Original Research Article

A Study of Relation of Hemoglobin A1c to Left Ventricular Diastolic Function in Patients with Type 1 Diabetes Mellitus and Without Overt Heart Disease

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Abstract

Introduction: Diabetes mellitusis a group of metabolic disease characterized by hyperglycemia results from defects in insulin secretion, insulin action or both. It affects more than 120 million worldwide.**Materials and Methods:** The Clinical materials were of Type-1 Diabetes Mellitus individuals selected from Endocrinology OP,Andhra Medical College,Vishakhapatnam. About 87 patients were subjected to initial assessment it included through clinical examination, routine blood investigation consisting of complete blood count, biochemistry investigation, ECG, estimation of HbA1c and echo cardiography were done from which 50 patients were included in the study.**Results:** In this study,left atrial area [19 ± 5.1] was more in group with HbA1C>7 i.e group II when compared to group (15.1±2.6)with HbA1C <7 i.e group I. Mean peak early mitral inflow velocity E wave [m/sec] was low [75 ± 1.1] in patients of Group II compared with Group I (77±0.9). Mean peak late mitral inflow velocity A wave [m/sec] was more [70 ± 14] in patients of Group II compared to patients of group I (48±15) with statistical significance (P 0.003). In this study, E/A ratio less (1.28±0.31) in group II patients when compared to group I (1.6±0.3) patients with statistical significance (P 0.01). Here in our study Isovolumetric relaxation time was prolonged (99±1) in group II compared to Group I (71±8) with statistical significance (P 0.003).**Conclusion:** The findings in our study concludes that left ventricular diastolic dysfunction represents the first stage of diabetic Cardiomyopathy preceding systolic dysfunction reinforcing the importance of early examination of ventricular function in patients with diabetes and importance of well controlled glycaemic status in diabetes.

Keywords: Type-1 Diabetes Mellitus, HbA1C, ECG, hyperglycemia.

Introduction

Diabetes mellitusis a group of metabolic disease characterized by hyperglycemia results from defects in insulin secretion, insulin action or both. It affects 120 million worldwide.Diabetes is usually irreversible and, although patients can have a reasonably normal lifestyle, its late complications result in reduced life expectancy and major health costs. These include macro vascular disease, leading to an increased prevalence of coronary artery disease, peripheral vascular disease and stroke, and micro vascular damage causing diabetic retinopathy and nephropathy.The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million In 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030. Approximately 1.5 million individuals (>20 years) were newly diagnosed with diabetes in 2005. DM increases with age.Type 1 diabetes is a disease resulting in insulin deficiency. In western countries almost all patients have the immune-mediated form of the disease (type 1A). Type 1 diabetes is prominent as a disease ofchildhood, reaching a peak incidence around the time of puberty, but can present at any age.The Diabetes Control and Complications Trial (DCCT) provided In DCCT[1] trial individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (7.3%) than individuals in the conventional diabetes management group (9.1%).

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definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM.The DCCT demonstrated that improvement of glycaemic control reduced non proliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycaemic control also slowed the progression of early diabetic complications.

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, Ml, and sudden death (risk increase from one- to fivefold) in DM.The increase in cardiovascular morbidity and mortality appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors.In the DCCT, the number of cardiovascular events in patients with type 1 diabetes did not differ between the standard and intensively treated groups during the trial but were reduced at follow-up 17 years later.

Effects of Diabetes on the Myocardium

Both systolic and diastolic abnormalities have been demonstrated in patients with Diabetes without symptomatic evidence of cardiovascular disease. These abnormalities correlate with glycaemic control, duration of diabetes and evidence of retinopathy/ neuropathy[1-5].

Aims and Objectives

1. To study about the echo cardio graphic findings in type -1 diabetic patients who are on regular treatment.
2. To study about glycaemic control
3. To detect early cardiac changes and prevent complications.

Materials and Methods

Type of Study: Prospective Study

The Clinical materials were of Type-1 Diabetes Mellitus individuals selected from Department of Endocrinology OP,Andhra Medical College,Visakhapatnam,Andhra Pradesh.About 87 patients were subjected to initial assessment it included through clinical examination, routine blood investigation consisting of complete blood count, biochemistry investigation, ECG, estimation of HbA1c and echo cardiography were done from which 50 patients were included in the study.

Exclusion Criteria: Patients with abnormal resting ECG suggestive of ischaemic heart disease or bundle brach block. Presence of co-morbid disease known to influence left ventricular dysfunction that is thyroid disease, alcohol, and hypertension.

- Peripheral vascular disease.
- Ciggarete smoking.
- Dyslipidaemia.

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

Place of Study: Andhra Medical College,KGH, Visakhapatnam, Andhra Pradesh from March 2013 to October 2014

Sample Number: 50(Selected from the list of 87).

