Original Article

Left Ventricular Dysfunction in Normotensive Diabetic Patients

M Ali[1], M Hafizur Rahman[2], M Kamruzzaman Khokan[3], M Helalur Rahman[4], M Haresur Rahman[5], M Belalul Islam[6]

Abstract:

Background: Diabetes is a major risk factor for impaired left ventricular function independent of coronary artery disease and hypertension. Left ventricular diastolic dysfunction is demonstrated in diabetic patients who are normotensive and have no symptoms of cardiac disease. Increased mortality is evident among type II diabetic patients with left ventricular failure with preserved ejection fraction also suggests its causative role diastolic dysfunction. **Objective:** To describe Left ventricular dysfunction in normotensive diabetic patients. **Method:** A Cross Sectional Study was undertaken in Comilla Medical College Hospital in 51 patients .29 diabetic patients with normal blood pressure (blood pressure ≤140/90 mmHg) who are not on anti-hypertensive medications and 22 healthy controls enrolled into the study. All patients and control subjects underwent transthoracic echocardiographic evaluation using GE LOGIQ V2 machine. The categorical variables described as frequencies and percentages, while continuous variables presented as medians and interquartile range (IQR) values and means and standard deviations. Continuous variables were compared using the Student's t- test, while categorical parameters were analyzed with the Chi-square test or two tailed Fischer's exact test as appropriate. A P-value of 0.05 or less was considered statistically significant. **Result:** Among 51 patients, 29 were cases and 22 were control. Male to female ratio was 1:1.7. The mean ages were 50.03±12.75 and 41.59±11.25 in case and control group respectively. The body mass index in two groups did not showed any significant difference (21.12±4.1 versus 20.91±3.60: P=0.374). The cases had a normal but significantly lower mean ejection fraction than controls (56.98±13.06 versus 62.48±7.73, respectively: P=0.033). Left ventricular diastolic filling pattern was abnormal in 17 (59%) cases and 6 (28%) in control group. The mean relative wall thickness (RWT) was higher in cases than controls. (0.47±0.11 versus .42±0.08; P= 0.014). Also the same difference observed in case of left ventricular mass index. (101.55±35.45 versus 86.98±28.01; P=0.053). The respondents were normotensive but abnormal filling pattern was observed in 17 (59%) and 6 (28%) in cases and control groups respectively which was significant. (P= 0.00018). **Conclusion:** Normotensive diabetic patients have asymptomatic diastolic dysfunction.

Keywords: Diabetes mellitus, diastolic dysfunction.

J Com Med Col Teachers Asso July 2024; 28(2): 53-57

1. Dr Mohammad Ali
   Associate Professor, Department of Medicine
   Dhaka Medical College, Dhaka
2. Dr Md Hafizur Rahman
   Associate Professor, Department of Medicine
   Dhaka Medical College, Dhaka.
3. Dr Muhammad Kamruzzaman Khokan
   Associate Professor, Department of Medicine
   Satkhira Medical College, Satkhira
4. Dr Md Helalur Rahman
   Associate Professor, Department of Medicine
   Comilla Medical College, Cumilla
5. Dr Mohammad Haresur Rahman
   Assistant Registrar, Department of Medicine
   Comilla Medical College, Cumilla
6. Dr Md Belalul Islam
   Professor, Department of Medicine
   Shaheed Tajuddin Ahmad Medical College, Gazipur

Address of correspondence

Dr Mohammad Ali
Associate Professor, Department of Medicine
Dhaka Medical College, Email:mltn7@yahoo.com

Introduction:

The prevalence of diabetes mellitus (DM) is increasing globally.[1,2] It is projected that 366 million people will be diabetic in 2030, 290 millions of whom will be living in developing countries.[3,4] According to WHO report, 2016, 8% (12.88 million) of total population of Bangladesh was affected by diabetes whereas 3% of total deaths of all-ages occurred due to diabetes[5]. Type II DM is a risk factor for cardiovascular disease and cardiovascular complications are a major cause of mortality and morbidity in diabetic patients.[7] Diabetes mellitus (DM) enhances coronary atherosclerosis and impairs microcirculation leading to left ventricular (LV) dysfunction. Ramifications of DM in the coronary circulation are quite broad. DM causes development of atheromatic plaques in coronary arteries, which leads to a narrowing of intravascular lumen and to thrombus formation. On the other hand, microcirculatory impairment is caused by the toxic effect of free radicals that are formulated due to persistent hyperglycemia and might provoke arteriolar

