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RESEARCH ARTICLE

DIASTOLIC DYSFUNCTION IN TYPE II DIABETES MELLITUS

Trpathi Prasad, A., *Mehra, D. and Kumar, A.

Department of Medicine Rohilkhand Medical College and Hospital, Bareilly U.P., 243006, India

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ABSTRACT

Introduction: Diabetes Mellitus is a categorized as a disease with multi-system complications. Congestive heart failure is one of the last resorts of cardiovascular complications, and is featured by the presence of diabetic cardiomyopathy, indicated by diastolic left ventricular dysfunction, which is easily assessed clinically and with echocardiography.
Objective: To study the prevalence of LV diastolic dysfunction in asymptomatic patients diagnosed as diabetes mellitus.
Method: The study was carried out on 100 diabetics and compared with 100 age and sex matched controls. In all the patients, complete history, general examination and relevant investigations was done to find out the prevalence of diastolic dysfunction in patients of diabetes mellitus.
Results: The prevalence of diastolic dysfunction, defined by echocardiograph criteria was observed in 53% of total subjects. E/A was a sensitive index of diastolic LV dysfunction. Left ventricular hypertrophy, as indicated by an increased LV mass, was an early marker of diabetic cardiomyopathy.
Conclusion: Echocardiography is a sensitive method to investigate the diastolic dysfunction. There is a high prevalence of diastolic dysfunction in diabetes, which is an early marker of diabetic cardiomyopathy.

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INTRODUCTION

Diabetes Mellitus is characterised as a group of common metabolic disorders that share the symptoms of hyperglycemia. It is associated with cardiovascular complications. Clinical, epidemiological and pathological studies had showed the increased occurrence of clinical congestive heart failure in patients of diabetes cardiomyopathy, which could take the form of diastolic and systolic left ventricular dysfunction (Zarich and Nesto, 1986; Raev *et al*., 1994). Left ventricular diastolic dysfunction represents the reversible first stage of diabetic cardiomyopathy, reinforcing the importance of early examination of diastolic ventricular function in patients of diabetes. The risk of heart failure is increased in diabetics with no clinical evidence of coronary artery disease. Myocardial involvement in diabetics occurs early in the course of disease, impairing early diastolic relaxation and when severe, it causes decreased myocardial contraction. Prior to the development of symptomatic congestive heart failure, sub-clinical left ventricular dysfunction exists for some duration (Rajput *et al*., 2002). With the availability of echocardiography and Doppler, the natural history of cardiac involvement from pre-clinical to clinical stage in patients with diabetes can be described.

Corresponding author: Mehra, D.
Department of Medicine Rohilkhand Medical College and Hospital, Bareilly U.P., 243006, India.

The present study was performed to assess normotensive diabetic patients by echocardiographic and Doppler parameters.

MATERIALS AND METHODS

This prospective study was undertaken in 100 patients of diabetes mellitus, who were selected from OPD and IPD from Rohilkhand Medical College and Hospital, Bareilly, over a period of one year. All subjects were determined to be otherwise healthy by a medical history and physical examination. A normal resting electrocardiogram and chest radiograph were taken in all patients initially. Plasma glucose was measured as FBS (8-14 hrs fasting) and PPBS (2 hrs after 75 gm glucose intake) and urine exmination was done. Biochemical investigations in the form of blood urea, serum creatinine, Fasting Lipid profile, Glycosylated haemoglobin were also carried out. A standard 12 lead electrocardiogram and a transthoracic echocardiogram in all its modes (M, 3d and colour Doppler) were also carried out. Following patients were excluded:

- Patients with symptoms of coronary artery disease.
- Patients with any other cardiac illness like ischemic, hypertensive heart disease, congestive heart failure and cardiomyopathy, LVEF < 55%

- 3 Any abnormality in ECG.
- Patients found as hypertensive (BP > 130/90 mmHg).
- Diabetes Mellitus type I / Stress hyperglycemia/ pregnancy.

The control group consisted of 100 healthy, non-diabetic individuals, confirmed by blood sugar values comparable for age and sex distribution to diabetic patients. Institutional approval was obtained for the study and informed consent was obtained from the subjects, who did not have to pay for any of the tests.

