Original Article

Correlation Between Type II Diabetes Mellitus and Left Atrial Function as Assessed by 2D Speckle-Tracking Echocardiography in Patients Without Coronary Artery Disease

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ABSTRACT

Background: Diabetes mellitus (DM) is associated with several comorbidities and complications such as hypertension, obesity, hyperlipidemia, nephropathy, and cardiovascular diseases. This study aimed to investigate the correlation between the left atrial (LA) function and DM via conventional and speckle-tracking echocardiography (STE).

Methods: In this prospective study, from 198 patients with sinus rhythms, 174 patients were included based on inclusion and exclusion criteria. Conventional and STE examinations were done for all the patients. The patients' demographics, comorbidities, and family history, as well as the results of their angiography or computed tomography angiography, electrocardiography, and echocardiography, were recorded. The variables were compared between the groups with and without DM, and the association between the LA function and DM was studied in the patients.

Results: Totally, 45.2% of the diabetic patients (n = 28) and 38.4% of the nondiabetic patients (n = 30) had diastolic dysfunction (P = 0.384). The diabetic patients had a lower mean of the left ventricular end-diastolic diameter, the LA peak strain during the reservoir phase, the LA pump, and the LA peak positive strain rate during ventricular systole (all Ps < 0.001) and a higher mean of the left ventricular mass index, the A-wave, the E/A, the LA peak negative strain rate during early diastole (all Ps <0.001), the left ventricular end-systolic volume (P = 0.001), the Ea (P = 0.008), the LA ejection fraction (P = 0.011), and the passive emptying volume (P = 0.026).

Conclusions: The results of the present study indicated LA and left ventricular dysfunction in diabetic patients. However, the LA function may be affected by several factors, and our nonrandomized patient selection could also have affected the results. Thus, it is suggested that future randomized clinical trials compare the LA echocardiographic parameters in matched groups. ***(Iranian Heart Journal 2020; 21(1): 82-93)***

KEYWORDS: Diabetes mellitus, Left atrium, Atrial function, Echocardiography, STE

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Diabetes mellitus (DM) is one of the world's most common chronic noncommunicable diseases with a high prevalence in most developing countries. [1] The prevalence of DM is estimated to be on the rise because of the increasing trend of diabetes risk factors, obesity, and the aging of the populations. [2] In Iran, although the general prevalence of DM is close to that of the global prevalence (8%–9%), its prevalence surges in the elderly and illiterate urban dwellers, approaching nearly 20%. [3,4] In addition to the high prevalence of DM, about one-third of patients are not aware of their disease and may be, thus, affected by the silent complications; this issue is associated with a great mortality rate. [5] The chronicity of hyperglycemia in diabetic patients predisposes them to numerous micro- and macrovascular complications such as nephropathy, retinopathy, neuropathy, cardiomyopathy, and vasculopathy. [6,7] Furthermore, DM is associated with several comorbidities including hypertension, obesity, and hyperlipidemia, which increase the risk of complications and mortality rates. [8]

The cardiac complications of DM are the most important diabetes-related complications and the first cause of mortality in diabetic patients, [9,10] with the evidence suggesting a 5-fold increase in the risk of myocardial infarction and ischemic stroke and a 2- to 4-fold increase in the risk of peripheral artery disease in diabetic patients compared with nondiabetics. [11,12] Several pathophysiologies are suggested for the etiology of cardiac complications in DM like inflammation, reactive oxygen, and endothelial dysfunction. [13-15] In addition to the complexity of DM, a wide range of changes is observed in diabetic hearts including left ventricular (LV) systolic and diastolic dysfunction (leading to heart failure), cardiomyocyte hypertrophy, myocardial interstitial fibrosis, and the apoptosis of cardiomyocytes. [16,17]

The effect of DM on the LV has been studied and the role of LV dysfunction has been confirmed in diabetic cardiomyopathy. [18,19] Nevertheless, there is insufficient evidence on the importance of changes in the left atrium (LA) in diabetic cardiomyopathy. [20] Some studies have shown no influence on the LA diameter, [21] while a significant increase in the LA index has been observed in other studies. [22,23]

Considering the lack of knowledge related to the LV function in diabetic patients and the predictive value of the LA in cardiovascular events, we aimed to study the association between LA dysfunction and DM in patients with stable cardiac function by conventional and speckle-tracking echocardiography (STE) methods.

