Original Article

Association of Glycosylated Hemoglobin with Left Ventricular Diastolic Dysfunction in Type 2 Diabetes Mellitus

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Abstract

Background: Diabetes is the leading cause of death and disability among cardiovascular disease patients. By 2025, India will have people with diabetes to one in every five diabetics worldwide. **Aim:** The study examines the relationship between glycosylated hemoglobin (HbA1c) levels and left ventricular diastolic dysfunction (LVDD) in type 2 diabetes patients. **Settings and Design:** This was a cross-sectional observational study. **Materials and Methods:** Over 2 years, 345 subjects with type 2 diabetes mellitus who gave informed consent and met the inclusion criteria were studied. The HbA1c test was performed using ion-exchange high-performance liquid chromatography. Electrocardiogram and two-dimensional echocardiography were used to evaluate cardiac dysfunctions. The relationship between potential variables and outcomes was determined using logistic regression. **Statistical Analysis:** All statistical analyses were carried out using STATA version 13 (College Station, TX: Stata Corp LP). **Results:** Mean HbA1c levels were found to be higher in patients with LVDD (10.40% ± 4.25%) compared to normal LVDD (7.51% ±3.18%) ($P = 0.004$) in the current study. The predicted left ventricular (LV) function with an area under the receiver operating characteristic curve of 0.883. **Conclusions:** LVDD is a common finding in people with type 2 diabetes. LVDD causes various cardiac complications, including LV hypertrophy, which is concerning. The current findings suggest that HbA1c is a reliable predictor of LVDD that can be used for screening in resource-limited areas where echocardiography is unavailable. In addition, regular HbA1c screening and blood sugar control can help prevent cardiovascular complications caused by LVDD in type 2 diabetic patients.

Keywords: Echocardiography, glycosylated hemoglobin, left ventricular diastolic dysfunction, type 2 diabetes mellitus

Introduction

Diabetes mellitus is speedily becoming one of the leading causes of death worldwide. Because the trait is more heritable in Indians, they are more sensitive than other ethnic groups. Diabetes complications can occur in almost any system of the body.[1] Diabetes is the leading cause of death and disability among cardiovascular disease patients. By 2025, India will have people with diabetes to one in every five diabetics worldwide.[2] Diabetes patients can develop congestive heart failure (HF) even if they do not have other risk factors, such as coronary heart disease, hypertension, or structural heart problems.[3] Diastolic left ventricle dysfunction is the most pervasive and possibly earlier hemodynamic abnormality in diabetic cardiomyopathy following the stage is systolic dysfunction.[4] Left ventricular diastolic dysfunction (LVDD) and left ventricular (LV) hypertrophy are complications of type 2 diabetes mellitus (DM). Hyperinsulinemia and hyperglycemia may affect the left ventricle size in normotensive patients.[5] It is well known that echocardiography has increased sensitivity in detecting LV dysfunction and hypertrophy.[6] Diabetes patients with high glycosylated hemoglobin (HbA1c) levels have a larger LV mass.[7] As blood sugar stability improves, the risk of LV hypertrophy decreases.[8]

Obesity and being overweight are associated with LV dilation, hypertrophy, insufficient relaxation, and diastolic dysfunction. Excess weight can exacerbate insulin resistance, high blood sugar levels, and the risk of developing cardiovascular

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/mj.mj_42_23

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Submitted: 08-Jul-2023 **Revised:** 11-Aug-2023 **Accepted:** 19-Aug-2023 **Published:** 30-May-2024

How to cite this article: Rakhecha D, Patil BU, Parakh A, Yelwatkar S. Association of glycosylated hemoglobin with left ventricular diastolic dysfunction in type 2 diabetes mellitus. Mustansiriya Med J 2023;22:208-13.

disease.[9] Nonenzymatic glycosylation of hemoglobin occurs when glucose binds to the N-terminus of the chain. With a 1% decrease in the mean HbA1c level, the microvascular consequences could be reduced by 37%. HbA1c assesses, monitors, and predicts diabetic cardiovascular risk. As blood sugar stability improves, it decreases.[8] In asymptomatic diabetic Indian patients, diastolic dysfunction was directly related to HbA1c levels. Due to a lack of data on the relationship between HbA1c levels and LVDD in this population, the current study was conducted on a group of people with type 2 diabetes in central rural India.[10,11] The study examines the relationship between HbA1c levels and LVDD in type 2 diabetes patients.

