Hyperuricemia and Albuminuria in Patients With Type 2 Diabetes Mellitus

Shokoofeh Bonakdaran,[1] Maryam Hami,[2] Mohammad Taghi Shakeri[3]

[1]Division of Endocrinology, Department of Internal Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Division of Nephrology, Department of Internal Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3]Department of Community Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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Introduction. Hyperuricemia is an independent risk factor for kidney dysfunction in diabetic patients. On the other hand, albuminuria is considered as the proxy of early stages of diabetic nephropathy. We investigated the correlation between hyperuricemia and albuminuria in patients with diabetes mellitus.
Materials and Methods. In a cross-sectional study of 1275 patients (555 men and 720 women) with type 2 diabetes mellitus, serum uric acid and urinary albumin-creatinine ratio were determined. Other metabolic parameters including lipid profile, hemoglobin A1c, glomerular filtration rate, body mass index, blood pressure, blood glucose were assessed, as well.
Results. The mean age of the patients was 52.45 ± 10.11 years old. Serum uric acid levels for normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 4.49 ± 1.22 mg/dL, 4.84 ± 1.52 mg/dL, and 6.15 ± 1.68 mg/dL, respectively. Among patients with clinical metabolic syndrome, 233 (27.5%) were in the forth upper quartile of uric acid level (> 5.3 mg/dL), but in diabetic patients without this syndrome, only 80 (18.7%) were in this group. There was a significant relationship between hyperuricemia and serum triglyceride, fasting blood glucose, hemoglobin A1c, glomerular filtration rate, and serum creatinine levels ($P < .001$). No significant correlation was found between hyperuricemia and cholesterol levels, age, duration of diabetes mellitus, and body mass index. Serum uric acid level correlated positively with urinary albumin-creatinine ratio ($P = .04$).
Conclusions. We showed that higher serum uric acid concentrations were associated with a greater probability of albuminuria in patients with type 2 diabetes mellitus.

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INTRODUCTION

Uric acid is an end product of purine metabolism, and approximately, one-third of it is degraded in the gut, and two-thirds is excreted by the kidneys.[1-3] Although decreased kidney function can be associated by hyperuricemia,[4,5] based on some epidemiological studies, hyperuricemia is an independent risk factor for kidney dysfunction in patients with diabetes mellitus (DM).[5] It is suggested that increased serum level of uric acid is an injurious factor for kidneys,[2] as it is shown that hyperuricemia-induced endothelial dysfunction, glomerular hypertension, and renal hypertrophy decrease renal perfusion via stimulation of the afferent arteriolar vascular smooth muscle cell proliferation.[6-10] In some studies on diabetic patients, it has been reported that hyperuricemia is associated with kidney damage independent of hypertension.[2] On the other hand, higher levels of serum insulin may decrease uric acid clearance by

the kidneys.[11] As a rule, hyperinsulinemia is the basis of type 2 DM pathophysiology.[11] Therefore, diabetic patients are more prone to uric acid injury. We know albumiuria is the main marker of diabetic nephropathy in this group of patients, independent of hypertension.[2] We studied the relationship between hyperuricemia and albuminuria in our diabetic patients.

MATERIALS AND METHODS

A total 1275 patients (555 men and 720 women) with type 2 DM from the outpatient DM clinics at the Ghaem Hospital of Mashad University of Medial Sciences were included in this study. Type 2 DM was diagnosed based on the World Health Organization criteria. None of the patients had diabetic ketoacidosis at the onset of disease. All of them were being treated by antidiabetic oral agents or insulin at the time of the study. For those receiving insulin treatment, insulin therapy had not been started in the first year of diagnosis of DM. Patients on treatment with uric acid lowering agents, or diuretics, and patients with acute illness, fever, urinary tract infection, a glomerular filtration rate (GFR) less than 60 mL/min were excluded.

Patients enrolled in the study were recommended not to have heavy exercise 24 hours before examination. Urine sample consisted of midstream urine spot test. Urinary albumin-creatinine ratio (ACR) was calculated by dividing the urinary albumin concentration in microgram by the urinary creatinine concentration in milligram. An ACR of 30.0 µg/mg or lower was considered as "normal," an ACR between 30 µg/mg and 299 µg/mg was considered as "microalbuminuria." Very high ratios (ACR ≥ 300 µg/mg) were defined as "overt albuminuria." Urine albumin was measured in a morning sample by an immunoturbidometry assay (Parsazmon, Karaj, Iran). Urine creatinine was measured by an enzymatic colorimetric assay (Parsazmon, Karaj, Iran).

