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Evaluation of the relationship between left ventricular diastolic function and longitudinal myocardial strain with echocardiographic parameters in Type 2 diabetic patients

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Abstract

Introduction: This study aimed to investigate the relationship between left ventricular diastolic function, longitudinal myocardial strain, and echocardiographic parameters in diabetic patients.

Methods: This cross-sectional analytical study included all eligible type 2 diabetes patients referred to Seyed al-Shohadah Hospital, Urmia, Iran from March 2021 to February 2022. All the participants had an echocardiography examination. Demographic characteristics including age, sex, duration of diabetes, smoking, and body mass index (BMI) were recorded at the time of the echocardiography examination.

Results: This study included 140 participants, 70 were diagnosed with type 2 diabetes mellitus (T2DM) and 40 were considered healthy control group. The mean age of participants was 47.79±7.08 years for diabetics and 47.23±6.5 years for controls. A significant correlation was observed between diabetes duration and the echocardiography values of E/e', DT, MPI, and D ($p < 0.05$). A significant correlation was observed between DT ($p=0.021$), IVPT ($p=0.037$), TRvel ($p=0.002$), and a-sep values ($p< 0.001$) and smoking in diabetic patients, with a negative correlation. Moreover, a statistically significant positive association was established between E/e´ ($p=0.043$), e' ($p=0.007$), e-lat ($p=0.046$), e-sep (0.003), and a-lat ($p=0.003$) values and smoking in diabetic patients. Furthermore, GLS scores and diastolic dysfunction exhibited a statistically significant association with smoking and BMI variables.

Conclusion: This study demonstrated a statistically significant association between diastolic dysfunction and global longitudinal strain (GLS) in both diabetic and control groups. This suggests that GLS can be utilized to assess the severity of diastolic dysfunction in diabetic patients during the early stages of heart failure.

Keywords: Type 2 diabetes mellitus, Global longitudinal strain, Subclinical LV dysfunction, diastolic heart failure

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Introduction

The presence of type 2 diabetes mellitus (T2DM) is independently associated with an increased risk of developing heart failure (HF), regardless of the presence of traditional risk factors for HF, including hypertension, obesity, hypercholesterolemia, coronary heart disease (CHD), valvular heart disease, and cardiac autonomic neuropathy [1,2]. In recent years, cardiovascular disease has emerged as the leading cause of morbidity and mortality among individuals with T2DM [3]. The pathological hallmarks of diabetic cardiomyopathy include myocardial apoptosis, fibrosis, and necrosis, which collectively contribute to the development of systolic and diastolic dysfunction, culminating in heart failure [4,5]. Early identification and intervention to preserve left ventricular function are crucial for preventing and managing diabetic cardiomyopathy [2].

In the early stages of diabetic cardiomyopathy, diastolic dysfunction is a prominent feature, while systolic dysfunction typically manifests later on [6,7]. Left ventricular diastolic dysfunction is widely recognized as an early hallmark of diabetic cardiomyopathy (DCM) [8]. However, preclinical systolic LV dysfunction has also been identified using echocardiographic strain measurements, a non-invasive approach for the early detection of myocardial dysfunction [9]. Strain is defined as the rate of deformation of a myocardial region and is expressed as a dimensionless quantity. Myocardial deformation imaging was initially enabled by tissue Doppler imaging (TDI), but more recently, myocardial speckle tracking with 2D echocardiography has provided more accurate strain measurements. These strain measurements have revealed LV longitudinal myocardial dysfunction in diabetic patients with preserved LV ejection fraction (LVEF) [10, 11] despite the absence of overt coronary artery disease or heart failure (HF) [1]. Moreover, global longitudinal strain (GLS) in diabetic patients has been reported to be significantly lower than in age-matched healthy controls despite similar LVEF values [8]. Notably, type 2 diabetic patients with preserved LVEF and GLS < 18.9 exhibit significantly poorer long-term cardiac outcomes [12,9]. These findings suggest that LV longitudinal myocardial dysfunction, rather than LV diastolic dysfunction, may serve as an early marker of a preclinical form of DM-related cardiac dysfunction in diabetic patients with preserved LVEF and the absence of overt HF [13].