METHODS

Study Design

In this prospective study, patients who referred to Modarres Hospital from March 2018 to July 2018 were considered the study population. The study sample size was calculated at 198. The inclusion criteria for this study were as follows: patients with sinus rhythms (determined according to the electrocardiogram [ECG] taken at baseline), an ejection fraction (EF) > 50% (determined based on echocardiography taken at baseline by the echocardiologist), and normal coronary arteries over the past month (determined based on angiographic or computed tomography [CT] angiographic assessments by the cardiologist). The exclusion criteria for this study were as follows: patients with atrial fibrillation or flutter (based on the initial ECG), EF < 50%, regional wall motion abnormalities, a left ventricular end-diastolic diameter (LVEDD) > 53 mm in women or > 58 in men, moderate-to-severe valvular regurgitation

and any degree of valvular stenosis, myocardial hypertrophy with a septal diameter > 12 mm or poor echo windows (based on the initial echocardiography), a history of ischemic heart disease (myocardial infarction, stent implantation, and coronary artery bypass graft surgery), a history of stroke, peripheral artery disease, uncontrolled blood pressure (> 160/110 mm Hg), chronic renal or liver or lung disease, and pregnancy. Accordingly, 24 patients were excluded from the study: 14 had a poor echocardiographic view, 6 had moderate-to-severe valvular disease, and 4 had moderate-to-severe hypertrophy. Finally, a total of 174 patients were investigated.

Primary Assessment

An ECG was recorded from all the patients at the baseline of the study. Furthermore, the height and weight of all the samples were recorded for calculating the body surface area (BSA). In addition, the researcher recorded the patients' demographics (age and sex), comorbidities (hyperlipidemia, hypertension, smoking, DM, and obesity), drug history, familial history of cardiovascular diseases, and the duration of DM in diabetic patients from the patients' medical records. Systolic pressure > 140 mm Hg and diastolic pressure > 90 mm Hg were considered high blood pressure. [24] Moreover, the diagnosis of DM was made in accordance with the American Diabetes Association criteria. [25]

Echocardiographic Assessment

Echocardiography was performed by conventional and STE methods (Siemens®, Health Care Acuson SC2000). STE was performed using eSie VVI software. All the patients had sinus rhythms during echocardiography, and an ECG lead constantly recorded the patients' ECG. Echocardiography was done in the left lateral position based on the American Society of Echocardiography protocol. [26] In addition, the LV and LA volumes were measured and interpreted based on the BSA.

Conventional Echocardiography

The ventricular details recorded in the conventional method were comprised of systolic parameters: the LVEDD, the LV end-systolic diameter, the LV end-diastolic volume, the left ventricular end-systolic volume (LVESV), the interventricular septal end-diastole, the diastolic posterior wall thickness diameter (PWTd), the left ventricular mass index (LVMI), and the left ventricular ejection fraction (LVEF). The LVMI was measured as LVM/BSA, and the LVM was calculated based on the following equation [26-28]:

$$0.8\times1.04\,[(LVIDd + LVPWTd + IVSTd)^3 - (LVIDd)^3] + 0.6.$$

The ventricular diastolic parameters consisted of diastolic dysfunction (DD), the deceleration time (DT), the S wave, and E and A waves and their ratio (E/A, Ea, and E/Ea).

The atrial details recorded encompassed the LA diameter, which is the maximum diameter of the LA in the parasternal long-axis view, the LA volume index or LAV_{max}, the left atrial minimum volume (LAV_{min}), the left atrial stroke volume (LASV) or the total emptying volume (TEV) (which is calculated based on the following formula: LAV_{max}- LAV_{min} and represents the LA

reservoir function), the left atrial volume before atrial contraction (LAV_{preA}), the left atrial ejection fraction (LAEF) or the active ejection fraction (AEF) (which is calculated based on the following algorithm: $\frac{LAVpreA-LAVmin}{LAVpreA}$ and describes the pump function of the LA at the end of diastole), the left atrial emptying fraction or total ejection fraction (TEF) (which is estimated as $LASV/LAV_{max}$ and indicates the reservoir function of the LA during systole), the active emptying volume (AEV) (which is calculated based on the following formula: LAV_{preA}- LAV_{min} and describes the pump function of the LA), the passive emptying volume (PEV) (which indicates the conduit role of the LA in early diastole and is calculated according to the following formula: LAV_{max}-LAV_{preA}), and the passive ejection fraction (PEF) (which describes the conduit role of the LA in early diastole and is calculated according to the following formula: $\frac{LAVmax-LAVpreA}{LAVmax}$). [26]

