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Early Detection of Diastolic Dysfunction in Diabetic Patients (Single Center Cross Sectional Study)

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Abstract

Background: Left ventricular diastolic dysfunction in asymptomatic patients with diabetes mellitus may represent the early stage of diabetic cardiomyopathy even in patients without structural cardiac disease or systemic hypertension and have a preserved left ventricular systolic function.

Objectives: To determine the prevalence of left ventricular diastolic dysfunction in asymptomatic patients with diabetes mellitus.

Methods: A cross sectional study was carried out on 86 diabetics and compared with 65 age and sex matched controls. Detailed history, physical examination , specific investigations and transthoracic echocardiography study (including conventional pulse wave Doppler and tissue Doppler imaging) were done to assess the diastolic function.

Results: Left ventricular diastolic dysfunction is more prevalent in diabetic patients comparing with control group (62.3% versus 12.8%, $p<0.05$) and this correlated independently with increasing age, duration of the disease and glycated hemoglobin level.

Conclusion: Diastolic dysfunction can occur in diabetic patients even in young patients and those with shorter duration of disease. Tissue Doppler imaging, left atrial size and peak tricuspid regurgitation velocity are sensitive indices of LV diastolic dysfunction.

Keywords: Diastolic dysfunction; Diabetes; Echocardiography; Diabetic cardiomyopathy

Introduction

Cardiac involvement in patients with diabetes mellitus may occur relatively early in the course of disease, impairing left ventricular (LV) relaxation (diastolic dysfunction) and later on can affect ventricular contraction (systolic dysfunction).

Studies have reported a high prevalence of pre-clinical LV diastolic impairment in diabetic patients [1] and this cardiac complication may represent the reversible early stage of heart failure which is termed diabetic cardiomyopathy.

Diabetic cardiomyopathy was first reported by Rubler et al. [2] in 1972 when they described four diabetic patients with heart failure, normal coronary arteries, and without obvious etiology for heart failure and stated that it was due to diabetic cardiomyopathy".

The pathogenesis of LV diastolic dysfunction in diabetic patients is not clearly understood but the most reported important mechanisms are: "metabolic disturbances (increased free fatty acids, carnitine deficiency, changes in calcium homeostasis), myocardial fibrosis (increases in angiotensin II, IGF-I, and inflammatory cytokines), small vessel disease (microangiopathy, impaired coronary flow reserve (CFR), and endothelial dysfunction), autonomic neuropathy and insulin resistance" [3,4].

The prevalence of LV diastolic dysfunction in diabetic patients seems to be higher than previously suspected, therefore the early screening for this abnormality of cardiac function is mandatory to improve prognosis of those patients.

Isolated diastolic dysfunction can lead to heart failure (heart failure with preserved ejection fraction) in 50% of patients with normal systolic function and predispose to significant morbidity, medical costs, and increase overall mortality.

Pre-clinical LV dysfunction (systolic or diastolic) may be present for many years before the progression to symptomatic heart failure but the frequency of this progression is not fully established at time being [5].

The classic echocardiographic and Doppler parameters have some limitations for the diagnosis of diastolic dysfunction because there is no clear and definitive diagnostic criterion [6-17]. Tissue Doppler imaging (TDI) is relatively a new technique and sensitive method that measures the velocity of the longitudinal motion (shortening and lengthening) of the mitral annulus and has an important role for early diagnosis of diastolic impairment in diabetic patients who may benefit from earlier treatment in order to prevent the progression to clinically overt heart failure [18-25].

The prevalence of diastolic dysfunction in Iraqi diabetic patients is not precisely estimated so we try in this study to highlight this complication in our diabetic patients applying updating echocardiographic criteria of diastolic dysfunction [26].

Objectives

To determine the prevalence of asymptomatic LV diastolic dysfunction in diabetic patients and its relation to age, duration of the disease, glycemic control and obesity indices.

Materials and Methods

Cross sectional prospective study include asymptomatic diabetic patients (insulin dependent or non-dependent), that are free from cardiac symptoms (e.g., exertional dyspnea and angina) with duration between 1-10 years and free of coronary artery disease (CAD) (normal resting 12 lead electrocardiogram (ECG), normal exercise stress test and or normal coronary angiogram) and apparently healthy age-sex matched control group who referred to echocardiography unit in medical department of Al-yarmouk teaching hospital, baghdad between March and September 2017.

A standard 12 lead ECG was prerequisites for participation. Plasma glucose (fasting or post prandial) or glycated hemoglobin (HbA1c) was checked before participation.

Diagnosis of diabetes mellitus

"Fasting blood sugar (FBS) ≥ 126 mg/dL (7.0 mmol/L) or 2-h blood sugar ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT) or HbA1c ≥ 6.5% or Classic diabetes symptoms + random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)" [25].