To our knowledge, limited population-based investigations have explored preclinical diastolic dysfunction in diabetic patients. Given the growing prevalence of diabetes and the substantial economic, psychological, and health-related burdens associated with heart failure, this study aimed to assess the relationship between left ventricular diastolic function, longitudinal myocardial strain, and echocardiographic parameters in diabetic patients.

Methods

This cross-sectional analytical study was conducted according to the Principles of the Declaration of Helsinki and after approval by the ethics committee of Urmia University of Medical Sciences (Code: IR.UMSU.REC.1400.419) and informed consent was obtained from all participants. This study recruited all eligible T2DM patients who presented to Seyed al-Shohadah Hospital in Urmia, Iran, between March 2021 and February 2022. Patients were randomly assigned to two groups: the case group (T2DM patients with suboptimal glycemic control before hospitalization) and the control group (healthy participants of similar age and sex).

Eligible T2DM patients were required to meet the following criteria: clinically diagnosed with type 2 diabetes mellitus according to World Health Organization (WHO) guidelines [14]; no history of any cardiovascular conditions, including congenital heart disease, coronary artery disease, hypertension, myocardial infarction, cardiomyopathy, valvular disease, atrial fibrillation, thyroid disease, neoplasm, or kidney failure; absence of obesity or dyslipidemia; and age between 18 and 60 years. All participants underwent coronary computed tomography [10] or coronary angiography to rule out coronary artery disease. All T2DM patients had a left ventricular ejection fraction (LVEF) greater than 55%. Healthy controls were recruited from the hospital's physical examination program. In these healthy controls, all physical and laboratory tests, including cardiac function assessments, electrocardiogram (ECG), and echocardiography, were within normal limits.

Anthropometric and biochemistry

Demographic characteristics of participants were recorded at the time of the echocardiography examination, including age, sex, duration of diabetes, smoking and body mass index (BMI).

Conventional 2D Doppler echocardiography

Patients underwent conventional 2D transthoracic Doppler echocardiography with a Vivid E9 equipped with an M5S 3.5–5 MHz transducer (GE Vingmed Ultrasound, Horten, Norway) by an experienced cardiologist. All of the patients were connected to ECG leads. Apical 4-chamber, 2-chamber, and long-axis views of three consecutive cycles with a standard high frame rate (> 45 s^{-1}) were stored for offline analysis. The examination of echocardiography and the measurement of fasting plasma glucose, HbA1c, TCH, TG, HDL and LDL were performed in the same day. Echocardiographic parameters of Early diastolic flow velocity (E), early diastolic septal/lateral annular velocity (e′), late diastolic flow velocity (A), late diastolic septal/lateral annular velocity (a), E/A, E /e, pulmonary vein diastolic flow (D), pulmonary vein systolic flow velocity (S), isovolomic relaxation time (IVRT), tricuspid regurgitation peak velocity (TR velocity), Deceleration time (DT), myocardial performance index (MPI), Left Atrial volume index (LA volume index), global longitudinal strain (GLS) were measured during the examination.

Sample size

Drawing upon the findings of the study conducted by Patil et al. [15], and considering that approximately 35-40% of patients referred and hospitalized have diabetes, and accounting for sample attrition, including an error percentage of 0.5%, 70 diabetic patients and 70 non-diabetic patients were examined.

Statistical analysis

All statistical analyses were conducted using SPSS 21.0 software (SPSS, Chicago, IL, USA). The Shapiro–Wilk test or Kolmogorov–Smirnov test was employed to assess the normality of all variables. The independent Student's t-test was used to compare differences between T2DM patients and normal controls for normally distributed variables. For non-normally distributed variables, the nonparametric Mann–Whitney test was employed. To compare means of quantitative variables across multiple independent groups, the ANOVA test was used. Bivariate and Pearson's correlation coefficient were used to assess the relationships between quantitative variables, while Spearman's correlation coefficient was used for non-parametric variables. A p-value < 0.05 was considered statistically significant in all analyses.

