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RESEARCH

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The association of serum uric acid level with metabolic risk factors in patients with type 2 diabetes and their relation to eGFR status

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Abstract

Background The importance of uric acid has been increasingly appreciated because of its association with the development of diabetes mellitus and related diseases, and with the increasing incidence of diabetes, studying the impact of hyperuricemia in patients with diabetes type 2 is necessary. So we aimed to measure serum uric acid (SUA) levels in patients with diabetes type 2 and to assess the relation between the estimated glomerular filtration rate (eGFR) and the SUA in patients with type 2 diabetes (T2DM).

Subjects and methods This study is a cross-sectional conducted on 142 adult patients who attended the Outpatients Diabetes Clinic and Endocrinology Center in the Department of Internal Medicine, Assiut University Hospitals, in the period from the 1st of November 2021 up to October 2022. We measured serum uric acid level, serum creatinine, cholesterol, low- and high-density lipoproteins, triglycerides, and eGFR.

Results Overall, 142 patients were enrolled in the study; all patients had type 2 diabetes. The mean age of the participants was 61.08 ± 9.73 years. Based on SUA level, 46 (32.4%) patients had normal SUA and 96 (67.6%) patients had high SUA. Sixty-nine (48.6%) patients had normal eGFR and 73 (51.4%) patients had reduced eGFR. We found that serum uric acid had a positive significant correlation with the number of metabolic syndrome criteria, cholesterol, low-density lipoproteins, and triglycerides. Meanwhile, it had a negative significant correlation with eGFR and high-density lipoproteins.

Conclusion Serum uric acid was strongly associated with metabolic syndrome components and reduced eGFR in patients with T2DM.

Keywords Serum uric acid level, Type 2 diabetes, Metabolic syndrome

Introduction

Metabolic syndrome (MetS) is a complex disorder. It is distinguished by insulin resistance and aberrant adipose deposition and function. It includes many risk factors for cardiovascular disease (CVD), type 2 diabetes, fatty liver, and several cancers. The relationship between SUA and diabetes, as well as its consequences, has received considerable attention. Urine metabolism produces uric acid as a byproduct. High SUA levels have been linked to chronic renal illness, CVD, and hypertension [1–3].

There are several definitions for metabolic syndrome, leading to some difficulty in comparing data from studies using different criteria. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is the most widely used. ATP III criteria define metabolic syndrome as the presence of any three of the following five traits:

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i. Abdominal obesity, defined as a waist circumference ≥ 102 cm (40 in) in men and ≥ 88 cm (35 in) in females
ii. Serum triglycerides ≥ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
iii. Serum high-density lipoprotein (HDL) cholesterol < 40 mg/dL (1 mmol/L) in males and < 50 mg/dL (1.3 mmol/L) in females or drug treatment for low HDL cholesterol
iv. Blood pressure ≥ 130/85 mmHg or drug treatment for elevated blood pressure
v. Fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

Increasing SUA levels have been associated with metabolic syndrome in both healthy people and T2DM patients. In subjects with aberrant fasting glucose levels, greater levels of SUA independently predicted T2DM development. SUA levels are higher in patients with prediabetes and T2DM than in healthy controls, according to the study. All-cause mortality risk has been established to have a positive association with SUA level, whereas cardiovascular mortality has been shown to be connected with SUA level in patients with hyperglycemia (pre-diabetes and T2DM) [4, 5].

The causes of elevated blood urea and creatinine in hyperuricemia are difficult to determine. However, values of estimated GFR were slightly lower in patients with elevated uric acid levels. Serum creatinine and urea levels were associated positively with SUA levels, with a substantial association reported in patients with normal eGFR. While eGFR has been demonstrated to be inversely linked with SUA levels in patients with aberrant eGFR levels. The amount of SUA increases when urine decreases, resulting in decreased uric acid excretion. As a result, a decrease in eGFR may cause SUA levels in these patients to rise [6].

As a result of the increasing incidence of diabetes, studying the effect of hyperuricemia in patients with T2DM is important. Thus, the current study's primary objective is to assess the association of SUA with all metabolic risk factors in patients with T2DM including obesity, hyperlipidemia, and hypertension and study their relation to the eGFR.

