Assessment of left ventricular functions in patients with type 2 diabetes mellitus using tissue Doppler imaging and its correlation with a novel cardiac biomarker

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Introduction
Cardiovascular diseases account for about 65% of diabetes-related mortality.

Objective
Noninvasive assessment of left ventricular functions in asymptomatic nonhypertensive nonischemic type 2 diabetics using echo heart and tissue Doppler imaging (TDI) for detecting structural and functional cardiac abnormalities, and correlating them with levels of Brain natriuretic peptide (BNP) for early planning of management before passing into overt heart failure (HF) were the objectives of this study.

Patients and methods
We studied 55 patients with type 2 diabetes and classified them into two groups: 26 patients with less than 10 years diabetes duration and 29 patients with more than 10 years duration. Full history, fasting blood glucose, postprandial blood glucose, glycated hemoglobin, creatinine, lipid profile, BNP, ECG, conventional echo, and TDI were performed for all patients.

Results
In all, 45 (80%) patients out of 55 patients have diastolic dysfunction, classified as 15 (27%) with type 1 diastolic dysfunction, 26 (47%) with type 2 pseudonormal diastolic dysfunction, and four (7%) patients with type 3 diastolic dysfunction. Systolic dysfunction (ejection fraction $<55$) was present in nine (16%) patients despite absent HF. BNP was significantly high in patients with longer diabetes duration ($P=0.008$). There was a statistically significant difference in the BNP level between those with diminished systolic function and those with normal systolic function, $P=0.001$; yet no statistically significant difference was found between BNP and different groups of diastolic dysfunction ($P=0.7$).

Conclusion
Diabetic cardiomyopathy is an important diabetes complication. It varies from subclinical ventricular dysfunction to overt HF. Echocardiography is the standard diagnostic tool for diabetic cardiomyopathy. TDI can be used to quantitatively assess global, regional, systolic, and diastolic myocardial functions. Plasma BNP can be a prognostic rather than diagnostic test.

Keywords:
- brain natriuretic peptide
- cardiomyopathy
- diabetes mellitus
- diastolic dysfunction

Introduction
Diabetes mellitus (DM) is a global health problem affecting millions of people. DM complication prevention is essential to decrease morbidity and mortality in those patients. Cardiovascular complications are responsible for nearly 75% of deaths from DM and are the most important causes of morbidity and mortality in diabetic patients [1]. Framingham study showed that heart failure (HF) is encountered twice as often in diabetic men, and five times more often in diabetic women, compared with nondiabetic individuals [2].

Multiple pathophysiological pathways can cause cardiac impairment in DM such as altered myocardial metabolism, endothelial dysfunction, microvascular disease, autonomic neuropathy, and altered myocardial structure with fibrosis [3]. Myocardial ischemia and/or coronary artery disease (CAD) and hypertension are usual in type 2 diabetes. When those factors are excluded, myocardial impairment is considered to be specific to diabetes, defining diabetic cardiomyopathy (DbCM) [4].

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DbCM is currently defined as a diastolic dysfunction, and several studies of DM patients have identified left ventricle (LV) diastolic dysfunction as the earliest dysfunction in its course [5,6]. On the other hand, LV longitudinal myocardial systolic dysfunction has been identified in DM patients with preserved left ventricle ejection fraction (LVEF) without overt CAD or HF [7]. Recently, investigations have found that LV longitudinal myocardial systolic dysfunction, rather than left ventricle diastolic dysfunction (LVDD), should be considered the first marker of a preclinical form of DbCM in DM patients with preserved LVEF without overt HF [8].

Early recognition of heart disease in diabetic patients is a highly desirable goal, and diastolic dysfunction, one of its earliest manifestations, can be assessed by tissue Doppler imaging (TDI) [9].

