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A Study of Relation of Hba1c to Left Ventricular Diastolic Dysfunction in Patients with Type 2 Diabetes Mellitus and Without Overt Heart Disease

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Abstract
Introduction:*Diabetes is usually irreversible and, although patients can have a reasonablynormal lifestyle, its late complications result in reduced life expectancy and majorhealth costs.* ***Material & Methods:****This was a prospective study done among all the patients with Type-2 Diabetes Mellitus individuals selectedfrom GENERAL MEDICINE out- patient and in-patient department in the Government General Hospital, Guntur.They were divided into two groups according to the Glycemic status one groupconsisted of HbA1C levels < 7, and the other group consisted of HbA1C levels > 7.All of them were subjectedto echocardiography.* ***Results****: In the present study, most of the participants belonged to >50 years age group. Out of the 50 participants in the study, 26 (52%) were male and 24(48%) werefemale. 14 participants out of 25 in group 1 were observed to have LV diastolic dysfunction. Out of which 11 (44%) were having grade 1 LVDD and 3(12%) were having grade 2 LVDD. 11 (44%) participants whose HBA1C was <7 were not diagnosed to have a LVDD.21 participants out of 25 in group 2 were observed to have LV diastolic dysfunction. Out of which 13 (52%) were having grade 1 LVDD and 8(32%) were having grade 2 LVDD. 4 (16%) participants whose HBA1C was >7 were not diagnosed to have a LVDD.****Conclusions****: In patients with type 2 diabetes without clinical evidence of heart disease and HbA1c >7, there was a diastolic dysfunction with higher trans mitral A/E ratio, more prolonged isovolumic relaxation time in comparison with patients with type 2 diabetes without clinical evidence of heart disease and hemoglobin A1C<7 subjects.*

Keywords*: type 2 diabetes mellitus, HbA1c, left ventricular diastolic dysfunction, complications*

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I. Introduction

Diabetes mellitus is a syndrome of chronic hyperglycemia due to relativeinsulin deficiency, resistance, or both.Globally, an estimated 422 million adults are living with diabetes mellitus,according to the latest 2016 data from the World Health Organization (WHO)[1].

Diabetes prevalence is increasing rapidly; previous 2013 estimates from theInternational Diabetes Federation put the number at 381 million people havingdiabetes[2]. The number is projected to almost double by 2030[3]. Type 2diabetes makes up about 85-90% of all cases[4,5]. Increases in the overall diabetesprevalence rates largely reflect an increase in risk factors for type 2, notably greaterlongevity and being overweight or obese[1].

Diabetes is usually irreversible and, although patients can have a reasonablynormal lifestyle, its late complications result in reduced life expectancy and majorhealth costs. These include macro vascular disease, leading to an increasedprevalence of coronary artery disease, peripheral vascular disease and stroke, andmicro vascular damage causing diabetic retinopathy and nephropathy.

CARDIOVASCULAR MORBIDITY AND MORTALITY:

Cardiovascular disease is increased in individuals with type 1 or type 2 DM.The Framingham Heart Study revealed a marked increase in PAD, CHF, CAD, MI,and sudden death (risk increase from one- to fivefold) in DM. The prognosis forindividuals with diabetes who have coronary artery disease or MI is worse than fornon-diabetics. CHD is more likely to involve multiple vessels in individuals with DM.After controlling for all known cardiovascular risk factors, type 2 DM increases thecardiovascular death rate twofold in men and fourfold in women.

The American Heart Association has designated DM as a "CHD riskequivalent," and type 2 DM patients without a prior MI have a similar risk forcoronary artery–related events as non- diabetic individuals

who have had a priorMI. The absence of chest pain ("silent ischemia") is common in individuals withdiabetes, and a thorough cardiac evaluation should be considered prior to majorsurgical procedures.

The increase in cardiovascular morbidity and mortality rates in diabetesappears to relate to the synergism of hyperglycemia with other cardiovascular riskfactors. In the UKPDS , the number of cardiovascular events in patients with type 2diabetes are not differ between the standard and intensively treated groups duringthe trial but were reduced at follow-up 17 years later (legacy effect) or (metabolicmemory).

