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Correlation Between Urinary Orosomucoid1 Level and Albumin to Creatinine Ratio in Type 2 Diabetic Patients

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ABSTRACT

Background: Orosomucoid 1, also known as alpha-1-acid glycoprotein is an acute-phase serum protein produced by the liver in response to inflammation and infection, plays an important role as an anti-inflammatory and immunomodulatory agent. The aim of this work was to evaluate the relation between urinary orosomucoid 1(UROM1) and albumin to creatinine ratio (ACR) in type 2 diabetes mellites (T2DM). **Methods:** This cross-sectional study was carried out on 90 patients with T2DM. Patients were categorized into two equal groups: Group I: T2DM patients with normal ACR (less than 30 mg/g). Group II: T2DM with increased ACR (>30 mg/g). **Results:** UROM1 was significantly increased in patients with renal impairment (ACR >30mg/dl) than those without (ACR < 30mg/dl). UROM1 was positively correlated with diabetes duration, fasting, postprandial blood glucose, haemoglobin A1C, urea, creatinine, TGs, cholesterol, and low-density lipoproteins, while negatively correlated with estimated glomerular filtration rate, albumin, and high-density lipoproteins. UROM1 for early detection of diabetic nephropathy, at cut off value 7.995 with 96.42% sensitivity and 91.11% specificity. **Conclusions:** UROM1 could be used as a biomarker for early detection of diabetic nephropathy in T2DM.

Keywords: Urinary Orosomucoid 1 Level, Albumin to Creatinine Ratio, Type 2 Diabetic Patients,

1. Introduction

Diabetes and its complications have become one of the most important public health issues in the recent years (Rodriguez-Saldana, 2003; Żyłka *et al.,* 2018). Diabetic kidney disease (DKD) is a major complication that occurs in about 30% to 40% of patients with diabetes, (Akhouri *et al.,* 2023) and it is the leading cause of end-stage kidney disease (Zou *et al.,* 2022).

Early kidney protective treatment has the most important role to prevent development of DKD and to improve the prognosis of diabetic patients (Żyłka *et al.,* 2018). Therefore, early screening and diagnosis of DKD are extremely essential.

Currently, definition and classification of DKD are based on albuminuria and glomerular filtration rate (GFR) (Levey *et al.,* 2011). So, the urinary albumin to creatinine ratio (ACR), and the estimated glomerular filtration rate(eGFR) are the most used biomarkers for screening of DKD.
Nevertheless, an increasing number of studies have reported that there can be a considerable rate of kidney impairment without albuminuria in diabetic patients, (Koye *et al.,* 2018) even in the elderly (Wang *et al.,* 2019). Therefore, ACR might has limited use as abiomarker for early screening and diagnosis of DKD.

Furthermore, Early kidney injury is often accompanied by glomerular hyperfiltration whereas, eGFR decline appears relatively late in the progression of DKD(Żyłka *et al.,* 2018; Trevisan, and Dodesini, 2017). Hence, early screening of DKD still remains a major challenge.

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Orosomucoid 1 is an acute-phase reactant, which is believed to have immunomodulatory and anti-inflammatory effects and plays an important role to maintain the barrier for the transendothelial transport of macromolecules (Magid *et al.,* 2005; Haraldsson and Rippe, 1987).

The molecular weight of orosomucoid 1 is 42 kDa which between albumin (an indicator of glomerular impairment) (Waller *et al.,* 1989) [11]at 69 kDa and alpha-1 microglobulin (an established marker of renal tubular dysfunction) at 26.7 kDa (Wang *et al.,* 2015; Weber and Verwiebe, 1992).

The concentration of orosomucoid 1 in urine is very low in healthy individuals (Ito *et al.,* 1989), but significantly increased in diabetic patients (Christiansen *et al.,* 2002; Jiang *et al.,* 2009). It is elevated by more than 8-fold in patients with DKD compared to healthy individuals (Jiang *et al.,* 2009).

