ORIGINAL ARTICLE

LEFT VENTRICULAR DIASTOLIC FUNCTION ABNORMALITIES IN PATIENTS WITH NON-INSULIN DEPENDENT DIABETES MELLITUS

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Objectives: Left ventricular diastolic dysfunction (LVDD) is a prevalent condition among patients with non-insulin dependent diabetes mellitus (NIDDM). The aim of this study was to determine the frequency of the LVDD in patients with NIDDM at a tertiary care cardiac center of Karachi, Pakistan.

Methodology: This descriptive cross-sectional study included NIDDM patients without history of ischemic heart disease, on anti-hypertensive medication, diagnosed with valvular heart disease, congenital heart disease, arrhythmias, chronic respiratory illness, or with clinically overt heart failure (HF) or history of HF or concomitant systolic dysfunction. Transthoracic echocardiography was performed and LVDD was diagnosed.

Results: A total of 114 patients with NIDDM of less than five years were included in this study. Most of the patients were 41 to 60 years of age with mean age of the 52.23±10.85 years. Out of 114 cases, 58(50.9%) were male. Frequency of LVDD was observed to be 61.4% (70/114). With respect to age groups, rate of LVDD was high in above 60 years of age patients that is 90% (18/20) and it was observed 64.9% (24/37) in 51 to 60 years of age. Rate of LVDD was also high in male patients than female with frequency of 70.7% (41/58) vs. 51.8% (29/56).

Conclusion: A significant number of patients with NIDDM were found to have LVDD. Increased frequency of LVDD was observed to be associated with male gender and increased age of the patients.

Keywords: non-insulin dependent diabetes mellitus, left ventricular diastolic dysfunction, heart failure, Pakistan

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INTRODUCTION

Diabetes mellitus (DM) is a prevalent endocrine illness that affects approximately 425 million individuals globally.[1] Even if there are no signs of myocardial ischemia and hypertension, preclinical myocardial dysfunction in people with type 2 diabetes mellitus (T2DM) can proceed to heart attacks.[2,3] T2DM, in particular, is one of the risk factor for heart failure with preserved ejection fraction (HFpEF),[4] a condition with reduced left ventricular (LV) diastolic relaxation and elevated myocardial stiffness despite adequate LV contractility.[5,6] Although, the methods through which T2DM might cause HFpEF symptoms (mostly dyspnea on exertion) are still unknown. Both Endothelial dysfunction (ED) as well as autonomic neuropathy is common T2DM consequences that influence about 1/3 of patients.[7] Both have been linked to an elevated risk of cardiovascular events. In the presence of maintained LV systolic function, ED and cardiac autonomic dysfunction have been hypothesized to negatively impair LV diastolic function, leading to changed LV filling designs along with signs of cardiac failure.[8,9]

The very complicated and diverse pathophysiology of HF in T2DM individuals falls under the umbrella of diabetic cardiomyopathy, a condition specific syndrome that can occur alone or in conjunction with coronary artery and hypertensive heart disease.[10] Good understanding of its initial phase risk factor and usual progress would enable the development of efficient preventative techniques, as repeatedly advised by present clinical practice guidelines that put emphasis on the need of timely detection and intervention in individuals at high risk.[10] Though, an important flaw in this strategy is the lack of agreement on the optimum strategy for detecting asymptomatic LV impairment that due to scarcity of data, specifically on the impact of anti-diabetic medications on LV presentation. The accessible strategies to precisely measure heart activities are too complicated or not too sensitive.[11]

LV diastolic dysfunction (LVDD) can be determine by the ED due to sub-endocardial ischemia that may leads to abnormal cardiomyocyte relaxation due to compromised endothelial nitric oxide production caused by the coronary microvascular dysfunction.[12]

A key underlying factor in the progress of some arrhythmias is LVDD, it is an important characteristic of diabetes cardiomyopathy prior to the onset of systolic dysfunction, recommending that diastolic indicators may be sensitive to early cardiac injury.[13] Diabetic cardiomyopathy is all likely to cause by a number of factors such as acute coronary atherosclerosis, persistent hypertension, microvascular illness, glycosylation of myocardial proteins, and autonomic neuropathy.[14]

Keeping in view the significant influence of type 2 diabetes and HFpEF on individuals and the society, it is critical to establish the actual incidence of LVDD in individuals with type 2 diabetes so that preventative measures for both LVDD and initial phases of HFpEF may be targeted. Therefore, our aim was to look at the abnormalities in the LV diastolic function in patients with non-insulin dependent diabetes mellitus without any other factors that may lead to abnormality in diastolic function.