Patients and methods

Studied participants

A cross-sectional study included 142 patients with T2DM who attended the Outpatients Diabetes Clinic, Endocrinology Center, Department of Internal Medicine, Assiut University Hospital, in the period from the 1st of November 2021 up to October 2022. This study adhered to the guidelines of Assiut University's Ethical Committee. The clinical protocol was registered in ClinicalTrials.gov with a registration number of NCT04575389. Every participant in this study provided informed consent.

Eligible criteria

Adult patients diagnosed with type 2 diabetes, of both sexes, age ranging from 35 to 80 years old, duration of diabetes from newly diagnosed patients to 20 years' duration who are attending in Outpatients Diabetes Clinic of Assiut University Hospital during the study period and accepted to participate in this research, were enrolled in the current study. The exclusion criteria were patients with diabetes type 1, those with secondary diabetes or gestational diabetes, patients taking drugs affecting uric acid levels, and those who refused to be enrolled in this study were also excluded.

Sample size estimation

This was calculated using Epi Info7. According to the results of a previous study [7], the prevalence of hyperuricemia occurred in 12.7% of patients with T2DM. Based on this percentage, confidence limits of 5%, and a confidence level of 90%, the sample needed for the study was estimated to be about 142 patients.

Methodology

For all participants, full history was taken including treatment of diabetes and hypertension to exclude drugs affecting uric acid levels, history of other complications and affection of kidney function, anthropometric assessment, and detailed systematic examination including vital signs. In addition to complete blood count (CBC), fasting plasma glucose (FBG), HbA1C, kidney function tests, the eGFR was calculated according to a new equation [8] estimated GFR = 175 × standardized Scr − 1.154 × age − 0.203 × 1.212 [if black] × 0.742 [if female], where GFR is expressed as mL/min/1.73 m^2 of body surface area and Scr is expressed in mg/dL; serum lipogram and SUA levels were also assessed.

Statistical analysis

Data were collected and analyzed by using the SPSS program (Statistical Package for the Social Science, version 22). Quantitative data with normal distribution are expressed as mean ± standard deviation (SD) and comparison was done by Student's *t* test. The correlation between SUA and other variables was determined by Pearson correlation. Nominal data are demonstrated as number (*n*) and percentage (%) and compared by the chi-square test. The accuracy of uric acid in the prediction of metabolic syndrome was determined by the receiver operator characteristics curve. The prediction of the level

of confidence was kept at 95%, and hence, the *P* value significance at level < 0.05.

Results

Baseline data

The mean age (SD) of all studied patients was 61.08 (9.73) years. Out of 142 studied patients, 54.2% of patients were males. The most frequent comorbidities included hypertension (59.2%), chronic kidney disease (51.4%), and ischemic heart disease (34.5%). Based on SUA levels, 32.4% of patients had normal SUA and 67.6% of patients had high SUA (Table 1).

Characteristics of the studied patients based on serum uric acid

The majority (53.1%) of patients with high SUA were males and the majority (69.6%) of patients with normal SUA were females ($p < 0.001$). There was a statistically significant higher frequency of hypertension, chronic kidney disease, metabolic syndrome, and reduced eGFR in hyperuricemic patients compared to patients with normal SUA.

Regarding laboratory data; there was a statistically significant increase in creatinine level, cholesterol, triglycerides (TGS), and LDL in patients with high SUA compared to those with normal SUA with *p*-values < 0.001, 0.01, 0.04, and < 0.001 respectively, while there was a significant decrease in HDL level in patients with high SUA compared to those with normal SUA with *p*-value 0.02 (Table 2).

Characteristics of the studied patients based on eGFR

Both groups of patients based on eGFR had insignificant differences as regards body mass index, age, waist circumference, and duration of diabetes ($p > 0.05$). Patients with reduced eGFR had a significantly higher frequency of hypertension (75.3% vs. 42%; *p* value < 0.001) and ischemic heart disease (47.9% vs. 20.3%; $p < 0.001$).

