International Journal of Advances in Medicine
Ilamaran M et al. Int J Adv Med. 2019 Jun;6(3):890-894
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20192259

Original Research Article

A study on diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function

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Received: 03 April 2019
Accepted: 02 May2019

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ABSTRACT

Background: Diastolic heart failure, otherwise called as heart failure with preserved ejection fraction, is common finding of hypertensive heart disease, but various studies report a high incidence of diastolic heart failure in patients with type 2 diabetes mellitus in spite of the absence of coronary artery heart disease and hypertension. The objectives of the study were to determine the prevalence of dysfunction of left ventricle in diastole in type 2 diabetes mellitus patients and to compare with the non-diabetic individuals with that of asymptomatic type II diabetes patients. To assess the correlation of diastolic dysfunction in diabetes with age of patients, HbA1c levels, duration of diabetes, retinopathy, autonomic neuropathy.
Methods: A prospective cross sectional among them 50 patients were diabetics and 50 were non-diabetic controls. Diastolic dysfunction was measured with standard echocardiographic parameters and the results were computed with corresponding variables of the patients. All the variables and their data were analysed for percentage, mean, standard deviation 't' test and chi square test. The 't'-test was used to study the quantitative data while chi square test was used to study the qualitative data.
Results: Among the study population 60% had diastolic dysfunction and 14% had diastolic dysfunction among cases and control group respectively. Diastolic dysfunction was present among 23.3% and the 76.7% of the age group groups of less than 45 and more than 45 years of age respectively. In this study poor glycaemic status was significantly associated with diastolic dysfunction, whereas duration of diabetes, retinopathy and autonomic neuropathy were not statistically significant.
Conclusions: Present study reveals moderately high incidence of diastolic dysfunction in asymptomatic diabetic; subjects and, this finding was correlated with the HBA1C levels but not with retinopathy and autonomic neuropathy.

Keywords: Autonomic neuropathy, Diabetes mellitus, Diastolic dysfunction, Glycaemic control, Retinopathy

INTRODUCTION

The incidence of diabetes mellitus (DM) is on the raise across the world and it is turning out to be an epidemic of non-communicable disease. Diabetic heart disease and diabetic cardiomyopathy as a separate entity has been proposed in the last couple of decades. Diastolic heart failure, otherwise called as heart failure with preserved ejection fraction, is common finding of hypertensive heart disease, but various studies report a high incidence of diastolic heart failure in patients with type 2 diabetes mellitus inspite of the absence of coronary artery heart disease and hypertension. Observations point to a diastolic dysfunction occurring before systolic dysfunction in the setting of myocardial damage due to diabetes. There is also prevalence of a pre-clinical diastolic dysfunction in diabetics.[1] The patho-physiology of an impaired diastolic dysfunction in diabetes is poorly

understood. Diabetic cardiomyopathy is proposed to be a disease independent coronary artery disease. Metabolic derangements involving hyperglycemia, hyperlipidemia, hyperinsulinemia, myocyte loss, interstitial fibrosis, autonomic neuropathy, microvascular dysfunction have all been proposed as underlying the development of diabetic cardiomyopathy.[2] A study done among 50 diabetics and 50 controls showed the prevalence of diastolic dysfunction, defined by echocardiographic criteria was 66%. E/A, DT and peak a velocity were sensitive indices of diastolic LV dysfunction.[3] The objective of this study is to find out the association between type 2 diabetes mellitus and diastolic dysfunction, even in the asymptomatic diabetic population. To ascertain the prevalence of left ventricular diastolic dysfunction and to determine its correlation with duration of diabetes mellitus, obesity parameters, HbA1c levels, patient's age and diabetic microvascular complications authors conducted this case control study.

The objectives of this study were to determine the prevalence of dysfunction of left ventricle in diastole in type 2 diabetes mellitus patients, to compare the prevalence of left ventricular diastolic dysfunction of non-diabetic individuals with that of asymptomatic type II diabetes patients to assess the correlation of diastolic dysfunction in diabetes with age of patients, HbA1c levels, duration of diabetes, retinopathy, autonomic neuropathy.

