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Microalbuminuria versus Cardiovascular Autonomic Neuropathy in prediction of left ventricular diastolic dysfunction in patients with type 2 diabetes

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Abstract

Cardiovascular autonomic neuropathy is one of the most common complications in diabetic patients. Microalbuminuria is associated with increased incidence of heart disease mortality in diabetic patients and it is considered as an early marker of cardiovascular diabetic complications. To clarify cardiovascular autonomic neuropathy and microalbuminuria as risk factors for prediction of Left ventricular diastolic dysfunction in patients with type 2 diabetes. This is a prospective study that was performed at Minia University Hospital, Egypt. The study included a total of 250 subjects (200 T2DM patients and 50 healthy controls) who were classified to Five age and sex matched groups as: group (I) CAN group (n=50) included 50 T2DM patients with CAN, group (II) Microalbuminuric group (n=50) included 50 T2DM patients with microalbuminuria, group (III) CAN + Microalbuminuria (n=50) included 50 T2DM patients with CAN + microalbuminuria, group (IV) DM only group (n=50) included 50 T2DM patients only (no CAN and no microalbuminuria) and group (V) Control (n=50) included 50 matched healthy control subjects. The heart rate variation (DP, Valsalva and 30/15) was significantly lower in CAN and microalbuminuric groups (group I, II and III) compared to group IV and V (diabetic only pts. and the control group) ($p<0.01$). No significant differences were found among groups regarding EF (%) and early diastolic filling velocity (E) (cm/s) however, the late diastolic filling velocity (A) was significantly higher in both CAN and microalbuminuric groups (83.9 ± 14.7 and 81.8 ± 10.7 cm/s) compared to the other Two groups ($p<0.01$). Microalbuminuria and CAN are significantly associated with increased likelihood of LVDD and could be considered as an independent risk factors and predictors for LVDD in type 2 diabetes patients.

Keywords: Microalbuminuria, Cardiovascular autonomic neuropathy, Prediction, Left ventricular diastolic dysfunction, Diabetes.

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1. Introduction

Diabetes mellitus is a major public health issue affect more than millions of people worldwide and many complications were associated it such as nephropathy, neuropathy, cardiovascular and renal complications, retinopathy, food related disorders [1]. Left ventricular diastolic dysfunction (LVDD) is defined as the inability of the ventricle to fill to a normal enddiastolic volume, both during exercise as well as at rest, while left atrial pressure does not exceed 12 mm Hg [2]. The prevalence of LVDD in the general population is approximately 20% to 30%, and increases with age and comorbidities, such as diabetes and hypertension. In patients with type 2 diabetes, LVDD prevalence is 40% to 75% as detected by echocardiography [3]. LVDD is an indicator of myocardial damage before heart failure becomes apparent and serves as a predictor of adverse cardiac events, hence, early identification of myocardial dysfunction and correction of potentially modified risk factors are very important in order to delay the onset of heart failure and unfortunately, subclinical cardiomyopathy is often still unrecognized in asymptomatic diabetic patients [4]. Cardiovascular autonomic neuropathy (CAN) is one of the most common complications in patients with diabetes, it is defined as an impairment of cardiac autonomic nerve fibers in the cardiovascular system after excluding other causes. It was reported that CAN is associated with increased risk of

morbidity and mortality in patients with diabetes and also it was shown to be an independent predictor of cardiovascular morbidity and mortality [5]. Some studies reported an association between CAN and left ventricular diastolic dysfunction [6-9]. Microalbuminuria is defined as urinary albumin excretion of 30-300 mg/day, or 20-200 µg/min, it is an earlier sign of vascular damage, it is considered as an early marker of cardiovascular diabetic complications [10]. It was estimated that the prevalence of microalbuminuria in patients with diabetes and without known kidney disease was 40% and the transition from normoalbuminuria to microalbuminuria is frequent despite adequate treatment [1]. Microalbuminuria is associated with increased incidence of coronary heart disease mortality in diabetic patients and the presence of microalbuminuria is associated with increased likelihood of LVDD in type 2 diabetes patients [11]. The present study aims to clarify cardiovascular autonomic neuropathy and microalbuminuria as risk factors for prediction of Left ventricular diastolic dysfunction in patients with type 2 diabetes.