Blood samples were collected after 10 hours fasting. They were evaluated for fasting blood glucose (FBG), uric acid, cholesterol, triglyceride, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), albumin, and creatinine levels. Fasting blood glucose was measured by the glucose oxidase method (Human, Freital, Germany). Uric acid, total cholesterol, triglyceride, and HDL levels were measured by an enzymatic method (Parsazmon, Karaj, Iran). The LDLC was calculated according to Friedwall formula in participants with a triglyceride level less than 300 mg/dL. The GFR was calculated using the Cockroft-Gault formula.

For all enrolled patients a questionnaire was filled out about age, gender, duration of DM, hypertension, and metabolic syndrome. Metabolic syndrome in these patients was assessed according to the Adult Treatment Panel III criteria. They were asked about type of antihypertensive drugs. Blood pressure was measured on the right arm after 30 minute resting and in sitting position with a mercury sphygmomanometer. Body height and weight were measured. Body mass index (BMI) was calculated by dividing body weight in kilograms by the squared body height in meters.

Data were shown as mean ± standard deviation or percentage. The correlation between serum uric acid concentrations and age, sex, duration of DM, BMI, GFR, creatinine, FBG, hemoglobin A1c (Hb A1c), cholesterol, triglyceride, and urinary ACR were examined by the Pearson correlation analysis. Uric acid concentrations were categorized into approximate quantiles. The resulting 4 categories were less than 3.5 mg/dL, 3.5 mg/dL to 4.3 mg/dL, 4.4 mg/dL to 5.3 mg/dL, and greater than 5.3 mg/dL. The Chi-square test was used to evaluate differences in distribution of covariates such as albuminuria, GFR, metabolic syndrome, hypertension, gender, FBG, and Hb A1c with each quartiles of uric acid level. The Kruskal Wallis test was used to evaluate relations between normoalbuminuria, microalbuminuria, and macroalbuminuria with uric acid levels, as the data had a skewed distribution. *P* values less than .05 were considered significant.

RESULTS

Clinical characteristics of 1276 patients with type 2 DM enrolled in this study are shown in Table 1. The mean serum uric acid concentration was 4.56 ± 1.33 mg/dL, which was significantly higher in men than in women (4.89 ± 1.36 mg/dL versus 4.30 ± 1.24 mg/dL, respectively; $P < .001$). Of the men, 89 (16.0%) were in the first quantile and 175 (31.5%) in the fourth quantile, while 231 women (32.1%) were in the first quantile and 137 (19.0%) were in the fourth quantile ($P < .001$). Relationships between

Table 1. Characteristics of Patients with Diabetes Mellitus*

Parameter	Value
Age	52.45 ± 10.11
Gender	
Male	555
Female	720
Dialysis duration, y	7.70 ± 6.21
Body mass index, kg/m^2	28.24 ± 4.42
Hemoglobin, g/dL	14.21 ± 1.54
MCV, fL	83.57 ± 6.01
Blood urea nitrogen, mg/dL	16.58 ± 8.04
Serum creatinine, mg/dL	0.95 ± 0.32
Serum cholesterol, mg/dL	208.97 ± 45.50
Serum triglyceride, mg/dL	202.02 ± 130.10
Serum LDLC	127.50 ± 33.07
Serum HDLC	43.05 ± 9.82
Urine ACR, mg/g	32.52 ± 54.96
Fasting blood glucose	191.32 ± 66.25
Hemoglobin A1c	8.68 ± 1.96
GFR, mL/min/1.73 m^2	102.68 ± 35.52
Serum uric acid, mg/dL	5.55 ± 1.47

*Values are mean ± standard deviations except for gender.

serum uric acid concentrations and other variables are shown in Table 2. There were significant correlations between serum uric acid concentration and serum triglyceride, FBG, Hb A1c, GFR, and serum creatinine ($P < .001$). Serum uric acid level correlated positively with urine ACR ($P = .04$). Serum uric acid levels for normoalbuminuric, microalbuminuric, and macroalbuminuric patients were 4.49 ± 1.22 mg/dL, 4.84 ± 1.52 mg/dL, and 6.15 ± 1.68 mg/dL, respectively ($P = .004$). There were significant relationships between serum uric acid concentrations and hypertension and metabolic syndrome ($P < .001$; Table 3).

