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Assessment of Serum Angiotensin Converting Enzyme 2 and Urine Albumin to Creatinine Ratio as Early Detection of Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is a chronic disease manifested by a decreased glomerular filtration rate (GFR) that leads to the progression of kidney failure and increased incidence of mortality and cardiovascular complications. Type 2 diabetes mellitus (T2DM) is a metabolic disorder that affects multiple organs, including the pancreas, as well as the kidneys, liver, brain, and eyes. Angiotensin-converting enzyme 2 (ACE2) is a component of the renin-angiotensin system, which is highly expressed in renal tubular epithelial cells. This study aims to measure ACE2 and the urine albumin-to-creatinine ratio (ACR) as early detection markers for DN among T2DM patients. The sample size consisted of 135 individuals, who were divided into three groups based on ACR criteria: macroalbuminuria, microalbuminuria, and normoalbuminuria, with healthy subjects as the control group. They were intended for Telafer Hospital in Mosul City. The data showed significant differences between patient groups and the control group for glycemic, lipid profile, and kidney function tests. Additionally, the results revealed a significant association between serum glycemic levels, lipid profiles, kidney function tests, and ACE2 and DN in T2DM patients. Based on the current data, it can be concluded that ACR and ACE2 play a crucial protective role in preventing progressive renal damage, which is a valuable indicator for the early detection of DN.

Keywords: Albuminuria, Albumin to creatinine ratio, Angiotensin converting enzyme-2, Diabetic nephropathy, Type 2 diabetes mellitus,

1. Introduction

One of the dominant and severe effects of diabetes mellitus (DM) is diabetic nephropathy (DN), which linked to higher mortality and morbidity rates in diabetic individuals (1). Up to 40% of people with type 2 DM (T2DM) will progress clinically obvious renal impairment over the course of their lives, DN occurs in 30 to 40% of DM patients. Half of all patients receiving dialysis treatment have DN, which is a primary leading of end-stage renal disease (ESRD) (2).The clinical syndrome of DN is manifested by albuminuria, higher arterial blood pressure (BP), and reduced in the glomerular filtration rate (GFR) (3).

Due to the multiple chronic problems that T2DM causes, DM is currently the 9th greatest cause of mortality. The albumin to creatinine ratio (ACR) is frequently used to determine the earliest signs of renal impairment. Compared to albumin levels, it has been showed to be a very accurate indication (4,5). Chronic hyperglycemia has been associated with ketoacidosis, DN, high BP, also foot diseases (6). Diabetes impairs the kidney's filtration function, initially making it leaking to greater blood proteins like albumin, which are subsequently lost in the urine, especially when the blood sugar is not well regulated (7). There are several disorders may alter on the delivery of blood to the renal arteries. Diabetes mellitus is one of these, which cause kidney disease and risk of microvascular complications (8). Because of deficiencies in insulin secretion and activities, T2DM is a chronic condition (9). According to American Diabetes Association, DM is first identified by many symptoms, a random blood glucose level of 200 mg/dL, ≥126 mg/dL for fasting blood glucose (FBG), ≥ 200 mg/dL for 2-hour post-load glucose, or levels of HbA1c ≥ 6.5% (10). Angiotensin-converting enzyme 2 (ACE2) is a monocarboxypeptidase with a single enzymatic binding site that acts as a key counter-regulatory component of the renin-angiotensin system (RAS) (11). The renin enzyme is produced by the kidneys and acts in converting angiotensinogen protein synthesis in the liver to angiotensin 1 by removing 10 amino acids from the peptide (12). Lung and kidney produce ACE to convert angiotensin I to angiotensin ĮĮ by removing 2 amino acids from peptide at positions 14 and 15. The ACE2 is the only known homolog of ACE; it shares 42% of sequence identity with somatic ACE and 61% similarity in the area surrounding the active site (13,14). It is expressed on the surfaces of endothelial and epithelial cells in a membrane-bound form (15) as well as in a soluble form in several tissues throughout the body, including the kidneys, heart, gastrointestinal tract, and lungs (16,17). ACE2 promotes the development of microalbuminuria and diabetic nephropathy (DN) (18). Urea and creatinine are nitrogenous end products of metabolism. Urea is the primary metabolite derived from dietary protein and the breakdown of tissue protein. Creatinine is the product of muscle creatine catabolism. Both are relatively small molecules that distribute through total body water (19,20). As creatinine is produced, it is filtered through the kidneys and excreted in the urine (21).