Body Mass Index (BMI) was calculated as: weight (kg) ÷ $[\text{height (m)}]^2$

Following patients were excluded from the study:

1. Patients with CAD diagnosed by symptoms, ECG or regional wall motion abnormalities on echocardiogram or prior coronary angiography.

2. Patients with heart failure diagnosed by signs and symptoms, chest radiograph or echocardiography.

3. Patients with significant valvular heart disease.

4. Heart rate <50 or >100 beat per minute, atrial fibrillation and other arrhythmias that may interfere with Doppler studies.

5. Hypertensive patients (Hypertension was diagnosed if the patient had a history of hypertension with ongoing treatment or the blood pressure was equal to or greater than 140/90 mmHg) [26].

6. Patients with long history of diabetes mellitus (>10 years) or advanced diabetic complications (e.g renal failure, severe peripheral arterial disease).

7. Subjects with poor transthoracic echocardiographic window.

Echocardiography

All transthoracic echocardiographic examinations were obtained using GE Vivid E9 ultrasound machine with 4 MHz probe and performed according to the recommendations of American Society of Echocardiography.

Subjects were examined using standard parasternal long axis, short axis and apical two and four chambers views. Conventional techniques (two-dimensional-2D, M-mode echocardiography, Pulsed-wave Doppler wave (PW) and TDI were used and concentrate on the following parameters:

1. LV internal dimensions: LV end systolic dimension (LVESD) and LV end diastolic dimension (LVEDD).
2. Ejection fraction (EF %) (Using Teichholz method).
3. E point (m/sec): Early diastolic velocities of mitral inflow (Doppler-derived).
4. Septal and lateral e point by tissue Doppler (m/sec): Early diastolic myocardial velocity, derived from tissue Doppler imaging.
5. E/e ratio: Ratio of early diastolic velocities of mitral inflow (PW-derived) and myocardial movement (TDI-derived) taken as left ventricular filling pressure.
6. Left atrial (LA) volume index (mL/BSA): In apical four and two-chamber views.
7. Peak tricuspid regurgitation (TR) velocity (m/sec). Systolic dysfunction was defined if LV Ejection fraction <50% [28].

Definition of LV diastolic dysfunction was indicated if 3 or more of these variables are abnormal [27]:

"Septal e <7 cm/sec

Lateral e <10 cm/sec)

E/e ratio >14

LA volume index >34 mL/m^2

Peak TR velocity >2.8 m/sec."

Diastolic dysfunction was divided into three grades (grade I; impaired LV relaxation, grade II ; pseudonormal filling pattern and grade III ; restrictive filling pattern) [27].

Statistical analysis

"Analysis of data was carried out using the statistical package of SPSS-22 (Statistical Packages for Social Sciences-version 22). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values)".

"The significance of difference of different means (quantitative data) were tested using Students-t-test for difference between two independent means. The significance of difference of different percentages (qualitative data) were tested using Pearson Chi-square test ($\chi 2$-test) with application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P value was equal or less than 0.05".

Results

We evaluate 151 subjects (86 diabetic patients and 65 apparently healthy non diabetic (confirmed by blood sugar values), age and sex-matched control subject) with a mean age 43 ± 5 and 44 ± 3 years, respectively. Out of 86 diabetic patients 49 (57%) were female and 37 (43%) male.

A total of 65 were age and sex control subjects; 36 (55.4%) female and 29 (44.6%) male **(Table 1)**. Mean of E/A ratio in the diabetic patients was significantly lower as compared to the control group (p=0.05).

Mean of E/e' ratio in the diabetic group was significantly higher comparing with the control group (p<0.05). No significant difference in LA volume index and peak TR velocity between both groups.

Out of 86 diabetic patients, 54 patients (62.8%) met the criteria of diastolic dysfunction while 8 (12.3%) subject in the control group had diastolic dysfunction , which statistically highly significant (p<0.05) **(Table 2).**

Diastolic dysfunction was significantly higher in patients with age >45 years, compared to age <45 years (70.9% versus 48.3%; p<0.05) **(Table 3).**

Patients with 6 years duration of diabetes and more had higher prevalence of diastolic dysfunction compared with those patients with less duration (83.67% versus 35.13%; p<0.02). No significant difference in the mean of BMI between diabetics and control group.

Subjects with HBA1c >7.5% had more prevalence of diastolic dysfunction, than subjects with HBA1c <7.5% (75.43% vs. 37.93%; p<0.05).

Forty-one patients (76%) had grade 1 diastolic dysfunction, 13 (24%) had grade 2 diastolic dysfunction and no patient had restrictive filling pattern (grade III) diastolic dysfunction while all eight control subjects with diastolic dysfunction had impaired relaxation (grade I).

Table 1 Baseline characteristics of study population.

