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The relationship between left ventricular diastolic dysfunction and hemoglobin A1c levels in the type 2 diabetes mellitus patient population

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ABSTRACT

Objectives: This study aimed to investigate the relationship between hemoglobin A1c (HbA1c) levels, which is a good marker for determining glycemic levels, and left ventricular diastolic dysfunction (LVDD) in the type 2 diabetes mellitus (DM) patient population.

Patients and methods: This retrospective study was conducted with 116 type 2 DM patients (62 males, 54 females; mean age: 58.4±9.5 years; range, 18 to 65 years) between July 2019 and November 2021. The patients were divided into two groups as those without LVDD (n=55, Group 1) and those with LVDD (n=61, Group 2). Early to late diastolic transmural flow velocity (E/A) ratio, the mean ratio (E/e') of mitral inflow (E) and mitral annular (e'), HbA1c levels, other hemogram and biochemical parameters, and demographic data were recorded.

Results: The HbA1c level was significantly higher in the group with LVDD (6.96±1.23 *vs.* 9.00±2.19, p<0.001). While the mean E/e' ratio was 9.69±2.73 in the group without LVDD, it was 16.00±1.69 in the group with LVDD, and there was a significant difference between the two groups (p<0.001). The mean E/A ratio was significantly higher in the group without LVDD (1.25±0.51 *vs.* 1.02±0.53, p=0.021). In regression operating characteristics analysis, a HbA1c cut-off value of 7.35 and was found to be a predictor of LVDD in the type 2 DM patient group with a sensitivity of 80% and specificity of 80% (AUC: 0.805; 95% confidence interval: 0.718-0.892; p<0.001).

Conclusion: Providing close glycemic follow-up and monitoring the HbA1c level can reduce heart failure and other comorbid conditions that may develop, particularly after LVDD.

Keywords: Diabetes mellitus, diastolic dysfunction, hemoglobin A1c.

Diabetes mellitus (DM) is one of the prominent health issues all over the world. Type 2 DM can cause microvascular damage in many organs, particularly the heart and kidney. Cardiovascular complications are the leading cause of mortality in patients with DM.[1] Diabetic cardiomyopathy (DCM) is generally considered to be the result of microvascular damage to the heart.[2] Diabetic cardiomyopathy may be considered in the etiology of heart failure (HF) when no other possible cause can be identified. Left ventricular diastolic dysfunction (LVDD) is the earliest functional change in DCM, followed by a progressive development of heart failure with preserved ejection fraction (HFpEF).[3] An effective treatment protocol for HFpEF has yet to be found. Therefore, it carries similar risks as systolic HF. Hyperglycemia in patients with DM can cause mitochondrial dysfunction, lipotoxicity, and abnormal substrate metabolism, and through this, it may also cause damage to the myocardial tissue.[4] One of the serological markers recommended for periodic glycemic control is Hemoglobin A1c (HbA1c), which has been the subject of research in recent years.[5] Hemoglobin A1c elevation may cause multisystemic adverse effects. In a recent study, it was revealed that the heart rate, cerebral oxygenation and cerebral perfusion were also lower in the group of patients with a higher HbA1c value who underwent cardiac surgery.[6] A 1% increase in HbA1c was associated with an 8% increased risk of developing HF, independent of other cardiovascular risks.[2] In addition, LVDD was found to be quite common in newly diagnosed

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DM patients and was associated with HbA1c levels, obesity, dyslipidemia, and the duration of diabetes.[7] Therefore, early diagnosis, follow-up, and treatment of DM patients before myocardial dysfunction and HF develop is crucial. Hemoglobin A1c can be an effective diagnostic method and screening tool in identifying patients with early changes in myocardial function.

This study aimed to investigate the relationship between HbA1c levels, which is a good marker for determining glycemic level, and LVDD in the type 2 DM patient population.

PATIENTS AND METHODS

This retrospective study was conducted with 116 consecutive type 2 DM patients (62 males, 54 females; mean age: 58.4±9.5 years; range, 18 to 65 years) at the Cardiology Departments of three hospitals, between July 2019 and November 2021. The patients included in the study were enrolled from three different centers. Inclusion criteria for the study were patients with a diagnosis of type 2 DM, who were evaluated by echocardiography (ECHO) and whose HbA1c level was followed. Exclusion criteria from the study were pregnant patients, active infection, malignancy, hematological diseases, rheumatological diseases, life expectancy <1 year, anemia, severe kidney or liver failure, acute coronary syndrome, coronary artery disease, moderate to severe heart valve disease, acute decompensated or cardiac failure, cardiac pacemaker implantation history, patients who were hypertensive at the time of examination (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), and patients with severe arrhythmia. The patients were divided into two groups as those without LVDD (n=55, Group 1) and those with LVDD (n=61, Group 2).