Results

This study included a total of 140 participants, comprising 70 T2DM patients and 40 non-diabetic individuals. The average age of T2DM patients was 47.51 ± 7.32 years, ranging from 34 to 59 years. The non-diabetic group had a mean age of 47.23 ± 6.5 years. The gender distribution of T2DM patients was 57.1% male and 42.9% female, and the gender distribution of the non-diabetic group was 52.9% male and 47.1% female. The mean duration of T2DM in the 70 studied patients was 3.08 ± 0.3 years, with a minimum duration of 1 year and a maximum duration of 12 years. In the diabetic group, 44.3% of patients were current smokers, while 35.7% of patients in the non-diabetic group were current smokers. The mean BMI was 28.02 ± 3 (kg/m²) in T2DM patients and 21.9 ± 4 (kg/m²) in non-diabetic patients. Grade 1 diastolic dysfunction was the most common in both T2DM and control groups (34.3% and 20%, respectively) (Table 1).

Table 1. Basic information of the T2DM and control group

	T2DM (n=7)	Normal (n=70)
Gender		
Male	57.1%	52.9%
Female	42.9%	47.1%
Mean Age (years)	47.51 ± 7.32	47.23 ± 6.5
BMI (kg/m^2)	28.02±3	21.9±4
Mean disease duration	3.08 ± 0.3	-
Smoking	44.3%	35.7%
Diastolic dysfunction		
Grade 1	24(34.3%)	14(20%)
Grade 2	3(3.4%)	0(0)
Grade 3	0(0)	0(0)
normal	43(61.4%)	56(80%)

Mean values for E/e', IVRT, Trvel, MPI, S, D, and A were elevated in T2DM patients compared to normal controls. However, statistically significant differences between the two groups were observed for E/e' (p< 0.001), MPI (p=0.004), D (p< 0.001), and A (p=0.01). Mean values for Lavi, DT, e-sep, and E/A were significantly higher in the control group compared to the T2DM group (p < 0.05) (Table 2).

Table 2. Comparison of echocardiography values between two studied groups

Echocardiography	T2DM (n=7) Mean ± SD	Normal (n=70)	P-value
E	0.75± 0.045	0.76±0.056	0.59
A	0.7±0.1	0.64±0.92	0.01
E/A	1.11±0.18	1.20±0.17	0.003
a-sep	0.088±0.007	0.088±0.008	0.75
a-lat	0.108±0.011	0.106±0.01	0.28
e-sep	0.075±0.011	0.081±0.009	< 0.001
e-lat	0.092±0.008	0.095±0.007	0.02
e´	0.084±0.009	0.088±0.007	0.01
E/e´	9.09±0.80	8.58±0.75	< 0.001
DT	197.7±11.7	224.15±15	< 0.001
IVRT	80.58±7.5	75.52±3.45	0.06
Trvel	2.53±0.15	1.81±1.45	0.052
MPI	0.40±0.036	0.38±0.027	0.004
S	0.38±0.037	0.29±0.029	0.9
D	0.32±0.05	0.29±0.32	< 0.001
Lavi	24.08±4.27	23.44±3.17	0.05
GLS	-17.42±2.3	-18.27±1.93	0.21

In light of the non-parametric nature of GLS and diastolic function, the Spearman test was used to evaluate the statistical relationship between these two variables in the diabetic group. The findings indicated a statistically significant correlation between these two variables (p-value < 0.001). Furthermore, a Spearman's rho value of 0.848 underscored a strong and direct correlation, demonstrating that higher GLS values are associated with improved diastolic function.

According to Table 3, no statistically significant connection was established between diabetes duration and diastolic dysfunction in the T2DM group (P-value = 0.452). The results failed to reveal a statistically significant correlation between these two variables (P-value = 0.537). Despite this, a significant correlation was observed between diabetes duration and the values of E/e', DT, MPI, and D (p < 0.05). No statistically significant differences were detected between other echocardiography parameters and diabetes duration in the diabetic group (Table 3).

