INTRODUCTION

The 2012 International Diabetes Federation figures for diabetes prevalence confirm that 371 million adults are living with diabetes worldwide,1 and more than half that number are unaware that they have the disease.

Patients with DM are at an increased risk for cardiovascular disease. Diabetes produces cardiovascular complications2 by accelerating atherosclerosis in large arteries and causing diabetic microangiopathy which may have a role in producing heart failure as well.3

Diabetics also have a worse prognosis from heart failure when compared with non-diabetic heart failure patients.4 A sub-group of diabetics with heart failure have been distinctly identified without any co-existing hypertension or coronary artery disease. For this particular sub-group, the term “diabetic cardiomyopathy” has been proposed.

Diabetic cardiomyopathy is associated with both type-1 and type-2 DM and presents as early-onset diastolic heart failure (HFNEF, heart failure with normal ejection fraction) and later-onset systolic heart failure (HFREF, heart failure with reduced ejection fraction).5 Diabetes inflicts a direct insult to the myocardium with functional, biochemical, and morphological myocardial abnormalities that manifest as the diabetic myocardial phenotype.6 Diabetic women tend to have a much greater ventricular mass and increase in left ventricular wall thickness and chamber size.7 Other abnormalities noted in diabetic heart include microvascular constriction, interstitial fibrosis, and oedema.8

The diagnosis of diabetic cardiomyopathy rests on noninvasive imaging techniques such as Doppler echocardiography and cardiac magnetic resonance imaging (MRI) that can demonstrate myocardial dysfunction. Echocardiography can detect significant abnormalities well before the onset of symptomatic heart failure. Early abnormalities are defined by the preserved left ventricular ejection fraction (EF) with reduced early diastolic filling. The diastolic dysfunction precedes systolic dysfunction in diabetic cardiomyopathy even before the presence of pathological findings on clinical examination.9-11 With further disease progression, left ventricular compliance becomes reduced and filling pressures begin to increase. Systolic dysfunction occurs late when patients have already developed significant diastolic dysfunction.12

The prevalence of diabetic cardiomyopathy varies from 29% to 75% attributed to the difference in population under study and the research definition of diabetic cardiomyopathy used by individual workers. Several
studies have shown a correlation between glycemic control and left ventricular dysfunction, whereas other studies have refuted any such association. This important condition has not been investigated in the local population. The aim of this study was to determine frequency of diabetic cardiomyopathy among indigenous population with type-2 diabetic patients who present with heart failure.

METHODOLOGY

This observational study, based on purposive sampling technique was conducted from April 2008 to July 2009 at the Department of Cardiology, Mayo Hospital, Lahore. A total of 100 men and women with type-2 diabetes mellitus, aged 45 – 70 years, with physician-diagnosed symptomatic heart failure (NYHA class I, II, III, IV) were recruited consecutively. Diabetics with evidence of hypertension, known coronary artery disease, valvular or congenital heart disease, and thyroid or overt renal disease were excluded. The exclusion criterion for hypertension was a blood pressure > 140/90 mmHg.

Written informed consent was obtained from all patients as a standard ethical requirement and specified. Approval was taken from Ethical and Research Committee of the Institute. All patients were examined by at least two cardiologists and diagnoses of heart failure were confirmed by history, clinical examination, and relevant laboratory and imaging tests. The history highlighted the duration and control of diabetes, presence of diabetic complications such as retinopathy, clinical neuropathy, or albuminuria, smoking, hypertension, coronary artery disease, treatment history, previous hospitalization, and relevant family history. All patients underwent appropriate tests including complete blood count, plasma glucose (fasting and random), haemoglobin A1c, serum creatinine, fasting lipid profile, resting electrocardiogram and a PA view chest X-ray.

Two-dimensional echocardiography and M-mode measurements were obtained in standard views in all patients. Echocardiographic measurements of diastolic and systolic left ventricular dimensions - left ventricle internal dimension (LVID), posterior wall thickness (PWT), and interventricular septum (IVS) were measured from the leading edge to leading edge of each interface of intersect for optimal measurement accuracy.

Ejection fraction (EF) was calculated by Simpson's method (LVEF % = EDV - ESV/EDV x 100). Left ventricular EF was considered normal when it was between 50 – 75%. Diastolic dysfunction was calculated by measuring E and A velocity across transmural inflow velocity. Coronary angiography was undertaken in all patients after cardiac stabilization to rule out coronary artery disease as a cause of heart failure. Clinically, coronary angiography was not indicated in all patients but it was performed as part of the study because without this, establishing diagnosis of diabetic cardiomyopathy was not possible. No mortality or morbidity occurred due to this.