They were divided in to 2 groups according to the glycaemic status Group 1 consisted of HbA1C< 7. Group 2 consisted of HbA1C l >7.

The number of patients included in to each group was 25. All of them were subjected to Echocardiography done at the department of Cardiology,Andhra Medical College,Visakhapatnam,Andhra Pradesh.

ALOKA 830 equipment which has the capabilities of performing two dimensional, M mode, Pulsed wave and continuous wave Doppler and colour flow imaging was used to obtain echo cardiogram images. Phased array transducers 2.5 - 3.5 MHz frequencies were used to obtain 2-D / M-mode echo cardiography. Images were obtained with subjects in 30 degree lateral decubitus position. All measurements were performed in the freezed images from all the patients, good quality images suitable for the measurements and interpretations were obtained and recorded.For assessment of LV systolic function the following parameters were calculated from the M- mode echocardiogram obtained at the level of mitral valve chordae.LV dimension (minor axis) diastole (LVId) systole (LVsd) and thickness of inter ventricular septum, left ventricular posterior wall thickness in diastole.

LV ejection fraction was calculated using the following formula, EF= LVEDV-LDESV/ LVEDVx 100

Specific attention was focused on diastolic function namely

1 Calculation of left ventricular inflow velocities(e),
2 Peak atrial contraction in Systole(a)
3 Calculation of e/a ratio and
4 Deceleration time
5 Isovolumic relaxation time.

Data Analysis

The mean and standard deviation of the all the parameters was analyzed using following formula. The patients divided into two groups according to their HbA1c level as taking cutoff value as 7. The echo parameter of the two groups are analysed using the independent t-test and the P-value got from the t-test table.

Observation and Results

Table 1:Clinical characteristics of the two groups

Characteristic	Group 1 HbA1C<7 [n= 25]	Group 2 HbA1C>7 [n=25]
Age	30±10	30±9
Men	13	14
Body mass index [Kg/ m^2]	24±7	26±6
Systolic blood pressure[mm/Hg]	112±8	112±9
Diastolic blood pressure[mm/Hg]	72±4	78±3
Heart rate [beats/ minute]	74±6	78±9

Table 2:Doppler Indices

Variable	Group 1 N = 25	Group 2 N = 25	P value
LV peak early transmitral flow velocity E [cm / sec]	75 ± 1.1	77 ± 0.9	0.3
Peak atrial contraction A [cm/sec]	48 ± 15	70 ± 14	0.003
E / A ratio	1.6 ±0.3	1.28±0.31	0.01
Decelelaration time [ms]	185 ± 36	209 ± 34	0.02
Isovolumic relaxation time [ms]	71 ± 8	99 ± 11	0.003

Table 3:Base Line Echocardiographic Characteristics of Two Groups

Characteristic	Group 1 HbA1C<7 N = 25	Group 2 HbA1C>7 N= 25	P
Left atrial area [cm]	15.1 ± 2.6	19 ± 5.1	.07
Left ventricular mass index [gm/m^2]	91 ± 36	106 ± 40	.06
LV ejection fraction [%]	65 ± 4	66± 5	.2
Posterior LV thickness [cm]	0.7 ± 0.1	0.91± 0.3	.001
Inter ventricular septal thickness [cm]	0.97± 0.2	1 ±0.2	0.33
LV end diastolic diameter [cm]	4 ±0.3	4 ±0.4	0.61
LV end systolic diameter [cm]	2.3 ± 0.4	2.4 ± 0.6	0.73

Discussion

In this study, we found a higher prevalence of asymptomatic diastolic dysfunction in type 1 diabetes mellitus, 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.

It showed that children and adolescents with type 1 diabetes had altered cardiac function compared with age-matched individuals without diabetes.

Subjects included in the study had no cardiac signs or symptoms or diabetes complications, and were not taking medications known to modify cardiac structure or function.

The most striking findings were recorded in patients with type 1 diabetes, who had reduced diastolic function compared with control subjects.Left atrial area [19 ± 5.1] was more in group with poorly controlled glycaemic status, that is HbA1C > 7 when compared to group [15.1 ± 2.6] with well controlled glycaemic status.

Mean peak early mitral inflow velocity E wave [m/sec] was lowest in patients of group whose diabetic condition was poorly controlled [75 ± 1.1] as evidenced by HbA1C > 7 when compared with group with well controlled glycaemic status [77 ± 0.9].Mean peak late mitral inflow velocity A wave [m/sec] was more in patients of group whose diabetic condition was poorly controlled [70 ± 14] as evidenced by HbA1C > 7, when compared to patients whose diabetic status was well controlled [48 ± 15] as evidenced by HbA1.In this study, we found low trans mitral E/A ratio in group with poorly controlled glycaemic status as an evidence by

1. reduced diastolic function,
2. reduced left ventricular chamber compliance,
3. 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 low E/A ratio.