Echocardiography

Echocardiograms were recorded with a commercially available ultrasound system. Subjects were examined in the left lateral decubitus and supine position using standard parasternal long axis, short axis and apical views. All recordings and measurements were obtained by the same observer and were always performed at midday to avoid the influence of circadian rhythm on left ventricular diastolic function (Voutilainen *et al*., 1996). The following steps ensures comprehensive assessment of diastolic function and the identification of heart failure related to diastolic dysfunction:

1. Look for M mode and 2D echocardiographic evidence for diastolic dysfunction. Abnormal myocardial relaxation, an integral part of diastolic dysfunction, decreases the slope (in M mode) and mitral annulus motion of early diastolic filling and increases LA size. LV wall thickness are usually but not necessarily increased.
2. Mitral inflow velocities reflect the Transmitral pressure gradient, which is usually predictable for various stages of diastolic dysfunction. Assessment of ventricular compliance is possible from the configuration of mitral inflow velocities. Pulmonary vein flow velocities are also helpful
3. Myocardial relaxation by tissue Doppler can be evaluated. Mitral annulus velocity during early diastole correlates reasonably well with the status of myocardial relaxation.
4. Mitral inflow velocities, Ea, mitral inflow propagation velocity and their combination can estimate LV diastolic filling pressure at rest and with exercise.

Criteria for left ventricular hypertrophy were based on values > 13mm for interventricular septum and left ventricular posterior wall. Systolic dysfunction was indicated by Ejection fraction < 50%; Fractional shortening; Regional wall motion abnormalities; and E point septal separation: normal value – 6-9 mm, with higher values indicating systolic dysfunction. Doppler echocardiography was carried out to assess left ventricular diastolic function.

Under simultaneous 2- dimensional echocardiographic visualization of cardiac anatomy in the apical four chamber view, a Doppler sample volume was positioned within inflow area of the left ventricle just below the mitral valve annulus (near the mitral valve tips and parallel to the presumed axis of blood flow) (Appleton *et al*., 1988). To minimize potential effects of transducer angulations, Doppler sampling volume was aligned in different planes until maximum diastolic flow velocities were recorded till optimal spectral pattern was obtained.

From the transmitral recording, following measurements were carried out:

- Peak E velocity in m/sec - peak early transmitral filling velocity during early diastole (normal: 0.5-0.8).
- Peak A velocity in m/sec – peak transmitral atrial filling velocity during late diastole (normal: 0.3-0.5).
- Deceleration time (DT) in msec – time elapsed between peak E velocity and point where extrapolation of deceleration slope of E velocity crosses the zero baseline (normal: 150-220).
- Acceleration time (AT) in msec – time elapsed between point where extrapolation of acceleration slope of E velocity crosses zero baseline and peak E velocity. (normal: 60-100)
- Isovolumic relaxation time (IVRT) in msec – duration between aortic valve closure and mitral valve opening (normal: 60-100).
- Ratio of peak E to peak A (E/A) (normal: 1-2).

The Echocardiographic Diastolic Dysfunction Criteria (6, 7) for enrollment in the study were as follows:

Diastolic Parameters	**Criteria**
Mitral E/A ratio	< 1 or > 2
Deceleration time (msec)	< 150 or > 220
Isovolumic Relaxation time (msec)	< 60 or > 100

Left ventricular mass was calculated using the following formula (8):

$$LV\ mass\ (gm) = 0.8 \times 1.04[(LVEDD + IVSD + PWD)^3 - (LVEDD)^3] + 0.6$$

All the data collected was analyzed statistically using the Z test. Statistical significance was estimated by calculating the 'p' value, with significance assigned at $p < 0.05$. p values < 0.01 were considered to be highly significant.

RESULT

Among the total of 100 patients 40% were males and 60% were females.

Effect of different parameters on Diastolic Dysfunction

Study parameter	Normal	Pseudo Normal	Impaired Relaxation	P value
Age (yrs)	52.67+11.72	51.66+6.58	54.53+11.02	0.629
Duration of Diabetes (yrs)	5+1.94	3.4+2.6	3.5+2.78	0.006
BMI (kg/m^2)	25.30+4.10	26.18+5.46	25.33+3.99	0.744
Total Cholesterol (mg/dl)	177+34.73	173.44+27.88	184.86+39.12	0.484
HDL Cholesterol (mg/dl)	46.84+14.12	42.68+14.09	40.8+11.22	0.126
LDL Cholesterol (mg/dl)	104.34+23.55	99.94+22.33	102.4+18.70	0.755
Fasting TGL (mg/dl)	187.57+80.55	216.61+67.68	179.66+63.45	0.228

In our study 22% were smokers and 18% were alcoholics. Duration of diabetes was <5 years in 56%, 5-10 yrs in 42% and only 2% had a duration of >2 yrs. In our group 80% of patients were on oral hypoglycemic agents, 13% patients were on Insulin and 7% patients were on both OHA and Insulin. The BMI was in the range of 20-25 kg/m^2 in 37%, 39% had in the range of 26-30 kg/m^2, 8% had in the range of 20 kg/m^2 and 16% had BMI of >30kg/m^2. 71% patients had serum cholesterol of <200 and 29% had >200. Serum HDL was <40 in 43% of patients and >40 in 57%. 38% had serum LDL <100, 49% had 100-130. In 30% of patients PPBS were in the range of 201-250, 17% were in the range of 151-200, 16% were in the range of 251-300, 15% were in between 301-400 and 13% patients were in 101-150 range.