Dyslipidemia is a significant factor in DN patients, characterized by higher levels of serum triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoproteins (VLDL), with low levels of high-density lipoprotein cholesterol (HDL-C) (22). Raised cholesterol levels are linked to the development of severe or moderate urine albumin excretion in T2DM patients. Lowering cholesterol and triglyceride (TG) levels in DM patients helps to reduce urine albumin excretion from a mild to a normal level (23). Albuminuria, which represents the degree of glomerular damage, and serum creatinine, which may be used to calculate estimated glomerular filtration rate (eGFR), are two parameters that can be used to assess the presence of DN (24). However, ACR is thought to be a more accurate and sensitive biomarker for identifying patients who are at high risk of developing DN (25). Patients with persistent microalbuminuria still develop to DN stages 3-5 (26). This study aims to measure the ACE2, urine ACR, and some factors associated with DN for the early detection of DN in T2DM patients.

2. Materials and Methods

A total of 135 participants aged 32-76 years with T2DM and albuminuria were included. Ninety T2DM patients were involved, and they were subdivided into three groups according to their albuminuria levels: 22 patients who had macroalbuminuria (ACR = 300 mg/g); 23 patients had microalbuminuria (ACR= 30–300 mg/g), and 45 diabetic patients had

normoalbuminuria (ACR = 30 mg/g). They were compared with a control group of 45 healthy individuals, and their clinical examination and disease history were collected. After a 12-hour overnight fast, venous blood samples were obtained from diabetic patients and healthy volunteers and placed into three different types of tubes. The samples were then processed as follows: The first tube was filled with whole blood sample and EDTA without centrifugation for the assay of glycosylated hemoglobin (HbA1c); the second tube was filled with potassium oxalate and sodium fluoride for the simultaneous assay of plasma glucose; and the third tube was filled with blood, which was centrifuged at 4000 rpm for 10 minutes. Aliquots of serum were quickly split and separated. On the same day that the blood was drawn, a single aliquot of serum was used to test the lipid profile. Also, it was used after being maintained at -20 °C to assess ACE2, which was evaluated using the BioSource manufacturer's enzyme-linked immunosorbent assay (ELISA) kit from the USA. Urine samples were collected in a clean glass tube for determining urinary ACR using the FUS 3000 Urinalysis device. The eGFR was calculated using the chronic kidney disease (CKD)-EPI formula (27).

$eGFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$ [For women and serum creatinine > 0.7 mg/dL].

$eGFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$ [For men and serum creatinine > 0.9 mg/dL].

2.1. Inclusion and exclusion criteria

This study included T2DM patients aged between 32 and 76 years, who had both albuminuria and normoalbuminuria. This study excluded patients with fever, polycystic ovaries, nephrotic syndrome, ESRD, osteoarthritis, thyroid disease, heart failure, and liver disease.

2.2. Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 22 was used to statistically analyze the data. The variables' means and standard deviations were reported. To ascertain whether there are statistically significant variations in the means of the four independent studied groups. One-way analysis of variance (ANOVA) was utilized for comparing the variables among the patients (macro-, micro-, normalbuminuria) and the control group.

3. Results

The demographic characteristics of the study groups are demonstrated in **Table (1)**. There was no significant difference in age and BMI among the groups.

Table 1. The demographic characteristics of the study groups

Variables	Mean ± SD				*p*-value
	Macroalbuminuria (n= 22)	Microalbuminuria (n= 23)	Normoalbuminuria (n= 45)	Control (n= 45)	
Age (Years)	54.76± 11.53	55.13± 10.13	53.59± 8.10	52.87± 8.77	0.767
BMI (kg/m^2)	25.97± 1.90	24.92± 2.57	25.57± 2.33	23.00± 1.95	0.620

*The collected data were presented as mean ± SD at the $p < 0.05$ level, BMI: Body mass index.

The results in **Table (2)** indicate that there were substantial (p= 0.001) variances in FSG among the patients and control groups. On the other hand, there was a significant increase (p= 0.045) in HbA1c levels in the macroalbuminuria group compared to the control group. Still, it was not significant when compared with the micro- and normoalbuminuria groups. The ANOVA results showed a significant increase in serum TC in the macroalbuminuria group compared to the other groups (p= 0.001). Also, there were substantial (p= 0.001) variances in TG, VLDL, and LDL-C among the groups. Compared to the HDL-C, the means for the macroalbuminuria group were statistically lower (p= 0.001) than those for the micro-,

normoalbuminuria, and control groups, indicating that the serum HDL-C level significantly differed among the groups, as shown in **Table (2)**.