METHODS

This study was conducted in Sivagangai Medical College over a period of 12 months. Patients were recruited to the study from medical OPD and diabetic OPD. A total of about 120 patients were selected and 20 of them were excluded as per exclusion criteria used. The remaining 100 patients were included in the study. Among them 50 patients were diabetics and 50 were nondiabetic controls. Informed consent was obtained from all patients. Diastolic dysfunction was measured with standard echocardiographic parameters and the results were computed with corresponding variables of the patients. For the purpose of the study it was hypothesized that the diastolic dysfunction occurring in diabetes would worsen with age of patients, duration of diabetes, hba1c values, obesity indices. A prospective cross-sectional study was done in a tertiary care hospital for a period of one year. The sample size was 100.

Inclusion criteria

- Asymptomatic type 2 diabetes patients who presented to the medical OPD and diabetic OPD,
- Healthy individuals between the age of 20-60.

Exclusion criteria

- Patients with evidence of previous coronary artery heart disease-determined by previous history of angina, Electrocardiographic changes in the form of ST elevation/ST depression/significant q waves, echo cardiographic evidence of regional wall motion abnormalities, Treadmill testing with positive testing for ischemia,
- Patients with evidence of valvular heart disease as confirmed by standard echocardiographic observation,
- Patients with evidence of systemic hypertension-determined by: history of systemic hypertension, history of drug intake for the hypertension, evidence of LVH with ST and T changes,
- Patients with poor trans thoracic window.

Data collection and outcomes measured

For all the 100 cases admitted, detailed clinical examination and history regarding diabetes, hypertension, coronary heart disease, valvular heart disease were obtained. Patients' anthropometric measurements were done. BMI and Waist hip ratio were calculated. Examination for autonomic dysfunction was done. Fundus examination for diabetic retinopathy was done. Investigations like blood sugar, ECG, HBA1C, lipid profile were obtained. Echocardiographic assessment of both systolic and diastolic dysfunction was done.

Statistical analysis

All the variables and their data were analyzed for percentage, mean, standard deviation, 't' test and chi square test. Those variables which were not distributed in normal distribution were transformed for the analysis. The 't'-test was used to study the quantitative data while chi square test was used to study the qualitative data. A 'P' value of<0.05 is considered as statistically significant.

RESULTS

Among the 50 patients in the case group 30 were male and 20 females. In the control arm among 50 patients 29 were male and 21 females were present. Among the study population 60% had diastolic dysfunction and 14% had diastolic dysfunction among cases and control group respectively. Relationship of diastolic dysfunction with other variables among the diabetic patients

Age group

Diastolic dysfunction was present among 23.3% and the 76.7% of the age group groups of less than 45 and more than 45 years of age respectively. Similarly, diastolic dysfunction was absent among 30% of less than 45 years and 70% of more than 45 years of age. The difference was found to be statistically not significant (Table 1).

HBA1C levels and diastolic dysfunction

About 53.3% of the diabetic patients had more than 7.5% HBA1c group had diastolic dysfunction whereas the

remaining 46.7% had less than 7.5% HBA1c levels had diastolic dysfunction. The chi square test values showed significance difference between two groups (P <0.05). Uncontrolled diabetic patients with high glycated hemoglobin levels had more chance of diastolic dysfunction than the patients with good glycemic control (Table 1).

Duration of diabetes

Duration of diabetes was classified as less than 10 years and more than 10 years. 73.3 % of the patients presented

with diastolic dysfunction with the duration of 6 to 10 years of diabetes. In present study duration of diabetes was not correlated with the diastolic dysfunction (Table 1).

Retinopathy and diastolic dysfunction

In the study all 100 subjects were examined clinically for the presence of diabetic retinopathy with fundus examination after using mydriatics. They were tabulated as either presence of non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR) and no diabetic retinopathy. Retinopathy was present among the 30% of the diastolic dysfunction patients whereas the remaining 70% presented with no retinopathy. It was statistically not significant (Table 1).

Table 1: Relationship of diastolic dysfunction with the dependent variables and corresponding 'p' values among diabetes patients.