Also, patients with reduced eGFR had significantly higher mean SUA (8.26 ± 2.34 vs. 4.23 ± 0.87 mg/dl; $p < 0.001$) with a higher frequency of high SUA (79.5% vs. 55.1%; $p < 0.001$) and metabolic syndrome (54.8% vs. 28.9%; $p < 0.001$) in comparison to those with normal eGFR. In addition, patients with reduced eGFR had significantly higher serum creatinine (470.59 ± 177.98 vs. 111.84 ± 82.24 mmol/L; $p < 0.001$), cholesterol (212.09 ± 43.98 vs. 160.11 ± 53.11 mg/dl; $p < 0.001$),

Table 1 Baseline data of the studied patients

	***N* = 142**
Age	61.08 ± 9.73
Sex	
Male	77 (54.2%)
Female	65 (45.8%)
Body mass index (kg/m^2)	28.35 ± 5.09
Comorbidities	
Hypertension	84 (59.2%)
CKD	73 (51.4%)
IHD	49 (34.5%)
CVS	20 (14.1%)
Others	29 (20.4%)
Class based on SUA	
Normal	46 (32.4%)
High	96 (67.6%)
Class based on eGFR	
Normal	69 (48.6%)
Reduced	73 (51.4%)
Metabolic syndrome	
Yes	60 (42.3%)
No	82 (57.7%)

Data are presented as mean ± SD or number (percentage)

IHD ischemic heart disease, *CVS* cerebrovascular stroke, *CKD* chronic kidney disease, *SUA* serum uric acid, *eGFR* estimated glomerular filtration rate

Table 2 Characteristics of the studied patients based on serum uric acid

	Serum uric acid		***P* value**
	Normal (*n* = 46)	**High (*n* = 96)**	
Age (year)	58.93 ± 8.96	62.10 ± 9.97	0.06
Sex			**< 0.001**
Male	14 (30.4%)	51 (53.1%)	
Female	32 (69.6%)	45 (46.9%)	
Body mass index (kg/m^2)	28.10 ± 4.79	28.46 ± 5.25	0.69
WC (cm)	106.19 ± 13.53	106.96 ± 15.18	0.77
Duration of DM (years)	7.71 ± 4.35	8.76 ± 5.89	0.39
Comorbidities			
Hypertension	19 (41.3%)	65 (67.7%)	**< 0.001**
CKD	15 (32.6%)	58 (60.4%)	**< 0.001**
IHD	14 (30.4%)	35 (36.5%)	0.30
CVS	8 (17.4%)	12 (12.5%)	0.29
Metabolic syndrome	10 (21.7%)	50 (52%)	**< 0.001**
Reduced eGFR	15 (32.6%)	58 (60.4%)	**0.01**
Creatinine (mmol/l)	156.44 ± 83.87	363.27 ± 101.85	**< 0.001**
HbA1C (%)	8.75 ± 2.34	9.15 ± 2.73	0.19
Cholesterol (mg/dl)	157.87.22 ± 43.34	201.77 ± 54.44	**0.01**
Triglycerides (mg/dl)	99.11 ± 13.54	121.45 ± 25.25	**0.04**
HDL (mg/dl)	39.33 ± 11.11	27.01 ± 4.44	**0.02**
LDL (mg/dl)	91.22 ± 7.89	122.09 ± 24.44	**< 0.001**

Data are presented as mean ± SD or number (percentage). Significance defined by $p < 0.05$

IHD ischemic heart disease, *CVS* cerebrovascular stroke, *CKD* chronic kidney disease, *SUA* serum uric acid, *eGFR* estimated glomerular filtration rate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

triglycerides (125.10 ± 25.10 vs. 88.11 ± 16.01 mg/dl; $p < 0.001$), and low-density lipoproteins (LDL) (120.43 ± 19.87 vs. 79.10 ± 7.77 mg/dl; $p < 0.001$) and significantly lower high-density lipoproteins (HDL) (29.11 ± 4.20 vs. 43.11 ± 9.76 mg/dl; $p = 0.02$) (Table 3).