Table 2. Serum glycemic and lipid profile for patients and control groups

Variables	Mean ± SD				*p*-value
	Macroalbuminuria (n= 22)	Microalbuminuria (n= 23)	Normoalbuminuria (n= 45)	Control (n= 45)	
FSG (mg/dL)	280.65± 14.47	248.29± 9.87	186.39± 9.91	97.67± 6.02	0.001
HbA1c (%)	10.49± 2.70	10.43± 2.37	8.49± 1.87	5.06± 0.21	0.045
TC (mg/dL)	227.76± 18.95	183.20± 13.75	171.89± 14.13	135.24± 8.87	0.001
TG (mg/dL)	280.48± 11.69	155.65± 9.12	164.78± 8.71	110.64±19.24	0.001
HDL-C (mg/dL)	36.80± 6.61	40.96± 7.71	39.98± 7.16	49.33± 6.28	0.001
VLDL (mg/dL)	56.08±13.12	31.13±14.6048	32.96±10.67	22.08±11.04	0.001
LDL-C (mg/dL)	134.88± 26.47	111.11± 37.08	98.22± 13.92	64.16± 28.76	0.001

*The collected data were presented as mean ± SD at the $p < 0.05$ level. FSG: Fasting serum glucose, HbA1c: Glycated hemoglobin, TC: Total cholesterol, TG: Triglycerides: LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, VLDL: Very low density lipoprotein.

The ANOVA results indicated that there were significant differences ($p < 0.001$) in serum urea and creatinine levels among the groups. Multiple pairwise comparisons showed that the mean serum urea and creatinine levels for macroalbuminuria were significantly ($p= 0.001$) higher compared to the micro- and normoalbuminuria groups and the control group. Moreover, the results of multiple pairwise comparisons showed that the mean ACR for macroalbuminuria was significantly ($p<0.001$) increased compared to the micro- and normoalbuminuria groups and the control group. There were substantial decreases in eGFR levels among the groups. The results of the ANOVA indicated that the macroalbuminuria group had the lowest eGFR value compared to the other groups, as shown in **Table (3)**.

Table 3. Descriptive statistics of kidney function parameter for pateints and control groups.

Variables	Mean ± SD				*p*-value
	Macroalbuminuria (n= 22)	Microalbuminuria (n= 23)	Normoalbuminuria (n= 45)	Control (n= 45)	
Urea (mg/dL)	153.86± 34.95	99.22± 40.91	60.33± 19.54	20.51±5.3412	0.001
Creatinine (mg/dL)	2.485.64± 865.52	0.70± 0.23	0.63± 0.196	0.6113±0.137	0.001
ACR (mg/g)	556.10± 369.20	111.74± 70.39	47.96± 38.34	20.51± 5.34	0.001
eGFR(mL/min/1.73 m^2)	38.38± 20.95	50.65± 35.11	119.61± 43.98	160.02± 40.49	0.001

*The collected data were presented as mean ± SD at the $p < 0.05$ level. ACR: Albumin to creatinine ratio, eGFR: Estimated glomerular filtration rate.

Table 4. Serum ACE2 for pateints and control groups

Variables	Mean ± SD				*p*-value
	Macroalbuminuria (n= 22)	Microalbuminuria (n= 23)	Normoalbuminuria (n= 45)	Control (n= 40)	
ACE-2 (ρg/mL)	2485.64± 865.52	2183.97± 1,012.09	0.62± 0.20	0.61± 0.14	0.001

*The collected data were presented as mean ± SD at the p < 0.05 level.ACE2: Angiotensin converting enzyme2

The ACE2 in discriminating between macroalbuminuria and control subjects had the best cutoff value of 153.85. Also, had sensitivity and specificity values of 95.45% and 97.78% at a cutoff value = 1085.23. The ACE2 had a sensitivity of 100.00 and a specificity of 93.33 at a cutoff of 918.349 in discriminating the microalbuminuria group from the control. For

differentiation of ACE2 in the normoalbuminuria group from control subjects, AUC = 0.704, which had sensitivity and specificity of 57.78 and 95.56 at a cutoff = 1017.43. The outcomes of this study revealed that serum ACE2 was higher in DN patients, especially those with macroalbuminuria and microalbuminuria, as illustrated in **Figure (1)** and **Table (5)**.

