Association between serum uric acid, urinary albumin excretion, and glycated hemoglobin in Type 2 diabetic patient

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ABSTRACT

Background: Diabetes mellitus (DM) is a chronic disease characterized by insulin deficiency or peripheral resistance resulting in hyperglycemia. Poor glycemic control leads to diabetic complications. Hyperuricemia has been reported with increased risk of renal insufficiency. The aim of this study was to evaluate the relationship between serum uric acid concentration, degree of urinary albumin excretion (UAE) and glycated hemoglobin (HbA1c) in Type 2 DM (T2DM) patients. **Materials and Methods:** Serum uric acid concentrations, urine microalbumin, and HbA1c were measured in fifty T2DM patients. We then evaluated relationship between uric acid concentrations, degree of UAE and glycemic control as well as other confounding variables. **Results:** Serum uric acid concentration correlated positively with UAE ($r = 0.323$, $P < 0.05$), age ($r = 0.337$, $P < 0.05$), age at onset ($r = 0.341$, $P < 0.05$), and duration of DM ($r = 0.312$, $P < 0.05$). Multiple regression analysis demonstrated that serum uric acid concentration ($\beta = 0.293$, $P < 0.0001$), duration of DM ($\beta = 0.261$, $P < 0.0001$), HbA1c ($\beta = 0.173$, $P < 0.005$), and systolic blood pressure ($\beta = 0.268$, $P < 0.005$) were independent determinants of UAE. **Conclusions:** Serum uric acid concentration is associated with microalbuminuria and HbA1c in T2DM patients.

Key words: Glycated hemoglobin, microalbumin, Type 2 diabetes mellitus, uric acid

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease characterized by insulin deficiency or its peripheral resistance resulting in hyperglycemia and nonenzymatic glycation of protein.[1] Although poor glycemic control has been associated with cardiovascular disease (CVD), nephropathy and retinopathy, CVD is the primary cause of mortality and morbidity in Type 2 DM (T2DM) patients; and several risk factors, including smoking, hypertension, and dyslipidemia, have been shown to accelerate the progression cardiovascular events.[2] Furthermore, elevated urinary albumin excretion (UAE) is associated with increased risk of CVD.[3]

Elevated serum uric acid concentration has been reported in patient with CVD.[4,5] Some investigators have suggested that uric acid plays a causal role in the development of CVD,[6] whereas others have concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, or dyslipidemia.[7] In addition, hyperuricemia is also an independent risk factor for renal dysfunction in a general population,[8] in patients with hypertension,[9] and in patients with diabetes.[10]

Although some study has previously shown the association between hyperuricemia and microalbuminuria in hypertensive patients.[11] No previous reports have examined a linear association between serum uric acid concentration, microalbuminuria as well as age, age at onset, duration

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of DM, blood pressure (BP), body mass index (BMI), and glycated hemoglobin (HbA1c) in T2DM patients.

MATERIALS AND METHODS

This cross-sectional study was carried out in the Department of Biochemistry with collaboration of Department of Internal Medicine, Universal College of Medical Sciences, Bhairahawa, Nepal. After the approval from Institutional Review Committee, a total of fifty T2DM patients were recruited for the study. Informed consent was obtained from all participants. Patients were excluded if they were taking any medications that might affect serum uric acid concentrations (e.g. uric acid lowering agents or diuretics). Patients with advanced renal dysfunction (serum creatinine level >2.0 mg/dL) or urinary tract infection were also excluded.

DM was diagnosed according to the WHO criteria.[12] Nephropathy was graded as follows: Normoalbuminuria, UAE <30 mg/L; microalbuminuria, 30–300 mg/L; or macroalbuminuria, more than 300 mg/L. Serum uric acid concentrations were measured by enzymatic method (uricase-peroxidase). The HbA1c was measured using the principle of dry chemistry. Similarly, UAE was measured with an immunoturbidimetric assay.

We then evaluated the relationship of uric acid concentrations, the degree of UAE as well as to HbA1c, age, age at onset, duration of DM, BP, BMI, current treatment of diabetes, smoking, and drinking habit.

Statistical analysis

Means and frequencies of potential confounding variables were calculated. All continuous variables are presented as the mean ± standard deviation unpaired *t*-test or analyses of variance were conducted to assess statistical significance of differences between groups using Statistical Package for the Social Sciences (SPSS-16, International Business Machine Corp, SPSS, New York, USA). The relationships between uric acid concentrations, UAE, and other variables were examined by Pearson correlation analyses and multiple regression analysis was used to find the independent determinants of UAE. $P < 0.05$ was considered statistically significant.

RESULTS

General characteristics of fifty T2DM patients enrolled in this study are shown in Tables 1 and 2. Mean serum uric acid concentration was 6.75 ± 1.36 mg/dL. Most of them was normoalbuminuric 72% ($n = 36$) and had good glycemic control 76% ($n = 38$). The frequency of hyperuricemia in T2DM patients was 30% ($n = 15$).

