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Correlation between diastolic dysfunction and HBA1C levels in type II diabetes mellitus patients

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Abstract
Aim: To determine the correlation between diastolic dysfunction (DD) and HBA1C levels in type II diabetes mellitus patients.
Materials and Method: The present prospective study was conducted in the department of General Medicine, OPD, Medical wards, Chattrapati Shivaji Subharti Hospital, Meerut among 200 patients of Type 2 diabetes mellitus. Diabetes was diagnosed according to American diabetes association guidelines. Reduction in peak velocity of early mitral flow (E) increase over peak velocity of late mitral flow (A) with E/A ratio of <1 and increase in left atrial (LA) size with preserved ejection fraction were considered as the evidence of left ventricular diastolic dysfunction. Reduction in E velocity increase over A velocity with E/A ratio of <1 and increase in left atrial (LA) size with preserved ejection fraction (EF) was considered as the evidence of left ventricular diastolic dysfunction. Data was collected and subjected to statistical analysis.
Results: 66.5% subjects had HbA1c level ≥8.1 and 33.5% subjects had <8.1. Left atrium volume index and E/e′ were significantly higher in subjects with HbA1c≥8.1 as compared to subjects with HbA1c<8.1. Isovolumetric relaxation time was significantly less in subjects with HbA1c≥8.1 as compared to subjects with HbA1c<8.1. Among the subjects with <8.1 HbA1c level, incidence of LVDD was present in 37.31% subjects whereas among the subjects with HbA1c level ≥8.1, incidence of LVDD was present in 61.65% subjects.
Conclusion: HbA1C emerges as an important indicator of diastolic dysfunction in early onset diabetes population in the study.

Keywords: Diastolic dysfunction, left atrial, e/a ratio, ejection fraction

Introduction
Diabetes mellitus (DM) is a chronic health problem that has high morbidity and is rapidly spreading. It is estimated that by the year 2045, patients with DM will compromise approximately 9.9% of the total world population. Owing to the high prevalence of obesity and sedentary lifestyle, type II diabetes (T2DM) is diagnosed in approximately 90% of diabetes cases [1]. T2DM is a metabolic disorder characterized by hyperglycaemia and insulin resistance which contribute to different cardiovascular risk factors, such as dyslipidaemia, hypertension and obesity [2, 3].
T2DM is also associated with abnormally high levels of inflammatory mediators and cytokines and has renal as well as vascular complications. Together, these factors increase the cardiovascular risks in diabetic patients. Diabetic cardiomyopathy (DCM) is a major cardiac complication in diabetic patients. Recently, it was defined as myocardial dysfunction in a diabetic patient with the absence of any other possible cause for heart failure [4, 5].
Cardiovascular complications are known to be the main cause of morbidity and mortality in Diabetics. Other cardiovascular risk factors like hyperlipidemia, hypertension and obesity are common in diabetics. Atherosclerosis of the coronary arteries is by far the most common cause of cardiac involvement in diabetic patients [6]. The different synchronized pathological processes lead to myocardial fibrosis, which is considered the main cause of diastolic and systolic dysfunctions in the diabetic heart [7]. Diastolic dysfunction (DD) has been broadly defined as left ventricular diastolic dysfunction (LVDD) indicating a functional abnormality of diastolic relaxation, elasticity or distensibility of the left ventricle (LV), regardless of whether the left ventricle ejection fraction (LVEF) is normal or abnormal and whether the patient is symptomatic or not [8]. Left ventricular diastolic dysfunction (DD) may represent the initial stage of diabetic cardiomyopathy thus reinforcing the importance of the early examination of diastolic function in individuals with diabetes [9].

Two-dimensional and pulsed wave Doppler echocardiography together will non-invasively provide reliable information about diastolic performance. Usual evaluation of diastolic function includes peak velocity of transmittal flow during early diastolic filling (E wave), peak velocity of transmittal flow during late diastolic filling (A wave), E/A ratio, deceleration time (DT) of early filling velocity and the isovolumic relaxation time (IVRT, time from aortic valve closure to onset of mitral inflow) [10, 11].

The assessment of diastolic dysfunction with risk factor and variables of DM may aid the early and precise identification of individuals at risk of having diabetic cardiomyopathy. Echocardiographic correlation with HbA1c will help in triage for the optimal management of diabetes as well as the prevention of diastolic heart failure. So far, very few population-based studies have been carried out in India, to demonstrate the correlation between DD and HBA1C levels in type II diabetes mellitus patients. The relationship between DD and glycemic control is still a matter of debate. Thus, this cross-sectional study was conducted with the aim of determining the correlation between diastolic dysfunction (DD) and HBA1C levels in type II diabetes mellitus patients.