Two hundred sixty-seven patients (21.0%) were on angiotensin-convertor enzyme inhibitors or angiotesin receptor blockers as antihypertensive treatment, who had higher levels of uric acid (35.2% compared to 21.5% of the remaining patients in the fourth quantile; $P < .001$).

Table 2. Correlation Between Serum Uric Acid Concentration and Other Variables*

Parameter	Uric Acid	
	R	*P*
Age	0.069	.10
Dialysis duration	-0.058	.15
Body mass index	0.037	.25
Total cholesterol	0.222	.04
Triglyceride	0.245	< .001
LDLC	-0.015	.39
HDLC	0.008	.44
Fasting blood glucose	0.215	< .001
Hemoglobin A1c	-0.182	< .001
Glomerular filtration rate	-0.165	.001
Serum creatinine	0.266	< .001
Urine ACR	0.097	.036
Blood urea nitrogen	0.163	.001

*LDLC indicates low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; and ACR, albumin-creatinine ratio.

DISCUSSION

We evaluated relationships between serum uric acid concentration and degree of urinary albumin excretion in patients with type 2 DM. Siu and colleagues reported lowering serum uric acid level in patients with hyperuricemia was associated with regression of kidney disease.[12] Since appearance of albuminuria is the first sign of kidney damage and onset of diabetic nephropathy in patients with DM,[11] the association between ACR and hyperuricemia confirmed the effect of hyperuricemia on diabetic nephropathy. In our study, a positive correlation was found between these two parameters.

Although it is true that elevated serum uric acid concentration can be a consequence of kidney dysfunction,[4] we found that the association between serum uric acid concentration and degree of urinary albumin excretion was significant even after adjustment for estimated GFR. On the other hand, our study demonstrated that serum uric acid concentration was significantly higher in patients

Table 3. Relationship Between Serum Uric Acid Concentration and Hypertension and Metabolic Syndrome

Parameter	Uric Acid				*P*
	First Quantile	Second Quantile	Third Quantile	Fourth Quantile	
Hypertension					
Yes	129 (20.9)	130 (21.1)	160 (26.0)	197 (32.0)	
No	191 (29.0)	189 (28.7)	163 (24.7)	116 (17.6)	< .001
Metabolic syndrome					
Yes	179 (21.1)	201 (23.7)	235 (27.7)	233 (27.5)	
No	141 (32.9)	119 (27.8)	88 (20.6)	80 (18.7)	< .001

with metabolic syndrome. Nakagawa and associates reported that uric acid has a causal role in metabolic syndrome.[13] Also, Bo and coworkers reported that hyperuricemia is associated with insulin resistance and onset or progression of nephropathy in type 2 diabetic patients.[11] Metabolic syndrome components include hypertension, hypertriglyceridemia, hyperinsulinemia, insulin resistance, and obesity.[5,13] In our patients, there were significant correlations between hyperuricemia and serum concentration of triglyceride, FBG, and HbA1c. We found a positive association between hyperuricemia and hypertension. It must be noticed that in our study, hypertension was defined as a blood pressure of at least 140/90 mm Hg or use of antihypertensive medication. Similar results were shown in some studies such as the study by Johnson and colleagues who reported hyperuricemia to be a risk factor for hypertension.[3] In spite of the significant relationship between hyperuricemia and metabolic syndrome, such a link was not found between serum uric acid concentration and BMI. Lohsoonthorn and colleagues found different results showing positive correlation between BMI, metabolic syndrome, and serum uric acid.[14] Although it has been reported that some drugs, such as losartan, can reduce serum uric acid concentration by their uricosuric effect, serum concentration of uric acid in our study was higher in patients that were on angiotensin-converting enzyme inhibitors. This may be due to their higher blood pressure.

CONCLUSIONS

We showed that high serum uric acid concentration was associated with albuminuria in patients with type 2 DM. As hyperuricemia is a common finding in this group of patients, and its treatment is easy and available, early diagnosis and treatment may be helpful to prevent or decrease the rate of development of overt kidney disease in this population of patients.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Maryam Hami, MD
Department of Nephrology, Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: +98 511 765 9556
E-mail: hamim@mums.ac.ir

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