, or
- E/E' ratio <8 OR > 15

The detailed medical history, physical examination, ECG and biochemical investigations (plasma glucose level, glycatedHbA1c and Lipid profile) were done as per study protocol and noted in IEC approved Case Report Form (CRF). Echocardiogram done to assess the presence of diastolic dysfunction. Echocardiograms were done using the commercially available GE Vivid S5.

Data Analysis

Data were analyzed by using statistical package for social sciences (SPSS) version 16 for windows. Data were expressed as medians and frequencies were expressed as percentages. For continuous variables, Non-parametric, Mann-Whitney test was used to identify the significant difference between two groups and for categorical variable, proportions were compared using chi-square test. A P-value of less than 0.05 was considered as statistically significant.

Results

A total of 122 patients, initially screened and 101 patients were included in the study, diastolic dysfunction was detected in 67 patients while 34 of them had normal echocardiographic findings. Among the 67 patients who had diastolic dysfunction, impaired relaxation was detected in 52 (51.48%) and pseudonormal pattern was detected in 15 (14.85%) which was unmasked by the valsalva maneuver (Table 1)

Table 1: Gender and Diastolic Dysfunction Grading

		Diastolic Dysfunction			Total
		Normal Diastolic Function	Grade I (Impaired Relaxation)	Grade II (Psudonormal)	Diastolic Function
Gender	Male	24(36.9%)	34(52.30%)	7(10.7%)	65
	Female	10(27.77%)	19(52.77%)	7(19.14%)	36
Total		34	53	14	101

Table 1: For Gender and Diastolic Dysfunction grading, Gade 1 LVDD, male and female equally have high risk whereas females had almost two times a higher risk for the development of grade II diastolic dysfunction as compared with men.

Table 2. Comparison of characteristics between subjects with normal and those with diastolic dysfunction.

Variables	Normal (n = 34) Median	Diastolic dysfunction (n = 67) Median	P value
Age (years)	46	52	< 0.001
Duration of diabetes (years)	2.50	5	< 0.001
Systolic blood pressure (mm Hg)	130	130	0.997
Diastolic blood pressure (mm Hg)	80	80	0.911
BMI (kg/m2)	23.45	23	0.954
Fasting plasma glucose (mg/dl)	89.50	129	0.001
Serum creatinine (mg/dl)	0.90	0.85	0.328
Total cholesterol (mg/dl)	170	175	0.097

HDL cholesterol (mg/dl)	41.0	40	0.095
Triglycerides (mg/dl)	161	145	0.032
LDL cholesterol (mg/dl)	101	110	0.369

Table: 2 displays the anthropometric characteristics of the study group. Median age, duration of diabetes, fasting plasma glucose and triglycerides were significantly (P=< 0.001, P=< 0.001, P=0.001, P=0.032) higher in the diastolic dysfunction patients than the normal patients. However, systolic blood pressure, diastolic blood pressure, serum creatinine, HDL and LDL were not statistically differing in both groups (P=0.997, P= 0.911, P=0.328, P=0.095, P=0.369).

Table 3. Echocardiographic parameters between subjects with normal and those with diastolic dysfunction

Echocardiographic parameters	Normal (n=34) Median (range)	Impaired relaxation (n=52) Median (range)	Pseudonormal pattern (n=15) Median (range)
Ejection fraction (%)	60 (55-70)	60 (55-70)	60 (50-60)
E wave (cm/s)	725 (560-850)	440 (320-570)	775 (738-895) 555 (475-595)*
A wave (cm/s)	570 (487-650)	719 (630-800)	640 (450-690) 690 (610-710)*
E/A ratio	1.2450 (1.15-1.58)	0.605 (0.45-69)	1.20 (1.14-1.64) 0.82 (0.74-1.40)*
DT (ms)	169 (152-215)	250 (236-280)	186 (142-200)
IVRT (ms)	79 (70-89)	104 (94-130)	82 (70-90)
E/E’	6.4 (5-8.2)	7 (5-9)	16 (13.8-17)

*expresses the values of E wave, A wave and E/A ratio after valsava manoeuvre.

Table 3: Out of 101 subjects, 33.66% were having normal diastolic function, while 51.48% were having impaired relaxation (grade I LVDD). 14.85% were initially having normal diastolic function but after performing valsalva, all parameters changed, depicting psuedonormal pattern (grade II LVDD) in which E/E’ was found to be above 15.

Table 4: Correlation of Normal & diastolic dysfunction with HbA1c Level

	HbA1C				
	< 6.3	6.4-7	7.1-8	8.1-10	>10
Diastolic dysfunction	0	7	14	40	6
Normal	18	6	5	5	0
TOTAL	18	13	19	45	6

Table 4: The results also revealed that HbA1C < 6.3 have no LVDD, however diastolic dysfunction increased gradually with the rise in HbA1c levels and it was statistically significant as shown in (Table 3) with 88.88% of patients between 8.1 to 10 HbA1c, and all patients with HbA1c >10 % were having diastolic dysfunction.

Table 5: Correlation of risk factors (Age and Duration of DM) with LVDD

		NORMAL DIASTOLIC FUNCTION	DIASTOLIC DYSFUNCTION
AGE[years]	<45 [n=17]	70.5% [n=12]	29.4% [n=5]
	>45 [n=84]	26.19% [n=22]	73.8% [n=62]
DURATION OF DIABETES [years]			

	1 [n=5]	80% [n=4]	20% [n=1]
	2 [n=12]	58.3% [n=7]	41.6% [n=5]
	3 [n=14]	35.7% [n=5]	64.2% [n=9]
	4 [n=14]	28.5% [n=4]	71.42% [n=10]
	5 [n=19]	26.3% [n=5]	73.68% [n= 14]
	6 [n=23]	26.0% [n=6]	73.9% [n=17]
	7 [n=12]	25% [n=3]	75% [n=9]
	8 [n=2]	O% [n=0]	100% [n=2]

Table 5: The potential risk factors for the development of diastolic dysfunction in type 2 diabetics that were determined were; (a) age ≥45 years was associated with an almost three times higher risk for the development of diastolic dysfunction, (b) patients with diabetes of more than two years' duration had a two times higher risk of developing diastolic dysfunction.

