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ORIGINAL RESEARCH

Elevated HbA1c Levels and Diastolic Discordance in Type 1 Diabetes: A Cardiac Echo Perspective

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ABSTRACT

Background: Type 1 diabetes mellitus (T1DM) predisposes individuals to cardiovascular complications, including diastolic dysfunction, even before overt heart disease manifests. Hemoglobin A1c (HbA1c) serves as a marker for long-term glycemic control and may influence cardiac function in T1DM. **Methods:** This cross-sectional observational study included 233 T1DM cases and 238 healthy controls to investigate the association between HbA1c levels and left ventricular diastolic function. Echocardiography assessed parameters including E/A ratio, E/e' ratio, left atrial volume index (LAVI), IVRT, DT, LV mass index, and LVEF. Statistical analyses included t-tests, correlation coefficients, and multivariate regression. **Results:** T1DM cases exhibited significantly impaired diastolic function compared to controls, as indicated by lower E/A ratio (0.85 vs. 1.20) and higher E/e' ratio (10.5 vs. 8.1), LAVI (28.4 vs. 24.3 mL/m²), IVRT (92.5 vs. 84.6 ms), DT (210.7 vs. 190.3 ms), LV mass index (95.2 vs. 88.1 g/m²), and slightly lower LVEF (62.5% vs. 64.1%). Elevated HbA1c levels correlated significantly with worsened diastolic parameters: negative correlation with E/A ratio ($r = -0.42$) and LVEF ($r = -0.22$), and positive correlations with E/e' ratio ($r = 0.39$), LAVI ($r = 0.35$), IVRT ($r = 0.30$), DT ($r = 0.28$), and LV mass index ($r = 0.25$) (all $p < 0.001$). **Conclusion:** Higher HbA1c levels are associated with impaired left ventricular diastolic function in T1DM patients without overt heart disease, highlighting the importance of glycemic control in mitigating early cardiac dysfunction. Regular monitoring and optimization of glycemic control may prevent the progression to symptomatic heart disease in T1DM.

Keywords: Type 1 diabetes mellitus, HbA1c, diastolic dysfunction, echocardiography, cardiovascular complications

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic condition characterized by autoimmune destruction of insulin-producing beta cells in the pancreas, leading to absolute insulin deficiency. This lifelong disease requires continuous management to maintain blood glucose levels within a target range, primarily through insulin therapy[1]. Despite advances in treatment, individuals with T1DM are at increased risk for various complications, both microvascular and macrovascular. Among these complications, cardiovascular disease stands out as a significant cause of morbidity and mortality[2]. While overt heart disease, such as coronary artery disease, is well-recognized in individuals with diabetes, there is growing interest in understanding subclinical cardiac abnormalities, particularly diastolic dysfunction, which may precede symptomatic heart disease[3].

Hemoglobin A1c (HbA1c) is a widely used marker for long-term glycemic control, reflecting average blood glucose levels over approximately three months. Elevated HbA1c levels are associated with a higher risk of diabetes-related complications[4]. The relationship between chronic hyperglycemia, as indicated by HbA1c, and cardiovascular complications in diabetes has been extensively studied. However, less is known about the specific impact of HbA1c on left ventricular diastolic function in patients with T1DM who do not yet exhibit overt heart disease[5].

Diastolic function refers to the ability of the left ventricle to relax and fill with blood during the diastolic phase of the cardiac cycle. Impaired diastolic

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function, or diastolic dysfunction, is an early marker of cardiac dysfunction and can occur independently of systolic dysfunction, where the heart's pumping ability is compromised. Diastolic dysfunction can lead to symptoms such as shortness of breath and exercise intolerance and may progress to heart failure with preserved ejection fraction (HFpEF), a condition where the heart pumps normally but is stiff and unable to fill properly[6].

Previous studies have indicated that diabetic cardiomyopathy, a specific form of heart disease in individuals with diabetes, may manifest as diastolic dysfunction before systolic dysfunction becomes apparent. Factors contributing to diastolic dysfunction in T1DM include hyperglycemia, insulin resistance, inflammation, oxidative stress, and myocardial fibrosis. Given the potential for early intervention to prevent progression to symptomatic heart disease, it is crucial to understand the relationship between glycemic control, as measured by HbA1c, and diastolic function in patients with T1DM[7,8].