B-type natriuretic peptide (BNP) level increases in the presence of both symptomatic and asymptomatic LV dysfunction. It has been shown in several studies that BNP levels are increased in patients with diabetic complications [10,11]. The diagnostic role played by BNP in early detection of asymptomatic diastolic dysfunction in type 2 diabetes is still controversial [12–16]. In clinical practice, it is difficult to submit all asymptomatic diabetic patients to echocardiographic laboratory so BNP may be considered to be a good marker for detecting preclinical LVDD in patients particularly prone to develop cardiovascular complications, such as uncontrolled DM patients, and could be a cheap, easy, and useful tool to screen diabetic patients with preclinical ventricular diastolic dysfunction [17].

Our study aimed at noninvasive assessment of LV functions in asymptomatic nonhypertensive nonischemic type 2 diabetics using echo heart and TDI for detecting structural and functional cardiac abnormalities and correlating them with levels of brain natriuretic peptide (BNP) for early planning of management before passing into overt HF.

**Patients and methods**

A total of 55 patients with type 2 diabetes with age below 55 years were enrolled in this study and were classified into two groups according to diabetes duration: 26 patients with diabetes duration less than 10 years (15 male and 11 female) and 29 patients with diabetes duration more than 10 years (11 male and 18 female). All participants were selected from outpatient endocrine and diabetes clinic, Ksar El Aini Cairo University Hospitals. Patients with a history of hypertension, significant valvular heart disease, congenital heart disease, persistent arrhythmias, and patients known or suspected to have ischemic heart disease as evidenced by history (including history of angina, dyspnea, and palpitation on exertion), resting ECG, and conventional echocardiography were excluded. Patients with resting segmental wall motion abnormalities by echocardiography were excluded from the study and were sent for further investigations with thalium scan and coronary angiography. LV mass was assessed and patients with hypertrophic cardiomyopathy and hypertrophic obstructive cardiomyopathy were excluded. Patients with morbid obesity, renal failure, and other major organ failure were excluded. The study protocol was approved by the ethics committee of our institution, and all patients gave informed consent before participation.

Full history and clinical examination, fasting blood glucose, postprandial blood glucose, glycated hemoglobin, creatinine, lipid profile (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, serum triglycerides), BNP levels with enzyme-linked immunosorbent assay, resting ECG, conventional echocardiography, including LV wall thickness, dimensions [left ventricular end systolic dimension (LVESD), LV end diastolic dimension, ejection fraction (EF), fractional shortening], pulsed Doppler (DW), and TDI, were performed for all patients.

**Detailed imaging studies**

**Two-dimensional echocardiography**

Each patient was examined in the left lateral decubitus position according to the recommendations of the American Society of Echocardiography. The study was conducted using an ATL HDI 5000 colored echocardiographic machine (Philips IE 33 Colored Echocardiographic Machine, USA) with TDI software incorporated in the device using 2.5–3.5 MHz transducer.

Systolic function: (a) LVEF was calculated as \[
\frac{\text{left ventricular end diastolic volume (LVEDV)} - \text{left ventricular end systolic volume (LVESV)}}{\text{LVEDV}} \times 100.
\] Systolic dysfunction was defined as EF below 55%. (b) Tissue Doppler: myocardial velocities were obtained using tissue Doppler settings, with the pulsed-wave Doppler sample volume at the septal mitral annulus in the apical four-chamber view. The Peak systolic (s') wave contraction ranged between 8 and 18 cm/s.
Diastolic function: Doppler echocardiography - transmitral flow velocities were recorded with pulsed-wave Doppler with the sample volume placed at the mitral valve tips from the apical four-chamber view. E wave: peak early filling diastolic transmitral flow velocity, A wave: diastolic atrial peak velocity, wave deceleration time (DT); interval between the peak of the E wave to the 0 baseline. Age-dependent thresholds for DT (<40 years <220 ms; 40–60 years 140–250 ms; >60 years 140–275 ms) were used to determine impaired relaxation (DT above normal limit) and restrictive pattern (DT below normal limit), [E to A ratio (E/A) was calculated]. N=0.75→1.5, ≤0.75=grade I diastolic dysfunction, 0.75<E/A<1.5 with DT>140=pseudonormal, E/A>1.5 and DT≤140=restrictive pattern.