Diabetic cardiomyopathy was defined as the presence of LV dysfunction by Doppler echocardiography with angiographic evidence of normal coronary arteries in diabetic patients, and the exclusion of other co-morbidities that causes similar myocardial abnormalities, i.e., hypertension, valvular heart disease and congenital heart disease.

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 15, in terms of percentages (relative frequencies) of variables. The variables included age, gender, duration of diabetes mellitus, use of insulin or oral hypoglycemic, haemoglobin A1c, Ejection fraction on Doppler echocardiography, NYHA class, and the number of coronary vessels involved on coronary angiography. Results were given as mean ± SD. Mean values were compared by unpaired student's t-test. Chi-square or Fisher's exact test were used for comparison of frequency proportions. The level of significance was set at p < 0.05.

RESULTS

A total of 100 subjects with type-2 diabetes mellitus were included in this observational study. There were 60 (60%) male and 40 (40%) female subjects. The characteristics of patients with and without cardiomyopathy are tabulated in Table I. Diabetic cardiomyopathy was found in 40 (40%) out of a total of 100 subjects comprising 24 males (60%) and 16 females (40%). The age ranged between 45 – 70 years; the age of patients with diabetic cardiomyopathy was found slightly higher than those without cardiomyopathy (p < 0.4623). All the subjects in the study had diabetes for more than 10 years but there were no significant differences between the cardiomyopathy and non-cardiomyopathy group (12.4 ± 10.3 years versus 11.8 ± 9.7 years, p < 0.347). Eighty patients (80%) received oral hypoglycemic agents and 20 patients (20%) were treated with insulin. The number of patients receiving insulin were not significantly different in diabetics with or without cardiomyopathy. Forty patients (40%) had ejection fraction < 30 %, 30 patients (30%) had EF between 31 to 50% and another 30 patients (30%) had normal EF (> 50%). Ejection fraction showed significant reduction in 40 diabetics with cardiomyopathy than in those without cardiomyopathy (29.6% ± 5% versus 50.4% ± 8.7%, p < 0.0003). Left ventricular mass of the diabetic patients with cardiomyopathy (227.8 ± 64.6 g) was much higher than those without cardiomyopathy (195.4 ± 87.3 g; p= 0.005).
Coronary angiogram was normal in 40 patients (40%), and this sub-group was labeled as diabetic cardiomyopathy. Single vessel disease was detected in 10 (10%) with 6 in left anterior descending artery (LAD), 2 in left circumflex artery (LCX) and 2 in right coronary artery (RCA). Forty patients (40%) had triple vessel disease which was diffuse. Ten patients (10%) had two vessel disease (5% in LAD and LCX and 5% in LAD and RCA). Patients with diffuse triple vessel disease had relatively lower ejection fraction among the diabetics without cardiomyopathy. Left ventriculogram was done in all patients who showed poor LV systolic function in 40%, moderate LV systolic function in 30% and normal LV systolic function in 30%. Among the 40 patients with diabetic cardiomyopathy, 70% had left ventricular systolic dysfunction, 14% had isolated diastolic dysfunction and 16% had both left ventricular systolic and diastolic dysfunction. The frequency of systolic dysfunction among diabetic cardiomyopathy was significantly higher than diastolic dysfunction (p < 0.001).

The average BMI of all the patients with diabetes was 24.2 ± 2.7 kg/m². The diabetics with cardiomyopathy were found slightly more obese than those without cardiomyopathy (p < 0.306). Glycemic control was poor in majority of our subjects: 80 patients (80%) having a haemoglobin A1c exceeding 8.0%. When compared between diabetics with and without cardiomyopathy, the difference in levels of haemoglobin A1c was not statistically significant in all three groups.

Serum cholesterol was found higher among the diabetics with cardiomyopathy than those without cardiomyopathy although not statistically significant (p < 0.230). High-density lipoprotein (HDL) cholesterol was found lower among the diabetics with cardiomyopathy (p < 0.216), and serum triglyceride and low-density lipoprotein (LDL) cholesterol were found insignificantly higher in the cardiomyopathy group (p < 0.076 and p < 0.138).

Serum creatinine was > 1.5 mg/dl in 40 patients (40%), among these 30 were diagnosed as diabetic cardiomyopathy.

Average systolic BP was 120 ± 13 mmHg and diastolic BP was 74 ± 15 mmHg in all patients and those with diabetic cardiomyopathy systolic and diastolic BP was 108 ± 11 mmHg and 76 ± 13 mmHg respectively. The difference was not statistically significant as patients with known or newly diagnosed hypertension were excluded from the study.