2. Patients and methods

This is a prospective randomized control trial that was performed at Minia University Hospital, Minia Governorate, Egypt. The study included a total of 250 subjects (200 T2DM patients and 50 healthy controls) who were classified to Five age and sex matched groups as: group (I) CAN group (n=50) included 50 T2DM patients with cardiovascular autonomic neuropathy, group (II) Microalbuminuric group (n=50) included 50 T2DM patients with microalbuminuria (ACR = 30-299 mg/g), group (III) CAN + Microalbuminuria (n=50) included 50 T2DM patients with CAN + microalbuminuria, group (IV) DM only group (n=50) included 50 T2DM patients only (no CAN and no microalbuminuria) and group (V) Control (n=50) included 50 matched aberrantly healthy control subjects. Inclusion criteria were; adult patients (20:60 years) and both genders, confirmed T2DM according to American Diabetes Association criteria guidelines and given approval and informed consent. While, exclusion criteria were; Type 1 DM, patients with stroke, hypothyroidism, alcohol addiction, and other causes of neuropathy except diabetes in addition to subjects with ischemic, valvular and congenital heart disease and congestive HF of any cause. All included cases were subjected to full history taking including medical history (diabetes and its duration of diabetes and type of treatment and hypertension, etc..), and clinical examination was done. Examination of CAN was performed according to four cardiovascular autonomic reflex tests (CARTs): heart rate variation during deep breathing (HRV_DP), HRV during Valsalva maneuver (HRV_Valsalva), HRV during the lying-to-standing test (HRV 30: 15), and blood pressure variability (BPV) in response to standing up [12]. Electrocardiogram (ECG) 12 lead ECG was obtained for every patient. The glomerular filtration rate (GFR) was calculated by the CKD-EPI equation, expressed as a single equation according to [13]: GFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] _ 1.159 [if black]. where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κor 1, and max indicates the maximum of Scr/κ or 1. Also, laboratory investigations were performed in terms of random blood sugar (RBS), HbA1C [14], complete blood count (CBC), urine analysis for detecting microalbuminurea, blood urea and creatinine, liver enzymes (AST and ALT) and lipid profile using commercial kits [15]. Echocardiography both two-dimensional and tissue Doppler imaging (TDI) was performed. Conventional transmitral flow was measured with pw-Doppler. Early (E), late atrial (A) transmitral peak flow velocities and the ratio (E⁄A) were measured. Pulse-wave tissue Doppler imaging was performed at the junction of the left ventricular wall with the septal mitral annulus. Early diastolic velocity (Em) was recorded. Ratio of E⁄Em was calculated. Reduced early diastolic tissue velocity (Em) and the E⁄Em ratio was used to classify left ventricular diastolic dysfunction according to the European Society of Cardiology consensus paper. Severe left ventricular diastolic dysfunction (pseudonormal pattern) was defined as an inverse E⁄A ratio 0.8–1.5 (> 60 years) or < 0.5 (< 60 years) with anE⁄ Em ratio > 15 or E⁄A > 1.5 with Em velocity < 8 cm⁄s (septal mitral annulus).

2.1. Statistical methods

Data analyses were performed using SPSS software (version 20, IBM, NY, USA) **[16]**. Number and percentage (N, %) were used to describe categorical variables while numerical variables were described by the mean and standard deviation (Mean ± SD) and range. As regards the comparison between groups, Chi-square or Fischer's exact tests were used for categorical data and while, One was ANOVA and Duncan test were used for continuous data however. P≤.05 was considered statistically significant& **P** ≤.01was considered highly significant.

3. Results

No significant differences were noticed among groups regarding age (p=0.29), sex (p=0.79), weight (p=0.40), height (p=0.57) and BMI (p=0.92). Duration of DM was significantly higher in group I, II and III compared to group (IV) (Table 1). The CAN and microalbuminuric groups had significantly higher heart rate, SBP, DBP and standing blood pressure compared to group (IV) and group (V) (diabetic only pts. and the control group) (p<0.01). In addition, the heart rate variation (DP, Valsalva and 30/15) was significantly lower in CAN and microalbuminuric groups (group I, II and III) compared to group IV and V (diabetic only pts. and the control group) (p<0.01), (Table, 2). Regarding the lipid profile, the results showed that total cholesterol, Triglyceride and LDL levels were significantly higher in CAN and microalbuminuric groups (group I, II and III) compared to group IV and IV (diabetic only pts. and the control group) (p<0.01) while, in contrary, HDL level was significantly lower in CAN groups (group I and III) compared to the other three groups. Both urea and creatinine levels were significantly higher in group II and III compared to CAN group and DM pts. group (group I and IV) while the lowest normal level was found in the control group. The lowest mean GFR was found in group II and III (78.6 ± 6.6 and 76.9 ± 6.9 mL/min/1.73 m^2, respectively) followed with a significant difference by the CAN group (82.7 ± 6.8 mL/min/1.73 m^2) and the DM pts. group (114.8 ± 5.9 mL/min/1.73 m^2), (Table, 3). Concerning the Echo findings among the studied groups, no significant differences were found among groups regarding EF (%) and early diastolic filling velocity (E) (cm/s) however, the late diastolic filling velocity (A) was significantly higher in both CAN and microalbuminuric