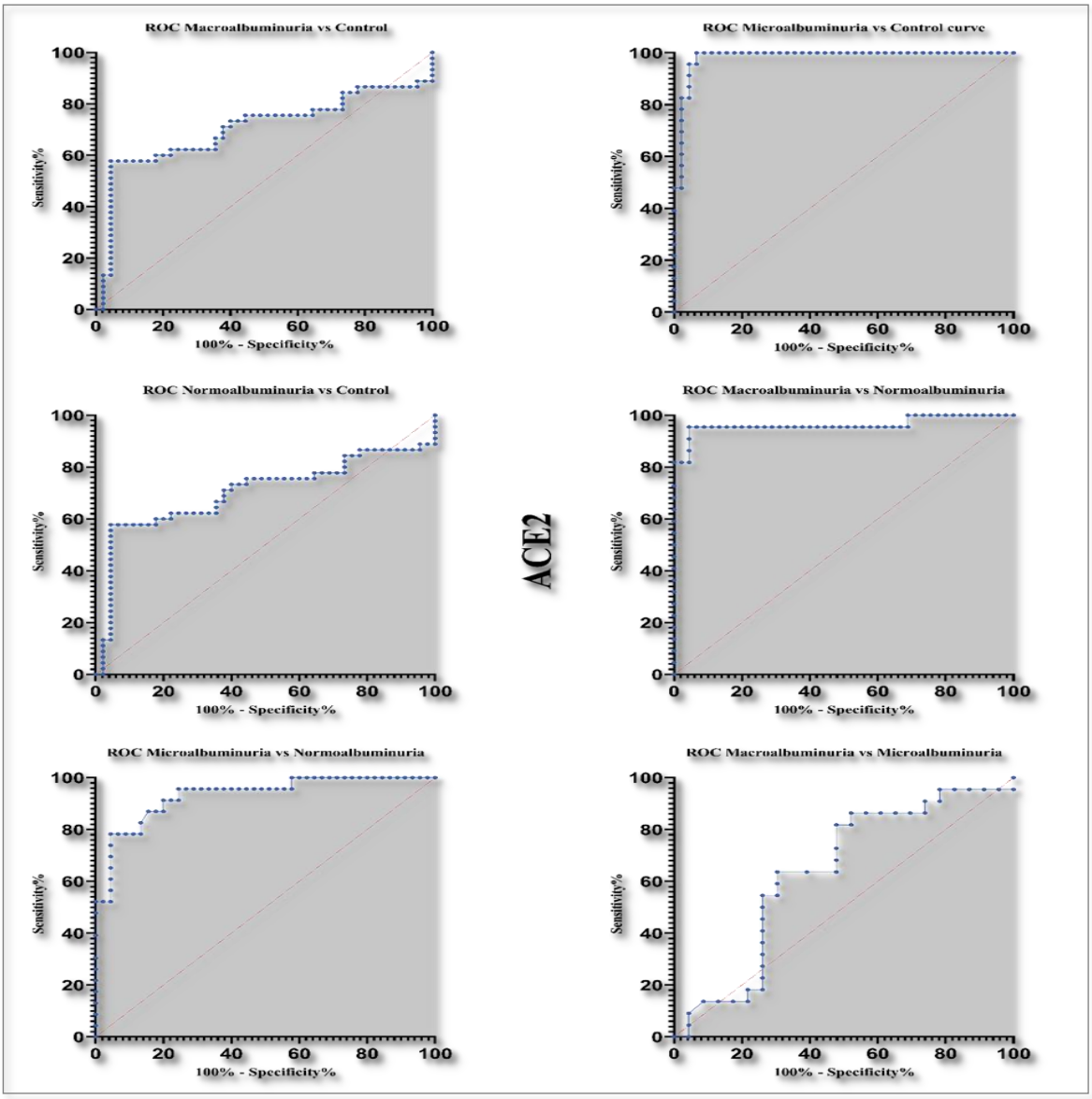

Figure 1. The ROC for ACE2 as differentiate across distinct study subgroups

Table 5. Comparison of ROC curve features for ACE2 as they attempt to differentiate across distinct studied subgroups.

ACE2 / Groups	AUC	SE	95% CI	Cutoff	Sense.	Spec.	*p*- value
Macroalbuminuria vs. control	0.98	0.017	0.911- 0.999	>1085.23	95.45	97.78	< 0.001
Microalbuminuria vs. control	0.984	0.012	0.918 -0.999	>918.349	100.00	93.33	< 0.0001
Normoalbuminuria vs. control	0.704	0.059	0.599-0.796	>1017.43	57.78	95.56	0.0006
Macroalbuminuria vs. Microalbuminuria	0.635	0.087	0.479-0.774	>1310.65	86.36	47.83	0.1200
Macroalbuminuria vs. Normoalbuminuria	0.963	0.031	0.885- 0.994	>1143.02	95.45	95.56	< 0.0001
Microalbuminuria vs. Normoalbuminuria	0.932	0.031	0.844-0.979	>1143.02	78.26	95.56	< 0.0001

AUC, Area under the curve; ROC, Receiver operating characteristic curve; SE, Standard error; 95% CI, 95% Confidence interval.

