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Serum Uric Acid Associations and Predictors in Patients with Type 2 Diabetes and Microalbuminuria

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ABSTRACT

Background: Diabetic nephropathy (DN) is a leading cause of end-stage renal disease (ESRD) with high morbimortality rates. Hyperuricemia is a predisposing factor for chronic kidney disease (CKD) in individuals with type 2 diabetes (T2D), even with normal renal function.

Objective: The current work aimed to determine the associations and predictors of serum uric acid (SUA) in cases with T2D with microalbuminuria.

Patients and Methods: This cross-sectional study included a total of 105 patients with T2D. Microalbuminuria, serum uric acid and other parameters were measured at the time of inclusion of patients.

Results: Among T2D cases, 42.9% had microalbuminuria (MAU). Higher levels of serum creatinine, uric acid, waist circumference (WC), mean blood pressure (BP), and low estimated glomerular filtration rate (eGFR) remained accompanied by an increased risk of microalbuminuria. A moderate predictive ability for serum uric acid level was found in predicting microalbuminuria, with a sensitivity of 84.4% and specificity of 61.7%. Uric acid showed significant positive correlations with WC, total cholesterol (TC) and significant negative correlation with HDL in those without microalbuminuria, as well as significant positive correlations with age, mean arterial pressure, TC and triglycerides (TGs) in those with microalbuminuria. In the group without microalbuminuria, WC and TC were positive predictors for high uric acid. In the microalbuminuria group, lower HDL was a significant predictor of serum uric acid.

Conclusion: The serum uric acid level may serve as a useful marker for predicting microalbuminuria. Both uric acid and microalbuminuria are predictors of nephropathy in patients with T2D. However, additional validation and consideration of other clinical factors are necessary for an accurate risk assessment.

Keywords: Microalbuminuria, Serum Uric Acid, Type 2 diabetes, Diabetic nephropathy.

INTRODUCTION

Diabetic nephropathy (DN), a common outcome of diabetic microangiopathy, is a primary cause of ESRD, with substantial morbimortality [(1)]. Inflammation is a fundamental pathogenetic process in diabetic nephropathy because factors of the diabetic environment activate kidney cells, causing chemokine release and cell adhesion molecule regulation. These conditions promote lymphocyte and monocyte infiltration into diabetic kidneys, as well as the generation of reactive oxygen products [(2)].

Microalbuminuria [(3)] is an early indicator of CKD and is linked to an increased risk of mortality and metabolic diseases, including T2D [(4)]. MAU is defined as a level of urine albumin that is higher than normal but lower than what can be determined with a standard dipstick. As a result, the rate of urinary albumin excretion (UAE) in MAU ranges from 30 to 300 mg/24 hours. In other measures, in addition, it could imply 30-300 mcg/mg creatinine or 20-200 mcg/min for two out of three urine collections.MA, in contrast, is defined as more than 100 mg/12 hours or 300 mg/24 hours [(5)]. MAU levels have been seen in the urine of people with DN [(6)]. Moreover, insulin resistance (IR) is favorably linked with MAU in diabetic individuals [(7)].

Although purine nucleotides are generated and destroyed in all organs, urate synthesis is concentrated in the liver and intestines due to the presence of the enzyme xanthine oxidase. Hyperuricemia causes gouty arthritis, urolithiasis, and kidney impairment. Urate is readily filtered by the glomerulus, secreted, and reabsorbed in the proximal tubules, and hyperuricemia caused by euglycemic hyperinsulinemia may occur before the onset of T2D, hypertension, cardiac diseases, and gout in subjects with metabolic syndrome (MetS) [(8)]. Furthermore, a correlation between UA and IR has been repeatedly proven, and UA is considered to have a substantial role in the progression of IR [(9)].

During the synthesis of UA, oxidants are produced, which can contribute significantly to kidney damage [(10)]. It has been demonstrated that free oxygen radicals generated by UA have a substantial influence on endothelial dysfunction, causing inflammation and contributing to the occurrence of DN [(3)]. Increased serum UA is linked to renal damage produced by glomerular hypertrophy and sclerosis; however there is inconsistent evidence in the literature about the correlation between UA levels and CKD [(11)]. However, hyperuricemia was considered as an independent predisposing factor for CKD development in people with T2D and normal renal function [(12)]. Furthermore, most people with T2D have renal glomerular and tubular damage before developing microalbuminuria [(13)].