No statistically significant association was found between smoking status in diabetic patients and the E, A, E/A, TR vel, S, and D, MPI, LAvi echocardiography parameters (p < 0.05). However, a significant correlation was observed between DT (p=0.021), IVPT (p=0.037), TRvel (p=0.002), and a-sep (p< 0.001) and smoking in diabetic patients, with a negative correlation coefficient. This indicates that these parameters were lower in smokers with diabetes than in non-smokers without diabetes. Moreover, a statistically significant correlation was established between E/e´ (p=0.043), e' (p=0.007), e-lat (p=0.046), e-sep (0.003), and a-lat (p=0.003) values and smoking in diabetic patients, with a positive correlation coefficient. This suggests that these values were higher in smokers with diabetes than in non-smokers without diabetes. Furthermore, GLS scores (p=0.032) and diastolic dysfunction (0.043) exhibited a statistically significant association with smoking status. The correlation coefficient revealed that smokers had higher grade diastolic dysfunction compared to non-smokers (Table 3).

A statistically significant correlation was established between all echocardiography parameters and BMI in diabetic patients. The positive correlation coefficient indicated a direct relationship between the values of a-sep, a-lat, E, E/A, E/e', IVRT, TR vel, MPI, S, and LAvi and BMI. On the other hand, a significant negative relationship was observed between the values of e-sep, DT, e-lat, D, and e'/A and BMI. This implies that higher BMI values correspond to lower values of these parameters. Additionally, a statistically significant positive correlation was found between GLS values and BMI. Using the Spearman's test, a statistically significant association was established between BMI and the severity of diastolic dysfunction (P-value < 0.001 and correlation coefficient=0.813). This indicates that higher BMI values correspond to higher grades of diastolic dysfunction.

In the non-diabetic group, a statistically significant correlation was observed between the grade of diastolic dysfunction and GLS (P-value < 0.001 and Spearman's rho = 0.603). This suggests that higher grades of diastolic dysfunction are linked to lower GLS values. No statistically significant correlation was found between echocardiography parameters, the degree of diastolic dysfunction, or smoking status in non-diabetic patients (p=0.54 and correlation coefficient=0.075). No statistically significant relationships were observed between the values of a-sep, a-lat, E/e', S, and LAvi and BMI in non-diabetic patients (p< 0.05).

A statistically significant inverse relationship was detected between the values of E, E/A, e-sep, e-lat, e', DT, and BMI in non-diabetic patients (p< 0.001 & correlation coefficient= -0.480). This indicates that higher BMI values correspond to lower values of these parameters. Moreover, a statistically significant direct relationship was found between the values of A, IVRT, TRvel, MPI, and D and BMI in non-diabetic patients (p< 0.001 & correlation coefficient= 0.581). This suggests that higher BMI values are linked to higher values of these parameters. A statistically significant positive correlation was also observed between GLS and BMI in non-diabetic patients (p< 0.001 & correlation coefficient= 0.480). This indicates a direct relationship between these two variables. A direct statistical relationship was established between BMI and the severity of diastolic dysfunction in non-diabetic patients (P-value = 0 and Spearman's rho = 0.581). This suggests that higher BMI values correspond to higher grades of diastolic dysfunction (Table 3).

Table 3. Correlation of echocardiography parameters with demographic variables between two studied groups

Echocardiography values	T2DM						Non-diabetic			
	Disease duration		Smoking		BMI		Smoking		BMI	
	P-value	Pearson Correlation	P-value	Pearson Correlation	P-value	Pearson Correlation	P-value	Pearson Correlation	P-value	Pearson Correlation
E	0.311	0.123	0.126	0.185	< 0.001	0.461	0.404	-0.101	0.003	-0.352
A	0.211	0.151	0.181	0.162	< 0.001	-0.703	0.555	-0.072	< 0.001	0.447
E/A	0.395	-0.103	0.237	0.143	< 0.001	0.735	0.68	0.05	< 0.001	-0.515
a-sep	0.657	0.054	< 0.001	-0.423	< 0.001	0.484	0.499	0.082	0.247	-0.14
a-lat	0.442	0.093	0.003	0.346	0.001	0.378	0.455	0.091	0.603	-0.053
e-sep	0.987	-0.002	0.003	0.348	< 0.001	-0.553	0.188	0.159	< 0.001	-0.411
e-lat	0.937	0.010	0.046	0.239	0.043	-0.242	0.265	0.135	0.025	-0.268
e´	0.981	0.003	0.007	0.318	< 0.001	-0.446	0.132	0.182	0.001	-0.384
E/e´	0.031	0.039	0.043	0.242	0.045	0.241	0.074	-0.215	0.597	0.064
DT	0.049	0.032	0.021	-0.276	0.003	-0.354	0.903	0.105	0.002	-0.358
IVRT	0.561	0.071	0.037	-0.249	< 0.001	0.601	0.487	0.084	0.001	0.383
TRvel	0.791	0.032	0.002	-0.367	0.001	0.388	0.596	0.064	< 0.001	0.593
MPI	0.025	0.004	0.298	0.126	< 0.001	0.502	0.233	0.144	0.001	0.375
S	0.580	-0.067	0.023	-0.271	0.001	0.38	0.309	-0.123	0.092	0.203
D	0.043	0/041	0.311	-0.123	< 0.001	-0.508	0.254	-0.138	< 0.001	0.433
LAvi	0.917	0.013	0.161	0.161	< 0.001	0.721	0.691	0.048	< 0.001	0.525
GLS	0.537	-	0.032	0.171	< 0.001	0.762	0.278	0.131	< 0.001	0.48
Diastolic dysfunction	0.452	-	0.043	0.131	< 0.001	0.813	0.54	0.075	< 0.001	0.581