Effect of different parameters on Diastolic Dysfunction

Study parameter	Study period	Normal	Pseudo Normal	Impaired Relaxation
E-wave	Pre valsalva	192.67+14.27	92.38+8.15	71.66+17.39
	Post valsalva	88.07+9.97	55.33+19.59	64.86+15.17
A-wave	Pre valsalva	77.46+15.09	74.72+9.50	84.83+16.18
	Post valsalva	76.73+6.82	65.44+16.95	84.46+14.87
E:A ratio	Pre valsalva	1.21+0.14	1.25+0.15	0.85+0.19
	Post valsalva	1.14+0.079	0.83+0.06	0.77+0.16
DT	Pre valsalva	179.32+49.66	189.77+50.34	184.43+34.83
	Post valsalva	140.9+23.26	171.22+19.90	156.1+62.84
IVRT	Pre valsalva	96.57+13.32	90.91+9.6	91.93+19.85
	Post valsalva	88.67+7.95	89.55+15.75	85.63+8.52

There was a significant difference in E-wave of patients between pre valsalva and post valsalva with duration of diabetes, p<0.0001. There was a significant difference in A-wave of patient between pre valsalva and post valsalva with duration of diabetes, p<0.0001. In present study diastolic dysfunction was well correlated with duration of diabetes.

DISCUSSION

The present study provides evidence that left ventricular diastolic function is impaired in patients with diabetes mellitus. Left ventricular diastolic function has been shown to be affected at an early stage in several myocardial diseases when systolic functions remain normal. Till the recent past, all importance was being given to systolic functions of the heart. But in the last decade clinicians and researchers have discovered that both reversible and irreversible abnormalities of left ventricular diastolic functions contribute significantly to symptoms and morbidity in individuals with a variety of cardiac disorders, including those with normal or near normal systolic function. Left ventricular wall thickness defined as the sum of ventricular septal and posterior wall thickness and LV mass were statistically significant both in systole as well as in diastole when compared with normal controls.

These data indirectly suggest that metabolic and/or hormonal factors may play a role in the development of a greater ventricular mass. Among these, insulin resistance with its associated hyperinsulinemia is the most likely candidate. The deceleration time (DT) of the E wave was an even more specific indicator of diastolic dysfunction, with a highly significant increase in its duration in the diabetic group. This index is an important variable to differentiate the diabetics with a normal filling pattern and normal diastolic function from those with a pseudonormalised pattern of diastolic dysfunction. The difference in the acceleration times (AT) of the E wave between diabetics and controls was not significant. The present study did not show any significant decrease in the ejection fraction in diabetics. Our results were compared with various studies. Patil *et al.* (Van Heerebeek *et al*., 2008) in their study of 127 asymptomatic Type II diabetics found a significant incidence (54.33%) of diastolic dysfunction in diabetics. Similarly, in the present study, 66% diabetics were found to have diastolic dysfunction. Van Heerebeek *et al.* (2008) in their study of 36 Type II DM patients stated that, the cardiomyocyte resting tension is more important when LVEF is normal. 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. Similarly, in the present study, 66% of subjects from the case group had diastolic dysfunction with normal LVEF. Sohail *et al.* (Ashraf *et al*., 2007) in their study of 212 diabetic population found that 30.76% patients with Type II DM had diastolic dysfunction. The LV diastolic dysfunction is much more prevalent in patients with Type II diabetes mellitus and LV diastolic dysfunction is an early marker of diabetic cardiomyopathy. In our study, the prevalence was 66%. (Patil *et al*., 2012) in their cross-sectional hospital based study found that in 64% of patients with Type II diabetes, myocardial damage affects diastolic dysfunction in diabetics before systolic dysfunction – very similar to the present study.

Conclusion

From the foregoing discussion, it can be concluded that diastolic dysfunction in patients of diabetes is present even when diabetes is present at a younger age, and is of a shorter duration. This dysfunction is suggestive of pre-clinical diabetic cardiomyopathy. E/A, DT and peak A velocity are sensitive indices of diastolic LV dysfunction. It is suggested that all patients of diabetes should be routinely and repeatedly subjected to 2-D color Doppler echocardiographic assessment of cardiac functions in the long-term management of this metabolic disease. This has important therapeutic implications and helps physicians planning early intervention strategies. Thus, diastolic dysfunction can be used as an early indicator, as it is a precursor to increased LV hypertrophy and clinical left ventricular dysfunction.

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