Correlations of serum uric acid with other variables among the studied participants

It was found that SUA had a significant positive correlation with the number of MetS criteria, serum creatinine, cholesterol, triglycerides, and LDL and a significant negative correlation with eGFR and HDL (Table 4).

Accuracy of UA in the prediction of metabolic syndrome

At cutoff > 6.9 mg/dl, serum UA had 54.8% overall accuracy for the prediction of metabolic syndrome in the current study with an area under the curve of 0.519 but of significant value ($p = 0.70$) (Table 5) Fig. 1.

Table 3 Characteristics of the studied patients based on eGFR

	eGFR		*P* value
	Normal ($n = 69$)	Reduced ($n = 73$)	
Age (year)	58.93 ± 8.96	62.10 ± 9.97	0.07
Sex			0.14
Male	28 (40.6%)	37 (50.7%)	
Female	41 (59.4%)	36 (49.3%)	
Body mass index (kg/m^2)	28.10 ± 4.79	28.46 ± 5.25	0.69
WC (cm)	106.96 ± 13.53	106.19 ± 15.18	0.39
Duration of DM (years)	7.71 ± 2.51	8.76 ± 4.04	0.77
Comorbidities			
Hypertension	29 (42%)	55 (75.3%)	**< 0.001**
CKD	0	73 (100%)	**< 0.001**
IHD	14 (20.3%)	35 (47.9%)	**< 0.001**
CVS	9 (13%)	11 (15.1%)	0.45
Others	11 (15.9%)	18 (24.7%)	**0.03**
Metabolic syndrome	20 (28.9%)	40 (54.8%)	**< 0.001**
Serum uric acid (mg/dl)	4.23 ± 0.87	8.26 ± 2.34	**< 0.001**
High serum uric acid	38 (55.1%)	58 (79.5%)	**< 0.001**
Creatinine (mmol/l)	111.84 ± 83.24	470.59 ± 177.98	**< 0.001**
HbA1C (%)	8.85 ± 2.62	8.91 ± 8.29	0.95
Cholesterol (mg/dl)	160.11 ± 53.11	212.09 ± 43.98	**< 0.001**
Triglycerides (mg/dl)	88.11 ± 16.01	125.10 ± 25.10	**< 0.001**
HDL (mg/dl)	43.11 ± 9.76	29.11 ± 4.20	**0.04**
LDL (mg/dl)	79.10 ± 7.77	120.43 ± 19.87	**0.01**

Data are presented as mean ± SD or number (percentage). Significance defined by $p < 0.05$

eGFR estimated glomerular filtration rate, *HbA1C* glycosylated hemoglobin, *LDL* low-density lipoproteins, *HDL* high-density lipoproteins

Table 4 Correlation of serum uric acid with other variables

	r value	*P* value
Age (year)	0.08	0.34
Body mass index (kg/m^2)	− 0.11	0.19
WC (cm)	0.13	0.36
Duration of DM (years)	0.16	0.67
Systolic blood pressure (mmHg)	0.09	0.96
Diastolic blood pressure (mmHg)	0.10	0.23
Number of MetS criteria	0.33	**< 0.001**
eGFR	− 0.40	**< 0.001**
Creatinine (mmol/l)	0.30	**< 0.001**
HbA1C (%)	0.04	0.56
Cholesterol (mg/dl)	0.31	**< 0.001**
Triglycerides (mg/dl)	0.28	**0.04**
HDL (mg/dl)	− 0.29	**0.01**
LDL (mg/dl)	0.32	**< 0.001**

Data expressed as *r* value (strength of correlation) and *P* value (significance of correlation and considered significant if < 0.05)

WC waist circumference, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *HbA1C* glycosylated hemoglobin, *LDL* low-density lipoproteins, *HDL* high-density lipoproteins, *MetS* metabolic syndrome

Discussion

Various CVD risk factors, including diabetes, hypertension, obesity, hyperlipidemia, the MetS, and subclinical atherosclerosis, are strongly associated with SUA levels. SUA has been linked to MetS and atherosclerosis in both the general and T2DM populations. Uric acid has also been associated with endothelial dysfunction because it inhibits the production of nitric oxide and increases inflammation. Uric acid is the byproduct of purine breakdown. Elevated uric acid induces a number of pathophysiological changes through inflammation, oxidative stress, and activation of the renin-aldosterone-angiotensin system (RAAS), promoting the onset and progression of many disorders, including metabolic syndrome [9].

