Association between albuminuria and abnormal cardiac findings in patients with type 2 diabetic nephropathy: role of urine albumin excretion

Ghada A. Mohamed[a], Marwa A. Gaber[b]

Departments of [a]Internal Medicine and [b]Medical Biochemistry, Assiut Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Ghada A. Mohamed, MD, Department of Internal Medicine, Assiut Faculty of Medicine, Assiut University, Assiut, Egypt
Tel: 01004301177; PO, Box; 71511;
e-mail: ghadaa1980@yahoo.com

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Background
Diabetic patients have higher morbidity and mortality from cardiovascular diseases compared with nondiabetic patients, particularly in the case of patients with high urinary albumin excretion (UAE). The main aims of our study were to detect abnormal cardiac findings in patients with type 2 diabetic nephropathy (DN) and its relation to increased levels of UAE.

Patients and methods
Our descriptive cross-sectional study consisted of 105 diabetic patients with documented DN who attended the diabetic outpatient clinic of the Internal Medicine Department, Assiut University Hospital, and underwent routine investigation, glycated hemoglobin (HbA1c), 24 h UAE, and transthoracic echocardiography.

Results
We evaluated 105 patients with type 2 DN (56 men and 49 women) who were divided into two groups: group I included those with microalbuminuria (39%) (age: 54.3 ± 14.4 years) and group II included those with macroalbuminuria (61%) (age: 59.7 ± 7.9 years). There was a significant relationship between the degree of albuminuria and occurrence of left ventricular hypertrophy and segmental wall motion abnormality in both groups ($P < 0.001$ and $P = 0.032$, respectively).

Conclusion
Our data indicate a possible link between abnormal cardiac findings and progression of DN. We suggest that assessment of cardiac morbidity by means of echocardiography in patients with DN be mandatory for early preventive strategies.

Keywords:
cardiovascular disease, diabetic nephropathy, urine albumin excretion

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Introduction

Diabetic nephropathy (DN) is a main and often life-threatening microvascular complication of diabetes mellitus (DM), giving rise mostly to cardiovascular disease, specifically heart failure, the incidence of which is about 15-fold more in patients with diabetic kidney disease (DKD) [1]. The all-cause mortality in patients with DN is ~20–40 times greater than in patients without nephropathy [2].

Microalbuminuria is the primary indicator of DN and can be defined as a persistent increase (in at least two of three consecutive urine samples) in albumin excretion rate to 30–300 mg/day [2]. Approximately 5–10% of diabetic microalbuminuric patients develop overt DN each year with consequential deterioration in the glomurular filtration rate [3].

A meta-analysis suggested a two- to three-fold rise in cardiovascular risk in microalbuminuric compared with normoalbuminuric type 2 diabetic patients [4] and a 10-fold increase in risk in macroalbuminuric patients [5]. Numerous traditional risk factors for atherosclerosis have been recognized in diabetic patients with microalbuminuria or macroalbuminuria, including elevated blood pressure (BP) levels, dyslipidemia, and procoagulatory state associated with endothelial dysfunction. Also microalbuminuria is currently considered a marker of generalized endothelial damage; it reveals transvascular albumin leakage, now known as an early event in atherogenesis [4,6]. Furthermore, the relationship of microalbuminuria with the marker of chronic inflammation (C-reactive protein) and with increased production of vascular endothelial growth factor was pronounced [7,8]. Thus, several mechanisms are tangled in the development and progression of cardiovascular complications both in microalbuminuric and macroalbuminuric diabetic patients and all these mechanisms should be considered the goal for therapeutic intervention [9].

Aim

The objectives of our study were as follows:

(1) Detect abnormal echocardiographic findings in patients with type 2 DN and its relation with levels of urine albumin excretion (UAE) (microalbuminuria and macroalbuminuria) in type 2 diabetic patients.
(2) Clarify whether UAE level could be a marker of cardiovascular complications.

Patients and methods

Participants

A cross-sectional study was performed in 105 type 2 diabetic patients who attended the diabetic outpatient clinic of the Internal Medicine Department, Assiut University Hospital. Type 2 diabetes was defined as per the criteria laid down by the American Diabetes Association [10]. Those patients were classified according to their UAE levels into two groups: group I included 41 (39%) microalbuminuric patients and group II included 64 (61%) macroalbuminuric patients.