Discussion

Left ventricular dysfunction has emerged as a prevalent comorbidity in individuals with diabetes [16]. T2DM-induced cardiac impairment encompasses microvascular dysfunction, metabolic disturbances, subcellular abnormalities, cardiac autonomic dysfunction, and an aberrant immune response [17]. Ultimately, T2DM leads to functional and structural modifications in the myocardium, even in the absence of coronary artery disease, a condition termed diabetic cardiomyopathy [18]. This study aimed to determine left ventricular diastolic function and GLS using echocardiographic parameters in diabetic patients.

Despite a normal LVEF, myocardial dysfunction can manifest as abnormal deformation in diabetic patients without CAD [19]. LVEF could be normal but myocardial dysfunction in terms of abnormal deformation is not [16]. GLS is an effective tool for detecting myocardial abnormalities before LVEF declines [20]. A recent study by Holland et al. assessed 10-year outcomes in subclinical myocardial dysfunction by analyzing GLS in 249 type 2 diabetic patients with normal LVEF [21]. Holland's findings revealed that nearly half of the patients (45%) exhibited evidence of subclinical LVD detected by GLS over a median follow-up period of 7.4±2.6 years. Independently of other factors, GLS was strongly associated with the primary endpoint, indicating that patients with LVD had a significantly worse outcome compared to those without. This study concluded that subclinical LVD is a common occurrence in asymptomatic type 2 diabetic patients and is detectable by GLS imaging, with independent prognostic implications [22]. Our study also demonstrated a significant reduction in GLS in diabetic patients compared to controls (p=0.001). Consistent with our findings, Liu et al. [23] investigated the prognostic value of GLS in T2DM patients and found that in T2DM patients without a history of cardiovascular disease, impaired GLS was associated with an increased risk of cardiovascular events.

The mean age of the patients with T2DM in our study was significantly younger (47.51 ± 7.32 years). This finding suggests that left ventricular dysfunction may manifest early in the course of the disease in diabetic patients with normal blood pressure and well-controlled blood sugar levels [24]. Our study also revealed a higher prevalence of T2DM among men compared to women. Similar findings were reported in another study, which indicated that the incidence of type 2 diabetes mellitus is rising in both genders, but men are typically diagnosed at a younger age and with lower body fat levels than women [25]. Conversely, a different study observed that women generally carry a greater burden of risk factors at the time of their type 2 diabetes diagnosis, particularly obesity [26]. Additionally, psychosocial stress may have a more pronounced impact on diabetes risk in women [27]. Throughout their lives, women experience more pronounced hormonal fluctuations and body changes due to reproductive factors compared to men [28].