groups (83.9 ± 14.7 and 81.8 ± 10.7 cm/s) compared to the other Two groups (p<0.01). While, both E/A and e`, early diastolic mitral annulus velocity were significantly lower in both CAN and microalbuminuric groups compared to the other Two groups (p<0.01) (Table 4).

4. Discussion

This study aimed to investigate cardiovascular autonomic neuropathy and microalbuminuria as risk factors for prediction of Left ventricular diastolic dysfunction in patients with type 2 diabetes. many studies investigated that association between CAN and LVDD in diabetic patients and others studied the association between microalbuminuria and LVDD in diabetic patients but, there was no available studies investigated the association between both CAN and microalbuminuria and LVDD in diabetic patients. Currently, the results showed that total cholesterol, Triglyceride and LDL levels were significantly higher in CAN and microalbuminuric groups (group I and II) compared to group III and IV (diabetic only pts. and the control group) (p<0.01) while, in contrary, HDL level was significantly lower in CAN group compared to the other three groups. These results agreed with [17] who reported that T2DM patients with CAN had higher levels of total cholesterol, Triglyceride and LDL compared to the normal controls or DM patients without CAN. Similar results were found by [18]. Furthermore, abnormal lipid parameters are associated with albuminuria or reduced kidney function [19]. The current results revealed that CAN and microalbuminuric groups had significantly higher heart rate, SBP, DBP and standing blood pressure compared to group III and IV (diabetic only pts. and the control group) (p<0.01). These results are in agreement with those of [20] who reported that T2DM patients with CAN had higher heart rate, SBP, DBP compared to the normal controls or DM patients without CAN. Also, this finding is concordant to the study by [21]. Regarding the main findings of the current study, both CAN and microalbuminuric groups had significantly higher late diastolic filling velocity (A) beside significantly lower both E/A and e` and early diastolic mitral annulus velocity compared to the other Two groups. These results indicate the strong association between CAN and microalbuminuria and deteriorated LVDD. Also, both CAN and microalbuminuria were found to be associated with LVDD and it could be considered as an independent risk factor for LVDD in type 2 diabetes (the more severe the CAN, the higher the LVDD occurrence and the more impaired diastolic function).