Despite these advances, there are numerous unsolved gaps in our understanding of the relationship between MAU and SUA, particularly in T2D patients. So, we aimed to investigate the relationship between SUA and MAU in cases with T2D.

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PATIENTS AND METHODS

This cross-sectional study included a total of 105 T2D patients, aged 40 to 60, attending Mansoura University Hospitals.

Exclusion criteria: Patients with renal diseases other than DN, as were situations that increase UAE, which include urinary tract infection, hematuria, fever, uncontrolled hypertension, and heart failure, as well as a history of renin-angiotensin system (RAS) inhibitor use, severe liver dysfunction, connective tissue disorders, pregnancy, or cancer.

All patients were subjected to comprehensive history, clinical examination and anthropometric measurements including BMI. After 5 minutes of rest, BP was measured from the right arm in a sitting position using a mercury sphygmomanometer with systolic (SBP) korotkoff sound 1 and diastolic (DBP) korotkoff sound 4. An average of two readings was recorded.

Laboratory investigations: HbA1C, serum creatinine, serum uric acid, fasting plasma glucose, and lipid profile were measured.

A random urine sample was obtained and stored at -20 until creatinine and albumin levels were measured for determination of ACR. The urine creatinine, urinary microalbumin, urinary ACR and serum uric acid were determined using the Cobas C311 automated system. The eGFR was measured using the Modification of Diet in Renal Disease (MDRD) Study formula: GFR (ml/min/1.73 m2) = 175 × (Ser Cr (mg/dl)) −1.154 x (age (years)) −0.203) with a correction factor of 0.742 in females.

Ethical approval:

This study was ethically approved by Mansoura University's Research Ethics. Written informed consent of all the participants was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis:

The collected data were analyzed by using SPSS v.20.0. The qualitative data was presented using frequencies and relative percentages. Use the X^2-test to compare qualitative variables across many sets. Quantitative data was expressed as the mean ± SD. The independent Student t-test was utilized to compare two groups of regularly distributed data, whereas the Mann-Whitney U test was employed for non-normally distributed data. Spearman's correlation coefficient was used to analyze the link between various research parameters. Logistic and linear regression analyses were used to evaluate the risk factors. A two-tailed P value of <0.05 was judged significant.

RESULTS

The current study was conducted on 105 T2D patients, 45 (42.9%) had MAU, while 60 (57.1%) had no MAU. Prediction of MAU among the studied cases was assessed. The predictors evaluated in this study included age, sex, eGFR, and levels of albumin/creatinine ratio, HbA1c, serum creatinine, uric acid , TC , TG, HDL cholesterol, LDL cholesterol, waist circumference, BMI, and mean arterial pressure (MAP).

Univariate analysis showed that higher levels of Ser Cr, uric acid, albumin/creatinine ratio, total cholesterol, TGs, LDL cholesterol, WC, and MAP were associated with an increased risk of microalbuminuria, while higher levels of eGFR and HDL cholesterol were associated with a decreased this risk. Age, sex, HbA1c, and BMI were not significantly associated with microalbuminuria in univariate analysis.

After adjusting for other factors, higher levels of serum creatinine, uric acid, WC, and MAP remained accompanied by an increased risk of microalbuminuria. Conversely, higher eGFR levels were associated with decreased risk, even after adjusting for other variables **(table 1)**.

Table (1): Univariate and multivariate analysis for prediction of microalbuminuria among studied cases .