Discussion

With the studies, data indicate that the DM subjects are at greater risk of cardiovascular morbidity and mortality, particularly congestive cardiac failure as compared with those without diabetes (Kannel, 1979). The study demonstrated that the LVDD represents the first stage of diabetic cardiomyopathy preceding systolic function, reinforcing the importance of early examination of ventricular function in individuals with diabetes (Cosson S, 2003). Another study o type 2 diabetic patients, found that diabetic patients with normal systolic ventricular function suffer a diastolic dysfunction (Schannwell C, 1999). In another study endorsed that 69% of diabetics had abnormalities of diastolic parameters (Holzmann, 2002). In Pakistan, studies (2008 & 2009) found a higher frequency of diastolic dysfunction in Type 2 diabetic patients, especially patients with worse glycaemic controlled even in the absence of cardiac disease. The left ventricular diastolic function was more impaired in those diabetic patients having poor glycaemic control. The prevalence of diabetic cardiomyopathy in type 2 diabetic patients is higher and diabetic cardiomyopathy is due to diastolic dysfunction caused by myocardial fibrosis, which occurs in response to hyperglycaemia (Hameedullah, 2009, Hameedullah, 2010). The prevalence of diabetes mellitus in the heart failure population is close to 20% as compared with 4 to 6% in control populations (Bauters, 2003). Diabetic cardiomyopathy was first described in 1972 by Rubler et al on the basis of post mortem findings and the diastolic dysfunction lies independent of ischemic, valvular, congenital, hypertensive or alcohol related heart disease (Raev, 1999).

This study results showed that the high prevalence of diastolic dysfunction in type 2 diabetic patients, mainly impaired relaxation and pseudonormal pattern of left ventricular filling. The study in Canada attempted to determine the prevalence of LVDD in middle-aged asymptomatic subjects with type 2 diabetes, the Left ventricular diastolic dysfunction was found in 60% subjects, 28% subjects had a pseudonormal pattern of ventricular filling and 32% subjects had impaired relaxation (Poirier, 2001). The study conducted in Kosovo demonstrated that LVDD was present in 68.8% of asymptomatic type 2 diabetic patients as compared to 34.9% in the control group without diabetes, which was due to the presence of asymptomatic diabetic cardiomyopathy which was present in the diabetic population (Bajraktari, 2004).

For gender prevalence, it was noted in our study that diastolic dysfunction was significantly more common among diabetic women with more advanced form of diastolic dysfunction. The Strong Heart study also demonstrated that diastolic dysfunction is more prevalent in women than in men (Devereuex, 2000). This could be due to hormonal changes that accompany after menopause.

For the age as a risk factor, in our study, we found that increase age is significantly associated with presence of LVDD. Patients with diastolic dysfunction were older. Similar results observed in the study, increase age is characteristics found in LVDD (Abhayaratna, 2006). Duration of diabetes was also found to be significantly associated with LVDD in our study result, however, it was also found to be present even in short duration. For 1 year were found to have LVDD and increases progressively, approaches to 100% in patients having diabetes for 8

years in our study. Similar results in the studies observed that LVDD was present in patients who were free of cardiovascular disease, had diabetes for less than 5 years and sometimes with less than 1 year. (Attali, 1998, From, 2009).

The relationship between diastolic dysfunction and glycemic control is still a matter of debate. Few studies support that presence of LVDD is related to concentration of fasting blood glucose and other do not. In our study, we found out a significant relation between fasting blood glucose levels and presence of LVDD debate. Assessing long term hyperglycemia by HBA1c levels also showed a significant relation between the two. LVDD was found to be more common in patients who have higher levels of HbA1C.

Our study found out a significant difference between the fasting blood glucose between the two groups. Holzmann and colleagues also demonstrated that the presence of diastolic dysfunction is related to the concentrations of fasting blood glucose (Holzmann, 2002). However, Poirier and colleagues did not find any difference in the glycemic indices and concluded that fasting blood glucose levels did not correlate with the presence of diastolic dysfunction in type 2 diabetes (Gaash, 1991). This was in accordance with Fiorina, who demonstrated that glycemic levels had an impact on diastolic dysfunction (Fiorina, 2000). There was one study done by Ann m. Grandi et al, showed a close relationship between glycemic control and left ventricular diastolic dysfunction in 36 type 1 diabetic patients, which improved with glycemic control (Grandi, 2006). It was also noted that normal body mass index could be due to the racial and dietary factors, which is different between the South East Asian population and the Caucasian and the Black population.

Limitation

The limitation of our study was that angiography was not performed due to financial strain, thus the possibility of coronary artery disease could not be completely excluded however the absence of clinical, electrocardiographic and echocardiographic evidence makes it unlikely.

Conclusion

DM is the strongest independent factor for LV diastolic dysfunction. This study confirms that asymptomatic diastolic dysfunction is more prevalent in subjects with type 2-DM especially more common in subjects with uncontrolled Glycemic control with significant correlation with increased age and more common in female.

For high prevalence of diastolic dysfunction in the high-risk population suggests that for LVDD screening should include procedures such as the valsalva maneuver to unmask the pseudonormal pattern of left ventricular filling.

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Conflict of Interest

There is no conflict of interest in publishing this study.

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