Original Research Article

Study of the Echocardiographic Changes in Patients with Diabetic Nephropathy

Abstract

Background: Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies. Cardiovascular changes are one of the important macro vascular complications which are a major cause of mortality in diabetic patients with diabetic nephropathy. The aim of this work was to evaluate the structural and functional cardiovascular changes using echocardiography in diabetic patients with diabetic nephropathy (DN) in comparison with those without diabetic nephropathy.

Methods: This observational cross-sectional study was carried out on 60 diabetic patients with type 2 diabetes mellitus (T2DM) only or had T2DM with DN Patients were subdivided in to two equal groups: group A included patients without DN and group B included patients with DN. All patients were subjected to laboratory investigations, echocardiography (tricuspid annular plane systolic excursion (TAPSE), pulmonary artery pressure measuring, left ventricular systolic and diastolic function assessment).

Results: There was a significantly lower Hb and significantly higher creatinine level and AL/CR ratio in group B compared to group A. There was significantly higher number of sclerotic aortic valve patients, higher numbers of low TAPSE, higher estimated systolic pulmonary artery pressure (ESPAP), higher end diastolic diameter (EDD), higher end systolic diameter (ESD), heavier left ventricular mass and thicker posterior wall thickness in group B compared to group A ($P \leq 0.05$). There was a positive relationship between AL/CR ratio and EDD, left ventricular mass, TAPSE, and posterior wall thickness, while negative relationship

between it and ESD in the two studied groups, and it was found that high EPASP and sclerosis of the Aortic valve were more prevalent with DN group.

Conclusions: Risks of cardiovascular events increase substantially with increasing stage of kidney disease in T2DM patients. Asymptomatic diabetic subjects are at high risk for major adverse cardiovascular events, such as those with, chronic diabetic kidney disease (DKD), or proteinuria.

Keywords: Echocardiography, Diabetic Nephropathy, Diabetes mellitus.

Introduction:

Diabetes mellitus (DM) is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbance of carbohydrates, fat and protein metabolism. This results from defects in insulin secretion, insulin action or both include long term damage and failure of various organs [1].

International Diabetes Federation (IFD) listed Egypt among the world top 10 countries in the number of patients with diabetes, the IFD estimated that 7.5 million individual have diabetes and around 2.2 million have pre diabetes in Egypt it is expected this number will increase to 13.1 million by 2035 [2].

There are many complications of DM that can be classified into macro vascular and micro vascular complications. Micro vascular complications are considered as an important group of hyperglycemia hazards that caused by increased endothelial permeability and can progress to sever impairment in several organs. Diabetic nephropathy (DN), retinopathy and neuropathy are the most common microvascular complications of hyperglycemia [3]**.** It was reported that 25–40% of patients with type 2 DM (T2DM) had DN [4].

Cardiovascular changes are one of the important macro vascular complications which are a major cause of mortality in diabetic patients with diabetic nephropathy [5], especially diabetic nephropathy of T2DM [6]. Study of prevalence of various cardiovascular changes in diabetic nephropathy patients would help in proper and timely intervention and reducing the mortality in diabetic nephropathy patients [7]. Echocardiography in recent years has become the gold standard in detecting structural and functional changes in heart of these patients [8].

The aim of this work was to evaluate the structural and functional cardiovascular changes using echocardiography in diabetic patients with diabetic nephropathy in comparison with those without diabetic nephropathy.

Patients and Methods:

This observational cross-sectional study was carried out on 60 diabetic patients with T2DM only or had T2DM with DN aged from 38-80 years attending the inpatient and outpatient clinics of Internal medicine department, Tanta university hospitals during the study period from June 2021 to June 2022. The study was done after approval from the approval of the Ethics Board of Tanta University. A written informed consent from all the subjects was obtained.

Exclusion criteria were type 1 diabetes mellitus, other known chronic cardiac diseases as (rheumatic heart diseases, coronary artery diseases or heart failure), renal diseases other than DM, pregnant patients with T2DM.

Patients were further subdivided in to two equal groups: group A included patients without diabetic nephropathy and group B included patients with diabetic nephropathy.

