EFFECT OF GLYCAEMIC STATUS ON LEFT VENTRICULAR DIASTOLIC FUNCTION IN NORMOTENSIVE TYPE 2 DIABETIC PATIENTS

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Background: Diabetes is associated with Left ventricular diastolic and systolic dysfunction known as diabetic cardiomyopathy. Echocardiography is helpful for the detection of diastolic dysfunction and Echocardiographic screening for asymptomatic diabetic cardiomyopathy should be performed in all asymptomatic diabetic subjects. Identification of diabetic cardiomyopathy should result in the initiation of therapies to prevent the progression of diabetic cardiomyopathy. The objectives of this Descriptive case series was to determine the effect of glycaemic status on left ventricular diastolic function in normotesive type 2 diabetic patients. **Methods:** This study was performed at Cardiology department, PGMI Lady Reading Hospital, Peshawar from March 2007 to September 2007. Sixty normotesive type 2 diabetic patients were enrolled, 20 well control, 20 moderately control and 20 poorly control (Group-3). Main outcome measures was Left ventricular diastolic function determined by Echocardiography. **Results:** Out of 60 patients there were 32 (53.3%) males and 28 (46.7%) females. Mean E/A ratio in Group 1 was 1.38±0.29, in Group 2 was 1.16±0.39 and in Group 3 was 0.60±0.15 (p<0.05). IVRT in Group-1 was 91±7.87 mSec, in Group-2 was 100±7.83 mSec and in Group-3 was 109±6.45 mSec (p<0.05). DT in Group 1 was 207.2±12.6 mSec, in Group 2 was 218±11.3 mSec and in Group 3 was 229.7±9.52 mSec (p<0.05). Mean Em at mitral annulus in Group-1 was 0.14±0.04 m/Sec, in Group-2 was 0.11±0.04 m/Sec and in Group-3 was 0.10±0.03 m/Sec (p=0.002). Left ventricular diastolic dysfunction was documented in 4 (25%) patients in Group-1, 9 (45%) patients in Group-2 and 16 (80%) patients in Group-3 (p<0.05). There was Strong correlation between HbA1c level and diastolic indexes (p<0.05). **Conclusion**: Diastolic dysfunction is more frequent in poorly controlled diabetic patients and its severity is correlated with glycaemic control.

Keywords: Type 2 diabetes mellitus, left ventricular diastolic function, Deceleration time

INTRODUCTION

Diabetes mellitus is associated with increased incidence of cardiovascular diseases.[1] Diabetic patients have a higher incidence of congestive heart failure as compare to age matched non-diabetic subjects.[1] Several causative mechanisms for diabetic cardiomyopathy have been postulated including microangiopathy, autonomic nervous dysfunction, defecting cellular calcium transport as well as structural changes in myocardial intracellular proteins and accumulation of collagens leading to increased stiffening of the ventricular wall.[1] Diabetic cardiomyopathy is associated with increased cardiovascular mortality.[2]

Diastolic dysfunction comprises about 30 to 50% of all patients hospitalised for heart failure.[3] The dramatic increase in hospitalization for heart failure among the elderly can be largely attributed to this condition.[3] Diabetes mellitus is considering an important independent factor in developing diastolic dysfunction.[4]

Doppler echocardiography is one of the most useful clinical tools for the assessment of left ventricular diastolic function.[5] Doppler indices of left ventricular filling are use not only for diagnostic purposes but also for establishing prognosis and evaluating the effect of treatment.[5] Tissue Doppler imaging has provided useful insight in the study of diastolic function.[5] Tissue Doppler imaging has been shown to provide an accurate assessment of diastolic function and appears to be relatively insensitive to the effects of pre-load compensation.[5] Tissue Doppler imaging has markedly improved the echocardiographic detection of diastolic dysfunction in asymptomatic patients with Type 2 diabetes mellitus.[6]

Left ventricular diastolic dysfunction may represent the first stage of diabetic cardiomyopathy reinforcing the importance of the early examination of diastolic function in individual with diabetes.[7] Several studies have shown a correlation between glycaemic control and left ventricular diastolic dysfunction with associated improvement in cardiac function after adequate treatment.[7] It has been shown that intervention such as aerobic exercise could beneficially influence diastolic function, the early and accurately detection of left ventricular diastolic dysfunction might have therapeutic implication.[7]

Therefore, this study was conducted to determine the effect of glycaemic status on left ventricular diastolic function in normotensive Type 2 diabetic patients. This study highlights the problem of left ventricular diastolic dysfunction to be taken in consideration while dealing patients with Type 2 diabetes mellitus who were free from symptoms of heart failure. Documentation of diastolic dysfunction

should result in the initiation of therapy to prevent advancement to heart failure.