Patients with any of the following conditions were excluded: type 1 DM, myocardial infarction within the past 6 months, hypertension stage 3 (BP ≥180/110), a history of stroke or occlusive peripheral vascular disease, heart failure, uncontrolled thyroid diseases, active urinary tract infection, and any type of other renal diseases. Patients who had undergone coronary artery bypass or angioplasty were not included either. The study was approved by the Scientific and Ethical Committees at Faculty of Medicine, Assiut University. Written informed consent was obtained from all participants.

Definition of diabetic nephropathy

DN is defined as a clinical syndrome characterized by albuminuria (microalbuminuria or macroalbuminuria), hypertension, and renal insufficiency. UAE was calculated from sterile 24-h timed urine samples by quantitative measurement of albumin/creatinine ratio by colormitric methods. Albuminuria was classified as follows:

(1) Microalbuminuria: A/C ratio from 30 to 300 mg/g.
(2) Macroalbuminuria: A/C ratio greater than 300 mg/g.

Echocardiography

Echocardiographic examination was performed with the patient in a partial left lateral decubitus position under a two-dimensionally guided M-mode echocardiography machine. Left ventricular systolic function was analyzed by calculating ejection fraction using the Teichholz techniques. EF less than 55% was considered systolic dysfunction. Left ventricular mass (LVM) was calculated by the regression equation $LVM = 1.04 \times [(IVST + LVPWT + LVDd)^3 - LVDd^3] - 13.6$. Left ventricular hypertrophy (LVH) was defined as LVM of at least 110 g/m^2 in women and 125 g/m^2 in men. Left Ventricular Mass Index (LVMI) (ratio of LVM/body surface area) was considered normal if less than 110 g/m^2 in women and less than 130 g/m^2 in men [11]. The transmitral diastolic flow Doppler tracing was imaged in the apical four-chamber view by using pulsed Doppler echocardiography with the sample volume sited at the tip of the mitral leaflets. The peak early transmitral filling velocity during early diastole (*E*), peak transmitral atrial filling velocity during late diastole (*A*), deceleration time of *E* velocity (*E*-Dec), and isovolumetric relaxation time were used as left ventricular diastolic function parameters.

Others

BMI was defined as weight in kilograms divided by square height in meters. BP was the average of two measurements in the supine position under a resting state using a mercury sphygmomanometer with an appropriately sized cuff on the left arm. A 12 h overnight fasting venous blood sample was collected for measurement of HbA1c, creatinine, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides using standard protocol [HbA1c (by Enzyme Linked Immunosorbent Assay (ELIZA) Stanbio. USA, normal range 2.7-4.3%), creatinine and the lipid profile by colorimetric method].

Data analysis

The clinical and laboratory data were categorized and processed using the statistical package for social sciences, version 16 (SPSS Inc., Chicago, Illinois, USA). The results were expressed as mean ± SD and as percentages. For statistical evaluation, the unpaired Student *t*-test was used to compare continuous variables between the two groups. The Mann–Whitney *U*-test was used to compare nonparametric variables between the two groups. Categorical data were analyzed by the χ^2-test. A *P* value less than 0.05 was considered statistically significant.

Results

Demographic, clinical, laboratory, and echocardiographic characteristics of the patients are depicted in Table 1. There was a significant difference between groups in terms of age, duration of DM,

and systolic blood pressure (SBP) and diastolic blood pressure. Serum creatinine levels and HbA1c were elevated in patients with macroalbuminuria compared with patients with microalbuminuria (P = 0.001). In contrast, there was a nonsignificant difference between the two groups regarding sex, BMI, HDL, LDL, serum triglycerides, total cholesterol, and history of hypertension.

As regards echocardiographic findings, we found a significant relationship between the degree of albuminuria and occurrence of LVH and segmental wall motion abnormality (SWMA) (P = 0.001 and P = 0.032, respectively) with no significant difference as regards diastolic dysfunction (Fig. 1 and Table 1).

In addition, we found that occurrence of LVH is significantly associated with increase in age (P < 0.001), duration of diabetes (P = 0.001), BMI (P = 0.043), SBP (P < 0.001), HbA1c, and serum creatinine (P < 0.001) (Table 2). Also, SWMA was significantly associated with increased age (P < 0.001), increased duration of diabetes (P = 0.001), smoking ($P \leq 0.001$), SBP and diastolic BP ($P \leq 0.001$), HbA1c, and serum creatinine (P = 0.001 and < 0.001, respectively) (Table 3).