STE

STE was done by using eSie VVI software. The STE images were recorded in 3 cardiac cycles at a frame rate (FR) of 40–60. For the assessment of the strain (S) and strain rate (SR) of the LA, the endocardium and epicardium were traced manually and automatically, respectively. The assessment of the S and SR of the LA was performed after the LA was automatically divided into 6 segments. The parameters that were evaluated by STE were as follows: the left atrial peak positive strain rate during ventricular systole (LASRS), the left atrial peak negative strain rate during early diastole (LASRE), the left atrial peak negative strain rate during late systole (LASRA), the left atrial peak strain during the reservoir phase (LARES) (before mitral opening), and the left atrial peak strain during the pump phase (LA-pump).

Statistical Analysis

The results were presented as the mean ± the standard deviation (SD) for the quantitative variables and were summarized as frequencies (percentages) for the categorical variables. The patients were categorized into 2 groups of diabetic and nondiabetic, and the categorical variables were compared between these 2 groups using the χ^2 or Fisher exact test. Additionally, according to the one-sample Kolmogorov–Smirnov test, the data were not normally distributed ($P < 0.05$); therefore, for the comparison of the numeric variables between the 2 groups with and without DM, the Mann–Whitney *U* test was used. The correlation between the variables was tested using the Spearman correlation coefficient. For the statistical analyses, the statistical software IBM SPSS Statistics for Windows, version 21.0, (IBM Corp 2012. Armonk, NY: IBM Corp) was used. A P value ≤ 0.05 was considered statistically significant.

Ethical Considerations

Before the enrollment of the patients into the study, the design and objectives of the study were explained to all the participants and written informed consent was obtained from those who were willing to participate in the study. The patients were reassured that they were free to leave the study whenever they wished to and that their participation would not affect their routine care at the medical center. All the ethical principles of Helsinki's declaration on human studies were met throughout the study. The protocol of the study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences.

RESULTS

Among 174 patients, whose details were analyzed, 96 (55.2%) patients were male and 78 (44.8%) patients were female. The mean

age of the patients was 53.71 ± 9.21 years (range = 29–75 y). DM was reported in 62 (35.6%) patients. The results of the Mann–Whitney *U* test indicated that the mean age of the patients was not significantly different between the groups with and without DM (54.40 ± 8.23 vs 53.32 ± 9.72 y, respectively; *P* = 0.345). Similarly, the frequency of male and female patients was not different between the groups with and without DM (*P* = 0.374). Table 1 demonstrates the frequency of comorbidities. The comparison of the demographics and the frequency of comorbidities between the patients with and without DM showed no statistically significant difference between the groups (Table 1).

Table 1. Frequency of the patients' sex and history of underlying diseases

Variable		Total, No. (%)	Diabetic Patients	Nondiabetic Patients	*P* value
Sex	Male	96 (55.2%)	37 (59.7%)	59 (52.7%)	0.374
	Female	78 (44.8%)	25 (40.3%)	53 (47.3%)	
Comorbidities	Hypertension	63 (36.2%)	23 (37.1%)	40 (35.7%)	0.856
	Hyperlipidemia	35 (20.1%)	10 (16.1%)	25 (22.3%)	0.329
	Smoking	31 (17.8%)	7 (4.02%)	24 (13.79%)	0.094
	Family history	18 (10.3%)	1 (1.6%)	17 (15.2%)	0.005
	Obesity	23 (13.2%)	5 (8.1%)	18 (16.1%)	0.135

At the baseline of the study, 45% (n=28) of the diabetic patients received insulin and 81% (n=50) received oral antidiabetic agents. The mean BSA was 1.88 ± 1.54 m^2 (mean ± SD); the results of the Mann–Whitney *U* test indicated that the mean BSA of the patients was not significantly different between the groups with and without DM (2.09 ± 2.57 vs 1.77 ± 0.13 m^2, respectively; *P* = 0.968).

