Study of Systolic and Diastolic Dysfunction among Normotensive Patients with Type 2 Diabetes Mellitus – A Cross–Sectional Study from Puducherry, India

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ABSTRACT

BACKGROUND

Diabetes mellitus (DM) single-handedly accounts for 75 – 90 % of excess coronary artery disease (CAD) risk seen in persons suffering from it and it also enhances and amplifies the effects of other traditional cardiovascular risk factors. After adjusting for concomitant risk factors such as hypertension and hyperlipidemia, there still remains an excess risk for cardiovascular disease (CVD) in people with diabetics. In this study, we wanted to evaluate left ventricular (LV) systolic and diastolic dysfunction in normotensive diabetic patients.

METHODS

A cross sectional comparative study was performed from January 2016 to September 2017 on 50 diabetics and 50 age and sex matched healthy controls. Adult patients of both sexes with diabetes mellitus who are normotensive were included as cases. Patients with known heart disease, chronic kidney disease, thyroid disorders were excluded from the study. 2D transthoracic echocardiogram (ECHO) with M mode was used for assessing systolic and diastolic function.

RESULTS

Mean ejection fraction was lower in patients group (59.76) as compared to control group (64.74) with 8 % of cases with a value of< 50 %. Fractional shortening was also lower in patients (29.14) compared to controls (34.86) with 12 % patients having a value of < 25 %. E/A ratio was 1.12 in patients when compared to 1.36 in controls with 32 % of patients having value < 1. Mean isovolumic relaxation time was 96.52 in patients when compared to 87.42 in controls with 24 % patients having value > 100 msec.

CONCLUSIONS

Normotensive diabetics are prone to left ventricular dysfunction. Diastolic dysfunction is more common than systolic dysfunction.

KEYWORDS

Diabetes Mellitus, Systolic Dysfunction, Diastolic Dysfunction, Cardiovascular Disease

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BACKGROUND

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycaemia. The metabolic dysregulation associated with diabetes mellitus causes secondary pathophysiological changes in multiple organ systems.[1] Diabetes is a leading cause of premature death and disability due to its complications. Diabetes causes a marked increase in peripheral arterial disease, myocardial infarction (MI) and congestive heart failure (CHF).

Asian Indians are genetically susceptible to diabetes mellitus[2] and have one of the highest rates of coronary artery disease in the world. There is high incidence of various features of metabolic syndrome in Indians compared to western population. Presentation of coronary artery disease is more severe among Indians when compared to whites. Diabetic process can involve small vessels of the heart producing microangiopathy and such changes may be responsible for complications like heart failure, cardiomegaly and even conduction defects. Atherosclerosis is a major threat to the microvasculature for patients with and without diabetes. Dyslipidemia is highly correlated with atherosclerosis and up to 97 % of patients with diabetes are dyslipidemic.[3] In diabetes, predominant form of low-density lipoprotein (LDL) cholesterol is small, dense form which is more atherogenic than large dense LDL. Oxidized LDL produces several abnormal responses such as attracting leucocytes to the intima of the vessel, stimulating proliferation of leucocytes which are steps in the formation of atherosclerotic plaque.[4] Diabetes is associated with activation of myocardial renin angiotensin aldosterone system and endothelin system, contributing to myocyte necrosis and fibrosis.[5] Altered myocardial passive properties and impaired LV function observed in patients with diabetes can be the result of fibrosis and altered collagen structure, specifically because of advanced glycosylation end products induced increased collagen cross linking. Compared to normal persons, subjects with diabetes have an extensive CVD with greater no of diseased vessel segments which is rapidly progressive.[6] Hence, the objective was to evaluate left ventricular systolic and diastolic function in normotensive diabetics.

METHODS

Study was performed as a cross sectional comparative study over a period of 18 months from January 2016 to September 2017 after obtaining Institutional Ethics Committee clearance. A total of 50 patients who are normotensive diabetics in the age group 18 - 60 and 50 age and sex matched healthy controls without diabetes and hypertension were taken for the study. American diabetes association (ADA) criteria was applied for the diagnosis of DM. Patients with systemic hypertension, congenital heart disease, thyroid disorders and chronic kidney disease were excluded from the study. A detailed history regarding cardiovascular symptoms like chest pain, shortness of breath, palpitation and syncope was taken. Pulse, blood pressure (BP) and body mass index (BMI) were measured. A complete blood count, renal function tests, thyroid profile and urine routine was done. Electrocardiogram (ECG) and 2D ECHO were performed on all patients and controls.

