Subclinical Left Ventricular Dysfunction in Asymptomatic Type Two Diabetes Mellitus Patients with an Echocardiographic Study

Abstract

Background: Left ventricular (LV) diastolic dysfunction represents the earliest pre-clinical manifestation of diabetic cardiomyopathy, preceding systolic dysfunction and evolving to symptomatic heart. The aim of this work was to detect subclinical LV dysfunction in asymptomatic patients with type two diabetes using various echocardiographic modalities.

Methods: This prospective cohort study was carried out on 30 patients aged above 18 years old, both sexes, with type II diabetes mellitus (DM) (Group I) and 20 healthy individuals as control (Group II). All patients were subjected to 12 lead Electrocardiogram and transthoracic echocardiography.

Results: Transmitral flow velocities derived from pulsed wave Doppler techniques, septal e', lateral mitral annulus early velocity (e'), septal early diastolic peak flow velocity (E)\e', Lateral E\e' and average E\e' were significantly different between both groups. EF was significantly lower in group I (P <0.001). LV end-systolic diameter (LVESD) was significantly higher in group I (P = 0.001). Systolic motion of mitral annulus (S`) septal, S` lateral and S` average was significantly higher among group II. Isovolumetric contraction time (IVCT) and myocardial performance index (MPI) were significantly higher in group I than group II. Ejection time (ET) was significantly lower in group I than group II. Fasting blood sugar, post-prandial blood sugar, glycated hemoglobin (HbA1C) was significantly higher in the study group compared to the control group (P <0.001).

Conclusions: History of DM, fasting blood sugar, post-prandial blood sugar, HbA1c, E/e´ ratio, LVESD, IVCT and MPI were significantly higher in patients with DM while EF and ET were significantly lower in patients with DM compared to healthy group.

Keywords: Left Ventricular Dysfunction, Asymptomatic, Diabetes Mellitus, Echocardiography

Introduction:

Early prediction of cardiac complications in patients with type two diabetes mellitus (DM) by using various modalities of echocardiography are of great importance to improve the outcome of heart failure. Cardiac complications contribute as a major cause of morbidity and mortality in diabetic patients [1].

Diabetes is a risk factor in 10-30% of patients who develop heart failure [2]. In type two diabetes, isolated abnormalities of diastolic relaxation in the absence of symptoms or signs of heart disease suggest a diagnosis of diabetic cardiomyopathy (DCM). This is thought to result from microangiopathy, deposition of collagen, decreased expression/activation of K+ channel and Na+ pump and decreased myofilament Ca2+sensitivity [3, 4]

Left ventricular (LV) diastolic dysfunction represents the earliest pre-clinical manifestation of DCM, preceding systolic dysfunction and evolving to symptomatic heart [5]. The prevalence of diastolic dysfunction increases with longer duration of diabetes. There was a linear progression of diastolic dysfunction with the increased age group [6].

Thus, LV diastolic dysfunction may represent the earliest stage of DCM and timely diagnosis of this entity can be vital in the management of patients.

The aim of this work was to detect subclinical LV dysfunction in asymptomatic patients with type two diabetes using various echocardiographic modalities.

Patients and Methods:

This prospective cohort study was carried out on 30 patients aged above 18 years old, both sexes, with type II DM and 20 healthy individuals as control. The study was done from March 2022 to March 2023. after approval from the Ethical Committee Tanta University Hospitals, Tanta, Egypt. An informed written consent was obtained from the patients.

Exclusion criteria were patients with evidence of coronary artery disease (CAD), CAD is an atherosclerotic disease which is inflammatory in nature (Ross, 1999), manifested by stable angina, unstable angina, myocardial infarction (MI) [7], patients with valvular disease (congenital or rheumatic) [8], hypertensive patients, systemic hypertension defined as systolic blood pressure of 140 mmHg or more and/or diastolic blood pressure of 90 mmHg or more measured on 3 separate occasions with or without treatment, patients with other known causes of diastolic dysfunction like hypothyroidism, restrictive cardiomyopathy and constrictive pericarditis.

Patients were divided into two groups: **Group (I) (n=30):** patients diagnosed with type two DM according to American Diabetes Association (ADA) [9]. Patient defined as having diabetes when he had previous history or current diagnosis of DM, according to American Diabetes Association the patient is diagnosed as diabetic if he has [HbA1C: 6.5 % or higher, Fasting blood glucose level: 126 mg/dl or higher and 2 hours post prandial blood glucose level: 200 mg/dl or higher] and **Group (II) (n=20):** normal individuals.

