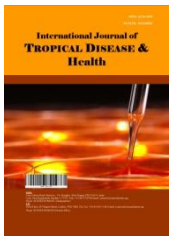

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Study of the Echocardiographic Changes in Patients with Diabetic Nephropathy

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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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).

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Results: There was a significantly lower Hb and significantly higher creatinine level and AL/CR ratio in group B in comparison 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 in comparison 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.

1. 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]. The study of the prevalence of different cardiovascular alterations in diabetic nephropathy patients might aid in appropriate and prompt management and the reduction of diabetic nephropathy-related mortality [7]. In recent years, echocardiography has become the gold standard for diagnosing structural and functional cardiac abnormalities in these individuals [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.

2. MATERIALS 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.

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.

2.1 Echocardiography

General Electric, Vivid 7 and Vivid E9 ultrasound were utilized. The offline analyses were conducted through the GE EchoPAC BT13 programme. A cardiologist with expertise in echocardiography conducted (>95%), evaluated, and confirmed the echocardiograms on the same day while being blind to patient data.

Left atrial (LA) end-systolic size was determined by the area-length approach, in which LA volume =8/3 (LA area in 4 chamber view LA area in 2 chamber view shortest/long axis length in both views) and increased LA size indexed for body surface area (BSA) was determined at >34mL/m^2.

Aortic root and ascending aorta measures were taken and assessed according to age and BSA area corrected normal values.

Using Simpson's biplane approach, the LV ejection percentage was evaluated, and a lower LV ejection fraction was regarded when 50%.

When the ratio of early mitral valve inflow velocity to septal early diastolic tissue doppler velocity (E/e′) was more than 15, it was determined that diastolic dysfunction was present. When the tricuspid annular plane systolic excursion was less than 1.7 cm, the right ventricular function was deemed diminished.

As proposed by the EAE24, an integrative method was used to determine the presence and severity of valvular heart disease, which was deemed present when in excess of moderate levels. During Valsalva, the anterior mitral valve leaflet's systolic anterior motion was visually observed, and Doppler measurements of left ventricular outflow tract gradients were recorded, if present [9]. An echocardiography was deemed abnormal if at least one of the aforementioned conditions was detected.

The patient was positioned in a partial left lateral decubitus under a two-dimensionally guided M-mode echocardiography equipment for the echocardiographic evaluation.

2.2 Tricuspid Annular Plane Systolic Excursion (TAPSE)

In a four-chamber view, TAPSE is assessed by inserting an M-mode cursor across the lateral tricuspid annulus. This measure is a valid indicator of RV longitudinal function, and cardiac MRI has demonstrated a strong correlation between it and RV EF. Less than 16 mm in adults and less than 10 mm in children indicate RV systolic dysfunction.

2.3 Pulmonary Artery Pressure

“The classic definition of pulmonary arterial hypertension is a rise in mean pulmonary arterial pressure (PAP m) ≥ 25 mmHg at rest, as measured by right heart catheterization (RHC)” [10]. Using tricuspid valve velocity (4v2 = TV pressure gradient), estimated CVP (=RA pressure), and the Bernoulli equation, Doppler Echo can estimate pulmonary artery systolic pressure (PASP). 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 = 20-40 mmHg, moderate = 41-55 mmHg, severe = > 55 mmHg.

2.4 Left Ventricular Hypertrophy (LVH)

LVH is an indicator of cardiac problem. In average, a measurement between 1.1 and 1.3 centimetres suggests mild hypertrophy, 1.4 to 1.6 centimetres shows moderate hypertrophy, and 1.7 centimetres or beyond indicates severe hypertrophy [11].

2.5 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

2.6 Left Ventricular Mass

LVH was characterised by a left ventricular mass (LVM) of at least 110 g/m2 in females and 125 g/m2 in males. LVM was computed via the regression equation:

LVM = 1.04 × [(IVST + LVPWT + LVDd) 3 − LVDd 3] − 13.6

(Indexed according BMI)

2.7 Left Ventricular Diastolic Function

Left ventricular diastolic function metrics included 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.

2.8 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.

3. RESULTS

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

There was a significantly lower Hb levels and significantly higher creatinine level and AL/CR ratio in group B in comparison to group A. No statistically significant difference in both groups regarding lipid profile and HBA1C.

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 in comparison to group A (P ≤ 0.05).

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

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 ≤ 0.05. AL/CR: Albumin creatinine ratio, HBA1C: Hemoglobin A1c*

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 ≤ 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*

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

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.

4. DISCUSSION

"Diabetes is associated with increased risk of atherosclerotic cardiovascular disease (CVD) up to 4-fold relative to the general population, and 30–40% of diabetics have chronic kidney disease characterised by diabetic kidney disease (DKD) or decreased glomerular filtration rate or even increased albuminuria" [12].

There was a significantly lower Hb levels in group B in comparison 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 in comparison 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 in comparison 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] They concluded that mitral regurgitation is a prevalent pathologic condition in individuals with type 2 diabetes and is independently related with an elevated risk of both all-cause and cardiovascular death, even if the severity of mitral regurgitation is mild. 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 in comparison 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 in comparison 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 in comparison 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 “In the absence of coronary artery disease, diastolic dysfunction, and pulmonary hypertension, TAPSE and tricuspid peak early to peak late diastolic flow velocities ratio (E/A) were considerably lower in diabetes patients in comparison to those of the control normal group”.

In our study, FS was low in (6%) of DN group, this come in agreement with a study which concluded their results as that our patients with CKD and DM had greater rates of inappropriate

left ventricular mass, systolic and diastolic dysfunction than 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 In the presence of albuminuria, myocardial microvascular function was decreased in comparison to normo albuminuria, and coronary calcification was greater in persons with T2DM in comparison to healthy control participants and in those with T2DM and albuminuria in comparison to normo albuminuria.

5. 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.

6. CONCLUSIONS

At the time of diagnosis, DM should primarily be evaluated by echocardiography. Some significant criteria, such as the existence of coronary artery disease or hypertension, poor management of diabetes, illness length, and clinical condition, may affect the frequency with which the test should be performed. Risks of cardiovascular events increase significantly with increasing stage of kidney disease in T2DM patients, suggesting that morbidity rates may be reduced if DKD can be identified earlier and its development controlled. Asymptomatic diabetics are at significant risk for having severe adverse cardiovascular events, such as those with chronic DKD or proteinuria, while asymptomatic diabetics without nephropathy have structural cardiovascular abnormalities.

ETHICAL APPROVAL AND CONSENT

The study was done after approval from the approval of the Ethics Board of Tanta University. A written informed consent from all the patient(s) was obtained.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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