Tissue Doppler imaging
To measure longitudinal myocardial velocities, the cardiac cycle is represented by three waveforms and was measured as follows.

(a) Sa: systolic myocardial velocity above the baseline as the annulus descends toward the apex; (b) Ea: early diastolic myocardial relaxation velocity below the baseline as the annulus ascends away from the apex; and (c) Aa: myocardial velocity associated with atrial contraction.

Myocardial velocities were obtained using tissue Doppler settings, with the pulsed-wave Doppler sample volume at the septal mitral annulus in the apical four-chamber view. Peak early diastolic septal mitral annulus velocity (e′) and peak active late diastolic septal mitral annulus velocity (a′) myocardial velocities were measured. E/e′ was calculated. In the presence of atrial dysrhythmia, transmitral, and tissue Doppler velocities were measured over five consecutive cardiac cycles. As previously described, thresholds for abnormal diastolic TDI were accepted as e′ less than 9.6 cm/s (myocardial relaxation below the lower 95% confidence limit of normal participants) or E/e′ more than 10.

Statistics
Data were analyzed by **Microsoft Office 2003 (excel)** and through statistical package of social science software program, version 16 (SPSS; SPSS Inc., Chicago, Illinois, USA). Statistical package for the social sciences was used along with Mann–Whitney U-test, Kruskal–Wallis test, NPar tests, and Pearson’s correlation test. Parametric data were expressed as mean±SD, and nonparametric data were expressed as number and percentage of the total. Determination of the relation between two studied parameters was done using correlation coefficient. *P* value less than 0.05 is considered significant.

**Results**

According to the duration of diabetes, the patients were classified into two groups: 29 patients with DM duration more than 10 years and 26 patients with DM duration less than 10 years. The laboratory data of all patients are shown in Table 1.

The echocardiographic data of all patients are shown in Table 2. The E/E′ represents LV end diastolic pressure and ranged from 5.3 to 38.4 cm/s with a mean of 11.3±6.1; S, which represents systolic forward flow, ranged from 4.3 to 9.8 cm/s with a mean of 6.7±1.3; A′, which represents late diastolic phase, ranged from 5.4 to 11.2 cm/s with a mean of 8.5±1.4; E′, which represents early diastolic phase, ranged from 3.20 to 14 cm/s with a mean of 6.5±2.2; E, which represents early filling velocity, ranged from 39 to 134 cm/s with a mean of 66.3±2; EF% ranged from 34 to 80% with a mean of 63.6±1.1; fractional shortening percentage ranged from 16.7 to 48.6% with a mean of 35±8.2; LVESD ranged from 3.5 to 6.7 cm with a mean of 3.2±0.7; and LV end diastolic dimension ranged from 3.5 to 6.7 cm with a mean of 5±0.6.

Table 3 showed that glycated hemoglobin, FBS, total cholesterol, and BNP levels were statistically significantly higher in patients with longer diabetes duration (*P*=0.04, 0.04, and 0.05, respectively).

Table 4 showed that there were statistically significant differences between the mean values of the variables (E′/E, A′,E′), which denotes all diastolic dysfunction in patients group with longer duration less than 10 years. The laboratory data of all patients with DM duration more than 10 years and 26 patients with DM duration less than 10 years. The laboratory data of all patients are shown in Table 1.

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duration of diabetes with \( P \) value of 0.016, 0.019, and 0.041, respectively, and 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 with a \( P \) value of 0.040.

A total of 45 (80%) patients out of 55 patients had diastolic dysfunction, classified as 15 (27%) with type 1 diastolic dysfunction, 26 (47%) with type 2 pseudonormal diastolic dysfunction, and four (7%) patients with type 3 diastolic dysfunction, as shown in Figs 1–3. Systolic dysfunction (EF<55) was present in nine (16%) patients despite the absence of HF and 46 (83%) patients with normal systolic functions (EF\( \geq \)55).