All patients were subjected to: complete history taking, clinical examination, laboratory investigations (complete blood count, fasting ,2-hour post prandial blood sugar and hemoglobin A1c (HBA1C), Serum creatinine, blood urea, urine analysis, albumin creatinine ratio (AL/CR) in urine, lipid profile) and radiological investigations.

Echocardiography:

It was performed with General Electric, Vivid 7 and Vivid E9 (GE Vingmed Ultrasound, Horten, Norway). The offline analyses were performed using GE EchoPAC software, BT13. The echocardiograms were performed (>95%) and interpreted and validated the same day by a cardiologist with specialty in echocardiography blinded to patient data.

Left atrial (LA) end-systolic size was calculated using the area-length method, where left atrial volume =8/3×π (LA area in 4 chamber view × LA area in 2 chamber view/shortest long axis length in either view) and increased atrial size indexed for body surface area was defined as >34mL/m^2.

Aortic measurements were performed in the aortic root and the ascending aorta and evaluated according to age and body surface area corrected normal values.

LV ejection fraction was assessed using Simpson's biplane method, and reduced LV ejection fraction was considered when <50%.

Diastolic dysfunction was considered present when the ratio of early mitral valve inflow velocity to septal early diastolic tissue doppler velocity (E/e′) was >15. Right ventricular function was assessed using tricuspid annular plane systolic excursion and considered reduced when <1.7 cm.

Presence and grading of valvular heart disease was performed with an integrative approach as suggested by the EAE24 and was considered present when more than moderate. Systolic anterior motion of the anterior mitral valve leaflet was visually identified and if present, Doppler measurements of left ventricular outflow tract gradients during Valsalva were recorded. An echocardiogram was considered abnormal when at least one of the above-mentioned was present [9].

Echocardiographic examination was performed with the patient in a partial left lateral decubitus position under a two-dimensionally guided M-mode echocardiography machine.

Tricuspid annular plane systolic excursion (TAPSE):

TAPSE is measured by placing an M-mode cursor through the lateral tricuspid annulus in a four-chamber view. This index is a reliable marker of RV longitudinal function and has been well correlated with RV EF by cardiac MRI. A value of less than16 mm is adults and <10 mm in children is indicative of RV systolic dysfunction.

Pulmonary artery pressure:

Pulmonary arterial hypertension is traditionally defined as an increase in mean pulmonary arterial pressure (PAP m) ≥25 mmHg at rest as assessed by right heart catheterization (RHC) [10]. Doppler Echo can approximate pulmonary artery systolic pressure (PASP) using

tricuspid valve velocity (4v2 = TV pressure gradient), estimated CVP (=RA pressure) and bernoulli equation:

PASP = RVSP (in the absence of RVOTO or pulmonic stenosis)

RVSP = 4v2 + CVP

Mean pulmonary artery pressure can be approximately calculated from systolic (by TR max method) and diastolic (by PR-end velocity method) pulmonary artery pressures:

M PAP = 2/3rd of PADP+ 1/3rd of PASP

Severity of pulmonary hypertension (mPAP): Mild = 20-40mmHg, moderate = 41-55mmHg, severe = > 55mmHg.

Left ventricular hypertrophy (LVH):

LVH is a marker for heart disease. In general, a measurement of 1.1-1.3 cm indicates mild hypertrophy, 1.4-1.6 cm indicates moderate hypertrophy, and 1.7 cm or more indicates severe hypertrophy [11].

Left ventricular ejection fraction (EF):

Fractional shortening (FS) is obtained from M-mode tracings or 2D imaging in the PLAX view at the tips of the mitral valve leaflets or in the PSAX view at the level of the papillary muscles. Left ventricular function may be objectively classified: normal function (FS 26–45%), mild (FS 20–25%), moderate (FS 15–19%) and severe dysfunction (FS ≤14%). The left ventricular end-diastolic dimension (LVEDD) is measured at R-wave of cardiac cycle and left ventricular end-systolic dimension (LVESD) obtained at end of T-wave, and the FS is calculated using the following equation:

(LVEDD - LVESD / LVEDD) x 100

Left ventricular mass:

LVH was defined as left ventricular mass (LVM) of at least 110 g/m^2 in women and 125 g/m^2 in men. LVM was calculated by the regression equation:

$$LVM = 1.04 \times [(IVST + LVPWT + LVDd)\ 3 - LVDd\ 3] - 13.6$$

(indexed according BMI)

Left ventricular diastolic function:

The peak early trans mitral filling velocity during early diastole (E), peak trans mitral atrial filling velocity during late diastole (A), deceleration time of E velocity (E-Dec), and iso volumetric relaxation time were used as left ventricular diastolic function parameters.