The urinary orosomucoid 1 excretion rate is related to the development of DKD and can be considered as a novel DKD-related biomarker (Jiang *et al.,* 2009).

However, the value urinary orosomucoid 1 protein (UORM1P) for the early screening of renal impairment in type-2 diabetic patients (T2DM) remains unclear, and the cut-off value for detecting kidney damage in T2DM also needs to be determined (Trombetta *et al.,* 2005).

Therefore, our aim was to evaluate the relationship of UORM1 and the Albumin-to-creatinine ratio (A/C R) in early screening of renal impairment in T2DM.

2. Patients and Methods

This cross-sectional study was carried out on 90 patients with T2DM recruited from endocrinology and diabetes outpatient clinics and inpatient wards of Internal Medicine department of Tanta University Hospitals, Egypt from August 2021 to June 2022. The study was done after approval from the Ethical Committee Tanta University Hospitals, and a written consent was obtained from the patients.

Exclusion criteria were age below 18 years, kidney disease other than DKD, known inflammatory disease or an autoimmune disease (such as systemic lupus erythematosus), liver disease and/or sever cardiovascular disease and Pregnancy.

Patients were further categorized into two equal groups: Group I: T2DM with normal ACR (less than 30 mg/g). Group II: T2DM with increased ACR (more than 30 mg/g).

All patients were subjected to:

Full history taking including disease history, surgical history, diabetes duration, hypertention, and angiotensin converting enzyme inhibitor (ACEI)/angiotensin II receptor blocker use.

Clinical examination: Measurement of systolic and diastolic blood pressure, chest, cardiac and abdominal examination to exclude subjects with any abnormal findings, measurement of body weight and height with calculation of body mass index (BMI).

Laboratory investigation: Fasting and two hours post prandial blood sugar, glycated haemoglobin (HbA1c), complete urine analysis, urinary albumin to creatinine ratio, renal function tests (serum creatinin and blood urea), estimation of glumerular filtration rate (eGFR), serum albumin, triglycerides and total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).

Blood sampling and processing

Under quality control and safety procedure for sample collection, 8ml venous blood sample was collected in plain vactainer tubes. 2ml EDTA for CBC assay. serum was separated from the other 6ml for all specimens using centrifugation at 3000 rpm for 15 min, serum sample for assayed for urea, creatinine, albumin.

Urea and creatinine were measured in serum using Diamond, Egypt on Kone lab Arena 20 XT (Thermoscientific) USA. CBC: automated by fully automatic blood cell counter ERMA PCE-210 N Germany. Serum albumin: using Modified bromocresol green colorimetric method by Diamond, Egypt on Kone lab Arena 20 XT (Thermoscientific) USA.

Estimation of Glomerular filtration rate: by using EPI equation based on creatinine, age and sex. (141*min (SCr/1) a* max (SCr/1)-1.209*0.993age*1.018[if female] * 1.159[if black]).

Urinary albumin to creatinine ratio was measured in supernatant of urine samples. Urinary microalbumin level was measured by turbidmetric method using Thermo scientific, USA on Kone lab Arena 20 XT (Thermo scientific) USA. The creatinine level was measured in diluted urine (1:49)

using Diamond, Egypt on Kone lab Arena 20 XT, USA. The urinary ACR was calculated using the following formula: Albumin in mg/dl / creatinine in g/dl, and the results were expressed in mg albumin/creatinine.