The present study aims to investigate the relationship between HbA1c levels and left ventricular diastolic function in patients with T1DM who do not have overt heart disease. By focusing on a population without clinical heart disease, this study seeks to identify subclinical cardiac changes that could serve as early indicators of future cardiovascular risk. Echocardiography, a non-invasive imaging modality, will be used to assess diastolic function parameters, including E/A ratio (early to late ventricular filling velocities), E/e' ratio (early diastolic transmitral flow velocity to early diastolic mitral annular velocity), and left atrial volume index[9,10].

AIM

The primary aim of this study is to evaluate the association between HbA1c levels and left ventricular diastolic function in patients with type 1 diabetes mellitus without overt heart disease. Specifically, the study seeks to determine whether higher HbA1c levels are correlated with impaired diastolic function as assessed by echocardiographic parameters. By elucidating this relationship, the study aims to contribute to a better understanding of the cardiovascular risks associated with T1DM and to highlight the importance of optimal glycemic control in preventing subclinical cardiac abnormalities.

MATERIALS AND METHODS

Study Design and Population

This study is a cross-sectional observational study designed to investigate the relationship between hemoglobin A1c (HbA1c) levels and left ventricular diastolic function in patients with type 1 diabetes mellitus (T1DM) without overt heart disease. A total of 471 participants were recruited for the study, comprising 233 cases with T1DM and 238 healthy controls. Participants were selected from outpatient department.

Inclusion and Exclusion Criteria

Inclusion Criteria

1. **Cases:**
- Diagnosis of T1DM for at least one year.
- Age between 18 and 60 years.
- No clinical evidence of overt heart disease.
- HbA1c levels measured within the last three months.

2. **Controls:**
- Age- and sex-matched healthy individuals.
- No history of diabetes mellitus or cardiovascular disease.
- Normal fasting blood glucose levels.

Exclusion Criteria

- History of coronary artery disease, heart failure, or other significant cardiac conditions.
- Presence of renal disease (defined as eGFR < 60 mL/min/1.73 m²).
- Hypertension (blood pressure > 140/90 mmHg) or use of antihypertensive medications.
- Other systemic diseases or conditions that might affect cardiac function (e.g., thyroid disease, chronic inflammatory conditions).
- Pregnancy.

Data Collection

Clinical Data: Detailed clinical histories were obtained from all participants, including duration of diabetes, current medications, and presence of any diabetic complications. Physical examination was performed to measure body mass index (BMI), blood pressure, and heart rate.

Laboratory Data: Blood samples were collected to measure HbA1c, fasting blood glucose, lipid profile, serum creatinine, and estimated glomerular filtration rate (eGFR).

Echocardiographic Assessment

Echocardiography was performed on all participants using a standardized protocol by a trained cardiologist blinded to the clinical status of the participants. The following echocardiographic parameters were assessed to evaluate left ventricular diastolic function:

- **E/A ratio:** Ratio of early (E) to late (A) ventricular filling velocities.
- **E/e' ratio:** Ratio of early diastolic transmitral flow velocity (E) to early diastolic mitral annular velocity (e').
- **Left atrial volume index (LAVI):** Left atrial volume indexed to body surface area.

Statistical Analysis

Data were analyzed using SPSS software (version XX.0; IBM, Armonk, NY). Continuous variables were expressed as mean ± standard deviation (SD) and compared using the Student's t-test or Mann-Whitney U test as appropriate. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test.

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Primary Analysis: The primary analysis involved comparing echocardiographic parameters between cases and controls. Pearson or Spearman correlation coefficients were calculated to assess the relationship between HbA1c levels and diastolic function parameters in the T1DM group.

Multivariate Analysis: Multivariate linear regression analysis was conducted to adjust for potential confounders such as age, sex, BMI, blood pressure, and duration of diabetes. The dependent variables were echocardiographic measures of diastolic function, and the independent variable of interest was HbA1c level.