### DISCUSSION

Diabetic cardiomyopathy presents as left ventricular dysfunction and heart failure in patients with diabetes mellitus. After exclusion of macrovascular (coronary artery) disease and hypertension, it remains unclear whether it is a small vessel disease in diabetics with subsequent ischaemia, or a myopathy resulting from direct injury to cardiac musculature, or a sequence of cardiac autonomic neuropathy, or a combination of multiple etiologies.

In this study, diabetic cardiomyopathy was found in (40%) of the type-2 diabetic subjects. Sixty percent of this were males, which has also been reported by other researchers from Subcontinent. The work done elsewhere, however, shows a higher proportion of females with diabetic cardiomyopathy.

Most of the clinically well-recognized population with evidence of heart failure (70%) exhibited left ventricular systolic dysfunction. Only a small proportion (14%) of cases had isolated left ventricular diastolic dysfunction. The frequency of left ventricular systolic dysfunction among diabetic cardiomyopathy was found to be significantly higher than diastolic dysfunction. These results do not match with the findings reported by other authors due to following likely reasons: firstly, the strict...
requirement of angiographic exclusion of large vessel coronary artery disease before labelling the subjects as diabetic cardiomyopathy; secondly, all patients enrolled in this study had clinical heart failure; and thirdly, most of these subjects (80%) had poor glycomic control. High variation in the prevalence (29 – 75%) of diabetic cardiomyopathy reported by other authors may be attributed to the definition of diabetic cardiomyopathy used and the differences in patient population under study. Most workers have selected well-controlled asymptomatic diabetics without clinical evidence of heart failure. Recruiting such cases, Fang et al. observed a higher number of left ventricular diastolic dysfunction (29%) than left ventricular systolic dysfunction (24%), and 17% of the diabetics in their study had both diastolic and systolic dysfunction.9 Other studies of well-controlled type-2 diabetic subjects showed that around 30% had diastolic dysfunction.10,18,19 However, this prevalence was based on standard echocardiography testing in which mild and early diastolic dysfunction is not detectable in approximately one-third of subjects. With the use of more rigorous Doppler methods, early and mild diastolic dysfunction can be diagnosed. Using these methods in India and in Minnesota, 54% and 52% of diabetic subjects respectively were shown to have diastolic dysfunction.17,20 Using similarly sensitive methods, Porier et al. showed the prevalence of diastolic dysfunction to be 60% in well-controlled type-2 diabetic patients.21 This figure, however, included 32% patients with impaired relaxation, a very milder of diastolic dysfunction.

In their normotensive type-2 diabetic subjects, Hameedullah found a significant correlation between the frequency of LV diastolic dysfunction and degree of diabetes control; LV diastolic dysfunction frequency of 25%, 45%, and 80% in well controlled, moderately controlled and poorly controlled diabetics respectively.13 Similar results were documented by Patil et al. and in the strong heart study where the extent and frequency of diastolic dysfunction was directly proportional to the haemoglobin A1c level.17,22 Like some previous studies,17,18 this study could not elicit such a correlation between the A1c and frequency of heart failure probably because a majority of these subjects (80%) had poor control of diabetes at enrolment and most of them (70%) had already developed LV systolic dysfunction.

This study also did not find any correlation between blood pressure, duration of diabetes, and BMI with presence of diabetic cardiomyopathy, which was also documented by other workers.18,23,24 Fang et al. did not find a significant difference in duration of diabetes, haemoglobin A1c levels and lipid profile, but did observe a significantly greater LDL cholesterol in the diabetics with LVH than the diabetics without LVH.9

Serum cholesterol, triglyceride, and LDL cholesterol levels were found higher and serum HDL cholesterol was lower among the diabetics with cardiomyopathy compared with those without cardiomyopathy.

In this study, ejection fraction was significantly lower among the diabetics with cardiomyopathy compared with the diabetics without cardiomyopathy due to a significantly higher occurrence of left ventricular systolic dysfunction. The left ventricular mass was more among the diabetics with cardiomyopathy compared with that of the diabetics without cardiomyopathy, which is statistically significant and this is consistent with the finding of other workers.7,9

**CONCLUSION**

Diabetic cardiomyopathy is a common cause of diastolic and systolic heart failure in long standing type-2 diabetic patients in the local population. There was no association between BMI, blood pressure, duration of diabetes, and glycemic control with diabetic cardiomyopathy. The level of serum cholesterol, triglyceride, and LDL cholesterol were higher and serum HDL cholesterol was lower among the diabetics with cardiomyopathy compared with those without cardiomyopathy.

**REFERENCES**