Measurement of urinary levels of UROM1protein

Measurement was by enzyme linked immunoassay (ELISA) kits. (Fine test, catalog no, EH4326, Wuhan Fine Biotech Co., Ltd. Wuhan, China (430075). The first or second morning urine sample from each subject was centrifuged and then stored at -800c until the complete set of samples had been collected. The plate was washed two times with a wash buffer. The standard stock was reconstituted with a 1 ml sample buffer. Then, seven tubes were labelled, and 0.3 ml of the sample dilution buffer was added to each tube, 0.3 ml of standard solution was added into first tube, mixed thoroughly and then 0.3 ml was transferred from the first tube to the second tube and then repeated serially to make a serial dilution of standards. Standards and test samples (diluted 1:1 with sample dilution buffer), were added on the per-coated plate. 100ul of properly diluted sample was added into test sample wells. The plate was incubated at 370c c for 90 minutes. The plate content was discarded, and then washed two times with wash buffer. 100ul Biotin-labeled antibody working solution was added into wells Then the plate was incubated at 370c for 60 minutes. The plate was washed three times with wash Buffer. 100ul of SABC (Streptavidin conjugate) was added and the plate was incubated at 370c for 30 minutes. The plate was then washed five times with a wash buffer. 90ul of TMB substrate was added into each well, and the plate was incubated at 370c in dark within 10-20 minutes. 50ul of stop solution into was added into each well, and the OD absorbance was measured at 450nm on Microplate Reader (Techan Spectra, AUSTRIA).

Statistical analysis

Statistical analysis was performed by SPSS version 25 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Parametric variables were expressed as mean and standard deviation (SD) and were compared using ANOVA test among the three groups with post hoc (Tukey) test to compare each two groups. Non- parametric variables were expressed as median and interquartile range (IQR) and were analyzed using Kruskal-Wallis test; further analysis was performed by Mann–Whitney (U) test to compare each two groups. Categorial variables were expressed as frequency and percentage and were statistically analyzed by Chi-square test. A two-tailed P.

3. Results

There was insignificant difference as regard age, usage of angiotensin converting enzyme inhibitors and angiotensin receptor blockers (ACEI and ARBS), hypertension distribution, and BMI. There was statistically significant difference as regard diabetes duration, sex distribution and type of treatment (Table 1).

There was statistically significant decrease as regard fasting blood glucose (FBS), postprandial blood glucose (2h-PP), and haemoglobin A1C (HbA1C), albumin/ creatinine ratio (ACR) urea, creatinine, triglycerides, cholesterol, and low-density lipoproteins (LDL). There was statistically significant increase as regard estimated glomerular filtration rate (eGFR). There was insignificant difference as regard albumin and High-density lipoproteins (HDL) (Table 2).

There was statistically significant decrease between group 1 and group 2 also between groups as regard UROM1(Figure 1).

According to UROM1 for detection of T2DM with increased albumin to creatinine ratio: At cut off value 7.995 under the curve was 0.810, sensitivity 97.77%, specificity 91.1%, positive predictive value (PPV) 91.66%, and negative predictive value (NPV) 97.61%. With increased albumin to creatinine ratio (ACR > 300 mg/g): At cut off value 11.76 under the curve was 0.801, sensitivity 94.11%, specificity 82.4%, PPV 76.19%, and NPV 95.83%.

For detection of early DN: At cut off value 7.995 under the curve 0.779, the sensitivity 96.42%, specificity 91.11%, PPV 87.09%, and NPV 97.61%. Regarding creatinine for detection of type 2 diabetic patients with increased albumin to creatinine ratio: At cut off value 0.975 under the curve was 0.743, sensitivity 91.11%, specificity 77.77%, (PPV 80.39%, and NPV 89.74%.

Table 1: Comparison between all the studied groups as regard age, sex, diabetes duration, treatment, hypertension and BMI.