DOI:https://doi.org/10.3329/jcomcta.v28i2.77981

perivascular myocardial fibrosis, capillary obstruction and finally endothelial dysfunction[8]. Insulin resistance and glycemic dysregulation have detrimental effects on the systolic and diastolic function of left ventricle. Cardiac alterations in patients suffering from DM, without overt coronary artery disease, are referred as diabetic cardiomyopathy. Development of diabetic cardiomyopathy is a gradual process, which consists of the following alterations. Initially, thickness of left ventricular walls increases and left ventricular compliance declines. As a result, diastolic function is impaired and left ventricular end-diastolic pressure rises. Progressively, left ventricular volumes increase and left ventricular deformation deteriorates. Finally, heart failure syndrome occurs. As a result, diabetes has an important clinical impact in the development of cardiovascular adverse events[9]. Left ventricular dysfunction, increased left ventricular wall thickness, increased left ventricular mass, and specific diabetic cardiomyopathy are some of the cardiovascular complications associated with diabetes.[10] Left ventricular diastolic dysfunction has been demonstrated in diabetic patients who are normotensive and have no symptoms of cardiac disease.[11,12] Increased mortality among type II diabetic patients with heart failure with normal ejection fraction also suggests a role for diastolic heart failure.[13] The aim of this study was to determine the prevalence of left ventricular dysfunction in diabetic patients and to compare it with that of healthy adult Bangladeshi attended at Medicine Outpatients Department, Comilla Medical college Hospital, Cumilla.

Echocardiography is a time-sparing and cost-effective method that provides accurate and reproducible diagnostic and prognostic information in patients with DM[14]. The application of two-dimensional, doppler echocardiography help us to interrogate cardiac function in diabetics[15]. Recent data show that deterioration of LV diastolic function is quite usual among patients with DM, regardless of clinical status [15]. This means that asymptomatic diabetics manifest subclinical myocardial dysfunction and are prone to the development of clinical syndrome of heart failure, which has adverse impact on their prognosis. Consequently, echocardiographic assessment in a timely manner is critical for the optimal management of patients with DM in order to detect such subclinical abnormalities. Echocardiographic abnormalities are present in diabetics, despite the fact that symptoms or clinical characteristics do not mandate echocar diographic assessment. Jorgensen et al. studied 1030 patients with DM type 2 and revealed remarkable abnormalities through echocardiographic assessment. More precisely, in half of these patients, researchers unveiled diastolic dysfunction with normal or elevated end-diastolic pressure, left atrial dilatation or LV hypertrophy. These findings were not associated with patient's clinical profile and, as a result, clinical details could not discriminate subjects with deteriorated diastolic function, as assessed by echocardiography. Thus, it is implied that echocardiographic assessment should be an essential screening tool for diabetic patients, regardless of their clinical characteristics[17].

Methodology:

A Cross Sectional Study was undertaken in51 patients.DM Of them 29 patients with normal blood pressure (blood pressure ≤140/90 mmHg) and are not on anti-hypertensive medications who will give informed consent will be enrolled into the study. 22 apparently healthy adults matched for age, sex, and body mass index were recruited for comparison. All patients and control subjects undergo trans thoracic echocardiographic evaluation using GE LOGIQ V2 machine. Normotensive type II DM patient were included in this study. Symptoms attributed to left ventricular dysfunction, hypertensive patient, history of coronary artery disease, congenital heart disease, valvularheart disease, pregnancy, unwilling to give consent.The variables analyzed in the study will divided into categorical and continuous variables. The categorical variables will be described as frequencies and percentages, while continuous variables will be presented as medians and interquartile range (IQR) values and means and standard deviations. Continuous variables were compared using the Student's t- test, while categorical parameters were analyzed with the Chi-square test or two tailed Fischer's exact test as appropriate. A P-value of 0.05 or less was considered statistically significant. All statistical analyses will be performed using Statistical Package for Social Sciences (IBM SPSS Statistics 26.0)

Result:

Total 51 patients were enrolled. Among them 29 were cases and 22 were control. Male to female ration was 1: 1.7. The mean ageswere 50.03±12.75 and 41.59±11.25 in case and control group respectively. The mean fasting blood glucose and HbA1c were 9.82±4.45 and 9.87±2.89 respectively.