Materials and Methods

This cross-sectional observational study was conducted on patients with type 2 diabetes who met the inclusion criteria from August 2020 to September 2022. The Institutional Ethical Committee approved the current study (MGIMS/IEC/MED/41/2021; January 21, 2021). Those between 30 and 60 years old, regardless of gender, with type 2 DM according to World Health Organization criteria, and American Diabetic Association criteria 2017 recommended for DM. The patients with known diabetes or on anti-diabetes medications and HbA1c >6.5% were included in the study. A patient with a drug abuse history, known high blood pressure with or without treatment, ischemic cardiovascular disease, cardiomyopathy, valvular heart disease, cardiac arrest, chronic pulmonary illness, severe anemia, or hemoglobinopathies were all excluded from participating.

Each patient's data were collected and recorded using a preprepared proforma. For each participant, a clinical history was taken, a thorough clinical assessment was performed, and fasting blood sugar (FBS), postprandial blood sugar (PPBS), and HbA1c levels were measured. The HbA1c test was performed using ion-exchange high-performance liquid chromatography. Electrocardiogram and two-dimensional (2D) echocardiography were used to evaluate cardiac dysfunctions. Imaging modes used in this study included dual 2D real-time, 2D and M mode, color Doppler, pulsed wave Doppler, and continuous wave Doppler. The same observer took all measurements and recordings, as the American Society of Echocardiography recommended. Patients were divided into two groups with or without LVDD by echocardiography.

With a 95% confidence interval and an expected frequency of 11% ±5%, the sample size was calculated using openEpi version-3 (because the expected frequency is higher in urban areas and lower in rural areas), confidence limits expressed as a percentage of 100 (absolute ± %) *d*: 5%, design effect (DEFF)-1 calculated using the following formula: $n = [\text{DEFFNp}\,(1 - \text{p})]$ sample size/$[(d2/Z21{-}\alpha/2\,(n - 1) + p\,(1 - p)]$. This resulted in a sample size of 345. A descriptive statistical analysis was performed, and the results of continuous measurements were classified into various value ranges and described in percentages (%). Next, a logistic regression analysis was performed to select the potential variables suitable for determining the association in the multivariable analysis. Finally, a multivariable logistic regression analysis was performed to determine the independent relationship of potential variables for the risk of LVDD. The logistic receiver operating curve was used to assess the predictive accuracy of the multivariable model. All statistical analyses were carried out using STATA version 13 (College Station, TX, USA: Stata Corp LP).

Results

The study included 345 people with type 2 diabetes who fulfilled the inclusion criteria. The majority of those aged 30–60 years (mean age: 50.63 ± 7.35) were males, with 209 (60.58%) outnumbering females (39.42%). Table 1 displays the baseline characteristics.

FBS, PPBS, and HbA1c levels were measured. All patients underwent echocardiography to assess LVDD. In 345 cases, 180 patients had LVDD and 165 had normal LVDD. LVDD was found in 180 (52.17%) cases, with 112 males and 68 females among them. No link was discovered between the study groups and the gender distribution shown.

The prevalence of LVDD varies between studies, which could be attributed to demographic and other risk factors. The diastolic dysfunction group had a higher mean age (47.08 ± 10.44 years in the normal group versus 59.17 ± 10.77 years in the dysfunction group; $P = 0.001$).

The baseline characteristics of patients with normal LV diastolic function and those with LVDD were compared. HbA1c, gender, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, and ejection fraction (EF) all showed no significant differences.

Mean HbA1c was found to be higher in the LVDD population (10.40% ±4.25%) than in the normal LVDD population (7.51% ±3.18%), which was statistically significant ($P = 0.004$).

A diabetic patient with a higher HbA1c level is at a higher risk of LVDD. As shown in Figure 1, the mean HbA1c value was 10.00 ± 4.18, the median was 9.5, the minimum was 5.2, and the maximum was 15.