There was a nonsignificant association of our echocardiographic findings (LVH, SWMA, and diastolic dysfunction) with sex, residence, diabetic therapy, history of hypertension, and lipid profile.

Discussion

The relationship between chronic kidney disease (CKD) and cardiovascular disease has long been acknowledged, and current guidelines recommend that patients with CKD be considered principally at high cardiovascular risk [12]. Although often transient and benign, the persistent existence of protein or albumin in the urine has obvious clinical significance as an early sign of underlying renal pathology, preceding tangible deterioration in renal filtration function. In addition to its role as a marker for CKD risk, it is now broadly established that proteinuria is an independent predictor of cardiovascular morbidity and mortality across different populations [13].

LVH is a pathological change that precedes/underlies ischemic heart disease, arrhythmias, and congestive heart failure [14]. In the current study, we found a clear association between higher rate of LVH (53.7 vs. 90.6% in patients with microalbuminuria and macroalbuminuria, respectively) and albuminuria status in type 2 diabetes mellitus (T2DM) patients with DN, which suggests that albuminuria could be

Table 1 Demographic, clinical, laboratory, and echocardiographic characteristics of the patient groups

Parameters	Group I (mean±SD) (n=41)	Group II (mean±SD) (n=64)	P value
Age (years)	54.3±14.4	59.7±7.9	0.016
Sex (female/male)	19/22	30/34	0.957
Duration of DM	4±3.3	10.2±4.3	0.001
Diabetes therapy			
Oral therapy	27	46	0.581
Insulin therapy	11	16	
Combined therapy	3	2	
Hypertension (n)	32	49	0.860
BMI (kg/m^2)	29.2±3.6	30.7±4.3	0.064
Systolic BP (mmHg)	147.6±6.6	161.7±6.1	0.001
Diastolic BP (mmHg)	92.7±6.3	98.6±6.9	0.001
HbA1c	6.2±0.7	9.6±1.4	0.001
Serum creatinine	1.8±0.1	3.1±0.4	0.001
HDL	46.2±10.7	44.4±11	0.404
LDL	116±38.7	113.8±38.3	0.779
Serum triglycerides	151.2±66.7	149.1±70.4	0.877
Total cholesterol	197.6±51	191.1±47	0.505
LVH (n)	22	58	0.001
Diastolic dysfunction (n)	10	15	0.911
SWMA	3	15	0.032

BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; LVH, left ventricular hypertrophy; SWMA, segmental wall motion abnormality.

Table 2 Demographic, clinical, and laboratory characteristics of patients with LVH and without LVH

Parameters	Patients with LVH (mean±SD) (n=80)	Without LVH (mean±SD) (n=25)	P value
Age	60±7.4	50±16.6	<0.001
Sex (female/male)	40/40	9/16	0.221
Duration of DM	8.7±4.4	5±5.6	0.001
Hypertension (n)	63	18	0.483
BMI	30.6±4.1	28.7±3.8	0.043
Systolic BP	158.3±8.4	149.6±9.3	<0.001
Diastolic BP	96.8±7.3	94.8±7.1	0.242
HbA1c	8.8±1.8	6.5±1.7	<0.001
Serum creatinine	2.7±0.7	2.1±0.7	<0.001
HDL	45.1±10.3	45.3±12.7	0.939
LDL	117.2±37.7	106.6±39.8	0.232
Serum triglycerides	146.6±66.3	160.3±76.2	0.387
Total cholesterol	194±45	192±59.3	0.892

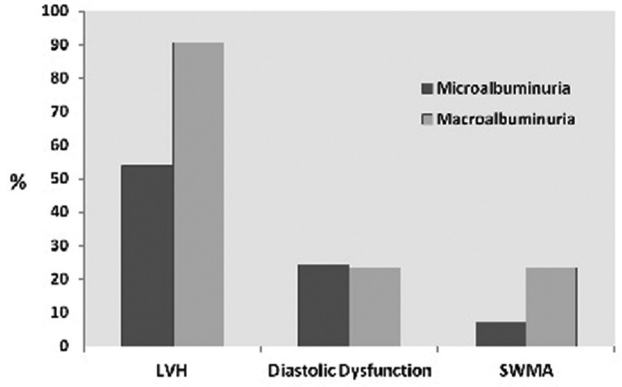
BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; LVH, left ventricular hypertrophy.