DOI:https://doi.org/10.3329/jcomcta.v28i2.77981

Table-I: Baseline characteristics

Characteristics	Case	Control
Age	50.03±12.75	41.59±11.15
Sex (M:F)	1:1.7	1:1.69
Height (cm)	156.65±7.47	156.77±7.96
Weight (kg)	52.76± 11.17	51.40±11.80
BMI (kg/m2)	21.12±4.1	20.91±3.60
BSA (m2)	1.5±0.18	1.49±0.19
FBS (mmol/L)	9.82±4.45	5.41±0.87
SBP (mmHg)	128.62±10.59	126.14±10.57
DBP (mmHg)	70.52±8.38	75.41±6.35
HbA1c (%)	9.87±2.89	6.12±0.73
Left Atrium (mm)	33.99±4.83	32.52±3.69
E velocity (m/s)	0.62±0.18	0.78±0.16
A velocity	0.74±0.11	0.66±0.16
E/A ratio	1:1.8	1.18 : 1
Dec. Time (ms)	165.96±54.55	174.09±38.15
EF(%)	56.98±13.06	62.48±7.73
LVMI	101.55±35.45	86.98±28.01
LVPWd (mm)	10.21±1.92	8.93±1.77
LVIDd (mm)	43.7±6.35	43.42±5.97
RWT	0.47±0.11	0.42±0.08

Body surface area(BSA), Fasting blood sugar (FBS), Systolic blood pressure(SBP),Diastolic blood pressure, (DBP), Peak velocity blood flow from left ventricular relaxation in early diastole (E velocity), Peak velocity flow in late diastole caused by atrial contraction (A velocity), Deceleration time (Dec,Time), Ejection fraction (EF), Left ventricular mass index (LVMI), Left ventricular posterior wall thickness (LVPWd), Left ventricular internal end diastolic diameter (LVIDd), Relative wall thickness (RWT)

The mean systolic and diastolic blood pressure were normal in both groups. The body mass index in two groups did not showed any significant difference although the mean BMI of case was more than that of controls. (21.12±4.1 versus 20.91±3.60: P=0.374)

Table-II: Demographic characteristics in subjects and controls

Variables	Subjects	Controls	P-value
Mean age (years)	50.03±12.75	41.59±11.15	0.0076
Mean BMI (kg/m2)	21.12±4.1	20.91±3.60	0.374
Mean SBP (mmHg)	128.62±10.59	126.14±10.57	0.203
Mean DBP (mmHg)	70.52±8.38	75.41±6.35	0.011

The cases had a normal but significantly lower mean ejection fraction than controls (56.98±13.06 versus 62.48±7.73, respectively: P=0.033). The mean early to late diastolic filling ratio (E/A ratio) in cases was 0.78±0.25 and 1.25±0.39 in controls. Left ventricular diastolic filling pattern was abnormal in 17 (59%) cases and 6 (28%) in control group. The mean relative wall thickness (RWT) was higher in cases than controls. (0.47±0.11 versus .42±0.08; P= 0.014). Also, the same difference observed in case of left ventricular mass index. (101.55±35.45 versus 86.98±28.01; P=0.053)

Table-III: Indices of Left Ventricular structure and function.

Indices	Subjects	Controls	P-value
Mean E/A ratio	0.78±0.25	1.25±0.39	1.629
Mean DT (ms)	165.96±54.55	174.09±38.15	0.267
Mean E (m/s)	0.62±0.18	0.78±0.16	0.0006
Mean A (m/s)	0.74±0.11	0.66±0.16	0.043
Mean EF (%)	56.98±13.06	62.48±7.73	0.033
MeanLVMI (kg/m2)	101.55±35.45	86.98±28.01	0.053
Mean RWT	0.47±0.11	0.42±0.08	0.014

All the respondents were normotensive but abnormal filling pattern was observed in 17 (59%) and 6 (28%) in cases and control groups respectively which was significant. (P= 0.00018)

Table-IV: Comparison of number of patients and controls with normal and abnormal diastolic filling pattern (by Chi Square test)

Filling pattern	Cases	Controls	P-value
Normal E/A >1	12(41%)	16(72%)	
Abnormal E/A <1	17(59%)	6(28%)	0.00018