E/A ratio less in group with poor glycaemic control where HbA1C greater than 7 [1.28± 0.31] when compared with group with good glycaemic status that is in those with HbA1C less than 7 [1.6± 0.3].

In more advanced heart failure, this pattern is often lost due to high left atrial and left ventricular pressure and the E/A ratio pseudo-normalizes or increases, complicating interpretation (Garcia et al (1998)[11].Prior studies have shown a correlation between HbA1c and diastolic function in older individuals with type 1 diabetes, suggesting that glycaemic control maybe an important determinant of diastolic function -Isovolumetric relaxation time is an interval in the cardiac cycle from the aortic component of the second heart sound that is closure of the aortic valve to onset of filling by opening of the mitral valve. It can be used as an indicator of diastolic dysfunction.

A normal Isovolumetric relaxation time is about 70 ±12 milli seconds and approximately 10 milli seconds longer in people over forty years. In abnormal relaxation, Isovolumetric relaxation time is usually in excess of 110 milli seconds. With restrictive ventricular filling it is usually under 60 milli seconds.So prolonged Isovolumetric relaxation time indicates poor myocardial relaxation and hence diastolic dysfunction.Here in our study Isovolumetric relaxation time is prolonged [99 ±11] in group with poor glycaemic control as evidenced by HbA1C greater than 7 when compared to group with good glycaemic control as evidenced by HbA1C less than 7 [71± 8]

Comparative Study

Effect of glycaemic status on left ventricular diastolic dysfunction in normotensive type 2 diabetic patients by Hameedullah et al 2009[5-10].

Table 1: Clinical characteristic of the subjects

Characteristics	Group 1	Group 2	Group 3	P-Value		
				Group 1 Vs Group 2	Group 1 Vs Group 3	Group 2 Vs Group 3
Age	51.1±8.52	57.3±11.61	57.25±9.62	0.05	0.98	0.09
SBP mm hg	121.9±9.82	120.1±10.1	123.4±6.25	0.57	0.09	0.08
DBP mm hg	69.80±6.95	73.9±8.93	69.7±7.88	0.11	0.33	0.30
BMI 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	Group 1 Vs Group 3	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 patients having LV diastolic dysfunction

Characteristics	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	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

60 normotensive type 2 DM patients enrolled and are divided in 3 groups.

Group 1- 20 well controlled [HbA1c < 8]
Group 2- 20 moderately controlled [HbA1c 8 -10]

Group 3- 20 poorly controlled [HbA1c -10]

In this study Left atrium was enlarged in poorly controlled diabetic patients [Group 3, 4.48±0.79] when 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].

Those patients with poor glycaemic status had worse left ventricular diastolic dysfunction in the form of pseudo normal pattern, these patients had higher level of HbA1C level with p<0.001.Mean peak early mitral inflow velocity E wave [m/sec] was lowest in patients whose diabetic condition was poorly controlled [Group 3, E = 0.48±0.08] as compared to patients whose diabetic condition was well and moderately controlled {[Group 1, E wave = 0.68±0.03] , [Group 2 , E = 0.62 ± 0.07] } with significance statistical difference.

This study demonstrated that patients whose diabetic condition was well controlled shows high E wave as compared to patients whose diabetic condition was not well controlled.Mean peak late mitral in flow velocity A wave [m/sec] was highest in patients whose diabetic condition was poorly controlled [Group 3 , A wave = 0.60 ± 0.15] as compared to patients whose diabetic status was well and moderately controlled { [Group 1 , A =0.51 ± 0.11] , [Group 2, A = 0.58 ± 0.15] } with significance statistical difference.This study document that A wave is higher in patients with poor metabolic control than patients with well controlled diabetes, the diabetic status was defined from the basis of HbA1C level and fasting blood sugar. E/A 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] and mean IVRT showed step wise decrease from poorly controlled diabetic group[Group 3,109±6.45] to those with moderately controlled Group 2[100 ±7.83] to well controlled diabetic group [Group 3 ,91.25 ±7.81] so E /A ratio which is an indicator of diastolic function is decreased both in type 1 diabetes with poor glycaemic control as shown by HbA1c greater than 7 in our study which is similar to study done by Hameedullah et al where E/A was gone decreasing as HbA1C increased , as evidenced by Group 3 where [HbA1C greater than 10] has E/A [0.6 ±0.15] compared to Group 1where HbA1C less than 8 with E/A [1.38 ±0.29]Isovolumetric relaxation time increased both inour study with poor glycaemic control with HBA1C greater than 7 value is [99±11] and in study done by Hameedullah at all study where Group 3 with HbA1C greater than 10 has isovolumetric relaxation time more [111.36±4.34] than Group 1 with HbA1C less than 8 with isovolumetric relaxation time [103±2.24][11,12]

Comparative Study

Diastolic dysfunction in diabetes mellitus by Nikhil et al[2013]

This prospective study was under taken in 50 patients with diabetes mellitus, who were referred to the O.P department of new civil hospital, Surat over a period of 6 months.