DM patients had an overall LVDD prevalence of 52.17%. Grade I LVDD was present in 42.22% of these patients, 23.88% in Grade II, 21.11% in Grade III, and 12.77% in Grade IV. Table 2 depicts the mean distribution of echo findings.

As shown in Figure 2, the mean HbA1c value in patients with Grade I LVDD was 9.60 ± 4.2, 10.56 ± 3.7 in Grade II patients, 11.15 ± 4.8 in Grade III patients, and 12.405.4 in patients with Grade IV LVDD. The mean FBS of the LVDD population was higher (231.52 ± 49.36) than the normal LVDD population (208.15 ± 42.01).

Table 1: The clinical characteristics of patients with type 2 diabetes who have normal left ventricle diastolic function and left ventricular diastolic dysfunction

Characteristic	Normal LVDD	LVDD	*P*
Cases, *n* (%)	165 (48.83)	180 (52.17)	
Sex, *n* (%)			
Male	97 (58.78)	112 (62.22)	0.09
Female	68 (55.14)	68 (37.77)	0.561
Age (years), mean±SD	47.08±10.44	59.17±10.77	<0.001
HbA1c, mean±SD	7.51±3.18	10.40±4.25	0.023
Triglyceride (mmol/L), mean±SD	132.08±12.13	133.06±10.14	0.813
High-density lipoprotein (mmol/L), mean±SD	65.97±7.23	67.90±8.24	0.551
Low-density lipoprotein (mmol/L), mean±SD	130.67±20.85	132.55±21.90	0.057
BMI (kg/m^2), mean±SD	24.23±3.03	27.12±3.02	<0.001
EF, mean±SD	66.34±4.55	66.82±4.80	0.182
FBS, mean±SD	198.15±32.40	231.45±34.20	0.019
PPBS, mean±SD	225.25±30.75	350.30±45.15	0.0267

HbA1c: Glycosylated hemoglobin, BMI: Body mass index, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, SD: Standard deviation, LVDD: Left ventricular diastolic dysfunction, EF: Ejection fraction

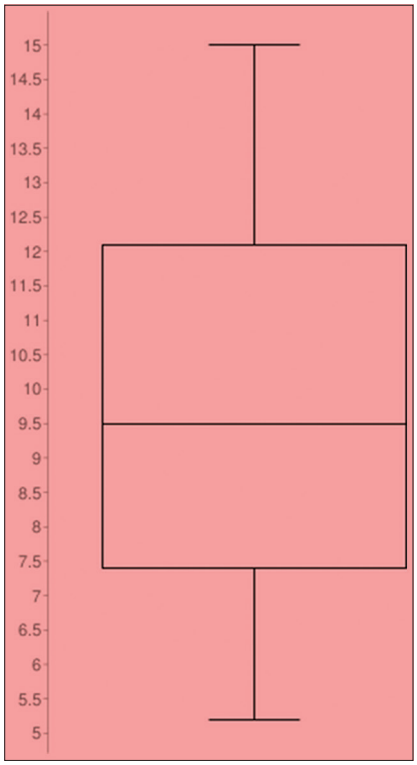

Figure 1: Box-and-whisker plot for glycosylated hemoglobin distribution

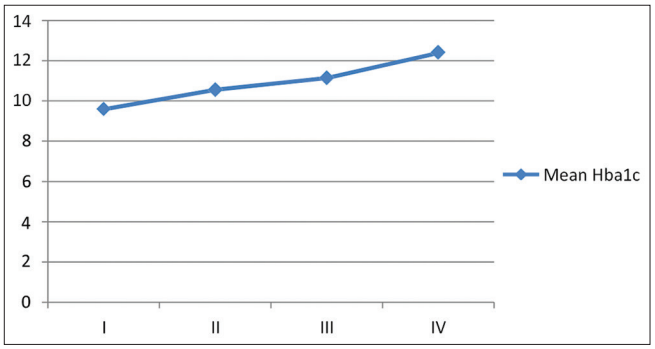

Figure 2: Mean distribution of glycosylated hemoglobin based on left ventricular diastolic dysfunction. HbA1c: Glycosylated hemoglobin

The mean PPBS of the LVDD population was also higher (362.24 ± 62.68) compared to patients with normal LVDD (313.54 ± 53.50), and the comparison was significant [Table 1]. This means that patients with diabetes will have a higher PPBS.[12]

As shown in Figure 3, the area under the curve for early rapid filling (E wave) and late filling (A wave) velocities (E/A) ratio prediction was 0.883, and for HbA1c, the prediction was 0.859. The best cutoff value for the E/A ratio for LVDD prediction was 0.8, with a sensitivity of 91.8% and specificity of 88.8%.