Concerning the association between CAN and LVDD, these results agreed with a study of [21] who evaluated the association between CAN and LVDD in T2DM patients. They concluded that CAN was an independent risk marker for the presence of LVDD in patients with diabetes. In study by [22], they found that CAN was diagnosed in 15 (28.8%) patients with T2DM and in six (12.5%) individuals with impaired glucose tolerance. The rates of left ventricular diastolic dysfunction were 81 and 33%in patients with and without cardiovascular autonomic neuropathy, respectively (P < 0.001). In the CAN group (n = 21), early diastolic relaxation velocity (Em) was significantly reduced (5.4 ± 0.9 vs. 7.3± 2.1 cm⁄s;P < 0.001) and the E⁄Em ratio was significantly higher (13.6± 4.6 vs. 10.3±3.4 cm⁄s, P < 0.001) as compared with the group without CAN (n = 79). These findings remained significant after adjustment for age, sex, coronary artery disease, hypertension and HbA1c. A severe form of LVDD was observed in 33 and 15% of patients with and without cardiovascular autonomic neuropathy, respectively (P = 0.001). They concluded that CAN is associated with a higher prevalence and a more severe form of LVDD in patients with DM or impaired glucose tolerance undergoing coronary angiography. Similarly, previous studies have revealed associations of CAN with altered left ventricular relaxation and filling, increased left ventricular mass, left ventricular hypertrophy, and impairment of myocardial blood flow regulation [23,24]. Also, an association of CAN with LVDD is well documented [25,26]. A study in Egypt by [27,28], they investigated if CAN is linked to left ventricular dysfunction in diabetic patients. They found that cases showed a statistically significant increase in LF/HF ratio compared to controls reflecting reduced HRV. Also, LV and RV diastolic function were reduced in cases compared to controls, there was a significant correlation between LV E/E' ratio (ratio of early transmitral velocity and average early mitral annular and basal septal velocities) and LF/HF ratio. LF/HF ratio was able to predict LVDD as expressed by the LV E/E' ratio with a sensitivity of 96%. In addition, T2DM patients with CAN who underwent coronary angiography showed reduced e' and increased E/e' ratio as assessed by TDI, after adjustment for age, sex, coronary artery disease, hypertension, and HbA1c [29]. Also, CAN is correlated with higher left ventricular mass and cardiac output, as assessed by cardiac magnetic resonance imaging [30]. CAN was further proved to be independently correlated with subclinical left ventricular dysfunction in type 1 diabetic patients with normal albuminuria, including systolic and diastolic functions, and coronary artery calcium score, evaluated by computed tomography [31]. Furthermore, it has been reported that CAN was shown to be an independent predictor of cardiovascular morbidity and mortality (after correcting for age, duration, glucose control, and cardiovascular risk factors) [32,33]. Several mechanisms could explain how CAN promotes mortality, including silent myocardial ischemia, fatal arrhythmia due to QT prolongation, and impaired respiratory response to hypoxia [34]. However, the exact mechanism remains unclear. Regarding the association between microalbuminuria and LVDD, this study revealed that microalbuminuria was significantly associated with LVDD and also it could be considered as an independent risk factor for LVDD in T2DM. These results agreed with a recent study by [5] who assessed association of microalbuminuria with LVDD in T2DM patients in India. They found that there was an increase in cholesterol, triglyceride, VLDL, and LDL levels and decrease in HDL levels in microalbuminuric group as compared to normoalbuminuric group. The regression analysis revealed that increase in age and a decrease in E/A ratio in patients with microalbuminuria was significantly associated with LVDD. They concluded that the presence of microalbuminuria is associated with increased likelihood of LVDD in T2DM patients.

Table 1: Baseline characteristics among studied groups.

Variable		Groups					P. value (Sig.)
		Group (I) DM + CAN	Group (II) DM + Microalb.	Group (III) DM + CAN + Microalb.	Group (IV) DM only	Group (V) Healthy control	
Age (year)		51.4 ± 9.1	52.2 ± 8.3	50.7 ± 9.4	49.9 ± 10.1	49.8 ± 10.5	0.29 NS
Sex (M/F)		30/20	31/19	28/22	25/25	28/22	0.79NS
Weight (kg)		93.2 ± 13.9	91.8 ± 14.5	89.4 ± 13.8	90.8 ± 14.1	87.8 ± 15.3	0.40NS
Height (cm)		170.2 ± 10.0	169.2 ± 11.2	168.1 ± 10.1	168.6 ± 9.9	167.1 ± 10.6	0.57NS
Body mass index (kg/m^2)		32.4 ± 6.6	32.3 ± 6.9	31.9 ± 6.5	32.3 ± 7.0	31.6 ± 5.7	0.92NS
Duration of DM (yrs)		9.2^a ± 3.9	8.6^a ± 2.9	9.5^a ± 2.6	6.1^b ± 2.8	-	**<0.01****
ttt of DM	**Insulin**	18 (36.0%)	14 (28.0%)	20 (40.0%)	12 (24.0%)	-	0.29 NS
	Oral	32 (64.0%)	36 (72.0%)	30 (60.0%)	38 (76.0%)	-	

Qualitative data presented as No. (%). Quantitative data presented as Mean ± SD

One way ANOVA and Chi-square were used to test significance among groups.

** highly Significant (p<0.01). NS Not significant.

a, b, c, Means in the same row with different superscript are significantly different (Duncan test).

Table 2: Heart rate and blood pressure and heart rate variation among studied groups.

