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SUBCLINICAL DIASTOLIC DYSFUNCTION AND ITS CORRELATION WITH LABORATORY PARAMETERS IN TYPE 2 DIABETES MELLITUS IN INDIA: A CASE CONTROL STUDY

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Abstract

Background: *This study was conducted to evaluate left ventricular dysfunction in diabetics and to find correlation with glycemic control and biochemical parameters compared to non-diabetic population.* ***Methods:*** *Thirty type 2 diabetics and thirty non-diabetic controls were recruited. Age, sex, body mass index of the controls were matched.* ***Results:*** *Mean duration of diabetes mellitus in study population was 10.97± 4.01years. Among study population both cases and controls had ejection fraction >55%(no systolic dysfunction). Among cases(n=16) 53.3% were having mean E/A ratio <1 and(n=14) 46.67% were had mean E/A ratio >1. In controls all of them had mean E/A ratio above 1. This difference of mean E/A ratio among cases and controls was statistically significant (p<0.001). Among patients with diabetes, 9.09% cases with a HbA1cbetween 6-7%, 33.33% between 7.1-8%, respectively 100% of cases with HbA1c>8.1% had diastolic dysfunction the differences between groups being statistically significant (p<0.001). Low density lipoprotein(LDL) was weakly and negative correlated with E/A ratio (r = -0.38) while fasting blood sugar (r = -0.53) respectively Hemoglobin A1c (r = -0.66) were moderately and negatively correlated. All these correlations were statistically significant.* ***Conclusion:*** *Subclinical diastolic dysfunction is prevalent among diabetic population. Diastolic dysfunction in patients with diabetes was correlated with FBS, HbA1C and LDL.*

key words: *Diabetes Mellitus, Diastolic dysfunction, Hemoglobin A1c.*

Background and Aims

The epidemic of diabetes represents a major burden to heath care systems around the world. Both type 1 and type 2 diabetes are increasing in children and adolescents. Most alarming factor is the increase in type 2 Diabetes in the youth related to obesity and physical inactivity [1,2]. Because of the increasing frequency of diabetes in the past 30 years, the incidence of cardiovascular disease attributable to diabetes will continue to increase, even as its incidence in the non-diabetic population continues to diminish [3]. Cardiovascular complications are

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known to be the main cause of morbidity and mortality in Diabetics [4]. Other cardiovascular risk factors like hyperlipidemia, hypertension and obesity are common in diabetics [5]. Atherosclerosis of the coronary arteries is by far the most common cause of cardiac involvement in diabetic patients. Diabetic cardiomyopathy has been proposed as an independent cardiovascular disease, and many mechanisms, such as micro vascular disease, autonomic dysfunction, metabolic disorders, and interstitial fibrosis, have been suggested as causative factors [6]. Despite similar left ventricular systolic function, patients with diabetes have more pronounced heart failure symptoms and have an adverse prognosis compared to those without diabetes; one putative explanation for these discrepancies is diastolic dysfunction of the left ventricle in diabetics [7]. The diastolic abnormalities may present in diabetics without diabetic complications of cardiovascular system [8]. Other prospective studies also have shown that diabetic patients have a significantly increased lifetime risk of developing heart failure and increased mortality from both Q-wave and non-Q-wave myocardial infarction [9,10]. This suggests that there is an additional aggression to diabetic myocardium which will predispose it to more extensive damage and subsequent failure.

Prior to the development of symptomatic congestive heart failure, subclinical left ventricular dysfunction (systolic or diastolic) exists for variable duration [11-13]. However, frequency of progression from pre-clinical to clinically evident myocardial dysfunction is not established. Echocardiography especially Doppler echo is simple, noninvasive and reproducible. Various studies were conducted worldwide to evaluate the left ventricular dysfunction in diabetes mellitus patients but very few studies conducted in India and the results are inconclusive. So, the aim of our current study was to evaluate the systolic and diastolic dysfunction in type 2 diabetes patients as compared to non-diabetics in Indian population and secondary aim of this study was to find out correlation between left ventricular dysfunction (systolic/diastolic) and any demographic parameters of the diabetic patients.