All patients were subjected to history taking, clinical examination, routine laboratory investigations [complete blood count (CBC), random blood sugar-fasting –postprandial – hemoglobin A1C (HBA1C), liver and renal function tests], 12 lead electrocardiogram (ECG) and transthoracic echocardiography.

12 lead Electrocardiogram:

Standard 12-lead ECG was obtained including limb leads I, II, III, aVR, aVL, aVF, and chest leads from V1to V6 for all patients and control group.

Transthoracic echocardiography:

Echocardiographic examination Two-dimensional, M-mode and subsequent TDE and quantitative analysis were conducted on parasternal long axis, short axis and apical four-chamber images according to the data provided by the American Society of Echocardiography [1]. LV systolic and diastolic functions were analyzed using standard two-dimensional (2D) echocardiography, M-mode echocardiography, pulsed wave (PW) echocardiography and TDE. Diameters of LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD) were obtained from the M-mode echocardiographic tracing under the guidance of 2D imaging. LV ejection fraction was calculated by the modified Simpson's method. The pulsed Doppler sample volume was positioned at the mitral leaflet tips. Early diastolic peak flow velocity (E), late diastolic peak flow velocity (A), E-wave deceleration time (DT) and E/A ratio were calculated.

The following measurements were obtained in each region as: myocardial systolic (S m) wave, myocardial early diastolic wave (Em) and atrial peak velocity (Am), Em/Am ratio, myocardial isovolumetric relaxation time (IVRTm), myocardial isovolumetric contraction time (IVCTm), myocardial ejection time (ETm). MPI was calculated by summing IVCTm and IVRTm and dividing by ETm value. In addition to these parameters, E/Em ratio, a reliable index of LV filling pressures was measured. All diastolic parameters were measured in three consecutive cardiac cycles and averaged. For data acquisition, three complete cardiac cycles were collected and stored in a cine-loop format. Data were acquired with the subjects at rest, lying in the left lateral position.

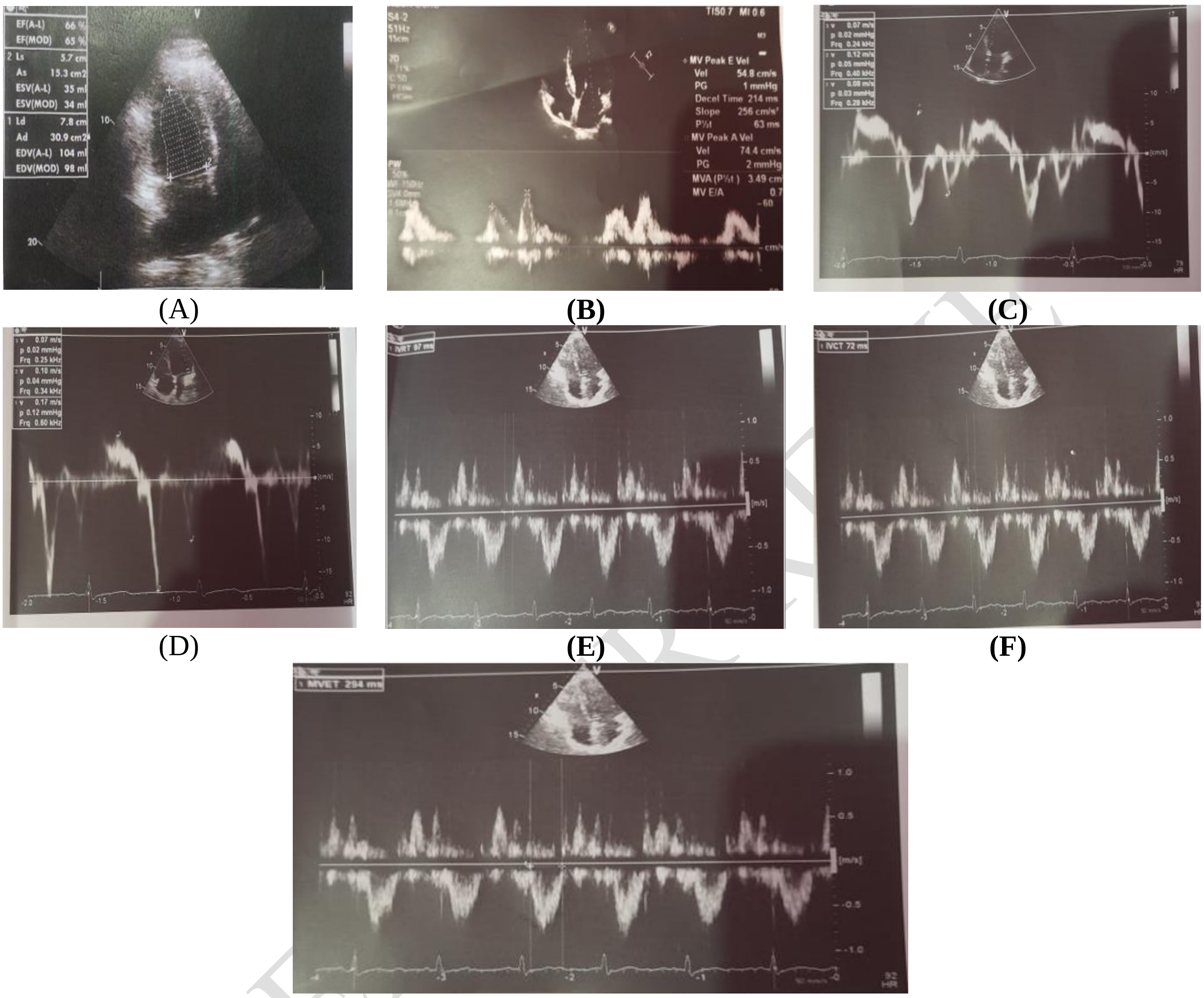
Two-dimensional (2D) echocardiography:

LV end-systolic volume, end-diastolic volume and Ejection fraction was quantified using the biplane Simpson 's method [10].

Assessment of diastolic function:

Pulsed-wave Doppler of the mitral valve inflow was obtained by placing the Doppler sample volume between the tips of the mitral leaflets. The early (E) and late (A) peak diastolic velocities and E-wave deceleration time (DT) and isovolemic relaxation time (IVRT) were measured.

E/e' average ratio was obtained by taking the average of (E / septal) and (E/lateral) which was measured using color TDI at the septal and lateral side of the mitral annulus respectively in the apical 4-chamber view [11, 12]. **Figure 1**



(A) **(B)** **(C)**

(D) **(E)** **(F)**

(G)

Figure 1: (A) Measurement of LVESV, LVEDV and EF by Simpson method, (B) E/A ratio and DT, (C) S` septal and e' septal, (D) S` lateral and e' lateral, (E) IVRT, (F) IVCT , (G) ET in a case study

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed P value < 0.05 was considered statistically significant.

Results:

Age, BMI, sex and clinical examination were insignificantly different between both groups. Family history of DM was significantly higher in study group (P <0.001). The mean duration of DM was 6.47 ± 2.46 years. **Table 1**

Table 1: Demographic data and clinical examination of the studied groups

		Group I (n=30)	Group II (n=20)	P
Age (years)		48.73 ± 12.21	51.3 ± 8.37	0.417
BMI (kg/m^2)		25.52 ± 3.9	24.81 ± 3.31	0.507
Sex	**Male**	7 (23.3%)	6 (30%)	0.844
	Female	23 (76.7%)	14 (70%)	
Family history of DM		19 (63.33%)	2 (10.0%)	**<0.001***
Duration of DM (years)		6.47 ± 2.46	---	---
Clinical examination				
Systolic blood pressure (mmHg)		127.83 ± 5.09	126.5 ± 3.8	0.323
Diastolic blood pressure (mmHg)		86.47 ± 4.73	85.2 ± 2.88	0.290
MAP (mmHg)		100.23 ± 4.32	98.28 ± 5.85	0.181

Data are presented as mean ± SD or frequency (%). *Significant p value <0.05. DM: diabetes mellitus, BMI: Body mass index, MAP: mean arterial pressure.

Hb, HCT, PLT, WBCs, AST, ALT, serum creatinine and Urea levels were insignificantly different between both groups. Fasting blood sugar, post-prandial blood sugar, HbA1C was significantly higher in the study group compared to the control group (P <0.001). **Table 2**

