

Study of Left Ventricular Diastolic Function in Patients with Diabetes Mellitus

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Introduction

Diabetic cardiomyopathy (DC) is defined as heart muscle disorder, due to or presumably due to Diabetes mellitus (DM). The relationship between DC and indices of metabolic control in DM is still a matter of debate.

Our aim was to determine the prevalence of DC in young diabetic patients and to find its correlation with age, duration of DM, and indices of glycemic control.

Patients and Methods

The study material consisted of 50 diabetic patients below 50 years of age and 50 age and sex matched control group. Echo was done to assess left ventricular function and to rule out other structural heart disease. Their metabolic indices were taken.

Results

Left Ventricular Function: all controls had normal LV function. Studied patients had normal LV systolic function. A total of 29 patients (58%) were found to have LV diastolic dysfunction. Grade I LVDD was most common (40%). LVDD was significantly correlated with duration of DM and age of the patient ($P < 0.05$). There was a trend towards higher grades of LVDD, as age of the patient and duration of DM increased. There was no significant correlation between fasting blood sugar level, serum lipid profile and LV diastolic dysfunction.

Conclusion

LVDD is very common in patients with DM. Its prevalence is related to age and duration of the disease while severity has a tendency towards these two variables but demonstrated no significant statistical value. Early detection of LVDD may have important diagnostic, prognostic and therapeutic implications

Introduction

Diabetic cardiomyopathy (DC) is defined as heart muscle disorder, due to or presumably due to Diabetes mellitus (DM). This entity was first reported by Rubler, et.al in 1972¹ to explain increased incidence of congestive heart failure (CHF) in diabetic patients. The famous Framingham study also reported a greatly increased risk of CHF in diabetic patients². The increased risk could not be solely explained by co-existent ischemic heart disease (IHD) or hypertension (HT) and has been attributed to DC, resulting from diastolic and/or systolic left ventricular dysfunction (LVD). Prevalence of DC in different surveys and clinical trials has ranged from 10 – 60 %³⁻¹¹. The relationship between DC and indices of metabolic control in DM is still a matter of debate. Some studies have found correlation between glycemic control and left ventricular diastolic dysfunction (LVDD), while other studies have found no such correlation. To the best of our knowledge prevalence of DC in young diabetic patients has not been studied before. The aim of this study was to determine the

prevalence of DC and age of patient, duration of DM, dyslipidemia and indices of glycemic control.

Patients and Methods

The study material consisted of fifty consecutive patients with DM defined according to the American Diabetic Association criteria¹². The patients were seen at the Outpatient Departments of Almana General Hospital, Jubail, Saudi Arabia between January 2002 and December 2005 and Academy Teaching Hospital, Khartoum, Sudan between May 2006 and April 2007. All the patients were at or below 50 years of age and gave informed consent. History and detailed physical examination were documented. Investigations done included complete blood count, blood urea, serum creatinine, and fasting and 2 hours plasma glucose concentration following 75 grams oral glucose tolerance test. Serum lipid profile, ECG and Echocardiogram were done in all the patients. Stress test was done in some patients where there was suspicion of underlying ischemic heart disease. Patients were excluded from the study if they had any of the following: history of hypertension, significant valvular heart disease, congenital heart disease, known or suspected ischemic heart disease, pericardial disease, thyroid dysfunction, chronic alcoholism, anemia, or renal failure. Fifty, age and sex matched, healthy non-diabetic subjects were enrolled in the study as a control group.

2D, Doppler and Color Doppler echo was done to assess left ventricular function and to rule

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out other structural heart disease using ATL-HDI 3000 and Ultrasound System (Philips) and MyLab CV30 (Esaote, Italy). All the measurements were taken at the same time, during morning hours to avoid influence of circadian rhythm on left ventricular (LV) diastolic function¹³. LV systolic function was measured by volume method of Cube. LV diastolic function was assessed by Pulse Doppler recordings at the tip of the mitral valve leaflets and at pulmonary vein. The following measurements were taken at mitral valve leaflet: E wave velocity; A wave velocity; E/A ratio; isovolumic Relaxation Time (IVRT); E wave deceleration time (EDT). The following measurements were taken at pulmonary vein: S wave velocity; D wave velocity; S/D ratio and Atrial Reversal (AR). Measurements were made at end expiration during normal breathing and were repeated during Phase II of Valsalva maeneuver¹⁴.