Material and methods

The study was conducted in the department of Medicine, Lady Hardinge Medical College and Associated Hospitals, New Delhi. Thirty type 2 diabetic patients who were diagnosed as per ADA criteria with minimum disease duration of 5 years were recruited from medicine OPD and diabetic clinic. Thirty patients with age, sex, body mass index matched to the non-diabetic controls were also recruited from medicine OPD from September 2014 to February 2016. Both cases and controls which fulfilled inclusion and exclusion criteria were selected and included in this study. The study was conducted after approval by the institutional ethics committee. The study protocol was explained to all participants and they gave their informed consent. Echocardiography was performed M-Mode and 2D measurements were made as per recommendation of American Society of Echocardiography (ASE) guidelines, among echocardiography parameters E/A ratio >1 was considered normal diastolic function, while E/A ratio >1 are considered diastolic dysfunction and all other laboratory parameters are done accordingly.

Inclusion Criteria (cases)

1. Patients with established diagnosis of type 2 diabetes mellitus by ADA criteria,

2. Disease duration of minimum 5 years since time of diagnosis,

3. Patients without any symptoms or overt complications of diabetes mellitus,

4. Age group 30 to 50 years independent of sex.

Inclusion Criteria (controls)

1. Healthy patients attending OPD for minor illness
2. Patients without evidence of diabetes mellitus (type1&2),
3. Age group 30 to 50 years independent of sex,

Exclusion Criteria (both cases and controls)

Patients with following conditions were excluded

1. Systemic hypertension.
2. Thyroid disease.
3. Peripheral vascular disease.
4. Established ischemic heart disease
5. Structural heart disease
6. Congenital heart diseases
7. History of rheumatic heart disease,
8. History of radiation exposure/cardio toxic drugs
9. History of chronic alcoholism, smoking, drug abuse
10. Any patient who did not give consent.

Categorical variables were presented as number of cases and percentage from the total of the group (%) while continuous variables were presented as mean ± SD and range. Quantitative variables were compared using unpaired t-test between the two groups. Qualitative variables were compared using Chi-Square test/Fisher's exact test. Pearson correlation coefficient was used to find out the association of E/A with various parameters. A p value of <0.05 was considered statistically significant. The data was collected using Microsoft EXCEL and analysis was performed using Statistical Package for Social Sciences (SPSS) version21.0.

Results

A total of sixty subjects (30 cases and 30 controls matched healthy controls) were included in this study. Mean age of the study populations (cases) was (40 ±5.3) years, and minimum age was 31 years and maximum age was 50 years. Mean age of controls was (38.37 ±4.47) years and minimum age was 30 years and maximum age was 46years.Mean duration of diabetes mellitus in the study population was (10.97±4.01) years. Maximum number of subjects were in 5-10 years duration of diabetes sub-group. Among the study population 73.33% cases and 50% controls were asymptomatic at the time of study. In case population 36.67%, 20% respectively 43.33% of patients were having HbA1cbetween 6-7%, 7.1-8% respectively>8.1%. Among controls all of them were having HbA1C below 6%. Table 1 showed demographic profile of study population.

Among study population all controls and 66.67% of cases (diabetics) were showing normal ECG. In rest of the diabetics, 1(3.3%) patient was showing LVH (Left ventricular hypertrophy), 4(13.3%) patients were showing nonspecific ST, T changes, 4(13.3%) patients were showing RBBB (Right bundle branch block), 1(3.3%) patient was showing other changes. The whole study population including cases and controls were showing ejection fraction above >55% means both cases and controls were showing no systolic dysfunction.

Table 1. Demographic profile of study population.

	Cases(n=30)		Control(n=30)		p-value
	Mean ±SD	Min-Max	Mean ± SD	Min-Max	
Age (years)	40±5.3	31-50	38.37±4.47	30-46	0.202
Duration (years)	10.97±4.01	5-22	0±0	0-0	<0.0001
Ht (cm)	159.12±7.86	142-169	155.85±7.65	143.5-172.5	0.108
Wt (Kg)	58.53±6.99	42.36-68.65	54.1±8.88	39.32-78.21	0.036

Table 1. *Continued*.