Materials and Method

The present prospective study was conducted in the department of General Medicine, OPD, Medical wards, Chattrapati Shivaji Subharti Hospital, Meerut among 200 patients of Type 2 diabetes mellitus. Ethical committee approval was obtained from the institutional ethical committee.

Diagnostic Criteria (American diabetes association) [12]

a. FBS ≥ 126 mg/dl,
b. 2 hr plasma glucose ≥ 200mg/dl during an OGTT,
c. RBS ≥ 200 mg/dl with symptoms (polyuria, polydipsia, polyphagia, weight loss),
d. HbA1C > 6.5%

Left Ventricular Diastolic Dysfunction [13]

Reduction in peak velocity of early mitral flow (E) increase over peak velocity of late mitral flow (A) with E/A ratio of <1 and increase in left atrial (LA) size with preserved ejection fraction were considered as the evidence of left ventricular diastolic dysfunction.

The subjects were recruited according to the following inclusion and exclusion criteria.

Inclusion Criteria

All Type 2 diabetes mellitus patients, diagnosed within last 5 years, who clinically have no cardiovascular symptoms and blood pressure of < 130/80 mmHg, with normal ECG.

Exclusion Criteria

- Extremes of age
- Moribund Patients
- Ischemic heart disease
- Hypertensive heart disease
- Congestive heart failure,
- Valvular heart disease
- Cardiomyopathy
- Connective tissue diseases
- Renal failure
- Thyroid dysfunction
- Known case of type 2 Diabetes mellitus >5 years duration

Investigations

a) RBS
b) Fasting Blood Sugar
c) Post Prandial Blood Sugar
d) Glycosylated haemoglobin (HbA1c)
e) Kidney Function Test (KFT)
f) Liver Function Test (LFT)
g) Fasting Lipid profile
h) Urine routine
i) ECG
j) Doppler Echo

In Doppler Echo study following values was evaluated

1. E - peak velocity of early mitral flow (N: 50-90 cm/sec)
2. A - peak velocity of late mitral flow (N: 30-70 cm/sec)
3. E/A ratio (N: 1-2)
4. Left atrial size (N: 3 – 4 cms)
5. EF (N: > 60%)

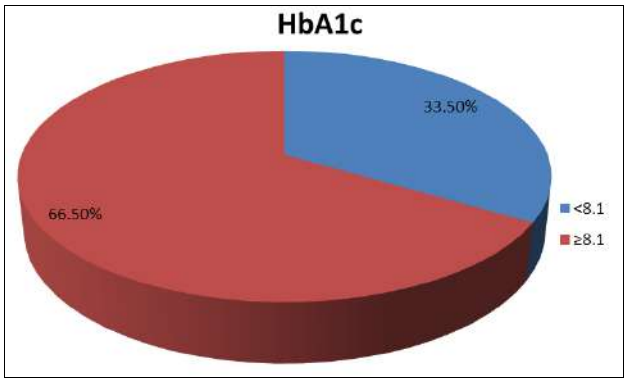
Reduction in E velocity increase over A velocity with E/A ratio of <1 and increase in left atrial (LA) size with preserved ejection fraction (EF) was considered as the evidence of left ventricular diastolic dysfunction. Data was collected and subjected to statistical analysis.

Statistical analysis

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p< 0.05$.

Results

The results showed that 66.5% subjects had HbA1c level ≥8.1 and 33.5% subjects had <8.1 (graph 1). It was found that among all the subjects with <8.1 HbA1c level, 21% were males and 12.5% were females while among all the subjects with ≥8.1 HbA1c level, 43.5% were males and 23% were females. The results were not statistically significant.



Graph 1: Classification of diabetic subjects according to HbA1c

It was seen that among the subjects with <8.1 HbA1c level, mean duration of diabetes mellitus was 4.11 ± 3.09 years while among the subjects with ≥8.1 HbA1c level, mean duration of diabetes mellitus was 4.93 ± 3.74 years. The

findings were not statistically significant. Subjects with <8.1 HbA1c level, mean BMI was 26.34 ± 4.28 while the subjects with ≥8.1 HbA1c level, mean BMI was 25.49 ± 3.95. All the findings were not significant statistically.
It was found that among subjects with <8.1 HbA1c level, mean urea (mmol/l) was 5.29±1.64, mean Creatinine (µmol/L) was 78.37±6.07, and mean eGFR (mL/min/1.73 m2) was 119.26±27.51. Among the subjects with HbA1c level ≥8.1, mean urea (mmol/l) was 5.56±1.79, mean Creatinine (µmol/L) was 74.03±5.93 and mean eGFR (mL/min/1.73 m^2) was 113.21±28.9. No statistical significance was seen (table 1).