A total of 70 (40.8%) patients had diastolic dysfunction, and the results of the χ^2 test showed that the frequency of diastolic dysfunction in the studied patients was not significantly different between the groups with and without DM (45.2% vs 38.4%, respectively; *P* = 0.384).

The echocardiographic parameters of the LV compared between the groups with and without DM are demonstrated in Table 2. As is shown in Table 2, the mean values of the LVEDD (*P* < 0.001) and the Ea (*P* = 0.008) were higher in the nondiabetic patients and the mean values of the LVMI, the A wave, the E/A (all *P*s < 0.001), and the LVESV (*P* = 0.001) were higher in the diabetic patients, while the other echocardiographic parameters including the deceleration time (DT), the E/Ea, and the S wave were not significantly different between the groups (*P* > 0.05).

The echocardiographic parameters of the LA compared between the groups with and without DM are demonstrated in Table 3. The LARES, the LA-pump, the LASRS, and the LASRE (all *P*s < 0.001) were higher in the nondiabetic patients. In addition, the LAEF (*P* = 0.011) and the PEV (*P* = 0.026) were higher in the diabetic patients. The other parameters of the LA were not significantly different between the groups (*P* > 0.05).

The correlations between DM and the LA echocardiographic parameters are presented in Table 4. As is depicted, the Spearman

correlation coefficient showed that DM had a significant association with the LASRE, the LA-pump, the LARES, and the LASRS (all *P*s < 0.001) (Table 4).

Table 2. Comparison of the values of the LV echocardiographic measures between the patients with and without diabetes

Variable	Total	Diabetic Patients	Nondiabetic Patients	*P* value**
LVEDD (mm)	48.28±6.08	45.24±7.96	49.96±3.85	<0.001
LVESD (mm)	29.48±3.94	29.69±5.19	29.37±3.04	0.573
IVSD (mm)	10.00±1.78	10.21±1.91	9.88±1.79	0.322
PWI (mm)	8.3678±1.73	8.71±1.82	8.17±1.65	0.074
LVMI	80.27±7.29	83.98±8.83	78.22±5.29	<0.001
LVEDV (cc)	72.05±6.32	73.34±7.80	71.33±5.23	0.237
LVESV(cc)	25.86±3.78	27.45±4.31	24.99±3.15	0.001
LVEF %	59.45±3.05	59.98±2.03	59.15±3.46	0.069
Peak E wave velocity (cm/s)	69.85±15.48	69.50±15.67	70.04±15.45	0.957
Peak A wave velocity (cm/s)	68.76±18.12	75.38±17.85	65.06±17.26	<0.001
Septal e' wave (Ea) (cm/s)	7.91±1.78	7.42±1.74	8.18±1.75	0.008
E/A	1.65±7.70	2.53±12.84	1.16±0.80	<0.001
E/Ea	8.49±2.27	8.89±2.45	8.26±2.13	0.065
D.T (ms)	147.33±26.40	152.14±31.74	144.63±22.60	0.208
Septal S' wave (cm/s)	7.42±1.00	7.24±1.09	7.52±0.93	0.278

LVEDD, Left ventricular end-diastolic diameter; LVESD, Left ventricular end-systolic diameter; IVSD, Interventricular septal end-diastole; LVEDV, Left ventricular end-diastolic volume; LVESV, Left ventricular end-systolic volume; LVIDd, Left ventricular diastolic internal diameter; PWI, Diastolic posterior wall thickness; LVMI, Left ventricular mass index; LVEF, Left ventricular ejection fraction; DT, Deceleration time

** The results of the Mann–Whitney *U* test

Table 3. Comparison of the values of the LA echocardiographic measures between the patients with and without diabetes