		Group (1) (n=45)	Group (2) (n=45)	Test of sig.	P-Value
Age (Years)		57.69 ± 3.16	56.44 ± 4.26	t= 1.571	0.120(a)
Diabetes duration (Years)		7.09 ± 2.04	12.22 ± 2.92	t= -9.697	< 0.001**(a)
Sex	**Male**	29 (64.4%)	9 (20%)	X^2= 18.970	<0.001**(b)
	Female	16 (35.6%)	36 (80%)		
Treatment					
Dimicron		7 (15.6%)	1 (2.2%)		
Mixtardand Cidophage		1 (2.2%)	6 (13.3%)		
Amaryland Cidophage		11 (24.4%)	2 (4.4%)		
Lantus		5 (11.1%)	7 (15.6%)	X^2=23.362	0.001**(b)
Insulin		16 (35.6%)	27 (60%)		
Amaryl		5 (11.1%)	1 (2.2%)		
Gliptus andzanoclide		0	1 (2.2%)		
ACEI and ARBS	**No**	27 (60%)	25 (55.6%)	X^2=0.182	0.696(b)
	Yes	18 (40%)	20 (44.4%)		
Hypertension	**No**	20 (44.4%)	16 (35.6%)	X^2=0.742	0.389(b)
	Yes	25 (55.6%)	29 (64.4%)		
BMI (kg/m^2)		31.89 ± 5.38	30.07 ± 3.44	t = 1.904	0.06(a)

Data are presented as Mean ± SD or frequency (%), n: number, (a): Independent-Sample T Test, (b): Chi-Square Test, ACEI and ARBS: angiotensin converting enzyme inhibitors and angiotensin receptor blockers, T, BMI: body mass index Test **: Statistically significant at p ≤ 0.001.

Table 2: Comparison between the studied groups as regard diabetic profile, renal profile, albumin and lipid profile

	Group 1 (n=45)	Group 2 (n=45)	Test of sig.	P-Value
FBS (mg/dL)	171.42 ± 40.34	231.34 ± 47.06	t=- 6.484	< 0.001**(a)
2h-PP (mg/dL)	222.98 ± 46.75	275.47 ± 41.63	t=- 5.624	< 0.001**(a)
HbA1C (%)	7.84 ± 1.62	9.78 ± 1.86	t=- 5.237	< 0.001**(a)
ACR (mg/g)	12 (6)	176 (490)	H=0.001	< 0.001**(b)
Urea (mg/dL)	30.67 ± 6.12	43.44 ± 15.98	t=- 5.007	< 0.001**(a)
Creatinine (mg/dL)	1.08 ± 0.14	1.27 ± 0.27	t=- 4.102	< 0.001**(a)
eGFR (mL/min/1.73m^2)	70.23 ± 12.30	60.57 ± 14.16	t=3.453	< 0.001**(a)
Albumin (g/dL)	4.35± 0.53	4.13 ± 0.53	t=1.958	0.053(b)
Triglycerides (mg/dL)	163.63± 7.35	194.75± 62.26	t=- 3.229	0.002*(a)
Cholesterol (mg/dL)	224.73± 3.59	261.24 ± 59.4	t=- 3.831	< 0.001**(a)
LDL (mg/dL)	141.24± 4.74	176.19± 53.17	t=- 3.654	< 0.001**(a)
HDL (mg/dL)	50.77 ± 5.44	50.47 ± 5.39	t= 0.203	0.840(a)

Data are presented as Mean ± SD or frequency (%), L: liter, (a): Independent-Sample T (b): Mann-Whitney U Test, T Test, **: Statistically significant at p ≤ 0.001.

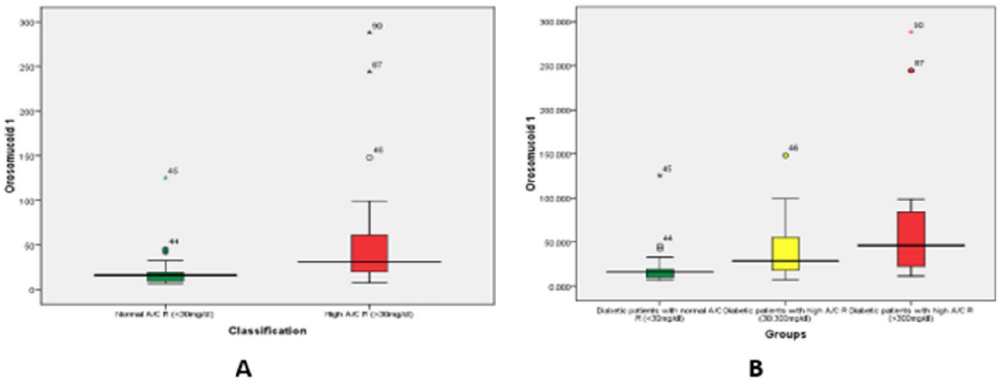

Fig. 1: Box plots of orosomucoid 1 in group 1 and group 2 (A) between groups (B) shows the median, interquartile range, and outliers.