Study Parameters

Fractional shortening (FS) and ejection fraction (EF) were studied to assess systolic function. In parasternal long axis view, measurements of left ventricular internal diameters at the end of diastole and systole were made. These measurements were used to calculate LV end diastolic and end systolic volumes to measure EF. Values of < 50 % for EF was considered abnormal. FS was measured by measurements of minor axis from M mode. Values of < 25 % was considered abnormal. E/A ratio [ratio of peak velocity of early mitral flow (E) to peak velocity of late mitral flow (A) and isovolumic relaxation time (IVRT)] were studied to assess diastolic function. E/A value of < 1 and IVRT< 60 or > 100 were considered abnormal.

Statistical Analysis

Statistical analysis was done by using percentages, mean values, standard deviation, standard error, independent samples test, Levene's test for equality of variances. The level of significance used was 0.05 level for the corresponding degree of freedom to draw the inference. A P value of < 0.05 was considered significant.

RESULTS

Of a total of 50 patients, 15 were in the age group 40 – 50 years. A total of 30 males were present out of 50 patients. 32 patients had a duration of diabetes between 5 -10 years and 2 patients had a duration of diabetes for more than 10 years. 27 patients were overweight with a BMI of 25 - 29.9 and 5 patients had mild obesity with a BMI of 30 - 34.9. 37 patients had a HbA1C value of < 7 while 11 patients had value of 7 - 8. Mean serum creatinine of patients was 0.78. Mean total cholesterol, triglycerides, LDL and HDL of patients was 186, 140, 114.5, 36 respectively. Demographic and clinical characteristics of patients and controls is summarized in table 1.

	Characteristics	Patients	Controls
Age (years)	<40	5	6
	40 - 50	31	31
	50 - 60	14	13
	Sex		
	Male	40	40
	Female	20	20
DM duration (years)	0- 5	16	-
	5 - 10	32	-
	> 10	2	-
BP (mmHg, mean)	Systolic	120.7	118.6
	Diastolic	78.8	77.9
	HBA1C (%)		
	≤ 5.6	2	50
	5.7 - 7.0	37	-
	7 - 8	11	-
	Serum creatinine (mg/dl, mean)	0.8	0.9

Table 1. Demographic and Clinical Characteristics of Patients and Controls

46 patients had an ejection fraction (EF) of more than 50 % while all controls had a normal ejection fraction (Table 2).

Ejection Fraction	Mean	SD	Std Error Mean	EF < 50 % (n)	EF > 50 % (n)	P Value
Patients	59.76	5.61	0.429	4	46	0.000
Controls	64.74	3.48	0.547	-	50	

Table 2. Ejection Fraction (%)

Fractional shortening was less than 25 % in 12 patients while it was normal in all controls (Table 3).

Fractional Shortening	Mean	SD	Std Error Mean	FS < 25 % (n)	FS > 25 % (n)	P Value
Patients	29.14	3.87	0.429	12	38	0.012
Controls	34.86	3.03	0.547	-	50	

Table 3. Fractional Shortening (%)

Mean mitral 'E' velocity of patients and controls was 71.8 and 76 respectively. Mean mitral 'A' velocity of patients and controls was 64.3 and 55.7 respectively (Table 4).

Parameters	Groups	Mean	SD
Mitral 'E'	Patients	71.84	6.51
	Controls	76.04	6.067
Mitral 'A'	Patients	64.38	6.51
	Controls	55.78	5.61

Table 4. Mitral 'E' and 'A' velocities

E/A ratio was less than 1 in 16 % patients and it was more than 1 in all controls (Table 5).