Variable		Groups					P. value (Sig.)
		Group (I) DM + CAN	Group (II) DM + Microalb.	Group (III) DM + CAN + Microalb.	Group (IV) DM only	Group (V) Healthy control	
Heart rate (beats/min)		95.7^a ± 13.1	82.1^c ± 11.4	88.9^b ± 15.3	76.7^d ± 8.0	75.4^d ± 7.1	**<0.01****
Blood pressure (mmHg)	**SBP**	141.1^a ±13.8	133.6^b ± 16.9	141.2^a ± 14.8	121.9^c ±12.9	117.1^c ± 8.3	**<0.01****
	SDP	100.1^a ± 8.1	93.5^b ± 11.8	99.8.1^a ± 9.3	85.4^c ± 8.8	81.9^c ± 5.8	
Standing BP (mmHg)	**SBP**	124.2^a ±12.2	117.5^b ± 14.9	120.4^a ±12.9	107.3^c ±11.1	103.1^c ± 7.3	**<0.01****
	SDP	92.8^a ± 7.5	86.9^b ± 11.0	90.9^a ± 8.6	79.4^c ± 8.2	76.2^c ± 5.4	
HRV (DP)		1.06^c ± 0.08	1.13^b ± 0.11	1.08^c ± 0.10	1.16^b ± 0.14	1.21^a ± 0.12	**<0.01****
HRV (Valsalva)		1.09^d ± 0.07	1.17^c ± 0.09	1.11^d ± 0.10	1.21^b ± 0.11	1.26^a ± 0.08	**<0.01****
HRV (30/15)		1.01^d ± 0.06	1.09^c ± 0.08	1.03^d ± 0.08	1.12^b ± 0.09	1.16^a ± 0.07	**<0.01****

One way ANOVA and Chi-square were used to test significance among groups.

** Highly Significant (p<0.01). NS Not significant.

a, b, c, Means in the same row with different superscript are significantly different (Duncan test).

Table 3: Laboratory investigations among studied groups.

Variable	Groups					P. value (Sig.)
	Group (I) DM + CAN	Group (II) DM + Microalb.	Group (III) DM + CAN + Microalb.	Group (IV) DM only	Group (V) Healthy control	
T. cholesterol (mg/dL)	$247.1^{a} \pm 33.8$	$225.0^{b} \pm 41.5$	$245.2^{a} \pm 31.4$	$229.5^{b} \pm 30.2$	$172.9^{c} \pm 23.6$	**<0.01****
Triglyceride (mg/dL)	$153.2^{a} \pm 20.9$	$139.5^{b} \pm 25.7$	$150.8^{a} \pm 23.9$	$142.3^{b} \pm 18.7$	$107.2^{c} \pm 14.7$	**<0.01****
HDL (mg/dL)	$32.9^{c} \pm 4.5$	$43.6^{b} \pm 5.7$	$34.8^{c} \pm 5.5$	$42.7^{b} \pm 7.9$	$46.9^{a} \pm 6.4$	**<0.01****
LDL (mg/dL)	$168.0^{a} \pm 22.9$	$152.9^{b} \pm 28.4$	$169.0^{a} \pm 20.8$	$156.1^{b} \pm 20.5$	$117.6^{c} \pm 16.1$	**<0.01****
HbA1C (%)	$9.28^{a} \pm 1.26$	$8.50^{b} \pm 1.56$	$9.34^{a} \pm 1.31$	$8.67^{b} \pm 1.14$	$6.20^{c} \pm 0.90$	**<0.01****
Urea (mg/dL)	$36.7^{b} \pm 5.73$	$41.9^{a} \pm 5.3$	$42.5^{a} \pm 5.9$	$35.6^{b} \pm 4.68$	$25.4^{c} \pm 3.67$	**<0.01****
Createnine (mg/dL)	$1.13^{b} \pm 0.18$	$1.50^{a} \pm 0.32$	$1.48^{a} \pm 0.28$	$1.15^{b} \pm 0.15$	$0.82^{c} \pm 0.12$	**<0.01****
GFR (mL/min/1.73 m^2)	$82.7^{b} \pm 6.8$	$78.6^{c} \pm 6.6$	$76.9^{c} \pm 6.9$	$114.8^{a} \pm 5.9$	$112.5^{a} \pm 5.5$	**<0.01****

One way ANOVA was used to test significance among groups.

** Highly Significant ($p<0.01$).

[a, b, c] Means in the same row with different superscript are significantly different (Duncan test).

Table 4: Echocardiography findings among studied groups.