Variable	Total	Diabetic Patients	Nondiabetic Patients	*P* value**
LA diameter	3.87±4.61	4.94±7.62	3.27±0.38	0.912
LAVI	26.77±5.91	27.05±6.18	26.62±5.77	0.751
LAV_{min}	11.93±3.83	11.50±4.23	12.16±3.59	0.147
LAV_{preA}	17.96±4.74	17.72±5.13	18.09±4.53	0.556
LAEF (AEF)	36.66±5.66	38.16±7.62	35.83±4.01	0.011
LAS.V	15.12±2.50	15.53±3.15	14.89±2.05	0.106
LATEF (TEF)	58.01±4.99	58.24±6.87	57.89±3.58	0.195
AEV	5.97±1.45	6.24±1.71	5.82±1.26	0.154
PEV	8.57±2.46	9.21±3.83	8.22±1.01	0.026
PEF	33.23±4.37	33.48±5.90	33.09±3.25	0.386
LARES	46.54±4.03	44.35±4.65	47.75±3.04	<0.001
LA-pump	18.70±2.64	17.22±3.16	19.52±1.86	<0.001
LASRS	2.53±9.64	1.29±0.58	3.22±11.98	<0.001
LASRE	-1.32±0.71	-0.96±0.58	-1.51±0.72	<0.001
LASRA	-1.48±0.69	-1.51±0.75	-1.46±0.66	0.586

LAVI, Left atrial volume index; LAV_{min}, Left atrial minimum volume; LAV_{preA}, Left atrial volume pre-atrial contraction; LAEF, Left atrial ejection fraction; AEV, Active emptying volume; PEV, Passive emptying volume; PEF, Passive ejection fraction; LASV, Left atrial stroke volume; LARES, Left atrial peak strain during the reservoir phase; LA-pump, Left atrial peak strain in the late diastolic pump; LASRS, Left atrial peak strain during systole; LASRE, Left atrial peak strain during diastole; LASRA, Left atrial peak strain during atrial systole

** The results of the Mann–Whitney *U* test

Table 4. Correlations between diabetes mellitus and echocardiographic parameters

Variable	Spearman Coefficient	*P* value
LARES	0.348	<0.001
LA-pump	0.416	<0.001
LASRS	0.277	<0.001
LASRE	-0.397	<0.001
LASRA	-0.41	0.587

LARES, Left atrial peak strain during the reservoir phase; LA-pump, Left atrial peak strain in the late diastolic pump; LASRS, Left atrial peak strain during systole; LASR-D, Left atrial peak strain during diastole; LASR-A, Left atrial peak strain during atrial systole

DISCUSSION

The results of the present study showed that among patients with a stable cardiac condition (sinus rhythms, LVEFs > 50%, and normal coronary arteries), the mean values of the LVEDD, the LARES, the LA-pump, and the LASRS were higher in the nondiabetic patients and the mean values of the LVMI, the A wave, the E/A, the LASRE, the LVESV, the Ea, the LAEF, and the PEV were higher in the diabetic patients. These results indicated that diabetic patients have several alterations in their LV including higher LV hypertrophy and LV dysfunction and several alterations in their LA, as discussed further.

Several roles have been established for the LA. It acts as a reservoir for the pulmonary venous return during the LV contraction and isovolumetric relaxation, transfers blood passively into the LV, and contributes to 15%–30% of the LV stroke volume by its contraction during the final phase of diastole; therefore its size and function imply LV compliance. [29] According to the evidence, the LA volume (size) is an appropriate predictor of adverse cardiovascular outcomes [30,31] and the LA function (indexed to the BSA) is associated with LV dysfunction, especially diastolic heart failure. [23,32] However, only a few studies have evaluated LA changes in diabetic patients.

A study by Gulmez et al [33] compared the echocardiographic parameters of 56 diabetic patients with 56 controls. The results showed higher LA diameter, indexed V_{max}, LAV_{preA}, LAV_{min}, AEV, and TEV in the diabetic patients, while the A and E waves and their ratio were not different between the groups. Furthermore, Gulmez and colleagues [34] reported high LA diameter, indexed V_{max}, LAV_{preA}, LAV_{min}, AEV, and TEV in their patients with prediabetes (n = 114) compared with their 70 controls. These results are regarding several LA changes in diabetic patients and no difference in the LA function between patients with and without (pre)diabetes. However, these are not associated with the current study, as we found significant differences between the groups in the A and E waves and their ratio (A wave, E/A, and Ea), without significant differences in the LAV_{preA}, the LAV_{min}, and the AEV. Nevertheless, the differences between our results and those of Gulmez et al [33,34] could be associated with several factors such as the duration of diabetes [35] and differences in the patients' body mass index and age, which can affect the LA function. [36] In addition, the results of a study by Kadappu et al, [37] in line with the present study, indicated significant differences in the E and A waves and their ratio between diabetic patients and controls.