With increased albumin to creatinine ratio (ACR > 300 mg/g): At cut off value 1.075 under the curve 0.760, sensitivity 94.11%, specificity 71.42%, PPV 66.66%, and (NPV 95.23%. For detection of early DN: At cut off value of 0.945; area under the curve 0.654, sensitivity 92.85%, specificity 88.88%, PPV 83.87%, and NPV 95.23%. According to eGFR for detection of type 2 diabetic patients with increased albumin to creatinine ratio: at cut off value 54.455 under the curve 0.700, sensitivity 88.88%, specificity 71.11%, PPV was 75.47%, and NPV was 86.48%. With increased albumin to creatinine ratio (ACR > 300 mg/g): At cut off value 51.40 under the curve was 0.702, sensitivity 82.14%, specificity 79.31%, PPV 68.75%, and NPV 83.33%. For detection of early DN: At cut off value 54.72 under the curve was 0.649, sensitivity 91.11%, specificity 75%, PPV 85.41%, and NPV 84%(Figure 2)

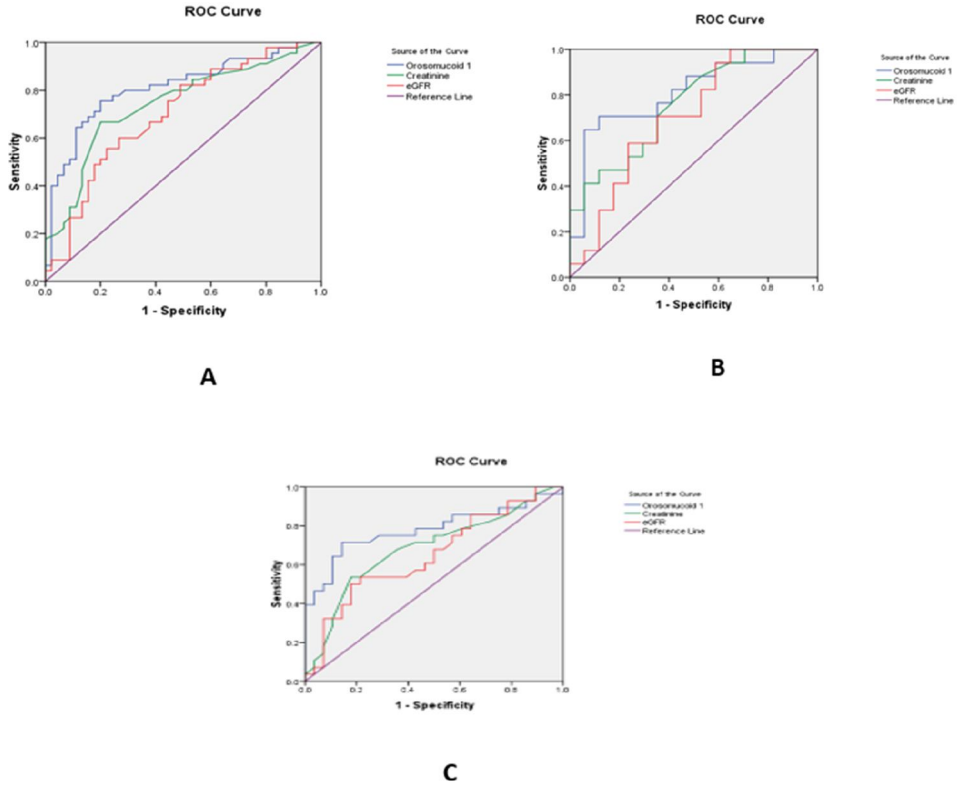

Fig. 2: ROC curve of orosomucoid 1, creatinine, and eGFR for (A) diagnosis of type 2 diabetic patients with increased albumin to creatinine ratio, (B) diagnosis of type 2 diabetic patients with increased albumin to creatinine ratio (ACR > 300 mg/g), and (C) early DN