Discussion:

Total 51 patients were enrolled. Among them 29 were cases and 22 were control. Male to female ratio was 1: 1.7. The mean ages were 50.03±12.75 and 41.59±11.25 in case and control group respectively. There was significant age difference observed between two groups. (P= 0.0076). Mean body mass index was 21.12 ± 4.1kg/m2 in patients and 20.91.09 ± 3.60 kg/m2 in controls. Mean ejection fraction was 56.98% ± 13.06% and 62.48% ± 7.73% in patients and controls,

DOI:https://doi.org/10.3329/jcomcta.v28i2.77981

respectively (P, 0.001). Fourteen (15.56%) patients had ejection fraction less than 55% compared to four (4.44%) in controls (P, 0.001; odds ratio = 3.96). Impaired diastolic function was found in seventeen (59%) of patients compared to twenty eight (6%)of controls (P, 0.00018). The left ventricular mass index was also higher in patients than in controls (101.55 ± 35.45 g/m2 versus 86.98 ± 28.01g/m2; P = 0.05).

There was significant age difference observed between two groups. (P= 0.0076). The role of elevated blood sugar in the causation of various cardiovascular diseases has been investigated by several researchers.[9,15,16] These studies have shown that DM causes structural and functional abnormalities that are independent of the effect of atherosclerosis and these abnormalities contribute significantly to adverse cardiovascular events8.Chronic hyperglycemia in DM expresses its toxicity by forming non-enzymatic glycation of tissue macromolecules, such as proteins, lipids, and deoxyribonucleic acid (DNA) to form irreversibly bound advanced glycated end products[17]. Such products have been found to accumulate in tissues such as the heart[18]. Abnormalities in cardiac structure of diabetic patients included a significant increase in LVMI and relative wall thickness compared to normal controls. The left ventricular mass index was also higher in patients than in controls (101.55 ± 35.45 g/m2 versus 86.98 ± 28.01g/m2; P = 0.05).

This change in cardiac structure has been postulated to be due to deposition of glycoprotein, fibrosis, and presence of microangiopathy.[8,19] In the diabetic heart, there is an increase in apoptosis leading to increased collagen deposition in a diffuse manner as a result of replacement fibrosis and connective tissue proliferation. Ultimately there is decreased ventricular compliance.[20] Left ventricular diastolic dysfunction has been proposed to be the first stage of the putative "diabetic cardiomyopathy".[21] A reduced E/A ratio has been shown to be independently associated with increased all-cause mortality as well as cardiovascular mortality.[22] These structural abnormalities may lead to increased wall stress, increased oxygen demand, ischemia, and the development of left ventricular diastolic dysfunction.[8] The prevalence of left ventricular diastolic dysfunction in these normotensive and asymptomatic diabetics without previous history of cardiac disease was quite high compared to controls (59% versus 28) but is comparable to findings by other workers using similar Doppler methods for assessing left ventricular function1.[7]

The present study also demonstrated a significant reduction in mean left ventricular ejection fraction in diabetics compared to healthy controls (56.98% versus 62.48%; P, 0.003), although the mean values were normal in both groups. This significant reduction in mean ejection fraction signifies early left ventricular systolic dysfunction in these diabetic patients despite absence of symptoms of cardiovascular disease. A reduced ejection fraction (55%) of 15.65% was found in diabetics compared to only 4.4% of control subjects. The findings of systolic dysfunction and increased prevalence of diastolic dysfunction has also been previously demonstrated[9]. Diastolic dysfunction was found in 28% of controls. This is probably because overweight and obese controls, who had to be matched with the overweight and obese in the diabetic group, were used in the study. Obesity is known to increase the risk of diastolic dysfunction and increase LVMI. This study is, however, different from most previous studies in Nigeria as it excluded hypertensive diabetic patients and assessed both systolic and diastolic function. Patients were also closely matched with controls for age, sex, and body mass index.

Conclusion:

Normotensive diabetic patients have asymptomatic diastolic dysfunction. Echocardiography with assessment of diastolic dysfunction will be helpful in reducing cardiovascular mortality and morbidity in normotensive diabetic patients.

Limitations: In this study sample size was small and coronary angiogram to rule out coronary artery disease was not done due to lack of facility

Disclosure: There is no conflict of interest in this work.

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