MATERIAL AND METHODS

This Descriptive case series study was conducted from March 2007 to September 2007. All normotensive Type 2 diabetic patients free from complications of diabetes presenting in out patient department (OPD) of Lady Reading Hospital were included. Based on strict criteria, patients were excluded from the study if they had a history of myocardial infarction (previous or recent), congestive heart failure, valvular heart disease, hypertension, cardiomyopathy, known coronary artery disease, connective tissue disease, thyroid dysfunction and renal disease.

Informed consent was taken from all patients. Complete history and full physical examination was done on every patient included in the study. The history highlighted the duration of diabetes, complications, ischemic heart disease, hypertension, heart failure and drug history.

Diabetic status was defined on the basis of HbA1c level. Three groups were made on the basis of HbA1c, Group-1 HbA1c <8, Group-2 HbA1c 8–10 and Group-3 >10. Resting ECG and Exercise tolerance test was performed on every patient to exclude ischemia. The study patients were undergone echocardiography (using Acuson CV70 Siemens system equipped with TDI technology). All patients were examined in the left lateral position. Measurements of the different chambers of the heart were done according to the recommendations of the American Society of Echocardiography. Wall motion abnormalities were detected; patients with wall motion abnormities were excluded from the study.

From apical four-chamber view pulse wave Doppler Mitral inflow velocities was recorded by placing sample volume at the tips of the Mitral valve. The transmitral peak early diastolic velocity (E), peak late diastolic velocity (A), E wave deceleration time (DT) and E/A ratio were measured. Isovolumic relaxation time (IVRT) was recorded from apical 5-chamber view by simultaneously recording of the mitral and aortic flows.

Tissue Doppler Imaging was performed by activating the TDI function. To assess the diastolic function two velocities peak early diastolic velocity (Em) and peak late diastolic velocity (Am) at Mitral annulus was determined. Four different sites on the mitral annulus i.e. Lateral, Anterior, Septal and Inferior were selected. For lateral and septal sites apical 4-chamber view and for anterior and inferior sites apical 2-chamber views were utilised. Mean values from above four sites were used to assess global diastolic left ventricular function.

The normal cut-off values for Doppler echocardiography and Tissue Doppler Imaging were adopted from the guidelines of American Society of Echocardiography. Impaired relaxation was defined as deceleration time >220 msec, Isovolumic relaxation time > 100 mSec, E/A <1. Pseudo normal was defined as deceleration time 150–200 msec, Isovolumic relaxation time 60–100 mSec, E/A >2. Restrictive filling was defined as deceleration time <150 mSec, Isovolumic relaxation time <60 mSec, E/A ratio >2. Diastolic dysfunction on Tissue Doppler imaging was defined as mean early diastolic mitral annulus velocity <0.11 m/Sec.[8]

Data were analysed using SPSS version 10. The variables were age, sex, duration of diabetes mellitus, Ejection fraction, Fractional shortening, Mitral inflow velocities, Isovolumic relaxation time and Mitral E wave deceleration time on Doppler Echocardiography and the Mean diastolic mitral annular velocities on TDI. Data were expressed as Mean±SD. Differences between groups of participants were assessed by analysis of variance followed by the Scheffe post hoc test. Chi square test was applied for comparison of Left ventricular diastolic dysfunction. A p-value of <0.05 was considered significant. Pearson's correlation analysis was used to measure the strength of association between pairs of variables.

RESULTS

A total of 60 normotensive type 2 diabetic patients were enrolled, 20 well control (Group-1, HbA1c <8), 20 moderately control (Group-2, HbA1c 8–10) and 20 poorly control (Group-3, HbA1c >10).