When predicting LVDD, the best HbA1c cutoff value was 9.5, with 85.8% sensitivity and 82.6% specificity. Using receiver operating characteristic analysis to compare the sensitivity and specificity of both scores, there appears to be a statistically significant difference in their ability to predict LVDD ($P = 0.001$) [Table 3].

Discussion

The participants' ages were between 30 and 60 years, with the mean age of the patients being 50.63 ± 7.35 years. Most patients are 51–60 years old, followed by 41–50 years. There was no relationship discovered between the study groups and gender distribution. DM patients had an overall LVDD prevalence of 52.17%.

The mean HbA1c in the LVDD population was found to be higher than in the normal LVDD population, which was statistically significant. This means that the higher the HbA1c of a diabetic patient, the greater the risk of LVDD. Table 4 summarizes studies that found an association between HbA1c and LVDD. Although the mechanism for the association of glycemic variability with LV diastolic function is not yet fully

Table 2: The mean distribution of echocardiography findings

Parameters	LVDD (n=180; 52.17)	No LVDD (n=165; 47.82)	P
E/A ratio	0.81±0.09	1.22±0.31	0.0120
LA diameter	33.17±9.12	27.6±12.31	0.0291
LVEF	63.13±6	67±5	0.0174
Deceleration time	230.45±56	220.40±45	0.0304
Grade of diastolic dysfunction, *n* (%)			
Grade I	76 (42.22)	-	-
Grade II	43 (23.88)	-	-
Grade III	38 (21.11)	-	0.054
Grade IV	23 (12.77)	-	-

E/A: Early rapid filling (E wave) and late filling (A wave) velocities, LA: Left atrial, LVEF: Left ventricle ejection fraction, LVDD: Left ventricular diastolic dysfunction

Table 3: Sensitivity and specificity of early rapid filling (E wave) and late filling (A wave) velocities ratio and glycosylated hemoglobin score for predicting left ventricular diastolic dysfunction

Test result variable	Area	SE	P	95% CI		Cutoff ≥	Sensitivity	Specificity
				Lower bound	Upper bound			
E/A ratio	0.883	0.042	<0.001	0.770	0.937	37.5	91 8	88.8
HbA1c	0.859	0.047	<0.001	0.737	0.921	6.5	85.8	82.6

E/A: Early rapid filling (E wave) and late filling (A wave) velocities, HbA1c: Glycosylated hemoglobin, SE: Standard error, CI: Confidence interval

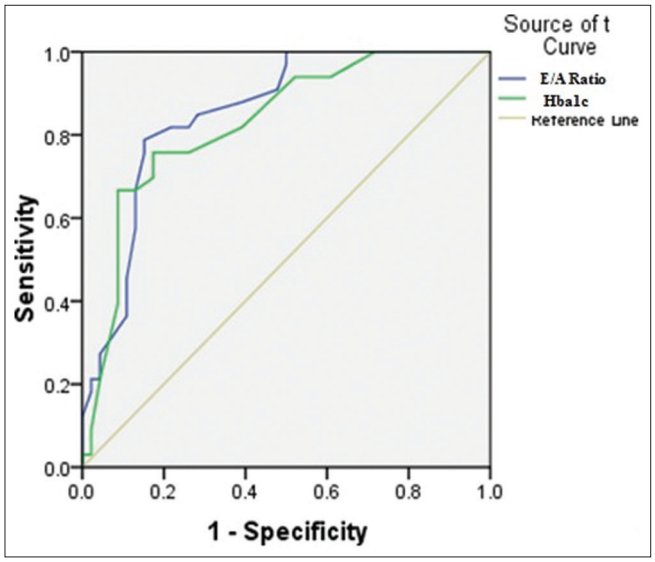

Figure 3: Receiver operating characteristic curve for predicting left ventricular diastolic dysfunction. HbA1c: Glycosylated hemoglobin