Exclusion criteria

1. Patients with Coronary artery disease diagnosed by symptoms, ECG , regional wall motion abnormalities on echo cardiogram.
2. Patient with blood pressure > 140/90.
3. Patients with congestive heart failure diagnosed by signs and symptoms, chest radiograph , or echocardiography.

Control group consisted of 50 healthy nondiabetic volunteers comparable for age and sex distribution to diabetic patients

Results

This study by Nikhil et al provides evidence that left ventricular diastolic function is impaired in patients with diabetes mellitus.

Out of total of 50% diabetics 33 [66%] patients had diastolic dysfunction.The average age of patients with diabetes observed was 43.88 ± 13.74 years. The mean age for control was 38.5 ± 14.36 years.All subjects showed normal systolic function. Interventricular septum thickness, left ventricular dimensions (both end systolic and end diastolic) and left ventricular posterior wall thickness were greater in the diabetic group [p< 0.01].Left ventricular mass was increased by 20% in patient group [223.4 ± 54.44 Vs 187 ± 29.87 , p <0.01] with regard to pattern of left ventricular diastolic filling , diabetic patients showed a higher atrial peak filling velocity [p< 0.01] and consequently reduced E/A ratio [p <0.01 }. The diabetic patients also showed prolonged Isovolumetric relaxation and deceleration times [p <0.01].It was observed that E/A ratio was significantly abnormal [< 1] in diabetics as compared to value in normal controls [> 1]. This abnormality was seen in 66% of diabetics.Left ventricular wall thickness defined as the sum of ventricular septal and posterior wall thickness and left ventricular mass were statistically significant both in systole and diastole when compared with normal controls. These data indirectly suggests that metabolic and hormonal factors may play a role in the development of a greater ventricular mass.The deceleration time [DT] of the E wave was an even more specific indicator of diastolic dysfunction, with a highly significant increase [236.5 ± 70.01] when compared to control group [181.2± 10.67].IVRT which is used as indicator diastolic dysfunction is prolonged [76.44 ± 7.99] in diabetic group when compared to control group [68.4 ± 7.34].When compared to our study E/A is low in diabetic group of Nikhil et all study [0.9 ± 0.27] which is similar to our study where patients with poor glycaemic status that is HbA1C > 7 have low E/A [1.28 ± 0.31] when compared with group with well controlled glycaemic status that is HbA1C < 7 [1.6± 0.3].In Nikhil et all study IVRT is prolonged in diabetic group [76.44 ± 7.29] when compared to control group [68.4 ± 7.34] which is similar to our study findings , where IVRT is prolonged [99 ± 11] in group with poorly controlled glycaemic status that is HbA1C > 7 when compared with group with well controlled glycaemic status that is HbA1C < 7.DT of E wave which is an even more specific indicator of diastolic dysfunction was more [236.5 ± 40.01] in diabetic group in Nikhil et al study compared to control group [181.2 ± 10.67] and these are similar to our study where DT [m/sec] was more [209 ±34] in group with HbA1C >7 when compared to group [185±36] with HbA1C <7. Hyperglycemia influences heart metabolism, the production of advanced glycosylation end products, oxidative stress, and protein kinase C activation Young et al (2003), young et al (2005)The relation between glycaemic control and diastolic indexes in study supports the hypothesis that hyperglycemia by itself can lead to Subclinical Cardiomyopathy[13,14]. Results indicate that diabetic patients with worse glycaemic control are at an increased risk of early diastolic dysfunction.Therefore, in our study, patients with type 1 diabetes had increased isovolumic relaxation time, and a decreased E/A ratio compared with normal volunteers. Also, diastolic dysfunction was closely related to the duration of diabetes.

Further Study Needed to Determine

Wheter Intensification of glycaemic control improves diastolic parameters. Drugs that could interfere at cellular level in cardiac metabolism Is diastolic dysfunction reversible, if so time limit.

Conclusion

The findings in our study concludes that left ventricular diastolic dysfunction represent the first stage of diabetic Cardiomyopathy preceding systolic function reinforcing the importance of early examination of ventricular function in patients with diabetes and importance of well controlled glycaemic status in diabetes.E/A ratio, left atrial size and isovolumetric relaxation time are significantly altered depending on glycaemic status in diabetic patients. Doppler echo identifies large percentage of diabetic subjects who have asymptomatic left ventricular dysfunction before abnormalities are detected with ECG or clinical examination.

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