Statistical analysis

Statistical analysis was done by SPSS v20 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and unpaired student t-test was used to compare between two groups. Qualitative variables were presented as frequency and percentage (%) and pearson chi-square was used to compare between two groups. Pearson correlation was used between two variables. A two tailed P value ≤ 0.05 was considered significant.

Results:

There was no statistically significant difference between the two groups with regard to age, gender, residence and duration of DM. Table 1

Table 1: Patient characteristics of the studied groups

		A	B	P-value
Age (Years)		61.467 ± 7.606	60.300 ± 10.127	0.616
Gender	**Male**	15 (50 %)	11 (36.67 %)	0.297
	Female	15 (50 %)	19 (63.33 %)	
Residence	**Urban**	8 (26.67 %)	16 (53.33 %)	0.065
	Rural	22 (73.33 %)	14 (46.67 %)	
Duration of DM (years)		13.533 ± 6.574	14.667 ± 7.599	0.539

There was a significantly lower Hb levels and significantly higher creatinine level and AL/CR ratio in group B compared to group A. There was no statistically significant difference between the two groups regarding lipid profile and HBA1C. Table

Table 2: Anemia, creatinine, albumin creatinine ratio, lipid profile and hemoglobin A1C in the studied groups

		A	B	P-value
Hb (g/dl)	**Mean ±SD**	12.5 ± 2.946	10.467 ± 3.776	0.043*
	Present	3 (10 %)	13 (43.33 %)	0.004*
Creatinine level		1.06 ± 0.161	1.895 ± 0.778	<0.001*
AL/CR		14.067 ± 5.212	111.1 ± 98.261	<0.001*
Lipid profile		214.167 ± 95.359	230.2 ± 116.063	0.561
HBA1C		8.213 ± 1.582	8.67 ± 1.55	0.263

Data is presented s mean ± SD and frequency (%), * significant as $p \leq 0.05$. AL/CR: Albumin creatinine ratio, HBA1C: Hemoglobin A1c.

There was no statistically significant difference between the two groups regarding the degree of the diastolic dysfunction, mitral valve regurge, tricuspid valve, FS, EF, inter ventricular septum thickness (IVSD), aortic root, and LA dilatation. There was significantly higher number of sclerotic aortic valve patients, higher numbers of low TAPSE, higher ESPAP, higher EDD, higher ESD, heavier left ventricular mass and thicker posterior wall thickness in group B compared to group A ($P \leq 0.05$). Table 3

Table 3: Echocardiographic parameters in the studied groups

		A	B	P-value
		N (%)	N (%)	
Grades of diastolic dysfunction	**Normal**	4 (13.33 %)	2 (6.67 %)	0.554
	Diastolic dysfunction G1	25 (83.33 %)	24 (80 %)	
	Diastolic dysfunction G2	1 (3.33 %)	2 (6.67 %)	
	Diastolic dysfunction G3	0 (0 %)	1 (3.33 %)	
	Diastolic dysfunction G3/G4	0 (0 %)	1 (3.33 %)	
Mitral valve	**Mild Regurge**	24 (80 %)	26 (86.67 %)	0.353
	Moderate Regurge	0 (0 %)	1 (3.33 %)	
Tricuspid valve	**Mild Regurge**	17 (56.67 %)	20 (66.67 %)	0.180
	Moderate Regurge	0 (0 %)	2 (6.67 %)	
Aortic valve	**Sclerotic**	0 (0 %)	4 (13.33 %)	0.038*
TAPSE	**Low**	0 (0 %)	7 (23.33 %)	0.005*
ESPAP	**HIGH**	3 (10 %)	11 (36.67 %)	0.015*
EDD (mm)		45.133 ± 4.240	50.2 ± 8.857	0.006*
ESD		29.5 ± 3.946	32.467 ± 6.776	0.043*
FS (%)		36.367 ± 5.756	33.667 ± 6.138	0.084
EF (%)		65.833 ± 4.935	62.8 ± 7.712	0.075
IVSD (mm)		10.233 ± 1.736	10.733 ± 1.856	0.286
Left ventricular mass		157.242 ± 40.686	218.583 ± 79.358	<0.001*
Posterior wall thickness (mm)		10.2 ± 1.472	11.067 ± 1.741	0.042*
Aortic root (mm)		28.8 ± 3.156	30.633 ± 4.972	0.094
LA (mm)		34.3 ± 4.655	36.633 ± 6.515	0.116