Table 5 Accuracy of uric acid in prediction of metabolic syndrome

	Indices
Sensitivity	67%
Specificity	46%
Positive predictive value	48%
Negative predictive value	66%
Accuracy	54.8%
Cutoff point	6.9
Area under the curve	0.519
P value	0.70

P value was significant if < 0.05

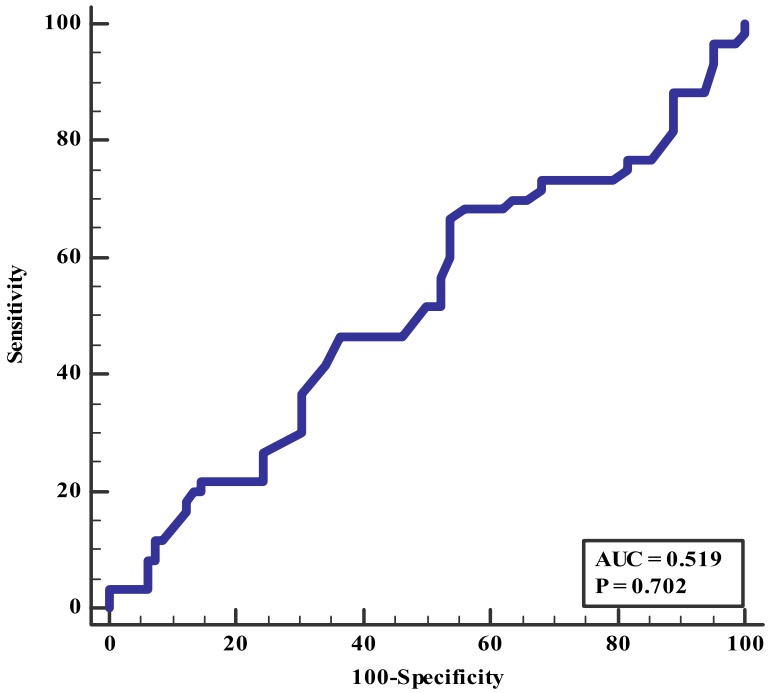

Fig. 1 Receiver operator characteristic curve for prediction of metabolic syndrome in the current study

Uric acid's effects on CVD incidence are most likely due to these factors. A population-based cross-sectional study found that SUA is related to MetS and is an independent risk factor for carotid atherosclerosis in T2DM patients [10, 11].

The current study was aimed to evaluate the relation of SUA levels with metabolic risk factors in type 2 diabetic patients and their relation to eGFR. We studied 142 patients with T2DM, and it was observed that 32.4% of patients had normal SUA and 67.6% of patients had high SUA. 48.6% of patients had normal eGFR and 51.4% of patients had reduced eGFR. A total of 42.3% of patients had MetS. In agreement with these findings, a previous study reported that high SUA occurred in 43% of patients with T2DM [12]. In contrast, other studies disagreed with the current study and reported a lower frequency of high SUA among patients with T2DM. Ma and colleagues found that out of 198 patients with T2DM, 15.6% of patients had high SUA [11]. Also, 26.3% with T2DM had high SUA [13]. This difference may be contributed to a small sample size, different studied populations, and selection bias.

Also, we found that patients with high SUA levels had a significantly higher frequency of HTN and CKD. The current study agreed with Fennon and colleagues who observed that the frequency of hypertension, older age, smoking, higher body mass index, and poor glycemic control were higher among patients with hyperuricemia [13].