UROM1 was positively correlated with diabetes duration, 2h-PP, HbA1C, ACR, urea, creatinine, triglycerides, cholesterol, and LDL. While UROM1 was negatively correlated with eGFR, albumin, and HDL(Figure 3)

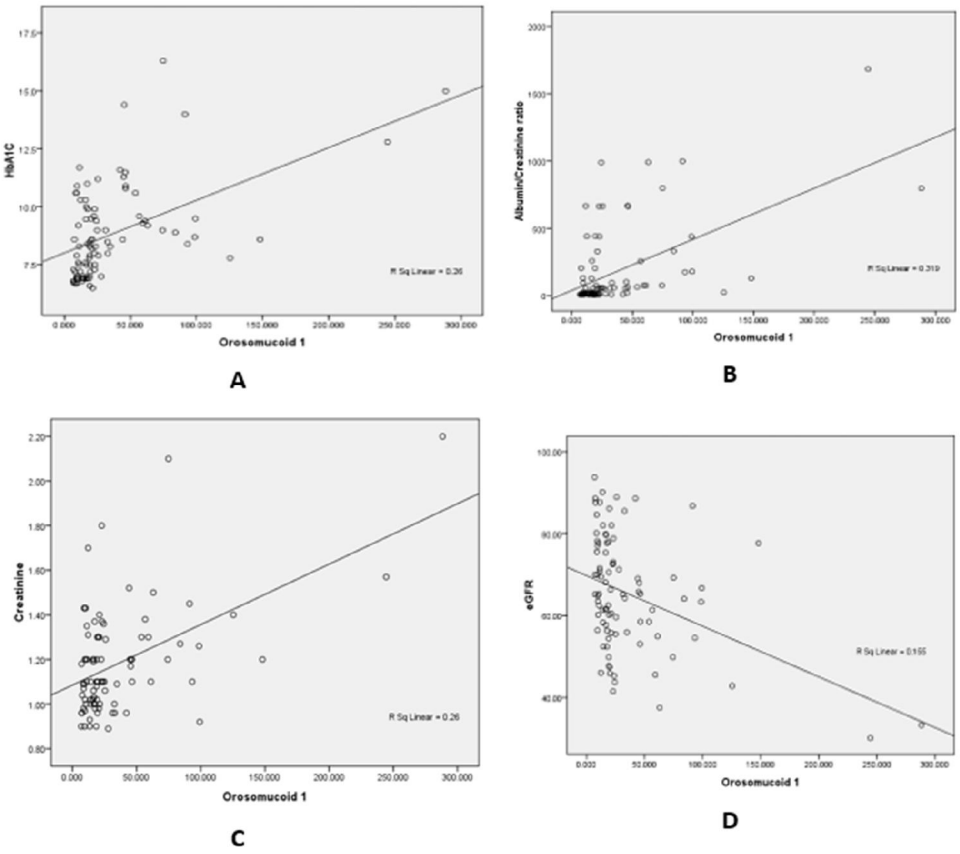

Fig. 3: Correlations between orosomucoid 1 and (A) HbA1C, (B) ACR, (C) creatinine and (D) eGFR

The regression analysis revealed that UROM1, age, diabetes duration, BMI, FBS, and HbA1C were significantly associated with affecting type 2 diabetic patients with increased albumin to creatinine ratio (Table 3).

Table 3: Regression analysis for predictor factors affecting patients.