	Cases(n=30)		Control(n=30)		p-value
	Mean ±SD	Min-Max	Mean ± SD	Min-Max	
BMI (Kg/m2)	23.32±3.14	18.3-28.91	22.26±3.04	17.2-28.38	0.192
Sys BP (mm Hg)	126±8.4	110-138	123.2±7.69	110-138	0.182
Dia BP (mm Hg)	81.07±5.22	68-90	79±6.66	70-88	0.186
PR (per min)	82.9±6.27	70-92	87.97±3.79	81-98	<0.0001
RR (per min)	14.63±1.4	13-17	15.1±1.18	13-17	0.169
FBS (mg/dl)	149.8±14.14	129-183	98.47±8.41	80-115	<0.0001
HbA1c (%)	8.09±1.47	6.3-11.5	4.72±0.2	4.5-5.1	<0.0001
Urea (mg/dl)	39.93±7.62	26-52	32.6±5.87	19-44	<0.0001
Creatinine (mg/dl)	0.89±0.2	0.6-1.2	0.85±0.19	0.4-1.2	0.388
Cholestrol (mg/dl)	209.17±13.53	178-236	204.45±10.48	172-226	0.137
LDL (mg/dl)	129.1±7.75	110-142	127.03±16.12	100-198	0.529
HDL (mg/dl)	40.27±3.37	35-47	40.97±1.59	37-43	0.31
Triglyceride (mg/dl)	161.53±13.56	140.24-201.4	149.8-10.15	136.27-171.6	<0.0001
EF (%)	57.5±3.33	55-60	58.67±2.45	55-60	0.053
E/A	0.99±0.26	0.64-1.6	1.18±0.15	1-1.6	0.002
E/E"	9.34±1.68	6.8-14	9.06±0.62	7.8-10	0.397
IVRT (ms)	90.82±8.69	74-112	88.77-7.38	74-108	0.329
DT(ms)	189.37±25.74	162-254	171.73±8.15	158-189	0.001

Table 2. E/A Ratio in study population

E/A Ratio	Group		Total	P value
	Case	Control		
≤1	16(53.33%)	0(0.0%)	17(28.33%)	<0.0001
≥1	14(46.33%)	30(100%)	43(71.67%)	
Total	30(100%)	30(100%)	60(100%)	

Table 2 is showing that among cases 53.3% were having mean E/A ratio <1 and 46.67% were having mean E/A ratio >1. In controls all of them having mean E/A ratio above 1. This difference of mean E/A ratio among cases and controls statistically significant (p<0.001). Among the diabetic cases, 9.09% of cases with HbA1C range 6-7%, 33.33% of cases with HbA1C range 7.1-8%, 100% of cases with HbA1C range >8.1% had diastolic dysfunction with the differences between groups being statistically significant (p<0.001) as Table 3.

Table 3. The distribution of diastolic dysfunction in cases according to HbA1c value.

HbA1c(%)	Diastolic dysfunction (E/A ratio<1)		Total	P value
	Absent	Present		
6 -7	10(90.91%)	1(9.09%)	11(100%)	<0.001
7.1-8	4(66.67%)	2(33.33%)	6(100%)	
>8.1	0(0.0%)	13(100%)	13(100%)	
Total	14(46.67%)	16(53.33%)	30(53.33%)	

Correlation of various demographic parameters with E/A ratio (diastolic function) as Table 4

The correlation between various demographic parameters with E/A ratio which is decreased in diastolic dysfunction was as follows: LDLc had a weak negative correlation with E/A ratio (r = -0.38) (Table 4, Figure 1), HbA1C was moderately and negative correlated with E/A ratio (r = -0.66) (Table 4, Figure 2) fasting blood sugar was negatively correlated with E/A ratio (r = -0.53) (Table 4, Figure 3) and all of these correlations were statistically significant. Hence LDLc, FBS and HbA1c were having significant positive correlation with diastolic dysfunction. rest parameters in this table was not showing significant correlation

Table 4. Correlation of demographic parameters with E/A ratio (diastolic function).