Venous blood samples were taken from all patients included in the study after an overnight fasting period. Blood was drawn from the anterior surface of the forearm in the supine position. For the complete blood count, blood was drawn into tubes containing standard EDTA, and measurements were made immediately after blood collection. Drugs used by the patients, demographic data, and echocardiographic data were obtained from hospital records.

Echocardiographic evaluation was performed with a GE Vivid 5 (5-1 MHz multi-frequency probe; GE Medical Systems, Milwaukee, USA) instrument using standard protocol. Echocardiographic images were obtained in four standard views (parasternal long axis, parasternal short axis, apical two chamber, and apical

Table 1
Demographic and comorbid characteristic results

	Group 1 (n=55)			Group 2 (n=61)			Total (n=116)			
Parameters	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			57.8±9.4			59.0±9.7			58.4±9.5	0.459
Sex										
Male			28±50.9			34±55.7			62±53.4	0.603
Systolic BP (mmHg)			124.15±17.8			131.48±18.9			128.0±18.7	0.034
Diastolic BP (mmHg)			69.44 ±10.6			72.67±11.7			71.1±11.3	0.123
Heart rate/min			72.9±11.7			74.0±13.9			73.5±12.9	0.635
Chest pain	28	50.9		32	52.5		60	51.7		0.868
Palpitation	13	23.6		15	24.6		28	24.1		0.905
Dyspnea	11	20.0		27	44.3		38	32.8		0.005
Smoker	21	38.2		29	47.5		50	43.1		0.309
Hypertension	26	47.3		31	50.8		57	49.1		0.703
Stroke/TIA	8	14.5		6	9.8		14	12.1		0.437
Hyperlipidemia	33	60.0		37	60.7		70	60.3		0.943
CKD	3	5.5		8	13.1		11	9.5		0.160

SD: Standard deviation; BP: Blood pressure; TIA: Transient ischemic attack; CKD: Chronic kidney disease.

four chamber) using the methods recommended by the American Society of Echocardiography.[8] The left ventricular ejection fraction was evaluated using Simpson's method from the biplane apical four-and two-chamber views.[8] Pulsed-wave Doppler-derived transmitral inflow velocities were measured in apical four-chamber imaging. While evaluating the diastolic parameters, a single measurement was made from an optimal image.

A detailed medical history was taken from all patients at the time of admission. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or using antihypertensive medication. Patients with a fasting glucose level ≥126 mg/dL, using antidiabetic agents, or HbA1c >6.5% were considered DM in accordance with the American Diabetes Association.[9] The tests were performed after anemia was excluded. The ratio (E/e') of mitral inflow (E) and mitral annular (e') velocities were obtained in apical four-chamber imaging using pulsed-wave Doppler. Patients with an early to late diastolic transmural flow velocity (E/A) ratio <1, mean E/e' >14, septal e' <7 cm/s, or lateral e' <10 cm/s were considered LVDD due to its high specificity.[10]

Statistical analysis

Data were analyzed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov and Shapiro-Wilk tests

Table 2
Hemogram, biochemical, and echocardiographic results

	Group 1 (n=55)			Group 2 (n=61)			Total (n=116)			
Parameters	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Uric acid (mg/dL)			5.30±1.02			5.41±1.02			5.36±1.02	0.590
Creatinine (mg/dL)			0.91±0.20			1.04±0.84			0.98±0.62	0.241
WBC (×10³/L)			8.11±2.06			8.62±2.62			8.98±2.18	0.202
Hemoglobin (g/dL)			13.64±1.28			13.48±1.59			13.55±1.45	0.566
Platelet (×10³/µL)			252.91±42.19			257.72±64.91			255.44±55.14	0.641
Total cholesterol (mg/dL)			195.78±57.18			182.34±48.10			188.72±52.80	0.172
Triglyceride (mg/dL)			156.16±76.54			171.09±135.31			164.01±111.17	0.473
HDL (mg/dL)			44.20±11.73			40.64±11.50			42.33±11.70	0.102
LDL (mg/dL)			118.73±55.64			119.98±93.56			119.38±77.60	0.931
Sodium (mEq/L)			137.58±13.72			139.36±2.79			138.52±9.66	0.324
Potassium (mmol/L)			4.48±0.39			4.51±0.47			4.49±0.43	0.686
HbA1c (%)			6.96±1.23			9.00±2.19			8.03±2.06	<0.001
TSH (µIU/mL)			2.01±1.28			2.25±1.41			2.13±1.35	0.345
LVEF (%)			57.9±5.3			57.8±4.3			57.9±4.8	0.950
LVEDD (mm)			47.09±3.49			47.77±4.81			47.45±4.23	0.390
LVESD (mm)			29.05±4.07			29.67±4.91			29.38±4.53	0.465
LVH	9	16.3		13	21.31		22	18.96		0.497
LA (mm)			35.31±7.25			36.38±5.27			35.87±6.28	0.361
E (cm/s)			104.52±37.32			85.51±29.58			94.53±34.67	0.003
A (cm/s)			87.81±25.14			91.39±24.27			89.7±24.65	0.438
Septal e′ (cm/s)			10.78±2.57			5.34±1.14			7.92±3.35	<0.001
E/A			1.25±0.51			1.02±0.53			1.13±0.53	0.021
E/e′			9.69±2.73			16.00±1.69			13.01±3.87	<0.001