Overall males were more 32 in number, i.e., 53.3% as compared to females 28 in numbers, i.e., 46.7%. The basic characteristics of the patients are shown in Table-1.

Mean age in Group-1 was slightly lower than Group-2 and 3 but the difference was not statistically significant.

There was no statistical significance difference between Group-1 and Group 2 and Group 2 and 3 regarding duration of diabetes, but there was significance difference between Group 1 and 3 (p=0.04).

The 2-D echocardiographic characteristic like LVESD, LVEDD, IVS, PW, EF and FS were compared between three groups with no difference of statistical significance (Table-2).

Regarding mean LA diameter there was no statistical significance between Group-1 and 2, but there was statistical significance difference between Groups-1 and Group-3 (p=0.001) and between Groups-2 and Group-3 (p=0.001) (Table-2).

Conventional Doppler and Tissue Doppler Imaging parameter were recorded and presented in Table-3.

Mean E wave was significantly difference between Group-1 and Group-3 (p=0.0001) and between Group-2 and Group-3 (p=0.0001) but not significantly different between Group 1 and Group 2 (p=0.05) (Table-3).

Regarding mean A wave there was no statistical significance between Group 1 and Group 2 (p=0.28), but there was statistical significance of between Group 1 and Group 3 (p=0.0001) and significance difference between Group 2 and Group 3 (p=0.01) shown in Table-3.

Mean E/A ratio was significantly difference between Group-1 and Group-3 (p=0.0001) and between Group-2 and Group-3 (p=0.001) but not significantly different between Group 1 and Group 2 (p=0.1) (Table-3).

Regarding mean IVRT (mSec) there was significance difference between Group 1 and Group 2 (p=0.001), significance difference between Group 1 and Group 3 (p=0.0001) and significance difference between Group 2 and Group 3 (p=0.002) (Table-3).

Mean DT wave was significantly difference between Group-1 and Group-2 (p=0.01) and between Group-1 and Group-3 (p=0.001) and between Group-2 and Group-3 (p=0.008) shown in Table-3.

Regarding mean Em (m/Sec) there was no significance difference between Group-1 and Group- 2 (p-value 0.05), but significance difference between Group-1 and Group-3 (p-value 0.0001) and significance difference between Group-2 and Group-3 (p=0.002) shown in Table-3.

Left ventricular diastolic dysfunction was detected in 5 patients (25%) in Group 1, 9 patients (45%) in Group 2 while 16 patients in Group 3 had Left ventricular diastolic dysfunction (80%) with p<0.05 (Table 3).

Diastolic filling parameters of the patients having left ventricular diastolic dysfunction were compared (Table 4).

Regarding E/A ratio (in patients having LVDD) there was significance difference between Group 1 and Group 2 (p=0.01), significance difference between Group 1 and Group 3 (p=0.0001) and significance difference between Group 2 and Group 3 (p=0.001) shown in Table-4.

Regarding IVRT (m/Sec) (in patients having LVDD) there was significance difference between Group 1 and Group 2 (p=0.03), significance difference between Group 1 and Group 3 (p=0.001) and no significance difference between Group 2 and Group 3 (p=0.08) shown in Table-4.

Regarding DT (m/Sec) (in patients having LVDD) there was no significance difference between the groups (Table-4).

Regarding Em (m/Sec) (in patients having LVDD) there was significance difference of p<0.05 between all Groups (Table-4).

HbA1c had a negative correlation between E wave (-0.73, p=0.0001), E/A ratio (-0.64, p=0.0001) and Em wave (-0.63, p=0.0001). HbA1c level had positive correlation with A wave (0.52, p=0.0001), IVRT (0.709, p=0.0001), DT (0.642, p=0.0001) and LA size (0.61, p=0.0001) shown in Table-5.

Table-1: Clinical characteristic of the subjects.