Parameters	E/A Ratio		Significant
	Correlation coefficient	P	
Age	0.026	0.89	Non-significant
BMI	0.011	0.95	Non -significant
Height	-0.005	0.98	Non-significant
Weight	0.326	0.07	Non -significant
Duration	0.022	0.9	Non -significant
SBP	0.075	0.69	Non -significant
Cholestrol	0.001	0.99	Non-significant
LDL	-0.382	0.03	Significant
HDL	0.059	0.79	Non-significant
TRI	0.129	0.49	Non -significant
FBS	-0.539	0.002	Significant
HbA1c	-0.66	0.0001	Significant

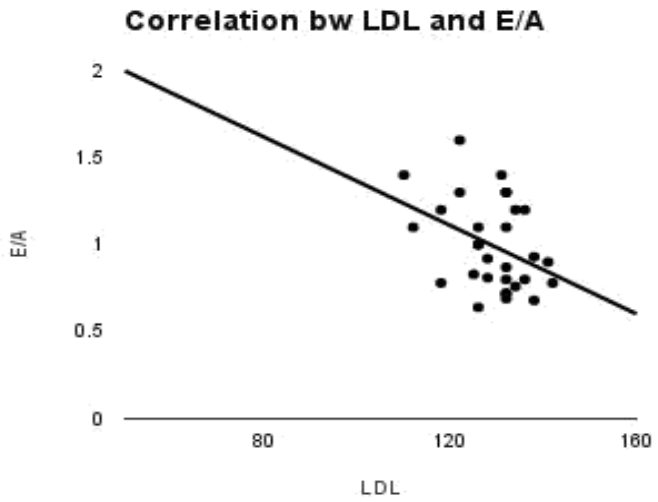

Figure 1. *Correlation between LDL and E/A ratio (showing a weak negative correction with E/A ratio (correlation coefficient- 0.38) by Pearson's correlation. statically significant p value 0.03.*

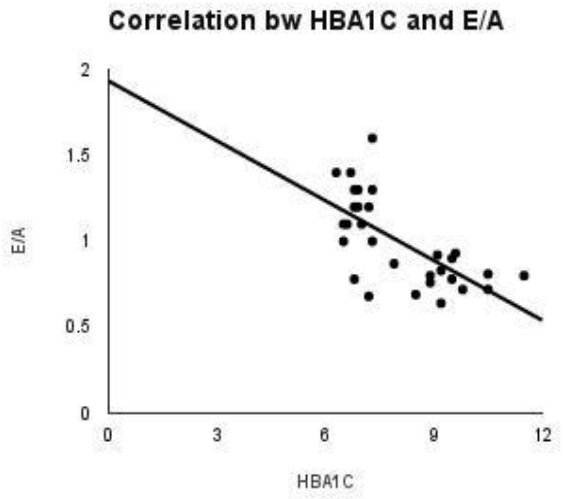

Figure 2. *Correlation between HbA1C and E/A ratio - moderately strong negative correlation with E/A ratio (correlation coefficient - 0.66) by Pearson's correlation which is highly statically significant p value -0.0001.*

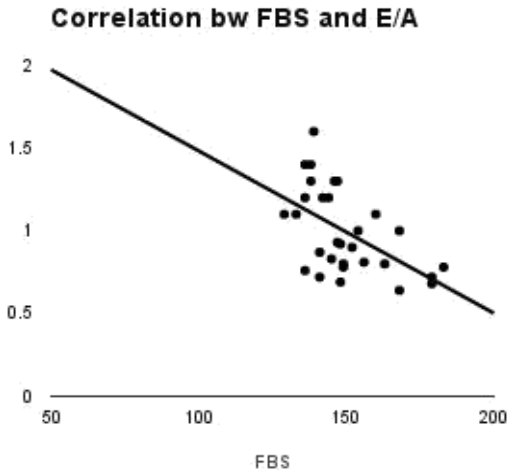

Figure 3. Correlation between FBS and E/A ratio (showing moderately strong negative correlation with E/A (Correlation coefficient - 0.53)

Discussion

This study was an Urban, public hospital based cross sectional case control study carried out jointly in the Department of Medicine Lady Hardinge medical college New Delhi during the study period of September 2014 to February 2016. A total of thirty diabetic patients who speak Hindi or English were enrolled in the study who fit into the prescribed selection criteria. Thirty age, sex, body mass index matched non-diabetic controls were also recruited from medicine OPD. In current study the mean age of study populations (cases) 40 years with standard deviation of 5.3, mean age of controls 38.37 years with standard deviation of 4.47. In Rajesh Rajput, Jagdish, et al in 2002 a study Group-A (Diabetic Patients) had an average age of 42 ± 4.78 years. Group-B (Control) had an average of 39.6 ± 6.27 years [14]. Both studies having similar age groups, there was no statistically significant difference of age between diabetics and non-diabetics. In current study, among the diabetic cases woman had an increased frequency of diastolic dysfunction (73.3%) as compared to men which had around 33.3% of them diastolic dysfunction without being statistically significant (p=0.06).