In our study, we found that the majority (53.1%) of patients with high SUA were males and the majority (69.6%) of patients with normal SUA were females with significant difference ($p < 0.001$). This finding was consistent with a previous study [13]. In contrast to this finding, Rafiullah et al. reported that high SUA was found in 13% of studied males and 18.5% of studied females [6].

Also, the current study stated that patients with high SUA had a significantly higher frequency of MetS and reduced eGFR. Similarly, Van Kleef and colleagues demonstrated that SUA has a strong association with MetS and hypertension in T2DM patients [14]. In addition, previous studies contribute the effect of uric acid in the development of atherosclerosis to other cardiovascular risk factors, such as obesity, MetS, hypertension, and chronic renal disease [14, 15].

Additionally, previous studies showed that serum TG, total cholesterol, and LDL-C levels have a positive correlation with SUA whereas serum HDL-C level is negatively correlated with SUA [16, 17]. A study of obese adults found that SUA does not appear to be associated with cardiovascular events, T2DM, hypertension, or dyslipidemia [18]. Therefore, further research on the association between SUA and components of MetS is needed.

Luis-Rodriguez et al. indicated that the uric acid-induced inflammatory pathway may be crucial in the pathophysiology of MetS. According to a recent study, higher SUA is associated with higher CRP and inflammatory cytokine levels, suggesting that SUA may contribute to subclinical inflammation [19].

Bonakdaran et al. evaluated 1978 patients with T2DM; the authors reported that the prevalence of MetS was 65.5%, and hyperuricemia was 12.7%. The occurrence of MetS was significantly higher in patients with higher SUA. In addition, SUA showed a significantly positive correlation with triglycerides, non-HDL cholesterol, and cholesterol level, while having a negative correlation with FBG, HbA1C, and HDL-cholesterol [7].

This study also found that patients with reduced eGFR had significantly higher mean SUA with a higher frequency of high SUA and MetS in comparison to those with normal eGFR. Also, we reported a significantly negative correlation between SUA and eGFR.

These findings were supported by Rafiullah et al. study which showed that SUA had a positive significant correlation with serum creatinine and a negative correlation with GFR. The authors added that in individuals with abnormal eGFR (less than 90 mL/min/1.73 m^2), increased incidence of CVD associated significantly with SUA [6]. Since chronic kidney illness itself raises SUA levels and hyperuricemia is associated with a decline in kidney function, it might be challenging to determine what is causing the elevated blood urea and creatinine levels [20, 21].

We stated that SUA at cutoff > 6.9 mg/dl, serum UA had 54.8% overall accuracy for the prediction of metabolic syndrome. Guqiao Nie et al. showed the cutoff value for UA 314.5 µmol/l [20]. Another study confirmed the ability of the baseline SUA level to predict the development of MetS was 0.65 (95% CI, 0.62–0.67) [21].

The main limitation of the current study was the small sample size and being conducted in a single center. We did not perform long-term duration of follow-up to assess the effect of SUA on the prognosis of those patients. Lastly, we performed only laboratory evaluation and we did not assess the correlation of SUA with radiological parameters as carotid intima thickness, and we did not take a control group to compare variables.

Conclusion

We could conclude that SUA had a significantly positive correlation with serum creatinine, cholesterol, triglycerides, and LDL and a significantly negative correlation with eGFR and HDL SUA sensitivity and specificity and *P* value in predicting metabolic syndrome are not of great value statistically and this could be explained by the small sample size in our study.

Abbreviations

SUA	Serum uric acid
eGFR	Estimated glomerular filtration rate
T2DM	Type 2 diabetes
MetS	Metabolic syndrome
CVD	Cardiovascular disease CVD
CBC	Complete blood count
FBG	Fasting plasma glucose
TGS	Triglycerides
LDL	Low-density lipoproteins
HDL	High-density lipoproteins

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Authors' contributions

RAM performed the data collection, performed the data analysis, and drafted the manuscript. SAA brought the concept of the study, participated in the data analysis, and revised the manuscript for important intellectual content. ETM performed the data collection and participated in the data analysis. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The ethical approval was granted by the ethical review institution board of Faculty of Medicine Assiut University (Approval no: 17101299). Consent was taken from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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