SD: Standard deviation; WBC: White blood cell; HDL: High density lipoprotein; LDL: Low density lipoprotein; HbA1c: Hemoglobin A1c; TSH: Thyroid stimulate hormone; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; LVH: Left ventricular hypertrophy; LA: Left atrium.

Table 3
The drugs used by patients

Parameters	Group 1 (n=55)		Group 2 (n=61)		Total (n=116)		
	n	%	n	%	n	%	*p*
Beta-blockers	34	61.8	41	67.2	75	64.7	0.544
ACE-I	16	29.1	16	26.2	32	27.6	0.731
ARBs	8	14.5	15	24.6	23	19.8	0.175
MRAs	4	7.3	7	11.5	11	9.5	0.440
Dihydropyridine CCB	11	20.0	8	13.1	19	16.4	0.317
Non-dihydropyridine CCB	5	9.1	2	3.3	7	6.0	0.189
Statin	37	67.3	45	73.8	82	70.7	0.443
Furosemide	4	7.3	7	11.5	11	9.5	0.440
Thiazide diuretic	8	14.5	14	23.0	22	19.0	0.249
Antithrombocyte drugs	44	80.0	52	85.2	96	82.8	0.455

ACE-I: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin receptor blockers; MRAs: Mineralocorticoid receptor antagonists; CCB: Calcium channel blockers.

were applied to determine whether the study data were normally distributed. Categorical variables were expressed as frequencies and percentages, and quantitative variables were expressed as the mean and standard deviation. Receiver operating characteristics (ROC) analysis was performed to determine the HbA1c cut-off value. The cut-off value was determined according to the Youden index. The significance level was accepted as p<0.05.

RESULTS

There was no significant difference between the groups in terms of mean age and sex (57.8±9.4 *vs.* 59.0±9.7, p=0.459; 50.9% *vs.* 55.7%, p=0.603, respectively). Dyspnea finding was significantly higher in Group 2 (44.3% *vs.* 20%, p=0.005). There was no significant difference between the groups in terms of hypertension (47.3% *vs.* 50.8%, p=0.703) and chronic kidney disease (5.5% *vs.* 13.1%, p=0.160) (Table 1). Other demographic data and comorbid diseases of the groups are given in Table 1.

The HbA1c level was significantly higher in Group 2 (6.96±1.23 *vs.* 9.00±2.19, p<0.001). There was no significant difference between the groups in terms of left ventricular ejection fraction (57.9±5.3 *vs.* 57.8±4.3, p=0.950) and left ventricular hypertrophy (16.3% *vs.* 21.31%, p=0.497). While the E/e' ratio was 9.69±2.73 in Group 1, it was 16.00±1.69 in Group 2, and there was a significant difference between the two groups (p<0.001). A significant difference was observed between the two groups in E/A ratio (1.25±0.51 *vs.* 1.02±0.53, p=0.021, Table 2). Other hemogram, biochemical, and echocardiographic parameters are summarized in Table 2. The patients are compared in terms of the medical treatments they received in Table 3.

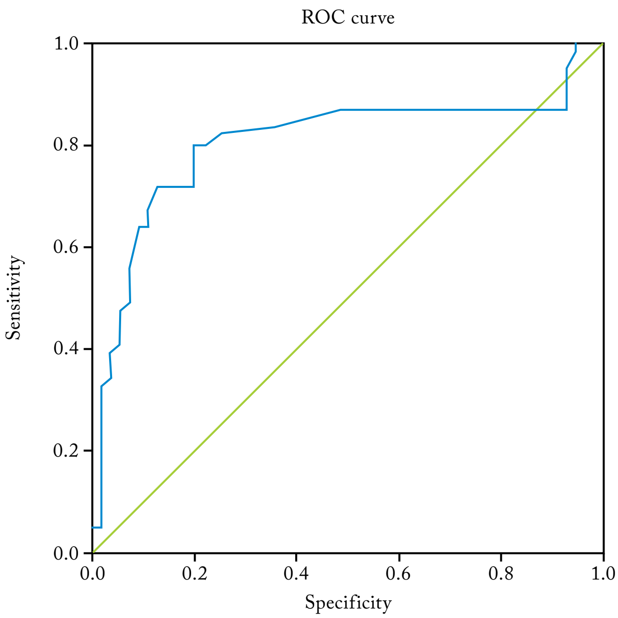

Figure 1. Cut-off value of HbA1c associated with LVDD in ROC curve analysis.
LVDD: Left ventricular diastolic dysfunction; HbA1c: Hemoglobin A1c; ROC: Receiver operating characteristics.