Parameter	Diabetic patients (N=86)	Control group (N=65)			P value
	Men (n=37)	Women (n=49)	Men (n=29)	Women (n=36)	
Age	44 ± 3	43 ± 5	42 ± 4	41 ± 6	NS
duration	5 ± 2	6 ± 2			
BMI	30.6 ± 2.7	31 ± 2.2	30.4 ± 3.9	29.8 ± 4.9	NS
HbA1C	8.4 ± 1.6	8.6 ± 1.4			
E/A ratio	0.87 ± 0.13	0.86 ± 0.17	1.23 ± 0.13	1.11 ± 0.21	0.05*
E/e ratio	14.4 ± 3.1	14.6 ± 2.8	7.2 ± 1.2	7.1 ± 1.3	0.05*
LA size	32.6 ± 1.8	32.4 ± 2.1	2.6.5 ± . 13	28.2 ± 1.5	NS
TR velocity	31.8 ± 1.2	32.7 ± 1.4	25.3 ± 1.1	27.8 ± 1.5	NS
EF	62 ± 4	61 ± 5	66 ± 5	65 ± 4	NS
Diastolic dysfunction	23(62.1 %)	31 (63.2%)	3 (10.3%)	5 (13.8%)	0.05*
"*P value <0.05 is considered statistically significant. BMI: body mass index, LA: left atrium, TR: tricuspid regurgitation, EF: ejection fraction					

Table 2 2D and doppler parameters in diabetics and controls.

Parameter	Diabetics mean +SD (n= 86)	Controls mean +SD (n=65)	p-value
E (m/sec)	0.54 ± 0.13	0.59 ± 0.05	NS
A (m/sec)	1.1 ± 0.23	0.8 ± 0.12	NS
E/A ratio	0.87 ± 0.25	1.21 ± 0.21	0.05*
Lateral e (m/sec)	0.8 ± 0.21	1.46 ± 0.2	0.05*
Septal e (m/sec)	0.68 ± 0.16	1.2 ± 2.7	0.05*
E/e ratio	14.2 ± 2	7.1 ± 1.3	0.05*
LA volume index (ml/m2)	33 ± 2	27 ± 3	NS
Peak TR velocity (m/sec)	3.4 ± 0.6	2.5 ± 0.5	NS
Diastolic dysfunction	0.628	0.123	0.05*
"*P value <0.05 is considered statistically significant"			

Table 3 Relation of diastolic dysfunction with dependent variables in diabetic patients.

Variables	Diastolic dysfunction Present	Diastolic dysfunction Absent	Total (%)	P-value
Age <45 years (n=31)	15(48.38%)	16	0.36	0.05*
Age >45 years(n= 55)	39 (70.9%)	16	0.64	
Duration of diabetes <5 years(n=37)	13(35.13%)	24	0.43	0.02*
Duration of diabetes>5 years (n=49)	41(83.67%)	8	0.57	
HbA1c <7.5 (n=29)	11 (37.93%)	24	0.3372	0.05*
HbA1c >7.5 (n=57)	43 (75.43%)	25	0.6628	

BMI <30 (n=35)	16(45.71%)	19	0.406 9	NS
BMI>30 (n=51)	38 (74.5%)	13	0.593 1	
"*P value <0.05 is considered statistically significant"				

Discussion

This study support the evidence that LV diastolic function may impaired early in patients with diabetes mellitus (the first 5 years from the diagnosis) before the development of symptomatic LV systolic or diastolic dysfunction and this is seems to be comparable to the previous reports.

In our study, we noted that there is a direct relation between the duration of diabetes mellitus and the presence of preclinical diastolic dysfunction and significant diastolic dysfunction occurs more than 5 years after the onset of the disease (p<0.05).

The diastolic dysfunction in diabetic patients also correlated with the poor glycemic control and HbA1c level which is comparable to the previous reports.

Hyperglycemia per se can lead to alteration in substrate supply and utilization by cardiac myocytes that represent the primary injury in the pathogenesis of diastolic function impairment and subsequently diabetic cardiomyopathy.

Celentano A et al. [29] reported that alteration in LV diastolic function seems to be related to level of fasting blood sugar and HbA1c even within normal limits.

"Each 1% increase in HbA1c level has been associated with an 8% increase in the risk of heart failure [28-31], and HbA1c > 8 has also been associated with diastolic dysfunction [32], although the glycemic control may not reverse the diastolic dysfunction" [33,34].

Importantly, improved glucose control may improve but no reverse diastolic impairment and a good glycemic control may decrease the risk of progression to overt heart failure.

In our study we found that 62.3% of asymptomatic diabetic patients have diastolic dysfunction which is comparable to the previous reports.

Nikhil et al. [35] reported in their study that 66% of diabetic patients had diastolic dysfunction.

Patil et al. [36] in their study of 127 asymptomatic type II diabetics found a significant incidence (54.33%) of diastolic dysfunction in diabetics.