According to the previous studies, the duration of DM has a significant role in LA enlargement [35] and patients who show no change in the LA diameter after 5 years' follow-up have significant changes after 20 years. [22] Therefore, no difference in the LA function between the groups in our study could be attributed to several factors affecting the LA diameter and function in diabetic patients.

Significant changes in the LA of diabetic patients in the present study included lower LARES, LA-pump (indicating the LA pump function), and LASRS (indicating the LA reservoir function), but higher LASRE (indicating the conduit function), LAEF, and PEV. Particularly, all the significant differences between the groups were in the STE parameters. Similar to these results, Mondillo et al [38] reported reduced LASRS, LARES, LA-pump, and LASRD in patients with hypertension and DM with normal LA volumes (< 28 mL/m^2). Kadappu et al [37] also indicated lower strain parameters in all 6 parameters and a higher LA volume index in diabetic patients. These results are consistent with those of ours, indicating several LA strain reductions in diabetic patients. Nevertheless, patients with DM had higher LASRE, LAEF, and PEV than the control group. A study by Liu et al [39] demonstrated lower LASRS and LARES in diabetic patients without significant differences in the LA-pump. These differences in the LA STE parameters between the studies on diabetic patients may be related to the accuracy of different imaging methods. [20] Studies have suggested that the accuracy of LA mechanics measurement by 2D and 3D echocardiography is comparable to that of CT imaging. [40,41] Furthermore, the measurement of strain rates by STE is considered a simple, feasible, sensitive, and reliable method for the evaluation of LA deformation [42] and the prediction of cardiovascular adverse events, [43] atrial fibrillation, and stroke. [44, 45] Additionally, LA strain is associated with LV diastolic dysfunction. [46] Thus, impaired LA deformation, as indicated by LA strain in the present study, is considered to be the most important finding, indicating LV diastolic dysfunction in diabetic patients.

Considering LV measurements, the results of our study showed a greater LVEDD in the nondiabetic patients and greater LVESV and LVMI in the diabetic patients. The results of a cohort study by Inoue et al [47] indicated the LVEDD as an independent predictor of all-cause mortality, better than other echocardiographic parameters. The LVESV, indicating LV dysfunction, is also recommended as a more accurate parameter, considering the shortcomings in the measurement of the LV end-systolic diameter. [48] The LVMI, indicating LV hypertrophy, is associated with a greater LA dimension and lower systolic and diastolic functions and is, thus, regarded as a predictor of heart failure. [49] The results obtained in the present study regarding LV changes also indicate significant LV dysfunction in diabetic patients, which is consistent with the results of previous studies. [18,19,50]

While the present study successfully compared 2 groups of diabetic and nondiabetic patients with similar baseline characteristics, this study, like any other, may have several limitations. One of the important limitations of the study is nonrandomized patient selection and grouping, which could have affected the results. Moreover, the LA appendix was not evaluated in the current study. It is, therefore, recommended that future studies take this factor into account. The positive point of the current study is that we considered any factors that could influence the results as the exclusion criteria to reduce the effect of confounding variables.

CONCLUSIONS

The results of the present study showed that the diabetic patients had a lower mean LVEDD and a higher mean LVESV and LVMI, indicating LV dysfunction in the diabetic patients. Studying LA parameters showed that the LA volume and function were not impaired in the diabetic patients. Additionally, the LAEF and the PEV were

higher in the diabetic than in the nondiabetic patients. Meanwhile, strain LA measurements showed lower LARES, LA-pump, and LASRS, but a higher LASRE. These results indicate several LA and LV dysfunction in diabetic patients. However, the LA function may be affected by several factors and our nonrandomized patient selection could also have affected the results. Thus, it is suggested that future randomized clinical trials compare LA echocardiographic parameters in matched groups.

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