Table 2: Laboratory investigations of the studied groups

	Group I (n=30)	Group II (n=20)	P
Hb (g/dL)	15.43 ± 1.78	15.27 ± 1.55	0.732
HCT (%)	47.12 ± 5.54	47.07 ± 6.24	0.976
PLT (*10^{3}cells/µL)	258.22 ± 82.54	244.88 ± 65.18	0.547
WBCs (*10^{3}cells/µL)	6.15 ± 1.72	5.74 ± 1.68	0.405
Fasting blood sugar (mg/dL)	173.64 ± 23.54	87.19 ± 5.44	**<0.001***
Post-prandial blood sugar (mg/dL)	258.74 ± 63.42	119.7 ± 13.5	**<0.001***
HbA1c (%)	7.34 ± 0.85	4.95 ± 0.21	**<0.001***
ALT (U/L)	33.37 ± 7.21	29.8 ± 4.85	0.073
AST (U/L)	27.86 ± 12.02	25.23 ± 12.8	0.464
Serum creatinine (mg/dL)	1.04 ± 0.27	0.89 ± 0.26	0.058
Urea (mg/dL)	29.37 ± 11.89	26.79 ± 9.52	0.421

Data are presented as mean ± SD. *Significant p value <0.05. Hb: hemoglobin, HCT: hematocrit, PLT: platelet count, WBCs: white blood cells, ALT: alanine aminotransferase, AST: Aspartate aminotransferase.

Transmitral flow velocities derived from pulsed wave Doppler techniques (E – E\A ratio – DT – IVRT), septal e’, lateral e’, Septal E\e', Lateral E\e' and average E\e’ were significantly different between both groups. EF was significantly lower in group I (P <0.001). LVESD was significantly higher in group I (P = 0.001). LVEDD was insignificantly different between both groups. **Table 3**

Table 3: Transmitral flow velocities derived from pulsed wave doppler techniques, tissue Doppler-derived E/e' ratio, EF, LVESD and LVEDD of the studied groups

	Group I (n=30)	**Group II (n=20)**	**P**
E (cm/s)	68.38 ± 20.77	58.75 ± 4.98	**0.048***
E/A ratio	1.32 ± 0.38	0.86 ± 0.17	**0.002***
DT (ms)	218.9 ± 39.21	189.5 ± 30.3	**0.011***
IVRT (ms)	88.7 ± 17.21	185.5 ± 17.8	**<0.001***
Tissue Doppler-derived E/e' ratio			
e' septal	10.04±3.69	7.56±1.49	**0.008***
e' lateral	8.25±2.58	10.12±0.62	**0.003***
E\e' septal	10.31 ± 4.61	7.66 ± 1.22	**0.016***
E\e' Lateral	9.06±3.68	5.81±0.49	**<0.001***
E\e' average	9.67±3.79	7.03±0.61	**0.003***
EF (%)	57.83 ± 4.23	65.15 ± 4.34	**<0.001***
LVESD (cm)	3.50 ± 0.45	2.65 ± 0.46	**0.001***
LVEDD (cm)	4.56 ± 0.72	4.43 ± 0.66	0.524

Data are presented as mean ± SD. *Significant p value <0.05. E/A: early and late ventricular filling velocity, DT: deceleration time, IVRT: isovolumic relaxation time, EF: Ejection fraction, LVESD: left ventricular end systolic diameter, LVEDD: left ventricular end diastolic diameter.

S` septal, S` lateral and S` average was significantly higher among group II. IVCT and MPI were significantly higher in group I than group II. ET was significantly lower in group I than group II. **Table 4**

Table 4: Pulsed wave tissue doppler of mitral annulus of the studied groups

	Group I (n=30)	Group II (n=20)	P
s` septal	7.32±1.57	8.67±1.54	**0.005***
S` lateral	8.71±2.23	10.39±1.81	**0.007***
S` average	8.03±1.31	9.54±0.99	**<0.001***
IVCT	71.33±16.84	65.22±6.71	**0.003***
ET	290.83±15.38	304.90±6.24	**0.016***
MPI	0.541±0.03	0.509±0.02	**<0.001***

Data are presented as mean ± SD. *Significant p value <0.05. IVCT: Isovolemic contraction time, ET: Ejection time, MPI: Myocardial performance index.

Discussion

Cardiovascular complications in type 2 DM patients account for more than 70% of the mortality. DM is the most common cause of ischemic cardiomyopathy, thus LV dysfunction. Macro and microvascular coronary disease, DCM and autonomic dysfunction produce myocardial damage in diabetic patients [13].

E (cm/s), E/A ratio, IVRT and DT (ms)) were significantly different between both groups. Septal e', lateral e', Septal E\e', Lateral E\e' and average E\e' were significantly different between both groups. EF was significantly lower in group in group I. LVESD was significantly higher in group I. LVEDD was insignificantly different between both groups.