There was a positive correlation between DM duration and E/E’ (indicates LV end diastolic pressure LVEDP) and negative correlation between DM duration and E’ (diastolic function of the LV), as shown in Table 5, Figs 4 and 5.

BNP level ranged between 100 and 868 mg/dl (217.8±172). BNP was significantly high in patients with longer diabetes duration (\( P=0.008 \)) (Table 3). In addition, there was a statistically significant difference in the BNP level between patients with diminished systolic function and those with normal systolic function (EF>55), with a \( P \) value of 0.001; yet there were no statistically significant correlations.
between BNP and diastolic dysfunction parameters (E’, E/E’, DT) and no statistically significant difference was found between BNP and different groups of diastolic dysfunction (P=0.7) (Tables 6 and 7).

**Discussion**

Diabetes affects heart either in the form of CAD owing to accelerated atherosclerosis or cardiac autonomic neuropathy; both conditions gain high awareness among clinicians compared with the third common yet under-identified modality of cardiac affection in diabetic patients, which is ‘DbCM’.

DbCM is a diagnosis of exclusion of myocardial dysfunction in diabetics with no CAD, HTN, or valvular heart disease [18].

Our study was conducted on 55 patients with type 2 diabetes. Patients with evidence of CAD by history, resting ECG, and conventional echocardiography were excluded. Hypertensive participants and those with evidence of valvular disease were also excluded.
Patients were classified into two groups according to the duration of diabetes: 26 patients with diabetes duration less than 10 years and 29 patients with diabetes duration more than 10 years.

In the current study, echocardiography, which is a relatively inexpensive tool for detecting structural and functional cardiac abnormalities, is the preferred diagnostic modality done for all patients; transthoracic 2-dimensional echocardiography with pulsed Doppler evaluation of transmitral inflow and TDI was performed to minimize the errors in assessing the diastolic dysfunction.

Measurement included the transmitral early diastolic rapid filling (E wave) and atrial contraction late filling (A wave) velocities, peak early diastolic septal mitral annulus velocity (e’), isovolumetric relaxation time and DT, E/e’ was calculated.

Quantitative assessment of global and regional myocardial systolic and diastolic functions by TDI that measures myocardial tissue velocities during cardiac cycle was done for all participants [19].

The earliest manifestation of DbCM is diastolic dysfunction [20] and is considered to be present if any of the following echo findings are seen: (a) E/A ratio <1 or >2, (b) DT <150 or >220 ms, (c) isovolumetric relaxation time <60 or >100 ms; or (4) E/e’ ratio >15; they can be categorized as follows: (a) normal pattern, (b) grade I (impaired relaxation), (c) grade II (pseudonormal pattern), and (d) grade III (restrictive pattern) [21].

Our study showed that 45 patients out of 55 (80% of cases) patients have diastolic dysfunction by means of conventional echo and TDI.

Results are in accordance with those of Schannwell et al. [22], who found subclinical isolated diastolic dysfunction in a majority of patients with type 2 diabetes.

In a study conducted by Romano et al. [17], diastolic dysfunction was found in 38% of diabetic patients without hypertension. The same findings were found in other study conducted by Virendra et al. [23], in which 127 asymptomatic diabetic patients with no evidence of coronary heart disease or hypertension were investigated; they found diastolic dysfunction in 69 (54%) of them, and all of them have normal systolic function.

Our study also showed that among 45 patients who had diastolic dysfunction 15 (27%) patients had type 1 diastolic dysfunction, 26 (47%) patients had type 2 pseudo normal diastolic dysfunction, and four (7%) patients had type 3 (restrictive pattern) diastolic dysfunction.