Variables	DD present	DD absent	Total %	P value
Age <45 years	7 (23.3)	6 (30)	13 (26)	>0.05 (NS)
Age>45 years	23 (76.7)	14 (70)	37 (74)	
HBA1C<7.5%	14 (46.7)	17 (85)	31 (62)	< 0.05 (S)
HBA1C>7.5%	16 (53.3)	3 (15)	19 (38)	
Duration of diabetes 6-10 years	22 (73.3)	16 (80)	38 (76)	> 0.05 (NS)
Duration of diabetes 11-16years	8 (26.7)	4 (20)	12 (24)	
Retinopathy present	9 (30)	3 (15)	12 (24)	>0.05 (NS)
Retinopathy absent	21(70)	17 (85)	38 (76)	
Autonomic neuropathy present	9 (30)	3 (15)	12 (24)	>0.05(NS)
Autonomic neuropathy absent	21 (70)	17 (85)	38 (76)	

Table 2: Mean and standard deviation of the variables under study.

Variables	Case male (Mean± SD)	Case female (Mean± SD)	Control male (Mean± SD)	Control female (Mean± SD)
Age in years	52±12	48±11	51±9	50±9
Duration of diabetes in years	12±5	11±3	-	-
Body mass index(kg/m^2)	27.4±2	26.2±2.4	23±1.5	24±1.2
Waist hip ratio	0.95±0.15	0.83±0.17	0.75±0.17	0.75±0.14
Total cholesterol	221±24	231±23	140±12	145±13
Triglycerides	206±26.7	197±25.4	130±10	128±12
LDL-cholesterol	145±17.8	149±13	95±13	103±9
HDL-cholesterol	40±7	38±6	45±3	44±2
Blood sugar level	136±20.1	134±19	90±6	85±8
HBA1C %	8.2±2.80	8.1±1.5	-	-
E/A ratio	0.80±0.12	0.79±0.13	1.20±0.2	1.18±0.10
IVRT (ms)	80±12	81±9	94±15	96±2
Ejection fraction%	55±3	54±2	59±5	58±3
Diastolic dysfunction	19 (63.33%)	11 (55%)	4 (13.79%)	3 (14.2%)

Autonomic neuropathy and diastolic dysfunction

In the study presence of cardiac autonomic neuropathy was defined when patient had orthostatic hypotension, which was defined as the fall in systolic BP >30mm of Hg or a diastolic BP fall of more than 10 mm Hg on standing for more than 3 minutes. For this the systolic and diastolic blood pressure was measured in all patients while sitting, immediately on standing and 3 minutes after standing. A sustained fall in SBP/DBP after 3

minutes is taken as positive and patients were computed as having autonomic neuropathy and not having autonomic neuropathy. Neuropathy was present among the 30% of the diastolic dysfunction patients whereas the remaining 70% presented with absence of autonomic neuropathy. It was statistically not significant (Table 1).

Table 2 shows the mean and SD of the study and control population with gender difference. The diastolic dysfunction was comparatively more among males (63.33%) than females (55%) among diabetic population. The E/A ratio was similar among both genders in diabetic population, but the E/A ratio was 1.2 and 1.18 among males and females in control population. The IVRT (ms) was 80 and 81 among males and females in diabetic population but it was 94 and 96 among males and females among controls respectively.