S` septal, S` lateral and S` average were significantly lower in group I. IVCT was significantly higher in group I, while ET was significantly lower in group I. MPI was significantly higher in group I.

In the present study, it was found that systolic blood pressure, diastolic blood pressure, and MAP were insignificantly different between both groups. In agreement with our results, Magdy et al. [14] there was no significant difference between control and cases groups regarding systolic and diastolic blood pressure . In line with our results, Kawata et al. [15] showed that there was no significant difference between control and cases groups regarding systolic and diastolic blood pressure (p value = 0.13, p = 0.075, respectively).

In the present study, it was found that Hb, HCT, PLT, WBCs, AST, ALT, serum creatinine and urea levels were insignificantly different between both groups. In agreement with our results, Ayman et al. [14] found that serum creatinine and urea levels were insignificantly different between both groups. In agreement with our results, Mahmoud et al. [16] revealed that AST, ALT, and serum creatinine levels were insignificantly different between both groups.

In the present study, it was found that transmitral flow velocities derived from pulsed-wave Doppler techniques (E/A ratio, DT and IVRT) were significantly different between both groups. In agreement with our results, Raafat et al. [14] highlighted that there was significant statistical difference between the studied groups as regard E/A ratio. In disagreement with our results, Ayman et al. [14] highlighted that there was no significant difference between both groups regarding E/A ratio, IVRT and DT.

In the present study, it was found that EF was significantly lower in group I . In agreement with our results, Diamant et al. [17] carried out a prospective study to evaluate myocardial function in relation to high-energy phosphate (HEP) metabolism in asymptomatic patients with uncomplicated type 2 DM using MR techniques about twelve male patients with uncomplicated type 2 diabetes and 12 age- and gender-matched healthy controls were studied highlighted that EF was significantly lower in the study group compared to the control group.

In disagreement with our results Ayman et al. [14] highlighted that there was no significant difference between both groups regarding Ef (p value =0.4).

In the present study, E/e´ ratio was significantly higher in group I compared to group II. In consistent with our results, Steele et al. [18] showed that E/e´ ratio was significantly higher in the study group compared to the control group. Parallel to our results, Magdy et al. [14] highlighted that E/e´ ratio was significantly higher in patients than in control group.

In the present study, LVESD was significantly higher in group I compared to group II. LVEDD was insignificantly different between both groups. In agreement with our results, Enomoto et al. [19] highlighted that LVESD was significantly higher in the study group compared to the control group. LVEDD was insignificantly different between both groups. On the contrary, Saglam et al. [14] highlighted that there was no significant difference between patient and control groups regarding LVEDD and LVESD. This contradiction between both studies may be justified by the larger sample size in their study.

In the present study S`medial, S` lateral and S` average was significantly lower in group I.

In agreement with our results, Raafat et al. [14] highlighted S`medial and S` lateral were significantly lower in diabetic groups than control groups. Supporting our results, Zakria et al. [14] found that there were statistically significant differences between the mean value of S, which denotes that systolic dysfunction is more in patients with duration of diabetes more than 10 years. Similarly, Magdy et al. [14] demonstrated that the `septal, S` lateral and S` average were significantly reduced in diabetic patients in comparison to control.

In the present study, IVCT was significantly higher in group I., while ET was significantly lower in group I. In disagreement with our results, Mahmoud et al. [16] revealed that IVCT does not differ between the prediabetic group and the control group. This difference may be because of different sample sizes. In agreement with our results, Mahmoud et al. [16] found that MPI values were significantly increased in the prediabetic patients compared to the control group.

Limitations of this study including that the sample size was relatively small. The study was in a single center. Exclusion of patients with cardiovascular disease, and negative exercise stress test may affect generalization of the results. Advanced imaging modalities such as stress myocardial perfusion scintigraphy, computed tomographic angiography and conventional coronary angiography were not applied.

Conclusions:

History of DM, fasting blood sugar, post-prandial blood sugar, HbA1c, E/e´ ratio, LVESD, IVCT and MPI were significantly higher in patients with DM while EF and ET were significantly lower in patients with DM compared to healthy group. There was insignificantly different between both groups regarding age, sex, systolic blood pressure, diastolic blood pressure, MAP, Hb, HCT, PLT, WBCs, AST, ALT, serum creatinine and Urea, transmitral flow velocities derived from pulsed wave doppler techniques (E/A ratio, DT and IVRT), TDI, pulsed doppler of mitral valve, and LVEDD.

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