METHODOLOGY

This descriptive cross-sectional study was conducted at a tertiary care hospital of Karachi, Pakistan for the duration of six months from January 2016 to June 2016. Patients referred to echocardiography department underwent transthoracic echocardiography (TTE) with the diagnosis of type II diabetes mellitus (DM) meeting the inclusion criteria were included in the study after obtaining the informed consent. Study was approved by the ethical review board of the Liaquat National Hospital (LNH), Karachi, Pakistan. Sample size of n=144 for the study was calculated with the 60% expected frequency of left ventricle diastolic dysfunction (LVDD) among type II DM patients and at 95% confidence level and 9% of error margin. Exclusion criteria were patients with history of ischemic heart disease, on anti-hypertensive medication, insulin dependent DM, diagnosed with valvular heart disease or congenital heart disease, presence of arrhythmias, permanent pacemaker (PPM) implanted, chronic respiratory illness, or patients with clinically overt heart failure (HF) or history of HF or concomitant systolic dysfunction

Coronary artery disease was ruled out clinically, blood pressure was taken and baseline ECG was obtained to rule out previous myocardial infarction or arrhythmias. Diabetes status was assessed according to the levels of HbA1c. The TTE parameter included transmitral peak early diastolic velocity (E wave), peak early diastolic velocity at mitral annulus (E' wave), peak late diastolic velocity (A wave), E wave deceleration time (DT), EA ratio, isovolumic relaxation time (IVRT)) performed by a trained cardiac sonographer and LVDD was reviewed and reported by experienced cardiologist.

Data was entered and analyzed by using the IBM SPSS version 19. A descriptive analysis (mean ± SD) was calculated for quantitative variables like age, weight and height of the patient. Frequency and percentages were computed for categorical variables such as gender, age groups, weight groups, height groups, and left ventricle diastolic dysfunction. Confounding variables such as gender, age groups, weight groups, and height groups were controlled through stratification and Chi-square test was applied with p-value ≤ 0.05 as significance.

RESULTS

A total of 114 patients with NIDDM of less than five years were included in this study. Most of the patients were 41 to 60 years of age with mean age of the 52.23±10.85 years. Out of 114 cases, 58(50.9%) were male. Frequency of left ventricular diastolic dysfunction was observed to be 61.4% (70/114). Summary of demographic and clinical characteristics of the patients are presented in Table 1.

Table 1: Summary of demographic and clinical characteristics

Characteristics	Total
Total (N)	**114**
Gender	
Male	50.9% (58)
Female	49.1% (56)
Age (years)	52.23 ± 10.85
≤ 40 years	12.3% (14)
41 to 50 years	37.7% (43)
51 to 60 years	32.5% (37)
> 60 years	17.5% (20)
Weight (kg)	65.28 ± 9.35
≤ 55kg	14% (16)
56 to 60 kg	26.3% (30)
61 to 70 kg	43.9% (50)
71 to 80 kg	9.6% (11)
> 80 kg	6.1% (7)
Height (cm)	163.44 ± 7.86
≤ 150 cm	7% (8)
150 to 160 cm	32.5% (37)
161 to 170 cm	50.9% (58)
> 170 cm	9.6% (11)
Left ventricular diastolic dysfunction	
Yes	61.4% (70)
No	38.6% (44)

Comparison of distribution of demographic and clinical characteristics for the patients with and without left ventricular diastolic dysfunction are presented in Table 2. With respect to age groups, rate of LVDD was high in above 60 years of age patients that is 90% (18/20) and it was observed 64.9% (24/37)

in 51 to 60 years of age. Rate of LVDD was also high in male patients than female with frequency of 70.7% (41/58) vs. 51.8% (29/56). Similarly rate of LVDD was above 70% in those cases with body weight of 56 to 60 kg and above 70 kg.

Table 2. Comparison of distribution of demographic and clinical characteristics for the patients with and without left ventricular diastolic dysfunction

Characteristics	Left ventricular diastolic dysfunction		P-value
	Yes	No	
Total (N)	**70**	**44**	**-**
Gender			
Male	58.6% (41)	38.6% (17)	0.038*
Female	41.4% (29)	61.4% (27)	
Age (years)			
≤ 40 years	7.1% (5)	20.5% (9)	0.007*
41 to 50 years	32.9% (23)	45.5% (20)	
51 to 60 years	34.3% (24)	29.5% (13)	
> 60 years	25.7% (18)	4.5% (2)	
Weight (kg)			
≤ 55kg	8.6% (6)	22.7% (10)	0.147
56 to 60 kg	31.4% (22)	18.2% (8)	
61 to 70 kg	41.4% (29)	47.7% (21)	
71 to 80 kg	11.4% (8)	6.8% (3)	
> 80 kg	7.1% (5)	4.5% (2)	
Height (cm)			
≤ 150 cm	11.4% (8)	0% (0)	0.029*
150 to 160 cm	35.7% (25)	27.3% (12)	
161 to 170 cm	47.1% (33)	56.8% (25)	
> 170 cm	5.7% (4)	15.9% (7)	