DISCUSSION

Our present study showed that, of the total 50 patients in the cases arm 30 had diastolic dysfunction which is 60% prevalence. On the control arm a total of 7 had diastolic dysfunction which equals to 14%. A total of 13 patients were of age <45 years of which 7 had diastolic dysfunction. This equals 53.8% prevalence. The remaining 37 patients were in the age group >45 years. A total of 23 patients in this category had diastolic dysfunction which equals 62.16%. 31 patients in cases arm had HBA1c less than 7.5 gm% and 19 had HBA1c greater than7.5gm%. 14 patients with HBA1c less than 7.5 gm% had diastolic dysfunction with a prevalence of 45.2%. 16 patients with HBA1c greater than 7.5 gm% had diastolic dysfunction with a prevalence of 84.2%. 38 patients had diabetes mellitus for 6-10 years and 12 had duration between11-15 years. 22 patients with duration 6-10 years had diastolic dysfunction with a prevalence of 57.9%. 8 patients with duration of diabetes 11-15 years had diastolic dysfunction with a prevalence of 66.67%. Present study also showed that a total of 12 patients had diabetic retinopathy while the remaining 38 did not show features of diabetic retinopathy. Of the 12 patients 9 had diastolic dysfunction with a prevalence of 75%. Similarly, a total of 12 patients had autonomic dysfunction and remaining 38 patients did not have autonomic dysfunction. Of the 12 patients with autonomic dysfunction 9 had diastolic dysfunction with an incidence of 75%. The mean body mass index, waist hip ratio, total cholesterol, LDL cholesterol, in cases was high when compared to controls. The mean HDL cholesterol was lower in cases than in the control group. The mean E/A ratio was lower in the cases that in the control group. 4 males and 3 females in the control arm had diastolic dysfunction with an incidence of 13.79% and 14.2%. Authors compared our results with various studies. Soldatos G et al, in their case control study of 55 individuals with type-2DM found that diastolic dysfunction, present in a significant proportion of population with type 2 DM.[4] Sacre JW et al, found that there was an independent association between global cardiac autonomic neuropathy (CAN) and left ventricular (LV) dysfunction in patients with type 2 DM.[5] These findings are comparable to present study, where diastolic dysfunction was present in majority of the subjects with autonomic neuropathy. Van Heerebeek L et al, in their study of 36 type-2DM patients stated that, the cardiomyocyte resting tension is more important when LVEF is normal.[6] Excessive diastolic left ventricular stiffness is an important contributor to heart failure in subjects with DM. Diabetes is presumed to increase stiffness through myocardial deposition of collagen and advanced glycation end products. Masugata H et al, in their case control study of 77 normotensive patients found that, the cardiac diastolic dysfunction without LV systolic dysfunction in patients with well-controlled type 2 DM is related neither to hypertension nor LV hypertrophy, but rather to aging and the duration of type 2 DM.[7] Annonu AK et al, in their case control study of 66 subjects found that there was an inverse correlation between the duration of diabetes and E/A ratio ($r = -0.4$, $P<0.005$).[8] Similarly present study findings are in line with the study conducted at Bangalore by Patil MB et al, showed that diastolic dysfunction was present in 32 (64%) of the patients.[9] Diastolic dysfunctions was more common among female sex (68.18%) compared to male (60.17%). Diastolic dysfunction was significantly associated with uncontrolled diabetes as assessed by HbA1c levels. Diastolic dysfunction was more common in patients who were on treatment with both oral hypoglycemic agents and insulin. The prevalence of diastolic dysfunction increased with longer duration of diabetes. There was a linear progression of diastolic dysfunction with the increase age group. Similar study among 46 men with type 2 diabetes who were aged 38-67 years; without evidence of diabetic complications, hypertension, coronary artery disease, congestive heart failure, or thyroid or overt renal disease; and with a maximal treadmill exercise test showing no ischemia. LVDD was found in 28 subjects (60%), of whom 13 (28%) had a pseudonormal pattern of ventricular filling and 15 (32%) had impaired relaxation. Systolic function was normal in all subjects, and there was no correlation between LVDD and indexes of metabolic control.[10]

CONCLUSION

Diabetes mellitus causes serious morbidities one of which is cardiovascular. The occurrence of coronary artery disease and systolic dysfunction are well known. However, the prevalence of a diastolic dysfunction even in asymptomatic patients independent of a CAD is a relatively new observation. It is also obvious that, diastolic dysfunction correlates well with diabetes duration, micro vascular abnormalities obesity index, lipid profile and HbA1c. Diastolic dysfunction, being a marker of diabetic cardiomyopathy, may be useful as the predictor of heart failure with preserved ejection fraction and mortality in the medium to long term. At present the treatment options for a diastolic heart failure with normal systolic function are very limited. It is prudent to screen

for diastolic dysfunction through the markers of insulin resistance for an early identification and treatment of the determinants so as to prevent the progression to full blown heart failure. All these determinants and diabetes in itself stem from the common patho-physiology of insulin resistance. Recently trials have shown a cardio-protective effect for metformin, probably because it increases insulin sensitivity. Studies are needed further to crystallize our knowledge, to understand the pathophysiology of diabetic cardiomyopathy which at present looks very complex and also to ensure better management so as to reduce the morbidity and mortality associated with diastolic dysfunction.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ilamaran M, Thangadhurai A, Kumar PS, Nagalingam S A study on diastolic dysfunction in asymptomatic type 2 diabetes mellitus with normal systolic function. Int J Adv Med 2019;6:890-4.