Independent variables	Odds ratio (95%) CI	P- value	P- correct
Orosomucoid 1	1.051 (1.02 – 1.084)	0.001**	0.001**
Age	0.597 (0.426 – 0.835)	0.003*	0.022*
Sex	0.181 (0.031 – 1.042)	0.056	-
Diabetes duration	5.788 (2.195 – 15.262)	0.001**	0.024*
ACEI and ARBS	0.927 (0.295 – 2.914)	0.897	-
BMI	0.848 (0.729 – 0.978)	0.033*	0.002*
FBS	1.037 (1.005 – 1.069)	0.023*	0.013*
2h-PP	0.993 (0.964 – 1.022)	0.630	-
HbA1C	1.514 (1.033 – 2.219)	0.033*	0.019*
Urea	1.122 (1.021 – 1.233)	0.016*	0.300
Creatinine	85.999 (1.776 – 4163.25)	0.024*	0.218
eGFR	0.972 (0.921 – 1.026)	0.31	-
Albumin	0.809 (0.264 – 2.478)	0.71	-
Triglycerides	1.005 (0.906 – 1.115)	0.920	-
Cholesterol	0.966 (0.585 – 1.594)	0.892	-
LDL	1.082 (0.656 – 1.786)	0.758	-
HDL	1.237 (0.737 – 2.076)	0.422	-

4. Discussion

Orosomucoid 1 (ORM1) is a highly glycated protein mainly synthesized in the liver and normal renal filtration results in loss of only a very small amount of it as it is almost totally reabsorbed (Henriksen *et al.,* 1982). Svendstrup *et al.* (2013) showed that UORM1 excretion can be used to independently predict mortality in diabetic patients with normoalbuminuria suggesting that UORM1 excretion is a better predictor of early mortality than albuminuria. Furthermore, the excretion rate of UORM1 is an independent predictor of DKD as it is significantly increased in patients with the condition (Varghese *et al.,* 2007; Jiang *et al.,* 2009). And so, UORM1 may be a novel biomarker for screening renal impairment in diabetic patients.

This is in disagreement with Wang *et al.* (2020) who found that participants who were male > 60 years old, had hypertension, had diabetes duration more than 10 years and took ACEIs / ARBs medications had the higher UORM1 level.

Also, Svendstrup *et al.* (2013), reported that T2DM patients with increased UORM 1 excretion were of older age and higher proportion was to male, had long diabetes duration, had higher prevalence of hypertension and took ACEIs / ARBs medications is disagree with our study.

Our results also in disagreement with Chen *et al.* (2021) reported that, the values of UORM1 were significantly higher among male patients compared with female patients ($P < 0.01$).

Regarding laboratory analysis among the studied groups, there was statistically significant decrease between group 1 and group 2 as regard FBS, 2hpp, HbA1c, urea, creatinine, eGFR, TG, Cholesterol and LDL (p value <0.05). Also, there was insignificant difference between groups as regard Albumin, HDL (P value >0.05).

Wang *et al.* (2020), reported that, the values of s. creatinine, eGFR, ACR, and HbA1C were significantly higher among participants with renal impairment than those without, and this in agreement with our results. On the other hand, they reported that, there was no statistically significant differences were observed for total cholesterol, TG, LDL between patients with and without renal injury and this disagrees with our results.

We found significant difference between two groups as regard HbA1C, TG, Cholesterol, and LDL, and this in contrast with Chen *et al.* (2021). who concluded that there was insignificant difference between patients.

Our study in agreement with Zhou *et al.* (2020) who found significant difference between patients with renal injury and those without as regard HbA1C, FBS, and eGFR but, disagree with them in that, they found insignificant difference as regard Cholesterol, TG, and LDL.

Regarding UORM1 we found that there was statistically significant difference between group 1 and group 2 (P value < 0.05), UORM1 is higher in patient with renal impairment than in those without (albumin to creatinine ratio < 30 mg/ g).