**significant at 5%*

DISCUSSION

The NIDDM is related to a considerable increase in the risk of cardiovascular and, specifically, coronary events. Coronary involvement can affect large epicardial arteries and coronary microcirculation.[15] On the other hand, various data shows that T2DM can also be the reason of causing direct abnormalities in cardiomyocyte metabolism and its function, leading to diabetic cardiomyopathy. T2DM has also consistently been found to be a significant risk factor for the progress of HFpEF syndrome[4,5] that normally consists of impaired LV relaxation in diastole. In fact, diastolic dysfunction has been observed in approximately 75 percents of T2DM patients, while for the individuals with signs of HFpEF has been found in roughly 30 to 40 percent of patients.[4] Though, the pathophysiologic reasons of diastolic dysfunction in T2DM are unknown. T2DM is associated with ED and cardiac autonomic dysfunction, both of which have pathophysiologic effects that may favor LVDD.[16]

Our study of 114 patients with NIDDM less than five years with mean age of 52.23±10.85 years with 58(50.9%) were male and 56(49.1%) were female. The results of our study found the frequency of left ventricular diastolic dysfunction was 61.4% (70/114). We also found increase in frequency of LVDD with respect to age and rate of LVDD was also high in male patients than female (70.7% vs. 51.8%). Similarly rate of LVDD was above 70% in those cases whose weight was 56 to 60 kg and above 70 kg of patients and similarly rate of LVDD was 100% in those patients whose height was below 150cm.

A study conducted by Chaudhary AK et al.[17] included newly diagnosed 100 normotensive, type 2 diabetic individuals aged between 30-60 years, the occurrence of LVDD, a sign of diabetic cardiomyopathy, and its relation with glycosylated haemoglobin (HbAIC) and additional factors such as age, body mass index (BMI), and total serum cholesterol were investigated. LVDD was present in 41 percent of patients, with grade l LVDD accounting for 87.8 percent of the cases, as observed by a delayed relaxation time pattern on pulsed Doppler echocardiography.

Diastolic dysfunction is thought to be an initial phase in the history of cardiomyopathy, and early detection helps to prevent or greatly postpone the start of congestive heart failure (CHF).[18] A study of 127 asymptomatic individuals, Patil et al., discovered that 54.33 percent of asymptomatic type 2 diabetics had diastolic dysfunction.[19] Because these individuals had already been diagnosed with diabetes and had been living with it for more than 5 years, the high incidence could be credited to the length of time they had been living with it. Because there were no patients with systolic dysfunction, diastolic dysfunction was the first symptom of diabetic cardiomyopathy.

Another study by Milwidsky A et al.[20] reported its high prevalence in individuals having impaired fasting glucose (IFG) and DM compared to euglycemic subjects (27%, 30%, and 15% respectively) among 3781 individuals screened in an annual health survey program. In many diabetic patients, LVDD leads to the development of HF, with a low or preserved EF. In fact, at the end of the seven year follow-up, individuals with prolonged type 1 DM were observed to develop CHF in 3.7 percent. Diastolic HF accounted for 85 percent of all HF patients.[21] A study in local population by Muhammad Z et al.[22] reported diabetic cardiomyopathy in 40 percent of the type-2 diabetic subjects, out of which 60% were men. Another local study by Khan AR et al.[23] included 150 consecutive individuals having type-2 diabetes mellitus with normal blood pressure and resting electrocardiogram and no signs of cardiac failure and diastolic dysfunction were observed in 48% of the patients. In the similar context, among patients referred to a preoperative visit clinic, the diastolic dysfunction was noted in 56.1%.[24]

A systematic review and meta-analysis by Bouthoorn S et al.[25] provide collective estimates regarding the occurrence of LVDD in type 2 diabetes patients, demonstrating that LVDD is a significant abnormality in males and females having type 2 diabetes, impacting not only around 35 percent (24% to 46%) of type 2 diabetes individuals in the society but also 48% (38% to 59%) of type 2 diabetes individuals in hospitals.

Our study, like others, has some limitations, it provides an account of relationships, the cross-sectional research pattern needs biological plausibility and inferences in terms of temporal relationships and causative associations. The study methods and findings are limited in their generalizability due to the use of non-probability sampling. Although the sample size for the study was estimated scientifically, the choice of an epidemiological study necessitates a bigger sample size to offer accurate estimates of frequency and occurrence.

CONCLUSION

A significant number of patients with NIDDM were found to have LVDD. Increased frequency of LVDD was observed to be associated with male gender and increased age of the patients. However, multicenter epidemiological studies with larger sample size are needed to accurately estimate the burden of LVDD in NIDDM and causative relationship between LVDD and heart failure in this population.

AUTHORS' CONTRIBUTION:

NAS, KAK, and MNK: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. NAS, KAK, SA, RR, IJB, STA, and MNK: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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