Characteristics	Group 1	Group 2	Group 3	*p*-value Group 1 vs Group 2	*p*-value Group 1 vs Group 3	*p*-value Group 2 vs Group 3
Age	51.1±8.52	57.3±11.61	57.25±9.62	0.05	0.98	0.09
Systolic blood pressure mmHg	121.9±9.82	120.1±10.1	123.4±6.25	0.57	0.09	0.08
Diastolic blood pressure	69.80±6.95	73.9±8.93	69.7±7.88	0.11	0.33	0.30
Body mass index (kg/m2)	22±6	23±9	23±8	0.45	0.45	0.45
Heart rate	65±8	66±7	69±10	0.06	0.78	0.91
Duration of diabetes.	8.5±2.16	9.05±2.8	10.75±3.27	0.49	0.04	0.08

Table-2: Echocardiographic characteristics of the subjects.

Characteristics	Group 1	Group 2	Group 3	*p*-value Group 1 vs Group 2	*p*-value Group 1 vs Group 3	*p*-value Group 2 vs Group 3
LA (cm)	3.29±0.6	3.67±0.59	4.48±0.79	0.17	0.001	0.001
LVESD (cm)	3.95±0.49	3.07±0.5	2.98±0.53	0.37	0.37	0.5
LVEDD (cm)	4.3±0.06	4.41± 0.67	4.41±0.67	0.54	0.35	0.37
IVS (cm)	0.81±0.13	0.84±0.13	0.86±0.17	0.23	0.8	0.9
PW thickness (cm)	0.82±0.15	0.80±0.10	0.88±0.19	0.09	0.09	0.09
LV EF (%)	65.8±2.65	66.1±2.67	65.92±2.78	0.77	0.09	0.06
LV FS (%)	30.8±0.9	31.1±1.1	30.7±0.96	0.37	0.78	0.56

Table-3: Conventional Doppler and Tissue Doppler imaging parameters of the subjects.

Characteristic	Group 1	Group 2	Group 3	*p*-value		
				Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
E wave (m/Sec)	0.68±0.03	0.62±0.07	0.48±0.08	0.05	0.0001	0.0001
A wave (m/Sec)	0.51±0.11	0.58±0.15	0.60±0.15	0.28	0.0001	0.01
E/A ratio	1.38±0.29	1.16±0.39	0.60±0.15	0.1	0.0001	0.001
IVRT (mSec)	91.25±7.87	100.3±7.83	109±6.45	0.001	0.0001	0.002
DT (mSec)	207.2±12.6	218.2±11.32	229.7±9.52	0.01	0.001	0.008
Em value (mSec)	0.14±0.04	0.11±0.04	0.10±0.03	0.05	0.0001	0.002
LV diastolic dysfunction	5	9	16	0.01	0.001	0.01

Table-4: Conventional Doppler and Tissue Doppler imaging parameters of patients having LV diastolic dysfunction.

Characteristic	Group 1	Group 2	Group 3	*p*-value		
				Group 1 vs Group 2	Group 1 vs Group 2	Group 2 vs Group 3
E wave	0.5±0.25	0.5±0.07	0.4±0.05	0.01	0.01	0.01
A wave	0.7±0.008	0.7±0.04	0.7±0.007	0.04	0.02	0.04
E/A ratio	0.9±0.04	0.7±0.01	0.5±0.08	0.01	0.0001	0.001
IVRT	103.0±2.24	108.22±1.39	111.56±4.34	0.03	0.001	0.08
DT	227.2±2.68	230.22±2.64	232.94±7.72	0.67	0.19	0.56
Em wave	0.08±0.008	0.06±0.007	0.05 ±0.01	0.04	0.001	0.001

Table-5: Strength of association between pairs of variables

		HbA1c level
Peak early mitral inflow velocity E wave, m/Sec	Pearson Correlation	-0.743
	Sig. (2-tailed)	0.000
Peak late mitral inflow velocity A wave, m/Sec	Pearson Correlation	0.523
	Sig. (2-tailed)	0.000
Mitral E/A ratio	Pearson Correlation	-0.644
	Sig. (2-tailed)	0.000
Isovolumic relaxation time IVRT, m/Sec	Pearson Correlation	0.709
	Sig. (2-tailed)	0.000
Mitral E deceleration time DT, m/Sec	Pearson Correlation	0.642
	Sig. (2-tailed)	0.000
Mean early diastolic velocity Em at mitral annulus, m/Sec	Pearson Correlation	-0.631
	Sig. (2-tailed)	0.000
Left ventricular diastolic dysfunction	Pearson Correlation	0.449
	Sig. (2-tailed)	0.000
Left atrium diameter	Pearson Correlation	0.614
	Sig. (2-tailed)	0.000

DISCUSSION

This present study was conducted to highlight that diabetic patients with worse glycemic control are at an increased risk of developing sever Left ventricular diastolic dysfunction.