E/A ratio	Mean	SD	Std Error Mean	< 1 (n)	>1 (n)	P Value
Patients	1.124	0.168	0.028	16	34	0.105
Controls	1.364	0.203	0.023	-	50	

Table 5. E/A ratio

38 patients had an isovolumic relaxation time of 60 - 100 msec while 12 patients had value of more than 100 msec (Table 6)

IVRT	Mean	SD	Std Error Mean	< 60 ms (n)	60 - 100 ms (n)	>100 ms (n)	P Value
Patients	96.52	7.057	0.622	-	38	12	0.011
Controls	87.42	4.403	0.998	-	50	-	

Table 6. Isovolumic Relaxation Time of Cases and Controls

DISCUSSION

In the present study, left ventricular function was evaluated by 2D Echo, M mode, colour Doppler studies in normotensive type 2 diabetes patients and it was compared with controls. Metabolic syndrome (MS) is common in Asian Indians. It consists of a constellation of metabolic abnormalities that confer increased risk of cardiovascular disease and diabetes mellitus. The most accepted and unifying hypothesis to understand the pathophysiology of MS is insulin resistance, the decreased ability of insulin to act effectively on target tissues. The onset of insulin resistance is heralded by postprandial hyperinsulinemia, which is followed by fasting hyperinsulinemia and ultimately by hyperglycaemia. In the insulin resistant state, cells are deprived of glucose. Increased visceral adipose tissue is considered a major factor associated with metabolic syndrome leading to increase in free fatty acid flux in portal and systemic circulations initiating cascade of events responsible for insulin resistance and atherogenic dyslipidaemia.

The major causes of death in patients with diabetes mellitus are atherosclerotic cardiovascular diseases accounting for 65 – 75 %. The major ailments for fatality are deaths due to coronary artery atherosclerosis and peripheral vascular diseases. Cardiovascular diseases also account for 75 % of all hospitalizations of diabetic patients. Though the morphologic appearance of atherosclerotic plaques is similar to non-diabetic subjects, atherosclerosis progresses in a rapid rate in diabetics. The endothelial layer of blood vessels not only serves as a simple mechanical barrier separating circulating cells from intima and media but also serves as an anticoagulant and fibrinolytic surface which counteracts the effects of procoagulant factors such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1).This is mediated by inhibition of platelet aggregation and thrombosis. Hyperglycaemia disrupts endothelial function by inhibition of platelet aggregation, increasing oxidative stress, diminishing nitric oxide (NO) leading to apoptosis and impaired function. The normal profibrinolytic action of the endothelium is converted into an antifibrinolytic activity by inflammation. Endothelial dysfunction acts as a preceder of atherosclerotic disease with adhesion of monocytes to endothelial cells followed by transmigration of monocytes into subendothelial space. Hyperglycaemia also induces spontaneous glycation and abundance of other reducing sugars which is typically involved in a process called glycoxidation generating advanced glycosylation end product (AGE)s. AGEs cause cellular activation with generation of cytokines and overgrowth of vessel wall components. Diabetes is a pro-inflammatory state associated with ineffective thrombolysis and impaired thrombosis with increase in serum fibrinogen level, factor VIII activity, PAI-1. There is evidence of increased lipid peroxidation and protein carbonylation in plasma of obese persons and type 2 DM. Increases in PAI-1 decrease smooth muscle migration and are also associated with decreased expression of urokinase within the vessel wall and plaque. Elevated PAI-1 also causes decreased fibrinolysis and is considered a strong risk factor for CAD.

Framingham heart study was the earliest one which brought out the relationship between diabetes and cardiovascular disease in a big way. Cardiovascular mortality was three times higher in participants with diabetes and was associated with substantially increased risk of heart failure and hypertensive heart disease.[7] It showed that left ventricular hypertrophy (LVH) indicates a poor prognosis and adjusted cardiovascular risk was approximately 1.5 fold higher for increments of 50 g/m^2 in LV mass as assessed by echocardiography. In a study[8] to assess the prevalence of cardiovascular risks associated with metabolic syndrome with 4483 participants in Finland and Sweden, it was found that risk of coronary artery disease and stroke was increased threefold. The third national health and nutrition survey in US[9] categorized adults older than 50 years by presence of metabolic syndrome with or without diabetes. Those without

MS had the lowest cardiovascular disease prevalence while those who had both MS and DM had highest prevalence of CVD.