Data is presented s mean ± SD and frequency (%), * significant as $p \leq 0.05$. G: grade, TAPSE: Tricuspid annular plane systolic excursion, ESPAP: Estimated systolic pulmonary artery pressure, EDD: End diastolic

diameter, ESD: End systolic diameter, FS: Fractional shortening, EF: Ejection fraction, IVSD: Inter ventricular septum thickness, LA: Left atrium.

There was a positive relationship between AL/CR ratio and EDD, left ventricular mass, TAPSE, and posterior wall thickness, while negative relationship between it and ESD in the two studied groups, and it was found that high EPASP and sclerosis of the aortic valve were more prevalent with DN group. Table 4

Table 4: Correlations between AL\ CR ratio and EDD, ESD, LV mass, PW, and TAPSE in studied groups

Diabetic	AL\CR	
	r	P-value
EDD (mm)	0.111	0.558
ESD (mm)	-0.029	0.879
Left ventricular mass	0.269	0.151
Posterior wall thickness (mm)	0.163	0.389
TAPSE (mm)	0.192	0.245

AL\CR: Albumin creatinine ratio, EDD: End diastolic diameter, ESD: End systolic diameter, TAPSE: Tricuspid annular plane systolic excursion.

Discussion

Diabetes is associated with a two - to fourfold increased risk for atherosclerotic cardiovascular disease (CVD) compared with the background population, and 30–40% with diabetes is affected by chronic kidney disease characterized by increased albuminuria or decreased glomerular filtration rate or diabetic kidney disease (DKD) [12].

There was a significantly lower Hb levels in group B compared to group A. This comes in agreement with the study in London [13] which reported that anemia is often more severe and occurs at an earlier stage in patients with diabetic nephropathy than in patients with chronic kidney disease (CKD), this results from erythropoietin deficiency even at relatively "normal" levels of serum creatinine .

There was a significantly higher creatinine level in group B compared to group A. This comes in agreement with the conclusion of multicenter involved study that studied the

relationship between HbA1c levels and risk of cardiovascular adverse outcomes and all-cause mortality in cardiovascular high-risk women and men with T2DM [14].

There was a significantly higher AL/CR ratio in group B compared to group A while there was no significant difference between the two groups regarding lipid profile. There was a study in China which observed a higher prevalence of hypertension (HTN), T2DM, HTN with T2DM, dyslipidemia, and CVDs in abnormal urinary albumin creatinine ratio and reveal a significant association of UACR, even within the normal range, with development of HTN, T2DM, HTN with T2DM, dyslipidemia, and CVDs [15].

There was no statistically significant difference between the two groups regarding the degree of the diastolic dysfunction. This comes in agreement with a study [16], that showed that diastolic dysfunction is one of the common findings after left ventricular hypertrophy and LV dilatation, while there is a study at Hospital of Soochow University that compared between diabetic and non-diabetic nephropathy patients in cardiac structure and function at the beginning of hemodialysis [17] and showed that patients with DN who are on HD tend to have worse LV diastolic function.

In our study, 86% showed mitral valve regurgitation, there were 40 % of cases with mild mitral regurgitation in group A and 43% with mild mitral regurgitation in group B and only one case with moderate MR in group B, while tricuspid valve regurgitation in (56.6%) of group A, and (66.6%) of group B. This agrees with a study [18] who found (32%) patients had mitral regurgitation (25% mild, 5% moderate, and 2% severe) and concluded that mitral regurgitation is a common pathologic condition in patients with type 2 diabetes and is independently associated with an increased risk of both all-cause and cardiovascular mortality, even if the severity of mitral regurgitation is mild, but on the other side the study in (RIMS) [16] reported that there were 25% of DN studied population showed no valve abnormality.