Variable	Groups					P. value (Sig.)
	Group (I) DM + CAN	Group (II) DM + Microalb.	Group (III) CAN + Microalb.	Group (IV) DM only	Group (V) Healthy control	
EF (%)	57.9 ± 8.8	58.1 ± 9.6	58.5 ± 9.73	60.6 ± 8.4	60.7 ± 4.5	0.16^{NS}
Early diastolic filling velocity (E) (cm/s)	69.9 ± 15.9	70.2 ± 12.8	71.3 ± 11.2	73.2 ± 13.6	74.2 ± 13.1	0.32^{NS}
Late diastolic filling velocity (A) (cm/s)	$83.9^{a} \pm 14.7$	$81.8^{a} \pm 10.7$	$82.9^{a} \pm 10.2$	$76.3^{b} \pm 11.7$	$72.3^{b} \pm 16.5$	**<0.01****
E/A	$0.85^{b} \pm 0.25$	$0.87^{b} \pm 0.09$	$0.86^{b} \pm 0.10$	$0.96^{a} \pm 0.07$	$1.03^{a} \pm 0.32$	**<0.01****
***e`*, early diastolic mitral annulus velocity (cm/s)**	$7.62^{b} \pm 2.21$	$7.75^{a} \pm 0.79$	$7.72^{a} \pm 0.82$	$8.62^{a} \pm 0.68$	$8.49^{a} \pm 1.56$	**<0.01****

One way ANOVA was used to test significance among groups.

NS Not significant ($p>0.05$) ** highly significant ($p<0.01$).

[a, b, c] Means in the same row with different superscript are significantly different (Duncan test).

Also, increase in age and decrease in E/A ratio show direct and independent association with LVDD in normotensive diabetic patients with microalbuminuria. Also, in a previous study by [8], they studied if the presence of microalbuminuria would correlate with cardiovascular autonomic dysfunction and insulin resistance in type 2 diabetic patients. They found that the presence of microalbuminuria in T2DM patients is characterized by depressed cardiovascular autonomic function and insulin resistance, and that the myocardial uptake of 123I-MIBG at delayed phase, fasting plasma insulin, and HOMA index are independent predictors of urinary albumin excretion. Also, these results agreed with previous study by [30] who investigated the association of microalbuminuria with LVDD in T2DM patients. They found that diastolic dysfunction was found in 73.7% of type 2 diabetic patients without microalbuminuria and 66.7% in type 2 diabetic patients with microalbuminuria. Neither type 2 diabetic groups with nor without microalbuminuria indicated any significant association to the occurrence of diastolic dysfunction. Previously, [31] found that microalbuminuria is independently associated with LV systolic and diastolic dysfunction in type 2 DM and this may explain in part the relationship of albuminuria to increased cardiovascular events in the DM population. It has been reported that microalbuminuria has been proposed to represent a marker of a generalized vascular dysfunction, and some studies indicated microalbuminuria is associated with cardiovascular disease in diabetic and non diabetic patients [33]. Also, the odds of having LVDD in Japanese T2DM patients with albuminuria was about eight times more than those without albuminuria (OR 7.95, 95% CI: 1.74–21.6, p = 0.005)[32]. In addition, microalbuminuria is one of the earliest markers of vascular changes, also known as endothelial dysfunction [29]. The presence of microalbuminuria in itself is associated with increased incidence of coronary heart disease (CHD) mortality in diabetic patients [35]. This study has some strength points such as the relatively suitable sample size and also has some limitations such as those related to clinical work and laboratory investigations. So, further studies with larger sample sizes and different settings are recommended to confirm our findings.

5. Conclusions

This study concluded that microalbuminuria and CAN are significantly associated with increased likelihood of LVDD and could be considered as an independent risk factors and predictors for LVDD in type 2 diabetes patients (the more severe the CAN, the higher the LVDD occurrence and the more impaired diastolic function). Also, early diagnosis of CAN are advocated for preventing LVDD and related cardiovascular comorbidities in T2MD patients. Periodic screening for microalbuminuria should be done in T2MD patients, along with other risk markers such as lipid profile and blood pressure, to get a more comprehensive risk assessment, for the development of cardiovascular complications.

Ethical considerations

The study protocol and all procedures were approved by the ethical committee of the Minia Faculty of medicine. A verbal consent was taken from patients before getting them involved in study. The steps, the aims, the potential benefits and hazards, all were discussed with the patients.

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Conflict of interest
None.

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