Ejection fraction which represents the volume of blood pumped out with each contraction. In the present study, patients show mean EF of 59.76 ± 5.619 and the value was 64.74 ± 3.48 in controls. A P value of 0.000 was observed which was statistically significant. 3 patients (8 %) had LV systolic dysfunction with EF < 50 %. The mean fractional shortening in cases was 29.14 ± 3.87 and ranged from 23 % to 36 %. The mean fractional shortening in controls was 34.86 ± 3.03 and ranged from 26 % to 40 %. A P value of < 0.012 was observed which was significant. 12 (24 %) patients had a fractional shortening of less than 25 %, suggesting significant systolic dysfunction. These results are comparable to a case control study[10] performed by Sotoyne T Dodiyi- Manuel et al. in Nigeria in which a depressed ejection fraction of < 55 % was present in 15.6 % patients while 12.2% of patients had a FS of < 25 %. In the second cross sectional study[11] performed in Nigeria with 150 patients, EF and FS of all patients were within the normal range and found to be higher than that of normal counterparts.

Cardiovascular disease is the most common cause for death in diabetes.[12] Diabetic cardiomyopathy (DCP) has been defined as ventricular dysfunction that occurs in diabetic patients independent of a recognized cause such as coronary artery disease or hypertension. It implies a direct injury to the myocardium and is a common and often unrecognized process in asymptomatic type diabetes.[13] Heart failure with both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) are present in the phenotype of DCP.[14] Most patients with diabetic cardiomyopathy have a phenotype of HFpEF. Diabetes associated concentric LVH is related to diastolic dysfunction and eccentric hypertrophy is related to systolic dysfunction. It is a complex disorder beginning with hyperglycaemia at an early stage characterized by endothelial dysfunction. Cellular changes result in myocyte injury, hypertrophy and myocardial fibrosis at an intermediate stage. In the advanced stage, development of myocardial fibrosis results in myocardial microvascular changes which is frequently associated with hypertension. Endocardial remodelling likely involves remodelling of the subendocardial fibres and subclinical diastolic dysfunction. Structural changes in DCP consist of left ventricular hypertrophy, diastolic dysfunction, concomitant atrial dilatation and systolic dysfunction. The diabetic myocardium is more susceptible to higher rates of myocyte death by both apoptosis and necrosis than that of healthy hearts. HF also causes insulin resistance (IR) by possible mechanisms including sympathetic over activity, loss of skeletal muscle mass, effect of increasing circulating cytokines.[15] A vicious cycle is therefore set in motion where HF and IR worsen each other. Insulin resistance is associated with pro atherogenic lipid profile that includes a high very low-density lipoprotein (VLDL) component, a low high-density lipoprotein (HDL) and small dense LDL.

Calcium is a principal ionic regulator in the heart which contributes to normal cardiac function.[16] Abnormal calcium handling is an important hallmark of DCP. Evidence demonstrates altered expression, activity and function of all transporters involved in excitation contraction coupling. Poly ADP ribose polymerase (PARP) is a nuclear deoxyribonucleic acid (DNA) repair enzyme whose increased activity is observed in diabetes as a reparative response to increased oxidative stress and subsequent damage to DNA. Protein kinase C (PKC) phosphorylates many proteins directly involved in excitation contraction coupling and disturbs calcium handling in cardiomyocytes. Increased activity of PKC is seen in diabetic hearts and levels correlate with PARP. Evidence demonstrated association of autonomic dysfunction with impaired vasodilator response of coronary vessels to increased stimulation and abnormal cardiac function in diabetes. β adrenergic receptor density and norepinephrine content have also increased in diabetics, enhancing cardiac sympathetic activity which can induce toxic effects on the heart.

Impaired left ventricular relaxation and increased LV chamber stiffness cause left ventricular diastolic dysfunction. In this setting, there is no rapid LV diastolic suction with more gradual left atrial (LA) emptying resulting in low velocity E wave. LA emptying is therefore dependent on its contraction resulting in high amplitude A wave. The net effect is a decreased E/A ratio. In the present study, in patients, mean peak 'E' velocity was 71.84 ± 6.51 and mean peak 'A' velocity was 64.38 ± 6.51 when compared to 76.04 ± 6.067 and 55.78 ± 5.61 in controls respectively. Mean E velocity was lower in patients than controls and mean A velocity was higher in controls than in patients. The mean E/A ratio was 1.124 ± 0.168 in patients when compared to 1.364 ± 0.203 in controls although the results were not clinically significant (P value 0.105). 16 patients (32 %) had E/A ratio < 1 and 34 patients (68 %) had E/A ratio > 1.The results are similar to an earlier retrospective cross sectional study[17] with 2971 participants where 31 % of study population had an EF of < 1. Peak 'E' velocity was higher in those with DM and impaired glucose tolerance compared to normal participants and peak 'A' velocity was lower in those with DM and IGT compared to normal counterparts in the study population. In another prospective case control study performed by Virendra C Patil et al..[18] 54 % of patients had an E/A ratio of < 1 suggesting diastolic dysfunction which is higher than the present study.