Jiang *et al.* (2009) assumed that, The possible mechanisms of increased UORM1 in DN may be due to enhanced glomerular filtration rate as a result of an elevation in UORM1 was closely related to the increase in glomerular permeability, and increased UORM1 may correlate with the inflamatory activation in patients with DN, also it may be due to renal secreation of orosomucoid 1 as it can be produced by glomerular endothelial cells in DN patients.

So, this study in agreement with Wang *et al.* (2015) who found that the level of UORM1 were about seven times higher in patients with renal injury than in those without.

Also, this study in agreement with Chen *et al.* (2021), who reported that, UORM1 level and NGAL levels were significantly higher among participants with renal insufficiency than among participants without, and the difference in UORM1 was relatively greater than the difference in NAGL values.

Regarding UROM1 as a predictor for early DN, our study revealed that, there was statistically significant decrease between the studied groups (P value<0.001), as UORM1 is low in patient with normal albuminuria (<30mg/g), and high in patient with micro-albuminuria (30:300mg/g), but higher in patients with macroalbuminurea (>300 mg/g).

Jiang *et al.* (2009), reported that UORM 1 was gradually increased in patients from normoalbuminuria (< 30mg/g) to macroalbuminuria group(>300mg/g) but significantly increased in micro (30:300mg/g) and macro albuminuria (>300mg/g), so there is agreement with our results. Also, it agrees with Zhou *et al.* (2020) who reported that levels of UORM1 gradually increase in renal damage (P value 0.05).

In the present study, urinary orthomucoid had a significant positive correlation with diabetes duration, 2hPP, HbA1c, ACR, urea, creatinine, TGs, cholesterol, and LDL, while negative correlation with eGFR, albumin and HDL.

This agrees with Wang *et al.* (2020) who reported that, the values of UORM 1 were significantly positively correlated with ACR, diabetes duration, creatinine, HbA1C, LDL, and urea, while UORM 1 levels were negatively correlated with e GFR and HDL.

Our results also agree with Jiang *et al.* (2009). who reported that UORM 1 had strong positive correlations with serum creatinine, HbA1c, and diabetes duration ($P < 0.001$) and a weak positive correlation with urea, CRP, and LDL, while UROM1 levels were negatively correlated with eGFR.

In agreement with our results Chen *et al.* (2021), reported that levels of UORM1 were positively correlated with ACR, HbA1c and creatinine but negatively correlated with eGFR.

In our study by using receiver operating characteristic curve (ROC) curves analysis of urinary UROM1, serum creatinine, eGFR, in detecting DN disease, DN patients with increased ACR >300mg/g, and early detection of DN (ACR 30:300 mg/g). The urinary UROM1 showed a sensitivity of 97.77%, 94.11 %, 96.42% and specificity of 91.11%, 82.4%, 91.11%, respectively. While for serum creatinine it revealed a sensitivity of 91.11%, 94.11%, 94.11%, and 92.85% and specificity of 77.77%, 71.42%, 88.88% respectively. For eGFR it revealed a sensitivity of 88.88%, 82.14% and 91.11%, and specificity of 71.11%, 79.31% and 75% respectively.

Some studies reported high sensitivity and specificity of urinary orosomucoid like, Zhou *et al.* (2020) who concluded that UROM1 has sensitivity of 94.1% and specificity of 84.2% in detecting diabetic nephropathy. El-Beblawy *et al.* (2016) found a sensitivity of 90% and specificity of 90% in diabetic nephropathy patients and this agrees with our study.

Limitations: Small number of patients, patients were enrolled in a single center, missing following up the patients by measuring urinary UROM1 levels before and after treatment.

5. Conclusion

Urinary orothomucoid 1 could be used as abiomarker of early detection of diabetic nephropathy in T2DM but further studies are needed, also it was significantly high in patients with renal impairment (ACR >30mg/g) than in those without and had a positive correlation with ACR and negative correlation with e GFR. Good glycemic control (by measuring HbA1C) is considered a protective factor against UROM1 increase.

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Conflict of Interest: Nil

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