Based on mitral valve and pulmonary venous recordings, four patterns of LVDD were identified¹⁵⁻¹⁷. **Abnormal relaxation pattern** – characterized by stiffness to LV filling. Characteristic pattern seen is-decreased E wave velocity, increased A wave velocity, E/A ratio <1, increased IVRT (>100 ms), and increased EDT (>240 ms) S/D ratio >1 and AR < 35 cm/s. **Pseudonormal pattern** characterized by normalization of LV filling pattern at the expense of increased LV filling pressure. Pulse Doppler recording at mitral valve leaflet shows normal filling pattern at rest and abnormal relaxation pattern with Valsalva maneuver. Evidence of increased LV filling pressure is increased AR velocity and duration. **Reversible restriction** depicts the following characteristics: pulse doppler recording (at mitral valve leaflet) showed increased E wave velocity, decreased A wave velocity, E/A ratio > 2.5, decreased IVRT (<70 ms) and decreased EDT (<150 ms), while pulmonary venous recording showed S/D ratio <1 and AR > 35 cm/s. In the early stages of restrictive filling, these findings are reversible with Valsalva maneuver. **Irreversible restriction** is characterized by features of restriction pattern not reversible with Valsalva maneuver. Based on clinical and Echocardiographic findings we graded the severity of LVDD into four grades according to the method suggested by Nashimura et al¹⁵:

Grade I – abnormal relaxation pattern + Functional class I-II of NYHA.

Grade II- pseudonormal pattern + Functional class II-III of NYHA.

Grade III- reversible restriction pattern + Functional class III-IV of NYHA.

Grade IV-irreversible restriction pattern + Functional class IV of NYHA.

Statistical Analysis

SPSS version 9 was used for all statistical analysis. Comparisons between groups with continuous variables were done using Students t-test and linear regression analysis. Groups with discrete variables were compared with Chi Square Test. Values were expressed in Mean ± SD. P value < 0.05 was taken as statistically significant.

Results

Demographic profile is shown in Table I.

Table: I .Baseline characteristics of study population

* Oral Hypoglycaemic Agent

Characteristics	Patients	Controls
No. of patients	50	50
Mean age	40.79±7.65 years (Range-22-50 years)	38.10±7.51 years (Range-21-50 years)
Age distribution		
21-30 years	8	8
31-40 years	14	14
41-50 years	28	28
Sex		
Males	47	47
Females	3	3
DM duration	6±3.59 years (Range-6 mo.-12 years)	
Fasting blood sugar	7.07±2.48 mmol/l	4.6±1.12 mmol/l
Serum lipids		
Total cholesterol	5.88±0.95 mmol/l	5.1±0.76 mmol/l
Triglyceride	2.75±0.67 mmol/l	2.23±0.53 mmol/l
HDL cholesterol	0.92±0.22 mmol/l	1.0±0.24 mmol/l
LDL cholesterol	3.79±0.81 mmol/l	3.1±1.11 mmol/l
Treatment modality		
*OHA	38	
Insulin	7	
Diet	5	
Nationality of patients		
Saudi	20	20
Indian	19	19
Sudanese	11	11

Baseline characteristics of patients and controls were compared. The study population consisted primarily of young patients, mainly males of mixed population, Saudis, Indians and Sudanese. Most of the patients were on some form of treatment and had dyslipidemia as defined by National Cholesterol Education Program Adult Treatment Panel III protocol.

Left Ventricular Function: all controls had normal LV function and none had LV systolic or diastolic dysfunction. All studied patients had normal LV systolic function. A total of 29

patients (58%) were found to have LV diastolic dysfunction. Grade I LVDD was most common (40%), followed by Grade II (18%) table II-III. None of the patients had Grade III or Grade IV LVDD.

There was significant correlation between age of the patients and prevalence of LVDD ($P < 0.05$). Prevalence of LVDD was lowest in the 21-30 years age group (12.5%), while 80% of patients in the 41-50 years age group had some degree of LVDD as shown in table II.

Table: II. Age of diabetics versus disease prevalence

Age group (Year)	No. Screened	CASES			Prevalence (%)	CONTROLS		
		No. Diseased GD I	GD II	Total		No. Disease Gd I	Gd II	Prevalence (%)
21-30	8	1	0	1	12.50	0	0	0
31-40	14	3	2	5	35.71	0	0	0
41-50	28	16	7	23	82.14	2	0	7.14
Total	50	20	9	29	58.00	2	0	4
Chi square=6.87		P value=0.032						

GD= Grade

Prevalence of LVDD significantly correlated with duration of DM ($P < 0.05$) as shown in table III. We also attempted to determine correlation between age of the patients and duration of DM versus severity of LVDD. There was a trend towards higher grades of LVDD as age of the patient and duration of DM

increased. However, it did not reach statistical significance. We did not find any significant correlation between indices of metabolic derangement and prevalence and severity of LVDD. There was no significant correlation between fasting blood sugar level, serum lipid profile and LV diastolic dysfunction.