LVDD was compared among gender showed 68.18 % female subjects had diastolic dysfunction compared to male 60.7% in the strong heart study by Devereuex and colleagues in 2000 [15]. Hence, both studies were showing similar observations. In current study increased HbA1c level was associated with a higher frequency of diastolic dysfunction in diabetic patients. It is comparable to a study by Runqing Huang, Sahar S, Abdelmoneim et al in 2014 [16] in which after adjusting for those possible confounders, HbA1c >7.0% remained significantly associated with abnormal MBFR (Myocardial blood flow reserve) (defined as <2) concluded that HgbA1c > 7.0% was an independent risk factor for having lower MBFR in T2DM patients. In Virendra C.P, Harsha V.P, Kuldeep B.S, Jay D.V et al [17] study also Subjects with HbA1c > 7.5% had a higher prevalence of diastolic dysfunction than subjects with HbA1c <7.5% (P < 0.02). Diastolic dysfunction was present in majority of the subjects with autonomic neuropathy and retinopathy. This current study had revealed high incidence of diastolic dysfunction in asymptomatic diabetic subjects and this finding was correlated with HbA1c levels.

Table 5. Comparison of diastolic dysfunction in current study with other studies

Eichelberger et al	62%
Poirier et al	60%
Virendra c patil et al	54.33%
Present study	53.3%

Comparison of HbA1C and diastolic dysfunction

The following table showing percentage of diastolic dysfunction in various studies as followed, Eichelberger et al [18] study was showing 62%, Poirier et al [19] study was showing 60%, Virendra c patil et al study was showing 54.3%, present study was showing 53.3%. So, the prevalence of diastolic dysfunction in current study was comparable with those studies mentioned above.

Comparison of the present study with Virendra et al study

Virendra et al study [17] had shown the mean HbA1c, Serum Cholesterol & Serum Triglyceride were significantly higher in diabetic patients as compared to non-diabetics. Mean systolic ejection fraction in diabetic patients was not significantly decreased in cases (54.5%), as compared to normal patients (55.5%). In present study also, there was not significant reduction in mean LVEF% in diabetes (57.5% ±2.33) than controls (58.67 % ±2.24) (p>0.05). In Virendraet al study there was diastolic dysfunction in diabetics (mean E/A is 0.8). In present study, control group had mean E/A 1.17±0.15 and diabetic patients had mean E/A 0.99±0.25 (p=0.001) thus diabetics were showing diastolic dysfunction as compared to controls in both study. Thus, the present study was comparable with the Virendra et al study, both studies had showed sub clinical left ventricular diastolic dysfunction in asymptomatic diabetic patients as compared to non-diabetics and associated with HBA1c level which was significant. In contrast to current study, Virendra et al study was showing significant difference in lipid profile of cases and controls. This may be due to small sample size of current study as compared to Virendra et al study.

Conclusions

There is no LV systolic dysfunction neither in cases nor controls. Hence, no significant association between LV systolic dysfunction and diabetes mellitus was found. There is LV diastolic dysfunction in 53.3% of cases as compared to controls in which no diastolic dysfunction was found. Hence, diabetes may be considered as an independent risk factor for LV diastolic dysfunction. This study confirms that

asymptomatic diastolic dysfunction is more prevalent in diabetic patients. In this study diabetics with LV diastolic dysfunction were significant positive correlation with the demographic parameters like HbA1c, FBS orLDLc level. In order to improve the current prognosis in subjects with diabetes mellitus, the treatment of diastolic heart failure must be optimized. Subject with type 2 DM should be screened for sub clinical diastolic dysfunction by echocardiography.

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