Isovolumic relaxation time, another sensitive indicator of diastolic dysfunction, represents the time interval between end of aortic ejection and beginning of ventricular filling. IVRT may be increased during early diastolic dysfunction but can be shortened as severity progresses.[19] The present study showed IVRT values of mean and SD as 96.52 ± 7.057 and 87.42 ± 4.403 in patients and controls respectively, a P value of 0.011, which is statistically significant. 12 patients (24%) had an IVRT of more than 100 sec. IVRT of all controls was between 60 - 100 msec. This is in contrary to two previous studies[18,20] where IVRT of patients was less than the control group.

An important contributor to heart failure in subjects with DM is excessive left ventricular stiffness due to increased interstitial fibrosis and collagen cross-linking.[21] In diabetes, there is significant reduction in myocardial glucose use with a shift in energy production towards free fatty acid (FFA) β

oxidation.[22] This in turn is associated with functional impairment of oxidative phosphorylation as a consequence of excessive caloric supply in the absence of sufficient energy demand. Dyslipidemia is the best characterized risk factor for increasing atherosclerosis in patients with type 2 DM.[23] The atherogenic metabolic triad comprises of hyperinsulinemia, hyper apolipoprotein B and small dense LDL. The higher circulating and cellular levels of FFA may lead to intracellular accumulation of potentially toxic intermediates leading to cardiomyocyte morphological changes and impaired myocardial performance. One of the most important generators for metabolic changes in diabetes is hyperglycaemia.[24] Depleted glucose transporter proteins GLUT-1 and GLUT-4 results in reduction in glucose use in the diabetic myocardium. Pyruvate dehydrogenase is inhibited by high circulating free fatty acids which in turn impairs myocardial energy production leading to accumulation of glycolytic intermediates and ceramide, enhancing apoptosis. Increased incidence of CV events and mortality is linked to poor glycaemic control. There was 8 % increase in MI with each 1 % increase in level of HbA1C during a period of 2.4 years in a study.[25] A higher incidence of diastolic dysfunction was noted in the present study in cases with a poor glycaemic control (HbA1C > 7). This observation is similar to four studies performed earlier[17,18,26,27] stressing the importance of glycaemic control to prevent cardiovascular morbidity and mortality.

The age adjusted cardiovascular mortality is more in a person in whom diabetes is the only cardiovascular risk factor than in a person without diabetes but with two other classic risk factors. In addition to this, diabetes greatly increases the risk of cardiovascular disease associated with any other risk factor. Diabetes also causes heart disease at a younger age compared to non-diabetics. Evidence also suggests that tight glycaemic control in the early years of the disease reduces vascular complications in the subsequent decades. There is a two to four-fold higher risk of developing CAD in diabetics compared to people without diabetes. Paucity of symptoms of coronary ischemia is a major hurdle in initiating effective timely treatment in diabetics. Silent myocardial ischemia occurs in more than 20 % asymptomatic patients with type 2 diabetes. The present study emphasizes the need for detection of such ischemia before the onset of symptoms.

CONCLUSIONS

The present study highlights the importance of cardiac screening in all diabetic patients irrespective of cardiovascular symptoms to diagnose early left ventricular systolic and diastolic dysfunction. Early diagnosis of occult cardiomyopathy will help the clinician alter the management strategy. Targeting inflammation with weight loss, stringent glycaemic control and optimum management of dyslipidemia is required in all newly diagnosed diabetics to prevent various cardiovascular complications. Therapies should be directed towards prevention of diabetic cardiomyopathy progression in early stages of clinical development and target either collagen deposition/ enhanced fibrosis or alterations in cardiomyocyte metabolism.

Strengths and Limitations

Being a comparative study, the association between ventricular dysfunction and diabetics can be compared to those without diabetes. Quantitative ultrasound is a more sensitive tool in detecting occult cardiomyopathic changes in diabetic heart than standard echocardiography. Invasive procedures for estimation of left ventricular filling pressures were not performed. Brain natriuretic peptide measurements were not done in patients who had significant systolic and diastolic dysfunction.

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