RESULTS

Table 1: Baseline Characteristics of Study Participants

Characteristic	Cases (n=233)	Controls (n=238)	p-value
Age (years)	35.2 ± 10.1	34.8 ± 9.8	0.652
Sex (Male/Female)	120/113	118/120	0.785
BMI (kg/m²)	25.1 ± 3.4	24.8 ± 3.6	0.489
Blood Pressure (mmHg)	120/80 ± 10/5	118/78 ± 9/6	0.324
HbA1c (%)	8.2 ± 1.5	5.1 ± 0.4	<0.001
Fasting Glucose (mg/dL)	150.3 ± 30.5	90.2 ± 10.1	<0.001
Duration of Diabetes (years)	15.4 ± 6.2	N/A	N/A

Table 1 presents the baseline characteristics of 233 patients with type 1 diabetes mellitus (cases) and 238 healthy controls. The average age and sex distribution are similar between groups, indicating appropriate matching. Body mass index (BMI) and blood pressure readings show no significant differences. However, significant differences are observed in HbA1c and fasting glucose levels, with cases showing higher values, reflecting poorer glycemic control. The average duration of diabetes in cases is 15.4 years. The p-values indicate statistical significance, with lower values (<0.05) for HbA1c and fasting glucose, confirming notable differences in these parameters between cases and controls.

Table 2: Echocardiographic Parameters

Parameter	Cases (n=233)	Controls (n=238)	p-value
E/A Ratio	0.85 ± 0.14	1.20 ± 0.18	<0.001
E/e’ Ratio	10.5 ± 2.1	8.1 ± 1.5	<0.001
Left Atrial Volume Index (mL/m²)	28.4 ± 5.6	24.3 ± 4.9	<0.001
IVRT (ms)	92.5 ± 12.3	84.6 ± 11.8	<0.001
DT (ms)	210.7 ± 25.4	190.3 ± 22.8	<0.001
LV Mass Index (g/m²)	95.2 ± 10.8	88.1 ± 9.7	<0.001
LVEF (%)	62.5 ± 5.4	64.1 ± 4.9	0.012

Table 2 shows significant differences in echocardiographic parameters between 233 type 1 diabetes mellitus patients and 238 healthy controls. Diabetic patients have a lower E/A ratio (0.85 vs. 1.20), higher E/e' ratio (10.5 vs. 8.1), larger left atrial volume index (28.4 vs. 24.3 mL/m²), longer IVRT (92.5 vs. 84.6 ms) and DT (210.7 vs. 190.3 ms), higher LV mass index (95.2 vs. 88.1 g/m²), and slightly lower LVEF (62.5% vs. 64.1%).

Table 3: Correlation of HbA1c with Echocardiographic Parameters in T1DM Patients

Parameter	Correlation Coefficient	p-value	Parameter
E/A Ratio	-0.42	<0.001	E/A Ratio
E/e’ Ratio	0.39	<0.001	E/e’ Ratio
Left Atrial Volume Index (mL/m²)	0.35	<0.001	Left Atrial Volume Index (mL/m²)
IVRT (ms)	0.30	<0.001	IVRT (ms)
DT (ms)	0.28	<0.001	DT (ms)
LV Mass Index (g/m²)	0.25	<0.001	LV Mass Index (g/m²)
LVEF (%)	-0.22	0.002	LVEF (%)

Table 3 shows the correlation between HbA1c levels and echocardiographic parameters in 233 type 1 diabetes patients. Significant negative correlations are observed with E/A ratio ($r = -0.42$, $p < 0.001$) and LVEF ($r = -0.22$, $p = 0.002$). Positive correlations are found with E/e' ratio ($r = 0.39$), left atrial volume index ($r = 0.35$), IVRT ($r = 0.30$), DT ($r = 0.28$), and LV mass index ($r = 0.25$), all with $p < 0.001$.

DISCUSSION

The present study investigated the relationship between HbA1c levels and left ventricular diastolic function in patients with type 1 diabetes mellitus (T1DM) without overt heart disease. By focusing on a population without clinical heart disease, this study aimed to identify subclinical cardiac changes that could serve as early indicators of future cardiovascular risk. Our findings reveal significant associations between elevated HbA1c levels and

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impaired diastolic function, suggesting that poor glycemic control may contribute to early cardiac dysfunction in T1DM patients[11].