Predictors	Microalbuminuria		Univariate analysis		Multivariate analysis	
	-ve (N=60)	+ve (N=45)	P value	COR 95%CI	P value	AOR 95%CI
Age (years)	49.92±5.67	52.27±7.32	0.067	1.06 (0.996-1.13)		
Sex Male Female	30(50) 30(50)	18(40) 27(60)	0.309	1.50 (0.686-3.28)		
Creatinine (mg/dl)	0.813±0.15	0.985±0.244	0.001*	5.22 (1.21-7.82)	0.001*	6.98 (1.25-10.58
e GFR	91.72±18.7725	72.66±17.88	0.001*	0.951 (0.928-0.975)	0.002*	0.961 (0.937-0.986)
Uric acid mg/dl	5.55±1.36	8.10±1.89	0.001*	1.49 (1.24-1.78)	0.001*	1.42 (1.18-1.72)
Albumin / creatinine ratio mg/gm	24.39±5.98	168.95±40.97	0.001*	4.1(1.3-6.50)	0.979	7.17 (0.25-8.98)
HbA1c %	7.32±1.79	8.22±1.59	0.07	1.17 (0.983-1.39)		
T. Cholesterol mg/dl	171.21±31.31	231.31±55.95	0.001*	1.02(1.01-1.05)	0.998	1.21(0.005-9.67)
TG mg/dl	137.73±33.64	163.18±40.42	0.016*	1.01(1.0-1.02)	0.994	1.28(0.05-8.7)
HDL mg/dl	56.48±13.76	44.98±11.13	0.001*	0.955 (0.931-0.981)	0.996	1.90(1.003-9.8)
LDL mg/dl	120.08±28.78	184.13±45.83	0.009*	1.01(1.01-1.02)	0.999	1.11(0.05-6.89)
WC (cm)	105.98±19.19	114.64±20.98	0.03*	1.02 (1.0-1.04)	0.035*	1.04 (1.0-1.07)
BMI (kg/m2)	29.38±4.79	30.95±5.16	0.111	1.07 (0.985-1.15)		
MAP (mm/Hg)	91.77±12.66	95.41±7.54	0.045*	1.04 (1.0-1.08)	0.02*	1.883 (1.794-1.980)
Overall % predicted =98.2%						

COR: Crude odds ratio , AOR: Adjusted odds ratio

The correlation of SUA with various demographic, clinical, and laboratory findings is presented for cases with and without microalbuminuria. Among individuals without microalbuminuria, a significant positive correlation was noticed between SUA and total cholesterol (r = 0.323, P = 0.012) and waist circumference (WC) (r = 0.432, P = 0.001), while a significant negative correlation was noticed between serum uric acid and HDL (r=-0.286, p=0.027). Conversely, in those with microalbuminuria, total cholesterol also showed a strong positive correlation with serum uric acid (r = 0.440, P = 0.003), alongside triglycerides (r = 0.418, P = 0.004) and mean arterial pressure (MAP) (r = 0.376, P = 0.01). Also, age demonstrated a positive correlation with serum uric acid in the microalbuminuria group (r = 0.309, P = 0.039), indicating that older individuals may have higher levels of uric acid when microalbuminuria is present. Other variables such as BMI and serum creatinine showed weaker correlations, suggesting that they may not be clinically significant or consistent across both groups. Overall, the results emphasize the significance of monitoring SUA levels in relation to metabolic parameters, particularly in patients with microalbuminuria where significant correlations are more pronounced **(table 2)**.

Table (2): Correlation of serum uric acid with demographic, clinical and other laboratory findings among cases with and without microalbuminuria.

	Serum uric acid			
	No micro-albuminuria		Micro-albuminuria	
	R	P	r	P
Age/years	0.180	0.168	0.309	0.039*
WC (cm)	0.432	0.001*	0.096	0.531
BMI (kg/m2)	0.155	0.237	0.261	0.083
MAP (mm/Hg)	0.01	0.937	0.376	0.01*
creatinine mg/dl	0.221	0.09	0.279	0.064
eGFR	0.003	0.984	-0.117	0.442
Albumin / creatinine ratio	-0.140	0.287	0.165	0.280
HBA1C (%)	0.126	0.337	0.107	0.486
Total Cholesterol mg/dl	0.323	0.012*	0.440	0.003*
Triglycerides mg/d	0.01	0.933	0.418	0.004*
HDL mg/dl	-0.286	0.027*	0.264	0.08
LDL mg/dl	0.097	0.460	-0.196	0.197

r:Spearman correlation coefficient , *statistically significant

In Table 3, the linear regression analysis identifies WC and total cholesterol as significant predictors of SUA levels in subjects without microalbuminuria. Both predictors have statistically significant p-values (P=0.003 and P=0.001, respectively), reinforcing their relevance in this population. In contrast, HDL does not appear to significantly affect serum uric acid levels, as indicated by its negative coefficient (-0.103) and a non-significant p-value (P = 0.595). This suggests that while WC and total cholesterol are positively correlated with serum uric acid, HDL levels may not play a meaningful role in this relationship among individuals without microalbuminuria. Among cases with no microalbuminuria, the level of serum uric acid could be predicted by applying the following equation: serum uric acid =7.91+[(0.449 ×total cholesterol)+ (0.561 ×WC)] **(table 3)**.