EFFECTS OF DIABETES ON THE MYOCARDIUM

Both systolic and diastolic abnormalities have been demonstrated in patientswith Diabetes without symptomatic evidence of cardiovascular disease. Theseabnormalities correlate with glycemic control, duration of diabetes and evidence ofretinopathy/neuropathy.The observation that myocardial dysfunction is present in the absenceof coronary artery disease, valvular disease, and the sequelae of associatedcardiovascular risk factors. "Diabetic cardiomyopathy" This term was first used in1972 by Rubler et al, [6] describing myocardial dysfunction in patients with diabetesin the absence of coronary artery disease, hypertrophy, or valvular heart disease.

II. Material & Methods

The Clinical materials were of Type-2 Diabetes Mellitus individuals selectedfrom GENERAL MEDICINE out-patient and in-patient department in the Government General Hospital, Guntur.Informed consent was taken from thesubjects.Ethical committee approval was obtained for this study.

Study design: Prospective study

Study period: During the period of year 2018-2019.

About 100 patients were subjected to initial assessment it included throughclinical examination, routine blood investigation consisting of complete blood count,biochemistry investigation, ECG, estimation of HbA1c and echocardiography weredone from which 50 patients were included in the study.

Patients with following criteria are excluded from the study

Patients with abnormal resting ECG suggestive of ischemic heart disease or
bundle branch block etc.

Presence of co morbid disease known to influence Left ventricular
dysfunction: - Thyroid disease, Alcoholism and Hypertension.

Evidence of heart disease and clinical heart disease patient,

Peripheral vascular disease,Cigarette smoking and Dyslipidemia

Only patients who were in sinus rhythm, free from signs and symptomscongestive cardiac failure, Hypertension, Anemia, Ischemic heart disease wereincluded for this study.

They were divided into two groups according to the Glycemic status one groupconsisted of HbA1C levels < 7, and the other group consisted of HbA1C levels > 7.The number patients included in to each group were 25. All of them were subjectedto echocardiography done at the Department of Cardiology, GGH, Guntur.

Echocardiography was performed in the post absorptive phase.ESOATE equipment which has the capabilities of performing two dimensional, Mmode, Pulsed wave and continuous wave Doppler and color flow imaging was usedto obtain echo cardiogram images.

Phased array transducers 2.5 - 3.5 MHz frequencies were used to obtain 2-D / Mmode
echocardiography. Images were obtained with subjects in 30 degree lateral
decubitus position. All measurements were performed in the freeze images from all
the patients, good quality images suitable for the measurements and interpretations
were obtained and recorded.

For assessment of LV function the following parameters were calculated from the
M- mode echocardiogram obtained at the level of mitral valve chordae.

Left Ventricular VOLUME

Left Ventricular MASS

Left Ventricular GEOMETRY –ratio of LV mass to volume
i.e. relative wall thickness(RWT)

Left Ventricular FUNCTION: Diastolic Properties

1. Calculation of Early left ventricular inflow velocities(E),
2. Peak atrial contraction in Systole(a)
3. Calculation of E/a ratio and
4. Deceleration time (DT)
5. Iso volumic relaxation time (IVRT)

6. Left atrial size
LV ejection fraction was calculated using the following formula, EF= LVEDVLDESV/
LVEDV x 100
Reduction in E velocity increase over A velocity with E/A ratio of <1 and increase inleft atrial (LA) size with preserved Ejection Fraction (EF) were considered as theevidence of left ventricular diastolic dysfunction.
Echo cardiographic grading was done in diastolic dysfunction into four grades.

Data analysis:Descriptive statistics was done for all the data and were reported in terms of meanvalues and percentages .suitable statistical tests of comparison were done.The datawas analyzed using SPSS version 16 and Microsoft Excel2007.

III. Observation And Results

In the present study, most of the participants belonged to >50 years age group. Out of the 50 participants in the study, 26 (52%) were male and 24(48%) werefemale.

Equal distribution of the two groups was done with 25 participants in each group i.e.Group 1(HBA1C<7) and Group 2 (HBA1C>7).

Some of the important parameters between the two groups found that 50.36 and 51.24 were the mean age of group 1 and group 2 respectively.The mean duration of suffering from diabetes is 4.20 and 4.92 in group 1 andgroup 2 respectively.Mean HBA1C levels are 6.39 and 8.01 in group 1 and group 2 respectively (pvalue=0.0001) and it was statistically significant.The mean FBS is 129.02 and 182.2 in group 1 and group 2 respectively.The mean PPBS was 211.02 in group 1 and 249.02 in group 2 and it was notstatistically significant.The mean BMI of group 1 was 26.87 and 26.85 was mean BMI of group 2.