Diastolic dysfunction is an early marker of cardiac dysfunction and can occur independently of systolic dysfunction. It is characterized by the left ventricle's impaired ability to relax and fill with blood during the diastolic phase of the cardiac cycle. In our study, we observed that T1DM patients had significantly lower E/A ratios and higher E/e' ratios compared to healthy controls[12]. These findings indicate that T1DM patients exhibit impaired diastolic function, even in the absence of overt heart disease[13].

The lower E/A ratio observed in T1DM patients suggests a reduced early diastolic filling velocity relative to late filling, which is indicative of impaired relaxation and increased stiffness of the left ventricle. Additionally, the higher E/e' ratio in T1DM patients indicates elevated left ventricular filling pressures, further supporting the presence of diastolic dysfunction[14,15].

Our study demonstrated significant correlations between HbA1c levels and various echocardiographic parameters of diastolic function. Higher HbA1c levels were associated with lower E/A ratios and higher E/e' ratios, as well as increased left atrial volume index, longer IVRT, longer DT, and higher LV mass index. These findings suggest that chronic hyperglycemia, as reflected by elevated HbA1c levels, may contribute to diastolic dysfunction in T1DM patients[16].

The mechanisms underlying the relationship between hyperglycemia and diastolic dysfunction are multifactorial. Chronic hyperglycemia can lead to insulin resistance, inflammation, oxidative stress, and myocardial fibrosis, all of which can negatively impact cardiac function. Hyperglycemia-induced advanced glycation end-products (AGEs) can also contribute to myocardial stiffness and impaired relaxation. These pathological processes may explain the observed associations between HbA1c levels and diastolic function parameters in our study[17-19].

The findings of this study have important clinical implications. Diastolic dysfunction is a precursor to heart failure with preserved ejection fraction (HFpEF), a condition where the heart's pumping ability is normal, but it is stiff and unable to fill properly. Identifying diastolic dysfunction at an early stage in T1DM patients could enable timely intervention to prevent the progression to symptomatic heart disease. Therefore, regular monitoring of diastolic function in T1DM patients, especially those with poor glycemic control, may be warranted[20-24].

Furthermore, our study highlights the importance of optimal glycemic control in preventing subclinical cardiac abnormalities. Targeting lower HbA1c levels through intensive insulin therapy and lifestyle modifications may help reduce the risk of diastolic dysfunction and subsequent cardiovascular complications in T1DM patients. Clinicians should emphasize the significance of maintaining good glycemic control to their patients, not only to prevent microvascular complications but also to protect cardiac function[25,26].

Limitations

Despite the strengths of this study, several limitations should be acknowledged. First, the cross-sectional design precludes establishing causality between HbA1c levels and diastolic dysfunction. Longitudinal studies are needed to confirm these findings and determine the temporal relationship between glycemic control and cardiac function in T1DM patients.

Second, our study relied on echocardiographic measures to assess diastolic function. While echocardiography is a widely used and non-invasive imaging modality, it may be subject to operator variability and technical limitations. Advanced imaging techniques, such as cardiac magnetic resonance imaging (MRI), could provide more detailed assessments of myocardial structure and function.

Third, the study population was recruited from a single institution, which may limit the generalizability of our findings. Future studies should include a larger and more diverse cohort of T1DM patients from multiple centers to validate the results.

Fourth, we did not account for other factors that might influence diastolic function, such as physical activity levels, dietary habits, and genetic predispositions. Including these variables in future studies could provide a more comprehensive understanding of the factors contributing to diastolic dysfunction in T1DM patients.

Lastly, while we excluded patients with overt heart disease and other significant comorbidities, the presence of subclinical atherosclerosis or early coronary artery disease could not be entirely ruled out. Coronary artery calcification scores or other assessments of subclinical atherosclerosis could be included in future studies to address this limitation.

CONCLUSION

In conclusion, our study demonstrates significant associations between elevated HbA1c levels and impaired diastolic function in patients with type 1 diabetes mellitus without overt heart disease. These findings suggest that poor glycemic control may contribute to early cardiac dysfunction in T1DM patients, highlighting the importance of maintaining optimal HbA1c levels to prevent subclinical cardiac abnormalities. Regular monitoring of diastolic function and intensive glycemic management should be considered in the clinical care of T1DM patients to mitigate future cardiovascular risk. Further research is needed to elucidate the underlying mechanisms and establish effective strategies for early intervention and prevention of cardiac complications in this population.

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