Van Heerebeek et al. [37] in their study found that, "the cardiomyocyte resting tension is more important when LVEF is normal and excessive diastolic LV stiffness is an important mechanism to heart failure in diabetic patients".

Sohail et al. [38] in their study reported that 30.7% of patients with type II diabetes mellitus had LV diastolic dysfunction.

Patil et al. [39] in their cross-sectional study found that in 64% of patients with type II diabetes, myocardial damage affects diastolic dysfunction in diabetics before systolic dysfunction.

Fawad et al. [40] found in their study that diabetes mellitus "was the strongest independent predictor of asymptomatic LV diastolic dysfunction in patients without structural heart disease or systemic hypertension".

In the current study ,most of patients with diastolic dysfunction (72%) had impaired LV relaxation (grade I), 16% had a pseudonormal filling pattern (grade II) which is comparable to Zabalgoitia et al. [41] study who reported that diastolic dysfunction was found in 47% of diabetic patients, 30% had impaired relaxation and 17% had a pseudonormal filling pattern.

No patient in our study had a restrictive filling pattern (grade III) and this is may be explained by our exclusion of patients with long history of diabetes mellitus (>10 years) or patients with advanced diabetic complications. Xiara et al. [42] reported in their study that 63.2% of diabetic patients had LV diastolic dysfunction, 77.4% of them had impaired relaxation pattern, 22.6% had pseudonormal pattern and no one had restrictive pattern of diastolic dysfunction.

Much effort was made to propose satisfactory diagnostic criteria for LV diastolic dysfunction with numerous echocardiographic parameters that are highly influenced by changes in volume status, blood pressure, and heart rate that causing difficulty in their interpretation in diabetic patients.

The "gold standard" procedure for assessing LV diastolic function is "Cardiac catheterization with simultaneous pressure and volume measurements is but it is invasive procedure and usually cannot be performed in the many patients".

During the last two decades, Doppler echocardiography together with more recently developed myocardial tissue Doppler imaging has emerged as an important noninvasive technique for the assessment of LV diastolic function.

In the current study we applied the last AHA and ESC guideline [27] in the assessment of LV diastolic function which depend mainly on the parameters of TDI in addition to LA volume index and peak TR velocity. Using these parameters seems to increase the rate of detection of diastolic dysfunction. These new techniques help as to overcome some technical limitations in the conventional Doppler echocardiographic techniques of diastolic function. The existence of the pseudonormal LV filling pattern (grade II) diastolic dysfunction, was not evaluated in most of the earlier reports. Therefore it is possible that many patients with diastolic dysfunction with a pseudonormal pattern would not have missed this diagnosis if these new techniques had been performed. This is may be the cause for the discrepancies in the prevalence of diastolic dysfunction that was noted between earlier and resent studies.

Boyer et al. detected "LV filling impairment in 46% in asymptomatic normotensive type 2 diabetic patients when screened by conventional Doppler, whilst newer techniques showed diastolic dysfunction in 75% of patients" [43].

Tissue Doppler Imaging is more sensitive method that measures "the velocity of the longitudinal motion (shortening and lengthening) of the mitral annulus" and it is a sensitive method for early detection of diastolic dysfunction.

Boyer et al. [43] reported that "TDI detected diastolic dysfunction more often (63%) than any other echocardiographic parameter".

Mitrovsca, et al. in their study reported that TDI[44].

On the other hand, Saraiva et al. [45] stated in their study that "tissue Doppler imaging identified diastolic dysfunction in 26.6% of diabetics, while classical criteria did so in 40.5% of the cases. The group identified by classical criteria did not differ significantly from patients without diastolic dysfunction, while in the group identified by TDI, significant differences were highlighted".

Ommen et al. [46] in their study found that the ratio of mitral velocity to early diastolic velocity of the mitral annulus (E/e) is better correlated with LV filling pressures than other Doppler parameters.

Conclusion and Recommendation

This study confirms that diastolic dysfunction may present in diabetic patients even in young diabetic patients or with a shorter duration of the disease and this abnormality may represent early stage of pre-clinical diabetic cardiomyopathy.

TDI , LA size and peak TR velocity are sensitive indices for early detection of LV diastolic dysfunction since this influence the outcome and prognosis of diabetic patients and has an important therapeutic implications.

Limitations of the Study

1. The rigorous exclusion criteria may explain the small number of included patients.

2. Other tests such as myocardial perfusion imaging, CT coronary angiography or coronary angiography to exclude CAD are as the underlying causes of the myocardial dysfunction rather than diabetic cardiomyopathy are not performed.

Nevertheless; the patients included in the study are relatively young and asymptomatic, so the possibility of CAD seems to be low.

3. This is a cross-sectional study so follow-up of the progression of the subtle LV diastolic abnormalities detected in this study would have added important information to the development of cardiac complications and congestive heart failure in diabetic patients.

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