Table: III. Duration of DM versus disease prevalence

Duration of Disease (years)	Number Screened	Number Diseased			Prevalence (%)
		GD I	GD II	Total	
0 - 3	15	2	0	2	13.33
4 - 6	12	6	1	7	58.33
7 - 9	13	7	3	10	76.92
10 - 12	10	5	5	10	100.00
Total	50	20	9	29	58.00
Chi Square = 9		P Value = 0.029			

Discussion

Early detection of LVDD has important diagnostic, prognostic and therapeutic implications. Patients of DM are at increased risk of heart failure¹⁸⁻²⁴. This increased risk is seen even in patients with normal LV systolic function. Similarly patients of myocardial infarction who are also diabetic are at higher risk of developing congestive heart failure than non diabetics²²⁻²⁵⁻²⁷. Studies have attributed this increased risk to DC. LVDD may represent the first stage of DC and may represent the potential marker of evolving heart disease^{19, 28, 29}. This reinforces the importance of early examination of diastolic ventricular function in individuals with diabetes mellitus. Indices of diastolic dysfunction like Early filling/ Atrial contraction [E/A] ratio may have important prognostic value. Retrospective studies have shown that mitral E/A ratio have equal or even superior prognostic value than left ventricular systolic indices³⁰. Apart from prognostic importance, early recognition of LVDD may have important therapeutic implications. Many interventions like exercise³¹, beta-blockers and calcium channel blockers³² have been shown to beneficially influence diastolic function. Therefore, early recognition of LVDD and early institution of therapeutic interventions may help halt or reverse its progression.

The prevalence rate of LVDD in our patients was 58% while non of our age and sex matched controls had LVDD, which indicates a true diabetic correlation in this young group of patients. The reported studies in normal subjects had shown that E/A reversal occurred at mean age of 78 years^{7, 33}. The mean age of the studied patients was almost half of that

The main finding of this study was a higher prevalence of LVDD (58%) in diabetic patients than was previously suspected. Some of the studies reported a lower prevalence rate³⁻¹⁰. However, these studies did not account for pseudonormal pattern, as they did not use maneuvers to unmask this type of ventricular filling. Therefore, difference in prevalence rate between our study and those studies relates to difference in the study design rather than difference in the true prevalence rate. Those studies, which accounted for pseudonormal pattern reported similarly high prevalence rate as our study^{11, 25, 34}. Pseudonormal pattern is usually seen in more advanced stages of LVDD. This pattern was seen in 18% of our patients and therefore, if we had classified subjects with pseudonormal pattern as subjects with normal

pattern, we would have missed a significant percentage of higher grade LVDD. Therefore, prevalence studies of LVDD should always include methods designed to unmask pseudonormal filling pattern and therefore Valsalva maneuver and pulmonary venous recording are essential tools^{14, 33, 35}

Can diastolic dysfunction be predicted?. To answer this question, we correlated different clinical and biochemical parameters with LVDD. We found a positive correlation between age of diabetic patients and prevalence of LVDD with an almost doubling of prevalence rate with each decade of age¹. Previous studies have also reported a higher prevalence in older patients.

As noted above we studied a younger age group. Nevertheless, the age correlation within this group was positive towards the relatively elderly patient. The conflicting results regarding the correlation of age to LVDD in diabetics may be attributed to sample selection, as noted above LVDD is affected by age and is prevalent in the elderly and is also correlated to IHD and hypertension³⁶ (which were with others are an exclusion criteria in this study). The negative prevalence in the control group as well as the fact that pseudonormal filling pattern is usually a pathological phenomenon and is not part of the aging process plus animal studies had shown that DM affects heart muscle independent of aging³⁷ all these facts may exclude the age as a cause but not as a predictor for DC (possibly because of the likely associated longer duration of diabetes with age as shown in the combined analysis)¹. The LVDD in our study appears to be related to longer duration of diabetes mellitus as the lowest prevalence of LVDD was seen in DM of short duration (13% in diabetes mellitus of ≤ 3 years duration) and the highest prevalence was seen in diabetes mellitus of longest duration (100% in DM of >9 years duration). This probably means that a longer duration of disease gives more time for LVDD to develop. This finding is in agreement with several previous studies³⁸. However, though there was a positive correlation between duration of DM and prevalence of LVDD, there was no significant correlation between duration of DM and severity of LVDD. LVDD was also not related to indices of metabolic derangement. We did not find any correlation between fasting blood sugar, serum lipid profile and LVDD. Some studies have shown correlation between glycemic control and LVDD with associated improvement in cardiac function after adequate treatment^{6, 39-41}, while other

studies have not found any such correlation^{3,5,10,42}. So it is still a matter of debate and a larger, more well designed studies are required to settle these differences. Our study did not find left ventricular systolic dysfunction in any patient of diabetes mellitus. Several studies before have reported similar finding^{11,34}.

Conclusion

Our study has shown that LVDD is very common in patients with DM. Its prevalence is related to age and duration of the disease while severity has a tendency towards these two variables but demonstrated no significant statistical value. Early detection of LVDD may have important diagnostic, prognostic and therapeutic implications

Limitations of the study

Beside DM, there are several other factors which can affect left ventricular diastolic function. We have tried to minimize these factors by excluding patients with structural heart disease or disorders that is suspected or known to affect left ventricular function. However, the confounding effect of age and occult coronary artery disease on left ventricular diastolic function cannot be completely removed. We used fasting blood sugar in the last three months as index of glycemic control, however Hb A₁C level would have been a better marker of glycemic control. Our study population consisted primarily of male patients because of inclusion of consecutive cases. A randomized stratified design to include equal number of males and females would have been much better.

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