understood, preliminary studies suggest glycemic fluctuations play a role in promoting endothelial toxicity, oxidative stress, and ischemia. Furthermore, it was observed that increased advanced glycemic end products decreased cardiac ryanodine receptors/calcium-release channels and myocyte contractility; increased ventricular stiffness and causes impaired ventricular filling Furthermore, it has been reported that rapid glucose swings are also associated with more profound endothelial toxicity than are tonic glucose elevations *in vitro*.[23,24]

The mean FBS of the LVDD population was found to be higher (231.45 ± 34.20) than that of the normal LVDD population (198.15 ± 32.40), which was statistically significant. The mean PPBS of the LVDD population was also high (350.30 ± 45.15) compared to the LVDD population (225.25 ± 30.75). A previous study included 101 asymptomatic type 2 diabetes patients without overt heart disease; LVDD was significantly and positively correlated with increased FBS concentration.[22]

We discovered a highly significant link between the mean E value and LVDD. Late mitral flow's average peak velocity was 75.98 ± 13.06 and between A and LVDD. The typical E/A ratio was 1.02 ± 0.27. The E/A ratio is higher in patients with Grade 3 LVDD. There was a significant statistical relationship between LVDD and mean E/A. The mean deceleration time (DT) was 202.27 ± 31.22. The amount of time required to slow down increases as the LVVD grade increases. The mean DT and LVDD had a highly significant correlation. The average isovolumetric relaxation time was found to be 103.28 ± 30.61 s. This could be explained by insulin resistance and subsequent hyperinsulinemia in diabetes 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.[17-21]

The lengthening of isovolumetric relaxation time was statistically significant as the LVDD grade increased. In general, left atrials (LAs) were 3.40 ± 0.39 cm in size. Patients with LVDD Grade 3 had a larger mean LA size than those with Grades 2 and 1. Higher rates of LVDD were associated with larger LAs. According to their findings, the average size of the LA is 58.32 ± 2.35 mm. The relationship between mean EF

Table 4: Various studies have reported an association between glycosylated hemoglobin and left ventricular diastolic dysfunction, as discussed