In this study higher prevalence of asymptomatic diastolic dysfunction in type 2 diabetes mellitus was found, even in the absence of hypertension and cardiac disease. These results support the concept of a specific subclinical diabetic cardiomyopathy, which may be related to glycaemic control.

In this study three groups were made on the basis of HbA1c level and these groups were not statistical different in age, gender and blood pressure. Wojciech *et al* showed no statistical significance difference between age, gender, blood pressure, smoking history and body mass index, proved that there are some other reasons (mechanism) behind the diabetic cardiomyopathy.[9]

LA was enlarged in poorly controlled diabetic patients (Group-3, 4.48±0.79) as compared to patient with well and moderately controlled diabetic status {(Group-1, 3.29±0.6), (Group-2, 3.67±0.59)} with statistical significance ($p<0.05$). Miguel *et al* showed that the mean LA size was more in diabetic patients whose metabolic status was not well controlled (40±3) as compare to well controlled (39±3).[9] Those patients with poor glycaemic controlled had worse Left ventricular diastolic dysfunction in the form of pseudonormal pattern, these patients had higher level of HbA1c level with $p<0.001$.[10]

Mean Peak early mitral inflow velocity E wave (m/Sec) was lowest in patients whose diabetic condition was poorly controlled (Group-3, E wave=0.48±0.08) as

compare to patients whose diabetic condition was well and moderately controlled {(Group-1, E wave=0.68±0.03), (Group-2, E wave=0.62±0.07)} with significance statistical difference. The Strong Heart Study documented lowest E wave in diabetic patients as compare to non-diabetic patients (p<0.05). This study demonstrated that patients whose diabetic condition was well-controlled shows high E wave as compare to patients whose diabetic condition was not well controlled.[11]

Mean Peak late mitral inflow velocity A wave (m/Sec) was highest in patients whose diabetic condition was poorly controlled (Group-3, A wave=0.60±0.15) as compare to patients whose diabetic status was well and moderately controlled {(Group-1, A wave=0.51±0.11), (Group-2, A wave=0.58±0.15)} with significance statistical difference. The Strong Heart Study results showed the peak A wave was higher in diabetic patients than in non diabetic patients.[11] This study document that A wave is higher in patients with poor metabolic control than patients with well control of diabetes, the diabetic status was defined on the basis of HbA1c level and Fasting blood sugar. Mehrdad *et al*, proved that the mean peak pulse Doppler A wave velocity was higher in diabetic group (when compare with non diabetic group, p<0.05) with positive correlation with HbA1c level.[12]

The E/A ratio in this study showed stepwise decrease from well controlled diabetic status (Group-1, 1.38±0.29) to those with either moderately controlled (Group-2, 1.16±0.39) to poorly controlled diabetic status (Group-3, 0.60±0.15) with statistical significance difference (p<0.05) between well control diabetic patients and poorly control diabetic patients. The E/A ratio in Strong Heart Study showed a stepwise decrease from the normotensive non-diabetic group to those with either condition to the combined hypertensive diabetic group.[11] The E/A ratio was more decrease in patients having worse glycaemic control (as indicated by higher levels of haemoglobin A1C and fasting glucose) than in patients having well controlled of diabetic status.[11] Mehrdad *et al*, showed a negative correlation of HbA1c with E/A ratio.[12]

Mean IVRT in this study showed a stepwise decrease from the poorly controlled diabetic group (Group-3, 109±6.45) to those with moderately controlled diabetic group (Group-2, 100±7.83) to the well-controlled diabetic group (Group-1, 91.25±7.87) (p<0.05) between all groups. Mehrdad *et al*, showed a positive correlation of HbA1c with IVRT.[12]