Table (3): Linear regression for predictors of serum uric acid among no microalbuminuria group.

No microalbuminuria	β	t	P value
WC (cm)	0.561	3.05	0.003*
Total Cholesterol mg/dl	0.449	3.80	0.001*
HDL mg/dl	-0.103	-0.534	0.595
Serum uric acid =7.91+(0.449 × total cholesterol) + (0.561 × WC)			

A linear regression analysis reveals several insights concerning the predictors of SUA levels among individuals with microalbuminuria. The model shows that HDL demonstrates a significant negative correlation with SUA, as indicated by its coefficient of -0.451 and a p-value of 0.004, highlighting the importance of HDL in this context. Conversely, triglycerides emerge as a notable predictor with a coefficient of 0.251 and a p-value of 0.07, suggesting a potential positive relationship, albeit just shy of conventional significance.

Age also approaches significance with a coefficient of 0.073 and a p-value of 0.09, indicating that older age may be accompanied by higher serum uric acid levels. Other variables such as SBP, DBP), serum creatinine, MAP, and total cholesterol do not show significant associations with serum uric acid levels, as evidenced by their respective high p-values. The overall model has a p-value less than 0.001 and an R^2 of 0.325, indicating that approximately 32.5% of the variability in serum uric acid can be explained by the included predictors, underscoring the complexity of factors influencing uric acid levels in this population **(table 4).**

Table (4): Linear regression analysis for prediction of serum uric acid among microalbuminuria group.

Microalbuminuria	β	t	P value
Constant	1.56	0.78	0.214
SBP	0.01	0.85	0.331
DBP	0.03	0.78	0.482
Serum creatinine	0.22	0.12	0.845
Age/years	.073	1.689	0.09
MAP	.196	-1.317	0.195
Total Cholesterol mg/dl	.109	-.416	0.680
Triglycerides mg/dl	.251	2.452	0.07
HDL	-0.451	3.1	0.004*
F=2.44 , P<0.001* , R^2=0.325			
Serum uric acid =1.56-0.451 ×HDL			

Receiver operating characteristic (ROC) curve was performed to evaluate the diagnostic accuracy of SUA levels in predicting microalbuminuria.

The AUC for serum uric acid was 0.776, with a 95% CI of 0.681–0.871, indicating moderate predictive ability. The best cutoff point for serum uric acid to detect microalbuminuria was determined to be 5.8. Sensitivity and specificity were 84.4% and 61.7%, respectively **(table 5 and Figure 1).**

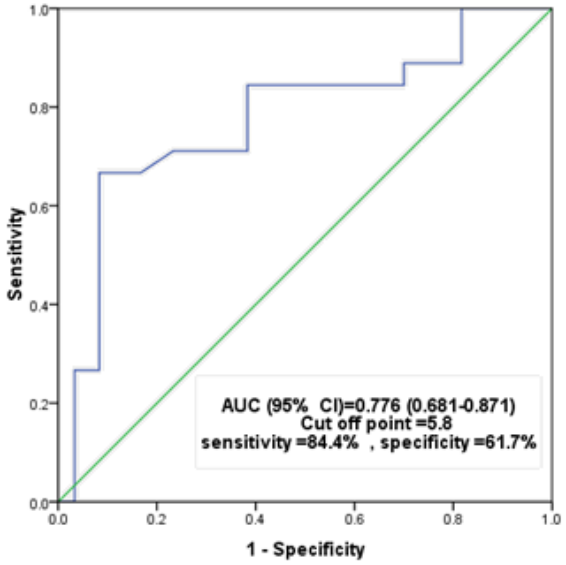

Figure (1): ROC Curve for SUA for prediction of microalbuminuria among studied T2D cases.