Author	Country	Sample size	Main findings
Guria *et al*.[13]	Ranchi, India	100	The population with LVDD had a higher mean HbA1c (11.07%±3.66%) than the population with normal LVDD (9.11%±2.95%), which was statistically significant
Ceriello *et al*.[14]	Italy	One thousand five hundred thirty-three people with type 2 diabetes without cardiovascular diseases	The correlation between HbA1c variability and cardiovascular complications development was confirmed in both the subgroups of subjects with a mean HbA1c ≤53 mmol/moL (recommended HbA1c target) or >53 mmol/moL during the exposure phase. Furthermore, the risk related to HbA1c variability was higher in people with mean HbA1c ≤53 mmol/mol for the primary outcome (*P* for interaction 0.004), for the expanded secondary outcome (*P* for interaction 0.001), and the stroke (*P* for interaction 0.001), even though HbA1c remained at the target during the follow-up
Priya and Rekha[15]	Bangalore, India	100 diabetic patients	Fifty-eight out of 100 patients had LVDD, with a higher prevalence of HbA1c at >8%. Patients with diastolic dysfunction had a diabetes duration of diabetes that was >8 years
Hassan Ayman *et al*.[16]	Egypt	100 patients	LVDD was found in 75% of diabetic patients with HbA1c ≥8.1. There is a significant relationship between diastolic dysfunction and diabetes duration, with a higher occurrence of HbA1c >8.1
Li *et al*.[17]	China	466 T2DM patients	The annualized changes in the left ventricular end-diastolic diameter, interventricular septum, left ventricular posterior wall, left ventricular mass index, LVEF, E/e.' ratio, and E/A ratio were all independently correlated with HbA1c (*P*=0.001)
Gupta *et al*.[18]	Bareilly, India	49 patients	HbA1c levels ranging from 6.5 to 10 were found in 52.1% of diastolic LV dysfunction patients, with more than ten found in 47%. In patients with systolic LV dysfunction, 52.6% had HbA1c levels ranging from 6.5 to 100, and 47.4% had >10
Chandey *et al*.[19]	Punjab, India	100 patients of type 2 diabetes mellitus o	No statistical correlation was found between gender, duration of diabetes, and HbA1c with diastolic and systolic dysfunction
Suresh *et al*.[20]	Mangalore, India	50 people with diabetes and 50 healthy controls	Diastolic dysfunction was found in 36 (72%) diabetic patients and 15 (30%) healthy controls, and with a sensitivity of 80.6% and specificity of 71.4%, glycated hemoglobin value >8.1% indicated an increased prevalence of diastolic dysfunction in diabetic patients
Di Pino *et al*.[21]	Italy	167 subjects	Patients with HbA1c prediabetes (*n*=106) had a lower E/A ratio (early diastolic; E wave, mitral inflow to late diastolic atrial filling velocity; A wave) than controls (*n*=61) (1.10±0.24 vs. 1.18±0.23; *P*<0.05). In addition, they showed a higher left atrium volume (28.4±5 vs. 22.1±3; *P*<0.05) and sphericity index (0.6±0.06 vs. 0.5±0.05; *P*<0.05). HbA1c is the major determinant of the E/A ratio, LAV, and SI
Dhar *et al*.[22]	Jaipur, India	100 newly diagnosed type 2 diabetes patients	Patients with HbA1c <8 have a 16% chance of developing LVDD, while those with HbA1c 8–10 have a 30% chance, with *P*=0.02 and *P*=0.01, respectively

E/A: Early rapid filling (E wave) and late filling (A wave) velocities, LVDD: Left ventricular diastolic dysfunction, HbA1c: Glycosylated hemoglobin, SI: Sphericity index, LVEF: Left ventricular ejection fraction

and LVDD was highly significant. This could be explained by increased cardiomyocyte resting tension in LVDD patients as observed in a study on hospitalized diabetic patients with LV endomyocardial biopsy.[25]

In addition, studies have revealed a paradoxical or J-shaped relationship between HbA1c and outcomes, implying that hypoglycemia may negate the benefits of lower HbA1c.[6] Higher HbA1c levels in HF patients have been linked to an increased risk of death.[11]

The LVDD group had a significantly higher body mass index (BMI) (27.12 ± 3.02) than the normal group. Given the preceding findings, it is reasonable to infer that LVDD, a precursor to diabetic cardiomyopathy, and a higher HbA1c level are directly related. In early-onset diabetics, HbA1c was a significant predictor of diastolic dysfunction. Although the relationship between increase BMI and LV dysfunction may be associated with hemodynamic and anatomic cardiac changes related to excess body mass, recent evidence suggests that the relationship is also mediated by obesity-related inflammatory response, metabolic and insulin resistance, and hormonal changes. Increased inflammatory cytokines such as interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 have been shown to be significant indicators of a greater degree of HF with preserved EF. In addition, high plasma levels of tumor necrosis factor-α and interleukin-6 might cause cardiac diastolic dysfunction by reducing diastolic calcium reuptake in myocytes.[26]

The risk factors for LVDD in newly diagnosed diabetics were predicted to be age at the time of type 2 DM diagnosis, duration, and BMI. The study's strength is an adequate sample size drawn from a nearby region with a large population. A large multicentric randomized controlled trial with a longer follow-up period is possible. Future studies may benefit from thoroughly examining LV systolic and diastolic functions using novel strain and strain rate techniques and diastolic stress testing.

Conclusions

LVDD is a common finding in people with type 2 diabetes. LVDD causes various cardiac complications, including LV hypertrophy, which is concerning. The current findings suggest that HbA1c is a reliable predictor of LVDD that can be used for

screening in resource-limited areas where echocardiography is unavailable. In addition, regular HbA1c screening and blood sugar control can help prevent cardiovascular complications caused by LVDD in type 2 diabetic patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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