None of our patients had symptoms of HF. Surprisingly, the study revealed that 46 (83%) patients have normal systolic functions (EF≥55), whereas nine (16%) patients have systolic dysfunction (EF<55) despite no symptoms; this is very important as this means that you need not wait for symptoms to investigate your patient, but in diabetic patients echocardiography has to be done routinely to assess cardiac functions [24].

Studies to date support that diastolic dysfunction develops earlier than systolic dysfunction in diabetic heart; however, Emande et al. [25], reported that systolic longitudinal strain rate was abnormal in 28% of diabetic patients with normal diastolic function and in 35% of those with diastolic dysfunction.

Our study showed that there were statistically significant positive correlations between DM duration and E/E’, E, with an $r$-value of 0.431, 0.297 and $P$ value of 0.001, 0.027, respectively, and there was a negative correlation between DM duration and E’ with an $r$-value of −0.292.

These results are in contrast to the study of thirty patients with type 2 DM, in which Fiorini et al. [26], found no correlation between duration of DM and diastolic dysfunction. However, Bertoni et al. [27], in the study of 26 young participants with type 1 DM of at least 3 years duration found that there is a correlation between diastolic dysfunction and duration of DM.

In our study, BNP level was found to be significantly higher in patients with longer diabetic duration, with a $P$ value of 0.008.

Also, there was a statistically significant difference in the BNP level between those with diminished systolic function compared with those with normal systolic function (EF>55), with a $P$ value of 0.001, whereas

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal (N=10) (20%)</th>
<th>Type 1 (N=15) (27%)</th>
<th>Type 2 (N=26) (47%)</th>
<th>Type 3 (N=4) (7%)</th>
<th>$P$ value</th>
</tr>
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<tbody>
<tr>
<td>BNP</td>
<td>215.9±230.9</td>
<td>238.6±212</td>
<td>201.3±119</td>
<td>252.5±196.1</td>
<td>0.7</td>
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BNP, brain natriuretic peptide.
we found no statistically significant difference in the BNP level between different groups of patients with diastolic dysfunction with a P value of 0.7; this may be attributed to the low number of patients in the advanced restrictive pattern, which invalidates good correlation in this group.

Our results are in accordance with the study conducted by Romano et al. [17], that failed to identify any difference between patients with normal function and those ones with LVDD regarding BNP value; the possible explanation of these results can be the presence of just impaired relaxation in the studied population, which represents the mild grade of LVDD. On the contrary, in the study by Albertini et al. [13] when 91 type 2 diabetic patients were assessed as regards levels of BNP, it was found to be significantly higher in those with LVDD, especially those with untreated hypertension.

Another study done by Kiencke et al. [12] on 100 patients analyzing BNP; if it can predict preclinical diastolic dysfunction in DbCM; they concluded that BNP have prognostic rather than diagnostic role.

Our study showed that there was a statistically significant difference between the mean values of two groups with BNP showing higher levels in patients with diminished systolic function (P=0.001); also our study showed that there were statistically significant negative correlations between BNP and systolic function of LV as represented by LVEsd and EF%.

Plasma BNP levels provide clinically useful information concerning the diagnosis and management of LV dysfunction and HF, which complements other diagnostic testing procedures such as ECGs, chest radiographies, and echocardiograms. Numerous studies have indicated that BNP can be used for patient diagnosis, prognosis, and therapy monitoring. Levels of BNP have been shown to be elevated in patients with cardiac dysfunction [28].

**Conclusion**

DbCM is an important but less well-recognized complication of diabetes; its manifestations can vary from subclinical ventricular dysfunction to overt HF. Echocardiography is the standard clinical diagnostic tool for DbCM at present. TDI can be used to quantitatively assess global and regional systolic and diastolic functions of the myocardium. Plasma BNP can be prognostic rather than diagnostic test.

**Limitations**

The limitations of this study are the small number of patients, which should be increased in future similar studies, and the lack of assessment of coronary flow reserve noninvasively to exclude microvascular dysfunction as a cause of diastolic dysfunction, such as cardiac MRI, which is a very expensive procedure.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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**References**