Table (5): ROC Curve for SUA for prediction of microalbuminuria among studied T2D cases

	Area under curve (95% CI)	P value	Best detected cut off point	Sensitivity	Specificity
Serum Uric acid	0.776 (0.681-0.871)	<0.001*	5.8	84.4%	61.7%

DISCUSSION

The present study demonstrated that several factors increase the risk of MAU, including higher serum creatinine levels, indicating reduced kidney functions, higher blood pressure, increased waist circumference, which is a marker of abdominal obesity, higher SUA levels. This agreed with others who found that BMI, WC and body fat content were significantly correlated with MAU [(14)]. Others reported that T2D cases with a high MAU concentration were more likely to have hypertension and hyperglycemia [(15)]. Others reported that MAU was significantly correlated with HbA1c and with the presence of high BP in T2D [(16)].

The present work showed that SUA levels may be a useful marker for predicting MAU, with sensitivity of 84.4% and specificity of 61.7%. According to others who have observed that high SUA levels are a predictor of MAU [(17)], frequent SUA level assessments may provide information for predicting the occurrence of MAU in T2D patients [(18)]. Both higher SUA and MAU levels were strongly related with diabetic chronic vascular problems, and monitoring both markers has a prognostic value for the occurrence of chronic vascular complications in T2D patients [(19)]. Others determined that the levels of SUA and MAU are strongly connected with nephropathy in T2D patients [(20)].

The current investigation found no significant relationship between HA1c and SUA in both MAU and non-MAU groups, although previous studies found that the development of MAU was related with inadequate glycemic management and the accumulation of advanced glycation end products [(21)].

In the non-MAU group, the current study found that greater WC values were related to higher SUA levels. In agreement with research found that SUA was positively connected with BMI [(22)], abdominal obesity increases the coexistence of high SUA, and weight loss is critical to lowering SUA levels [(23)]. SUA production may have a causative role in T2D and obesity [(24)], and greater SUA levels have been accompanied by an increased risk of obesity [(25)].

The current study found that higher TC and HDL levels were linked to higher SUA levels in non-MAU cases, while others demonstrated a positive correlation between SUA and hypertriglyceridemia [(26)].

SUA was significantly correlated with age, MAP, cholesterol TG, but not HDL in the MAU group in the current study. Others discovered that increased SUA and low HDL are substantially connected with IR, which may be utilized as an indication of IR in T2D patients [(27)], and that HDL cholesterol has an influence on raising SUA [(28)].

The present work stated that older age is related to greater SUA levels in those with MAU. This was consistent with previous research, which discovered that hyperuricemia was an independent predictor of incidence CKD in older T2D patients [(29)]. Furthermore, the SUA is significantly related with mortality in older hemodialysis patients [(30)].

The current investigation identified no significant connections between SUA and diabetes management, but preceding studies discovered that higher SUA was related with an increased risk of hypoglycemia and strengthened the link between modestly reduced eGFR and hypoglycemia in T2D [(31)]. Lowering SUA, even in

asymptomatic hyperuricemia, is helpful for reducing CKD progression [32].

We suggested equations depending on MAU status to predict SUA levels among T2D patients. Among cases with no MAU, the level of SUA could be predicted by applying the following equation; Serum uric acid =7.91+[(0.449 × total cholesterol)- (0.561 × WC)]. While, among cases with MAU, the level of serum uric acid could be predicted by applying the following equation; Serum uric acid =2.14+[(0.373 × age)+(0.651 × triglycerides)].The current study has some limitations, as small number of cases, and absence of follow up data, as well as correlation with treatment regimens.

The current study found that waist circumference and total cholesterol among those without MA could predict hyperuricemia, while in those with microalbuminuria, lower HDL could predict hyperuricemia. In agreement with a study that found that BMI could predict the potential risk of hyperuricemia [33]. Moreover, another study found that dyslipidemia could predict hyperuricemia [34]. On the other hand, others found that dyslipidemia could not predict hyperuricemia [35].

CONCLUSIONS

The SUA level may serve as a helpful marker for predicting MAU. Both SUA and MAU are correlated predictors of nephropathy in cases with T2D. However, additional validation and consideration of other clinical factors are necessary for an accurate risk assessment.

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