Table 1: HbA1c according to KFT

KFT	HbA1c				p value
	<8.1		≥8.1		
	Mean	SD	Mean	SD	
Urea (mmol/l)	5.29	1.64	5.56	1.79	0.43
Creatinine (µmol/L)	78.37	6.07	74.03	5.93	0.39
eGFR (mL/min/1.73 m^2)	119.26	27.51	113.21	28.9	0.66

Table 2 shows the comparison between echocardiographic findings (systolic and diastolic functions) of the study group classified according to glycated HbA1c. It depicted that only the parameters like left atrium volume index (LAVI -ml/m2), (ms) and E/e′ were significantly higher in subjects with HbA1c≥8.1 as compared to subjects with HbA1c<8.1. Isovolumetric relaxation time was significantly less in subjects with HbA1c≥8.1 as compared to subjects with HbA1c<8.1.

Table 2: Comparison between echocardiographic findings (systolic and diastolic functions) of the study group classified according to glycated HbA1c

Parameters	HbA1c				p value
	<8.1		≥8.1		
	Mean	SD	Mean	SD	
Ejection fraction (%)	66.19	3.84	64.89	4.66	0.16
Left atrium size (cm)	3.68	0.32	3.81	0.35	0.24
Left atrium volume index (LAVI -ml/m^2)	28.84	2.87	31.1	3.39	0.026*
E wave (cm/s)	55.82	14.5	51.41	16.66	0.09
E/A ratio	1.11	0.23	0.94	0.29	0.11
Deceleration time (ms)	203.98	45.25	224.57	56.16	0.22
Isovolumetric relaxation time (ms)	97.06	20.72	85.38	28.01	0.046*
E/e′	9.37	1.45	11.14	2.03	0.021*

*: statistically significant

Among the subjects with <8.1 HbA1c level, incidence of LVDD was present in 37.31% subjects whereas among the subjects with HbA1c level ≥8.1, incidence of LVDD was present in 61.65% subjects. The results were statistically significant (table 3).

Table 3: Incidence of Left Ventricular Diastolic Dysfunction (LVDD) according to HbA1c

LVDD	HbA1c						p value
	<8.1		≥8.1		Total		
	N	%	N	%	N	%	
Present	25	37.31	82	61.65	107	53.5	0.022*
Absent	42	62.69	51	38.35	93	46.5	
Total	67	100	133	100	200	100	

*: statistically significant

LVDD was present in 0.93% subjects of age group 18-30 years, followed by 7.48% among 31-40 years age group, 28.97% among 41-50 years age group and 62.62% among > 50 years age group. The results were statistically significant (table 4).

Table 4: Incidence of LVDD according to age

Age Group (in Years)	LVDD				p value
	Present (N=107)		Absent (n=93)		
	N	%	N	%	
18-30	1	0.93	7	7.53	0.041*
31-40	8	7.48	22	23.66	
41-50	31	28.97	36	38.71	
>50	67	62.62	28	30.11	

*: statistically significant

Discussion: The LVDD represents the earliest pre-clinical manifestation of diabetic cardiomyopathy, preceding the systolic dysfunction and being able to evolve to symptomatic heart failure. Diastolic dysfunction is the dominant cause of the heart failure in patients having diastolic heart failure. Prevalence of LVDD in T2DM varies from 47% to 71% in different studies. There is significant uncertainty about whether a correlation exists between glycemic control and LVDD with studies showing mixed results [14, 15]. This study was done to know the burden of LVDD in patients with type 2 diabetes. 200 patients with Type 2 diabetes presenting to the Medicine out-patient service and those admitted to the medical wards at Chattrapati Shivaji Subharti Hospital, Meerut were included in the present study.
It showed that among all the subjects with <8.1 HbA1c level, 21% were males and 12.5% were females while among all the subjects with ≥8.1 HbA1c level, 43.5% were males and 23% were females. The results were not statistically significant. Similar findings were revealed by Chaudhary *et al.* [16], Yadava SK *et al.* [17] and Hassan Ayman *et al.* [18] in their studies.
It showed that the subjects with <8.1 HbA1c level, mean BMI was 26.34 ± 4.28 while the subjects with ≥8.1 HbA1c level, mean BMI was 25.49 ± 3.95. All the findings were not significant statistically. According to Chaudhary *et al.* [16], BMI in their study was also not found to be correlated with LVDD.
Among all echocardiographic Doppler parameters, E/e′ was a powerful predictor of myocardial infarction and stroke, comparable to HbA1c and even superior to global longitudinal strain and LVEF. Therefore, performing diastolic stress testing using these novel Doppler techniques could be helpful for unmasking an advanced degree of diastolic dysfunction in diabetic patients with apparently normal diastolic function or with early-stage diastolic dysfunction[1]. Parameters like Left atrium volume index (LAVI -ml/m2), (ms) and E/e′ were significantly higher in subjects with HbA1c≥8.1 as compared to subjects with HbA1c<8.1. Isovolumetric relaxation time was significantly less in subjects with HbA1c≥8.1 as compared to subjects with HbA1c<8.1. This may be explained by insulin resistance and subsequent hyperinsulinaemia which may stimulate prohypertrophic changes in the myocardium. This in turn leads to increased diastolic LV stiffness and increased cardiomyocyte hypertrophy which are determinants for cardiomyocyte resting tension that are independent of pressure overload [19]. Furthermore, a study