Mean mitral E wave DT was higher in poorly controlled diabetic group (Group-3 229.7±9.52) and moderately controlled diabetic group (Group-2, 218.2±11.32) as compare to well controlled diabetic group (Group-1, 207±12.6) (p<0.05) between all groups. In Strong Heart Study DT was longer in diabetic group (201±2.7) as compare to non diabetic group (197±2.5) p-value <0.05.[11] The DT was in the range of LVDD (that is longer) in patients whose metabolic control was not optimally controlled when compare to those whose metabolic status was optimally controlled define on the basis of HbA1c level and Fasting Blood Sugar.

Mean Em velocity at mitral annulus showed a stepwise decrease from well controlled diabetic group (Group-1, 0.14±0.04) to those with moderately controlled diabetic group (Group-2, 0.11±0.04) to poorly controlled diabetic group (Group-3, 0.10±0.03) (p<0.05) when comparing poorly controlled diabetic group (Group-3) with either well controlled diabetic group (Group-1) or moderately controlled diabetic group (Group-2). Wojciech *et al*, proved the superiority of Tissue Doppler Imaging over the conventional Doppler echocardiography. In this study Em was lower in diabetic group (0.6±0.1) than non-diabetic group (0.8±0.1) (p=0.01). This study highlights the noxious effect of DM on myocardial function demonstrated as impairment in systolic and diastolic function.[9] Among the diabetes mellitus group, HbA1c had a negative correlation with Em (p=0.031).[13]

In Group 3 Left ventricular diastolic dysfunction was found in 80% patients comparing to 45% of patients in Group-2 and 25% of patients in the Group-1 with statistical significant differences (p<0.05). Diastolic function of the left ventricle in patients with diabetes is dependent on HbA1c level.[14–16] Markuszewski *et al*, concluded that diastolic function of the left ventricle in patients with diabetes is dependent on HbA1c level.[16] In this study diastolic dysfunction was observed in 43% of patients with HbA1c >6.1% comparing to 4.5% in the group with HbA1c level <6.1%.[17]

In this study asymptomatic Left ventricular diastolic dysfunction is common in patients with diabetes and that its severity is correlated with glycemic control. These results correlate well with the published data.[13]

In this study there is negative correlation of HbA1c level with E wave, E/A, and Em and positive correlation with A wave, IVRT, DT and LA size (p=0.0001). These results correlate well with results in a study conducted by Mehdi *et al.*[13] Among the diabetes mellitus group HbA1c level had negative correlation with Em (-0.43, p=0.003) and E/A ratio (p=0.01), positive correlation with A wave (p=0.005), E wave (p=0.2), IVRT (p=0.0001) and DT (p=0.03).[13]

Hyperglycaemia influences heart metabolism, the production of advanced glycosylation end products, oxidative stress, and

protein kinase C activation.[18,19] The relation between glycaemic control and diastolic indexes in our study supports the hypothesis that hyperglycaemia by itself can lead to subclinical cardiomyopathy. Our results indicate that diabetic patients with worse glycaemic control are at an increased risk of early diastolic dysfunction.

Further study is needed to determine whether intensification of glycaemic control improves diastolic parameters.

CONCLUSION

Diabetes and control of glycaemic status has direct effect on left ventricular diastolic function. In this study we found higher frequency of diastolic dysfunction in Type 2 diabetic patients especially patients with worse glycaemic controlled even in the absence of hypertension and cardiac disease. The left ventricular diastolic function was more impaired in those diabetic patients having poor glycaemic control.

The prevalence of diabetic cardiomyopathy in type 2 diabetic patients is higher and diabetic cardiomyopathy is due to diastolic dysfunction caused by myocardial fibrosis, which occurs in response to hyperglycaemia. A definitive diagnosis of diabetic cardiomyopathy can be made by Echocardiographic techniques, and Echocardiographic screening for asymptomatic diabetic cardiomyopathy should be performed in all asymptomatic diabetic subjects. Identification of diabetic cardiomyopathy should result in the initiation of therapies to prevent the progression of diabetic cardiomyopathy to CHF.

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