Diabetic patients demonstrated a significantly higher BMI compared to the non-diabetic group. Excess weight and obesity have been recognized as major contributing factors to type 2 diabetes and its complications in both genders [29]. Our findings align with previous studies that have demonstrated a stronger association between BMI and the onset of type 2 diabetes [30]. One study reported that Grade 1 diastolic dysfunction was the most prevalent form of diastolic dysfunction among T2DM patients [31]. The prevalence of diastolic dysfunction in diabetic patients is significantly higher (54.33%) than in the general population (11%) [15]. Numerous studies in patients with diabetes have identified diastolic dysfunction as the earliest functional alteration in the development of diabetic cardiomyopathy [32], [33]. A statistically significant association was observed between BMI and diastolic dysfunction grade, indicating that higher BMI values were linked to higher grades of diastolic dysfunction. Cardiovascular risk factors, including hypertension, diabetes, and elevated LV mass, adversely affect LV diastolic function [34]. However, BMI remained significantly associated with LV diastolic function parameters and was the primary predictor of LV mass [35].

On average, the values of E/e, IVRT, Trvel, MPI, S, D, and A were significantly higher in T2DM patients compared to the normal control group. This finding aligns with the results of a study by Zoppini et al. [36], which reported a significantly higher average E/e' ratio in patients with type 2 diabetes. These findings suggest that LVDD may be present in type 2 diabetes patients even in the absence of overt cardiovascular complications. Echocardiography parameters have been demonstrated to have a substantial prognostic value for various outcomes, such as all-cause mortality, cardiovascular death, and heart failure hospitalization [36]. Notably, a 4-year longitudinal study indicated that a progressive decline in the E/e' ratio was associated with an increased risk of developing heart failure [37].

Insulin resistance/hyperinsulinemia and pre-diabetic conditions, such as obesity, dysglycemia, and others, are the primary mechanisms that contribute to myocardial alterations in T2DM. These metabolic abnormalities may persist for years or even decades before the manifestation of overt diabetes, potentially leading to myocardial dysfunction during this preclinical stage [38]. Left ventricular diastolic dysfunction is prevalent in approximately 75% of T2DM patients. Additionally, considering the demographic characteristics of these patients, including younger age, normal blood pressure, and well-controlled blood sugar levels, it is reasonable to hypothesize that left ventricular dysfunction may develop early in the course of the disease [39].

No statistically significant relationship was detected between the duration of diabetes and the severity of diastolic dysfunction in this study. However, a study by Patil et al. reported a higher prevalence of diastolic dysfunction among patients with a diabetes duration of 11-15 years, suggesting a potential association between diabetes duration and the development of diastolic dysfunction [15]. The disparity between these findings could be attributed to possible inaccuracies in patients' self-reported diabetes diagnosis dates. Additionally, cumulative exposure to hyperglycemia may be a significant factor in the pathogenesis of LV diastolic dysfunction [40]. Consistent with previous studies [41], our study found that smokers exhibited a more severe form of diastolic dysfunction compared to non-smokers, and they also had lower GLS values.

Limitations of study

This study's primary limitations include its small sample size and single-center design. Additionally, some clinical data for the T2DM patients were incomplete. Another limitation was the absence of an assessment of the metabolic control status of the patients and its potential impact on the investigated parameters.

Conclusion

This study's findings revealed that the occurrence of diastolic dysfunction, its related parameters, and GLS dysfunction was markedly more prevalent among diabetic patients than non-diabetic patients. Additionally, diabetic patients who smoked and had a higher body mass index (BMI) exhibited more severe abnormalities in diastolic function parameters. This suggests that GLS can be utilized to assess the severity of diastolic dysfunction in diabetic patients during the early stages of heart failure.

Highlights

What Is Already Known?

The presence of T2DM is independently associated with an increased risk of developing HF.

What Does This Study Add?

This study's findings revealed that the occurrence of diastolic dysfunction, its related parameters, and GLS dysfunction was markedly more prevalent among diabetic patients than non-diabetic patients. Additionally, diabetic patients who smoked and had a higher body mass index (BMI) exhibited more severe abnormalities in diastolic function parameters. This suggests that GLS can be utilized to assess the severity of diastolic dysfunction in diabetic patients during the early stages of heart failure

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Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Urmia University of Medical sciences (No. IR.UMSU.REC.1400.419).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Author contributions

M H: Conceptualization, the original draft writing, investigation, writing including reviewing and editing and investigation and formal analysis; A R: Conceptualization, supervision, and project administration; A KH: Investigation, writing including reviewing and editing

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