4. Discussion

In this study, there were no substantial variances in the ages and BMI of different groups, as determined by the ANOVA test, compared to the control groups. This finding agrees with previous studies, which showed no significant difference in mean age among DN patient groups (28). Another study reported that the incidence of ESRD in T2DM increased with diabetes duration and age (29).

The current study was conducted on diabetic patients with nephropathy, who had hyperglycemia reflected by higher FSG and HbA1c levels, hyperlipidemia reflected by higher TC, TG, and LDL-C levels, and ACR, along with lower eGFR values, as dependent criteria for classifying patient groups. In addition to other factors such as urea and creatinine, the mentioned parameters refer to the progression of diabetic complications, i.e., diabetic kidney disease. In this study, the mean HbA1c level was significantly different between the diabetics and the controls. Measuring HbA1c value is commonly used in DM patients as a marker of glycemic control and also as a marker for adjusting treatment or even initiating insulin therapy when needed (30).

It has been reported that FSG was considerably greater in patient groups than in the control group in various studies, which is consistent with the results of this study (30, 31).

Albuminuria is used to diagnose and monitor kidney disease. Change in albuminuria may reflect response to therapy and risk for progression. A decrease in urine albumin may be associated with improved renal and cardiovascular outcomes.

In this study, the ACR increased in diabetic groups compared to control groups, reaching its maximum increase in the macroalbuminuria group, which is in agreement with a previous study (31). The two key markers for CKD are urine albumin and eGFR. The current study also found that the microalbuminuria group had significantly higher levels of urea and creatinine and lower eGFR compared to other diabetic groups and controls (32). Creatinine is a more sensitive marker than urea for the early detection of renal impairment. Thus, serum creatinine can be used to calculate GFR. Various studies have found that higher serum levels of urea and creatinine are associated with elevated blood sugar. The present data are consistent with prior research on diabetic patients, which demonstrated an increased level of urea and creatinine with the development of DN. Increased urea and creatinine levels have been reported in earlier studies (33) during diabetes, along with a decreased GFR. An increase in urea level is seen when there is damage to the kidneys. A higher blood urea level in the presence of high blood sugar in a diabetic patient indicates kidney damage (34).The findings of this study showed that estimating ACR and GFR could be helpful to markers in this situation for early detection of DN, prevention of overt nephropathy, and progression to ESRD (35). These results suggested that alterations in eGFR and albuminuria may contribute to the development of renal disease (36, 37). The eGFR is more accurate than serum creatinine alone. Serum creatinine is affected by factors such as muscle mass, age, sex, and race (38).

The ACE2, which is capable of reducing angiotensin II (Ang II) and promoting Ang (1–7), serves as a key protective enzyme by reducing oxidative stress, inflammation, and fibrosis. Compounds that increase ACE2 catalytic activity offer a unique approach to targeting tubular and glomerular ACE2, potentially participating in new treatment approaches for DM. Development of new ACE2 stimulators with clinical translational potential is necessary. Increased levels of ACE2 in the kidneys have been associated with elevated levels of renal Ang II (39). The ACE2 enzyme plays a crucial role in preventing progressive renal damage by reducing oxidative stress, inflammation, and fibrosis. The kidney possesses a fully

functional local RAS capable of producing Ang II, a major contributor to the progression of CKD. The ACE2 is highly expressed in the kidney and predominantly localized to proximal tubules and glomerular podocytes (40). In T2DM patients, increased levels of specific urinary biomarkers could be detected before the onset of significant albuminuria, and they can be used as early markers of DN (41).

5. Conclusion

The study revealed a significant association between serum glycemic levels, lipid profile, kidney function tests, and ACE2 and DN in T2DM patients. From the current data, it can be concluded that ACR and ACE2 play a key protective role in preventing progressive renal damage, which is a good indicator for early detection of DN.

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Conflict of Interest

None.

Funding

None.

Ethical Clearance

This research was approved by the Scientific Committee in the College of Science for Women at the University of Baghdad, in accordance with the instructions of the Iraqi Ministry of Health and Environment (No. 313/22 on 13/12022).

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