Receiver operating characteristics analysis was used to evaluate the power of HbA1c in predicting LVDD. Hemoglobin A1c was found to be a predictor of LVDD in the type 2 DM patients with a cut-off value of 7.35, sensitivity of 80%, and specificity of 80% (AUC: 0.805; 95% confidence interval: 0.718-0.892; p<0.001; Figure 1).

DISCUSSION

In our study, we determined that HbA1c levels may be a predictor of LVDD in type 2 DM patients. Hyperglycemia is a risk factor for HF in individuals with type 2 DM.[11] Structural, functional, and metabolic disorders develop as a result of the relationship between DM and HF. This leads to the emergence of more comorbid diseases and a worse prognosis. In addition, LVDD can be defined as the earliest functional change in type 2 DM patients.[12] Type 2 DM is known as an important factor associated with hypertension or obesity, as well as HFpEF, which often manifests as LVDD. Additionally, higher HbA1c levels have been associated with increased mortality in HF patients.[13] Hyperglycemia has deleterious effects on the myocardium. It up-regulates the renin-angiotensin-aldosterone system, increases oxidative stress, leads to the accumulation of glycation end products, and causes interstitial fibrosis in the heart muscle.[14] The HbA1c level is now recommended as the standard for testing and monitoring diabetes.[15] Giorda et al.[16] found that HbA1c is correlated with LVDD in patients with type 2 DM. Zuo et al.[17] revealed that the correlation between LVDD and HbA1c in type 2 DM patients was higher in patients with a normal body mass index. In a study by Di Pino et al.,[18] elevated HbA1c levels were associated with subclinical cardiac changes in patients with prediabetes, resulting in a lower E/A ratio and higher left atrial volume. Additionally, an independent relationship was found between E/e' ratio and HbA1c in this study.[18] In a recent study, it was emphasized that an E/e' ratio higher than 15 was associated with diastolic dysfunction.[19] This is consistent with our findings and previous studies conducted on patients with alterations in glucose homeostasis. Stahrenberg et al.[20] demonstrated in their study that glucose metabolism is associated with LVDD and HbA1c is associated with E/e' ratio. In another recent study, it was reported that hypoglycemia may also affect diastolic functions.[21] In addition, another study on the risk of atherosclerosis reported that the E/e' ratio was often within the normal range but was also positively associated with HbA1c.[22] These results reveal that HbA1c may be a marker of asymptomatic LVDD, the most prominent feature of DCM.[23] It has also been reported that a 1% increase in HbA1c level is associated with an 8% increase in the risk of HF.[24] Jain et al.[25] reported that the frequency of LVDD increases as the HbA1c level increases. Hameedullah et al.[26] found a strong correlation between HbA1c levels and diastolic indices in their study on 60 patients with type 2 DM. The results we obtained in our study support all these findings in the literature. As mentioned earlier, the pathogenesis of cardiac dysfunction associated with DM is multifactorial. Type 2 DM is thought to play a key role in the development of LVDD-related HFpEF.[23] Since there is still no effective pharmacological treatment in HFpEF patients, the importance of simple glycemic control with HbA1c monitoring becomes evident.

The main limitations of this study are its retrospective design and the relatively limited number of patients. In this respect, the results of the study cannot be generalized. In addition, we did not measure left atrial volume index (LAVI) during ECHO. In this respect, we did not examine all parameters indicative of diastolic dys function. Although we excluded many parameters that may affect diastolic functions, we could not exclude parameters that may affect diastolic functions such as chronic kidney disease, hypertension, and age. However, since there was no significant difference between the groups in terms of these parameters, we think that our study has a limited effect on the results. A single HbA1c value may not reflect the effect of hyperglycemia on diastolic function. In addition, we could not exclude the use of drugs that may have an effect on diastolic parameters.

In conclusion, as LVDD is quite common in the type 2 DM patient population and hyperglycemia is closely related to LVDD, providing close glycemic monitoring with HbA1c levels can reduce HFpEF development due to LVDD. Preventing the development of HFpEF is also of great importance in preventing long-term comorbid conditions.

Ethics Committee Approval: The study protocol was approved by the Bakırçay University Çiğli Training

and Research Hospital Ethics Committee (Date/no: 29.04.2022/580). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, data collection and/or processing, literature review, writing the article: T.G.; Idea/concept, design, control/supervision, data collection and/or processing, literature review, critical review: M.K.; Control/supervision, data collection and/or processing, analysis and/or interpretation, critical review: O.Ş.

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