on hospitalized diabetic patients with symptomatic HF which included obtaining a left ventricular endomyocardial biopsy reported that cardiomyocyte resting tension was more important for the progression of LVDD in diabetic patients with normal LV EF, as seen in our study.

Similarly Hassan Ayman *et al.* [18] found that differences in the E/e′ ratio and LAVI were significant, with a higher degree of diastolic dysfunction in subjects having HbA1c level ≥8.1. Similarly, Agrawal *et al.* [20] observed that most of his patients with LVDD (73%) had impaired LV relaxation, 16% had a pseudonormal filling pattern and no patient had a restrictive filling pattern. On the other hand, Seferovic-Mitrovic *et al.* [2] found LVDD in only 11% of his patients, and all of them had only impaired relaxation, which can be explained on the basis of different study designs. Long-standing hyperglycaemia affects diastolic LV stiffness by multiple direct and indirect mechanisms.

Among the subjects with <8.1 HbA1c level, incidence of LVDD was present in 37.31% subjects whereas among the subjects with HbA1c level ≥8.1, incidence of LVDD was present in 61.65% subjects. The results were statistically significant. Accordingly, early detection of LVDD at the time of DM diagnosis and competent control of hyperglycaemia could interfere with the progression to overt HF and might even improve the prognosis of such patients.

Regarding the prevalence of LVDD, our results meet the findings of previously published reports. Poirier *et al.* [22] found that LVDD was present in 60% (28 out of 46) of asymptomatic patients with T2DM aged 38–67 years. Patil *et al.* [23] reported that 54% of patients with T2DM had asymptomatic LVDD. In a study by Jain *et al.* including 212 patients, 30% were found to have LVDD.

Because of the high prevalence of LVDD in T2DM, Mishra *et al.* [24] concluded that T2DM is a strong independent predictor of asymptomatic LVDD in the absence of other structural heart diseases. Similarly Hassan Ayman *et al.* [18] in their study revealed that incidence of LVDD was more in subjects having HbA1c level ≥8.1. Kumar *et al.* [25] stated that patients with HbA1c > 7.5% had a higher prevalence of diastolic dysfunction compared to HbA1c < 7.5%. Suresh *et al.* [26] found that patients with HbA1c>8.1% had a higher prevalence of diastolic dysfunction compared to HbA1c < 8.1%. However, Exiara *et al.* [27] in Greece in 2010 demonstrated 63.2% prevalence of diastolic dysfunction in well controlled T2DM (HbA1c<6.5) patients.

It was seen that LVDD was present in 0.93% subjects of age group 18-30 years, followed by 7.48% among 31-40 years age group, 28.97% among 41-50 years age group and 62.62% among > 50 years age group. The results were statistically significant. Hence age of patients was a risk factor for LVDD. Yadava SK *et al.* [17] in their study found that the prevalence of diastolic dysfunction increases with age: 23.1% in patients of age 30–39 yrs to 65.8% in patients of age 50–60 yrs. According to Chaudhary *et al.*[16], incidence of LVDD was also found higher in older patients group specially above 50 year and this correlation was most significant (p=0.0012).

Limitations

1. This cross-sectional study involved a relatively small number of patients in a single centre.
2. Lack of a control group and follow-up. Future studies with larger patient populations and a longitudinal cohort design including a control group are necessary to support our findings.
3. A coronary angiogram was not performed to rule out CAD, which may lead to the inclusion of subclinical or undiagnosed CAD cases.

Our current findings demonstrated a high prevalence of subclinical LVDD in asymptomatic early diagnosed T2DM patients. This high burden of LVDD was clearly manifested in the uncontrolled group and correlated with HbA1c.

Conclusion

This study shows that higher HbA1C level is strongly associated with presence of LVDD, considered as precursor of diabetic cardiomyopathy. HbA1C emerges as an important indicator of diastolic dysfunction in early onset diabetes population in the study. Age at the time of diagnosis of type 2 DM was predicted as the most important risk factor for LVDD in these patients.

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