With regards to duration of diabetes mellitus, In group 1, majority of the study participants (24)were suffering from diabetes forthe last 7 months. The remaining 1 participant is suffering from diabetes from 8-12months.In group 2, majority of the study participants 19 were suffering from diabetes for thelast 7 months. The remaining 6 participant is suffering from diabetes from 8-12months.

Distribution according to complication found that 52% of the study populationswere not presenting any complication associated with diabetes. 26% of the studypopulation presented with albuminuria, 16% with autonomic neuropathy, and 6%with Retinopathy.In group 1, 68% of the study population were not presenting any complicationassociated with diabetes. 20% of the study population presented with albuminuria,12% with autonomic neuropathy.In group 2, 36% of the study population were not presenting any complication associated with diabetes. 32% of the study population presented with albuminuria,20% with autonomic neuropathy, and 12% with retinopathy.

Table 1: Distribution of study groups based on imaging findings

		GROUP 1		GROUP 2			
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**P value**
Ventricular Septal wall thickness	25	0.84	0.08	25	0.846	0.12	0.83
LV POSTERIOR WALL THICKNESS	25	0.81	0.12	25	0.79	0.086	0.49
LV end diastolic dimension in cm	25	4.2	0.39	25	4.31	0.43	0.34
LV end systolic dimension	25	2.8	0.28	25	2.77	0.30	0.22
Fractional shortening	25	30.8	5.3	25	29.85	5.98	0.55
EF%	25	57.36	2.70	25	57.84	2.3	0.50
aorta root dimensions	25	2.78	0.47	25	2.82	0.45	0.75
left atrial dimension	25	2.91	0.30	25	2.85	0.33	0.50
E wave	25	60.48	5.67	25	60.64	4.57	0.91
A Wave	25	63.41	3.79	25	63.25	4.64	0.89
E/A ratio	25	0.95	0.11	25	0.96	0.09	0.72
IVRT (ms)	25	94.48	10.02	25	92.80	11.33	0.58
Deceleration time	25	244.02	6.31	25	246.02	5.70	0.24

Table 1 showing the distribution of the study groups based on the important parameters in imaging. There was no statistical significant difference observed in imaging between the groups.

Table 2: Distribution of the study population based on LV diastolic dysfunction

	Group 1		Group 2	
LVDD	Frequency	Percentage	Frequency	Percentage
Normal	11	44	4	16
Grade 1	11	44	13	52
Grade 2	3	12	8	32
Total	25	100	25	100

	Group 1		Group 2		P value
LVDD	Frequency	Percentage	Frequency	Percentage	
Normal	11	44	4	16	
With LVDD	14	56	21	84	
Total	25	100	25	100	0.03

Table showing distribution of study population based on LV Diastolic dysfunction.

- 14 participants out of 25 in group 1 were observed to have LV diastolic dysfunction. Out of which 11 (44%) were having grade 1 LVDD and 3(12%) were having grade 2 LVDD. 11 (44%) participants whose HBA1C was <7 were not diagnosed to have aLVDD.
- 21 participants out of 25 in group 2 were observed to have LV diastolic dysfunction. Out of which 13 (52%) were having grade 1 LVDD
- and8(32%)werehavinggrade2LVDD.4(16%)participantswhoseHBA1Cwas>7were not diagnosed to have aLVDD. The result was found to be statistically significant with p value<0.05.

IV. Discussion

In this study, we found high Trans mitral A/E ratio as an evidence of reduced diastolic function, left ventricular chamber compliance, and changes in the left atrial pressure. In the presence of mild diastolic dysfunction, early filling is often reduced, leading to an exaggerated atrial contribution to left ventricular filling and a high A/E ratio.

In more advanced heart failure, this pattern is often lost due to high left atrial and left ventricular pressure and the A/E ratio pseudo- normalizes or increases, complicating interpretation

Hameedullah et al [7] in their study population of 60 patients with type 2 DM found that there was strong correlation between HbA1c level and diastolic indices ('P' < 0.05). Diastolic dysfunction was more frequent in poorly controlled diabetic patients, and its severity is correlated with glycemic control.