Table 3 Demographic, clinical, and laboratory characteristics of patients with SWMA and without SWMA

Parameters	With SWMA	Without SWMA	P value
Age	70.9±6.6	54.8±9.8	<0.001
Duration of DM	11.6±4.7	7±4.6	<0.001
BMI	30.1±3.2	30.1±4.2	0.997
Systolic BP	164.4±7.8	154.5±8.7	<0.001
Diastolic BP	103.3±5.9	94.8±6.6	<0.001
HbA1c	9.7±1.6	8±2	0.001
Serum creatinine	3.2±0.7	2.5±0.7	<0.001
Serum cholesterol	195±37.6	193.3±50.6	0.894

BP, blood pressure; DM, diabetes mellitus; HbA1c, glycated hemoglobin; SWMA, segmental wall motion abnormality.

Figure 1



Comparison between patient groups as regards abnormal echocardiographic findings. LVH, left ventricular hypertrophy; SWMA, segmental wall motion abnormality.

used, even in the early state of DKD, as a marker for cardiovascular events. This association can be explained by accumulation of advanced glycation end products, activation of protein kinase C, transforming growth factor-b1, and reactive oxygen species, which are closely related to the development of DKD [15]. Activation of these pathways also affects myocardial energy metabolism, decreases the activity of reactive oxygen species metabolic-related enzyme, causes cardiomyocyte hypertrophy, and results in excessive accumulation of collagen fibers in the myocardium, all of which are involved in the occurrence and progression of LVH [16]. Accordingly, it can be said that renal damage, persistent albuminuria, and LVH share some similar mechanisms. Our results are compatible with those of Liu *et al.* [17] who revealed an increased rate of LVH in T2DM patients with macroalbuminuria (49%) compared with that in patients with microalbuminuria (31%). Also, Nobakhthaghighi *et al.* [18] reported that patients with T2DM and increased UAE should be assessed for increased LVM. In addition, our study showed a significant association ($P \leq 0.001$) between LVH and SBP in patients with T2DM and DKD. This was in agreement with the results of Eguchi *et al.* [19] and Weber *et al.* [20]. Wu *et al.* [21] revealed no statistically significant association of SBP with LVMI ($P = 0.0578$). Age is another important factor in the relationship between albuminuria and LVH and this was seen in our result. We also established that patients with LVH had higher BMI, which was in agreement with the observation made by Cao *et al.* [22], who reported that BMI was independently correlated with LVMI and was an independent risk factor for LVH. LVH is a condition in which the cardiac muscle of the left ventricle becomes enlarged in response to increased pressure or volume overload. In obesity, cardiac output is elevated because of increased blood volume causing a chronically elevated preload condition that in turn increases ventricle size, wall stress, and LVM leading to the occurrence of eccentric ventricular hypertrophy [23]. LVM in diabetic patients may also increase with the HbA1c level. Thus, a poor glycemic control is also associated with more probabilities of having LVH [24], as evident in our study, which showed significant association between occurrence of LVH, increased HbA1c level ($P \leq 0.001$), and poor glycemic control. Data from the Prevention of Renal and Vascular Endstage Disease study and the Multi-Ethnic Study of Atherosclerosis trial revealed that microalbuminuria is independently associated with ECG indicators of myocardial ischemia and accompanied by increased coronary artery calcification scores [12,25]. We also clarified that the degree of albuminuria was significantly associated with the occurrence of ischemic heart disease ($P = 0.03$). This was in agreement with the study conducted by Klausen *et al.* [26], who reported that microalbuminuria is a strong and independent determining factor of coronary heart disease and death. We also found that patients with SWMA were older, smokers, and had a long duration of diabetes when compared with patients with normal wall motion. Our data illustrated that there were no significant differences between the microalbuminuric and macroalbuminuric groups as regards prevalence of diastolic dysfunction, which was in agreement with the study conducted by Cakır *et al.* [27]. In contrast, Andersen *et al.* [28] reported that diastolic dysfunction is closely related to increased UAE.

Conclusion

In summary, the results of the current study extended the previously identified association of albuminuria with cardiovascular morbidity in T2DM patients to a relative early stage of DKD. In addition, we confirmed that higher level of albuminuria (macroalbuminuria vs. microalbuminuria) is associated with increasing LVH and IHD.

Recommendation

Our results encourage the use of UAE (albuminuria detection) as an early reasonable marker for cardiovascular diseases in T2DM patients. Also early assessment of cardiac morbidity in patients with DN by echocardiography is mandatory for early preventive strategies.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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