There was significantly higher number of sclerotic aortic valve patients in group B compared to group A. there was research [19] that found that the prevalence of diabetes was higher among those with aortic stenosis than in the general population. The same paper also noted that diabetes creates and worsens pro-inflammatory factors that also affect the aortic valve.

In our study, there was no statistically significant difference between the two groups regarding IVSD. There was significantly higher EDD, higher ESD, heavier left ventricular mass and thicker posterior wall thickness in group B compared to group A. this comes in agreement with the Northern Manhattan Study (NOMAS) study [20], which reported that T2DM was independently associated with increased LV hypertrophy independent of various covariates in the multi-ethnic sample by about 1.5-fold, and it possibly interacted with central obesity. On the other hand in diabetic nephropathy population there was a study [21] that reported that left ventricular hypertrophy was demonstrated in 42 out of the 49 DN patients (85%), and found that it increased in severity with increasing renal impairment.

The present study demonstrated that 36% of studied cases in group B had pulmonary hypertension, 10% with pulmonary hypertension in group A. This comes in agreement with commentary published in Diabetes Metabolism Research and Review [22] that PH is more common among those with diabetes compared with those without and have a 1.6-fold higher risk for restrictive lung function impairment compared with those who do not have diabetes.

There was significantly higher numbers of low TAPSE in group B compared to group A. This is in agreement with a study [23] which concluded that presence of atherosclerotic disease, baseline urinary albumin concentration, and HbA1c level were indicators for further development of CHF. On the other hand, one report [24] cited that TAPSE and tricuspid peak early to peak late diastolic flow velocities ratio (E/A) in the diabetic patients were significantly lower than those of the control normal group in the absence of coronary artery disease, diastolic dysfunction, and pulmonary hypertension.

In our study, FS was low in (6%) of DN group, this come in agreement with a study which concluded their results as that the rates of inappropriate left ventricular mass, systolic and diastolic dysfunction were higher in our patients with CKD and DM than in those without DM. In contrast to our study the study [8] reported that (10%) of studied diabetic patients without complication had low FS.

In the present study, there was no statistically significant difference between the two groups regarding EF. This agrees with study [25] which reported that there were no significant differences in aortic root diameter or EF in whole diabetic cases. While a study [26] in India reported that the LVEF worsened with increasing stage of CKD and was significantly reduced in diabetic patients.

In this study, the echo finding of left atrial dilatation was found in 30% of group B while 6.6% of group A. This agrees with a study [27] that reported LA diameter was significantly higher in the DM2 group compared with the controls. While in DN there was a study in China [28] showed LAD was positively correlated with mesangial sclerosis, tubular-interstitial lesions, interstitial fibrosis, as well as tubular basement membrane thickness.

There was a positive relationship between AL\CR ratio and EDD, left ventricular mass, TAPSE, and posterior wall thickness, while negative relationship between it and ESD in the two studied groups, and it was found that high EPASP and sclerosis of the aortic valve were more prevalent with DN group. This is in agreement with a study [29] which reported that myocardial microvascular function was impaired in the presence of albuminuria compared with normo albuminuria, and coronary calcification was higher in individuals with T2DM compared with healthy control subjects and in individuals with T2DM and albuminuria compared with normo albuminuria.

Limitations: It was only one year study on 60 patients that may reduce the reliability of the conclusions. It was single-center study at only Tanta university Hospitals, so we need a

multicenter, more number of patients over longer period study to find out the prevalence of structural and functional cardiovascular changes in T2DM patients and whose with nephropathy in our locality for proper management of these cases.

Conclusions:

DM should essentially be assessed by echocardiography at the time of the diagnosis. Some key factors, such as presence of coronary artery disease or hypertension, poor diabetes control, disease duration and clinical status, may determine how often the examination should be repeated. risks of cardiovascular events increase substantially with increasing stage of kidney disease in T2DM patients, suggesting that rates of morbid events might decrease if DKD can be detected more readily, and its progression slowed. Asymptomatic diabetic subjects are at high risk for developing major adverse cardiovascular events, such as those with, chronic DKD, or proteinuria as there were structural cardiovascular changes in asymptomatic diabetic individual without nephropathy.

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