Prior studies have shown that the prevalence of diastolic dysfunction in asymptomatic newly diagnosed Type 2 diabetics as 42%. Mean of HbA1C (%) was found higher in group with as compared to group without LVDD.-S kumar et al suggesting that glycemic control may be an important determinant of diastolic function[8] .

Dikshit NM et al in a prospective study to assess normotensive diabetic patients by echocardiographic and Doppler parameters found a total of 50 diabetics out of which 33 (66%) patients had diastolic dysfunction[9].

In a study done by Attali et al it was observed that LV diastolic dysfunction was present in patients who were free of cardio vascular disease, had diabetes of less than 5 years[10].

Hyperglycemia influences heart metabolism, the production of advanced glycosylation end products, oxidative stress, and protein kinase C activation that leads to Left ventricular diastolic dysfunction which is earlier manifestation of diabetic cardiomyopathy.

The relation between glycemic control and diastolic indexes in study supports the hypothesis that hyperglycemia by itself can lead to Subclinical Cardiomyopathy.

Results indicate that diabetic patients with worse glycemic control are at an increased risk of early diastolic dysfunction.Therefore, in our study, patients with type 2 diabetes had increased isovolumic relaxation time, and a increased A/E ratio compared with normal volunteers.

These results are consistent with prior studies in asymptomatic normotensive type 1 and 2 diabetic patients zabalgoitia M (2001) [11] ,Shivalkar (2005)[12].Also diastolic dysfunction was closely related to the duration of diabetes.

There was one study done by Ann m. Grandi et al, showed a close relationship between glycemic control and left ventricular diastolic dysfunction in 36 type 1 diabetic patients which improved with glycemic control[13].

Hiramastn et al found that a short term glycemic control resulted in adecrease in diastolic dysfunction which was found in 48 out of 246 patients who were randomly selected and treated with insulin for 6 months. Doppler Echo was donetwice, at 1 and 6 months after the initiation of insulin treatment and results were comparable[14].

The diagnostic role played by BNP in early detection of asymptomatic diastolic dysfunction in type-2 diabetes is still controversial.

Dencker et al [15] demonstrated that BNP was significantly higher in patients with abnormal diastolic dysfunction (26.0 ± 3.4 vs. 5.3 ± 3.4, $p < 0.001$) in a cohort of 33 patients with poorly regulated type 2 diabetes.

A 17-year follow-up of 1441 patients from the DCCT trial more unambiguously demonstrated the benefit of intensive glycemic control in T1DM. They indicate finally that indicate that intensive glycemic control reduced the long term risk of CVD in patients with T1DM.Intensive therapy in the UKPDS significantly improved the rate of micro vascular disease in T2 DM patients.

Dungan et al .study glycemic liability index, indicating increased glycemic variability, was associated with higher mortality, independent of hypoglycaemia [16].

Clinical implication concerns the possibility to better control glycemic profile in order to reduce heart disease progression or even to reverse it, especially in patients with short duration of diabetes without history of cardiovascular event[17] In fact, in the early stages of diabetes, structural modifications seem to be partially reversible [18].

The occurrence of HF in diabetic patients is responsible for increased mortality in this population. The evidence of increase incidence of HF in diabetes is strongly supported by the results of numerous clinical trials, metabolic disturbances; interstitial fibrosis, cardiacmyocyte loss, small vessel disease, and cardiac autonomic neuropathy are incriminated.

It is crucial to actively screen for patients at risk and institute appropriate therapy as soon as possible. The multifactorial nature of cardiac dysfunction in diabetic patients indicates that various strategies might be effective for preventing or delaying the development of HF and its complications. Presently, tight glycemic control and use of ACE inhibitors seem to be basic therapeutic strategies.

Dueto the diabetogenic potential, it seems reasonable to avoid concomitant therapy with thiazide diuretics and β-blockers.

V. Conclusions

In patients with type 2 diabetes without clinical evidence of heart disease and HbA1c >7, there was a diastolic dysfunction with higher trans mitral A/E ratio, more prolonged isovolumic relaxation time in comparison with patients with type 2 diabetes without clinical evidence of heart disease and hemoglobin A1C<7 subjects.Furthermore, HbA1c correlated with diastolic Doppler indices.

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