When we compared different confounding and biochemical variables between male ($n = 29$) and female ($n = 21$), there were no significant differences ($P > 0.05$) of these variables

Table 1: General characteristics of Type 2 diabetic mellitus patients

Variables	Frequency (%)
Total number (*n*)	50 (100)
Sex (male/female)	29 (58)/21 (42)
Smoking habit (none/past/current)	27 (54)/23 (46)/0 (0)
Alcohol intake (none/past/current)	28 (56)/20 (40)/2 (4)
Dietary habit (vegetarian/nonvegetarian)	5 (10)/45 (90)
Current treatment (diet/OHA[†]/insulin)	0 (0)/20 (40)/30 (60)
Glycemic control (good/poor)	12 (24)/38 (76)
Nephropathy (normo/micro/macroalbuminuria)	36 (72)/14 (28)/0 (0)

[†]OHA – Oral hypoglycemic agent

Table 2: General characteristics of biochemical variables of Type 2 diabetic mellitus patients (*n*=50)

	Mean±SD
Age (year)	58.94±13.80
Age of onset (year)	49.50±7.94
Duration of diabetes (year)	9.26±6.48
BMI (kg/m²)	23.11±3.28
Systolic blood pressure (mmHg)	137.60±28.10
Diastolic blood pressure (mmHg)	84.80±15.01
Uric acid (mg/dL)	6.75±1.36
HbA1c (%)	8.12±2.14

BMI – Body mass index; SD – Standard deviation; HbA1c – Glycated hemoglobin

Table 3: General characteristics of biochemical variables in male (*n*=29) and female (*n*=21)

	Male	Female	*P*
Age (year)	58.96±14.21	58.90±13.56	0.988
Age of onset (year)	49.58±8.79	49.47±6.80	0.962
Duration of diabetes (year)	9.37±6.40	9.09±6.73	0.880
BMI (kg/m²)	24.16±3.34	21.65±2.61	0.006
Systolic blood pressure (mmHg)	137.93±28.45	137.14±28.30	0.923
Diastolic blood pressure (mmHg)	84.82±15.49	84.76±14.70	0.988
Uric acid (mg/dL)	7.06±1.38	6.32±1.24	0.060
HbA1c (%)	8.39±2.33	7.74±1.82	0.294

Values are presented as mean±SD. SD – Standard deviation; BMI – Body mass index; HbA1c – Glycated hemoglobin

in both the sexes except BMI ($P < 0.05$) as shown in Table 3. This shows the matching of the most of these variables in both sexes.

Serum uric acid concentration did not differ between patients treated with and without insulin (6.99 ± 1.49 vs. 6.39 ± 1.07 mg/dL, $P = 0.130$). In addition, serum uric acid concentration did not differ between patients with and without alcohol intake (6.50 ± 1.33 vs. 6.96 ± 1.37 vs. 8.15 ± 0.49 mg/dL, $P = 0.173$), smoking habit (6.69 ± 1.41 vs. 6.82 ± 1.32 mg/dL, $P = 0.749$), and also in vegetarian and nonvegetarian (6.16 ± 1.30 vs. 6.82 ± 1.36 mg/dL, $P = 0.309$) although high values were found in the latter group in every cases. Serum uric acid concentration was higher in patients with microalbuminuria (7.54 ± 1.39 mg/dL) than in patients with normoalbuminuria (6.44 ± 1.23 mg/dL, $P = 0.009$). In addition, serum uric acid concentration was higher ($P = 0.002$) in

patients with hypertension (7.26 ± 1.48 mg/dL), than in patients without (6.10 ± 0.82 mg/dL), and also no significant differences (P = 0.858) in the serum uric acid concentration were noted between the patients with good glycemic control (6.69 ± 1.12 mg/dL) and poor glycemic control (6.77 ± 1.44 mg/dL) [Table 4].

Serum uric acid concentration correlated positively with age (r = 0.337, P < 0.05), age at onset (r = 0.341, P < 0.05), duration of DM (r = 0.312, P < 0.05), and UAE (r = 0.323, P < 0.05). No significant correlations were found between serum uric acid concentration and BMI, HbA1c, BP [Table 5].

Multiple regression analysis demonstrated that serum uric acid concentration (β = 0.293, P < 0.0001), duration of DM (β = 0.261, P < 0.0001), HbA1c (β = 0.173, P < 0.005), and systolic BP (β = 0.268, P < 0.005) were independent determinants of UAE [Table 6].

DISCUSSION

In this study, the average serum uric acid and HbA1c concentrations were (6.75 ± 1.36 mg/dL) and (8.12 ± 2.14 g%), respectively. We found lower serum uric acid concentration in none smokers than in past smokers. Serum uric acid concentrations were higher in current alcoholic patients than in the past alcoholic than in none alcoholic. The association between serum uric acid concentration, degree of UAE and HbA1c in T2DM patient is a new finding in several regards. Several studies had shown that serum uric acid concentration is associated with abnormal UAE in both individuals with and without diabetes.[10] Fukui M *et al*.[13] reported that hyperuricemia is associated with the insulin-resistant syndrome and with early onset or increased progression to overt nephropathy in patients with T2DM. Serum, uric acid concentration, was higher in patients treated with insulin than in patients treated with oral hypoglycemic agent. No correlation was found between serum uric acid concentration and BP in this study; however, serum uric acid concentration was higher (P = 0.002) in patients with hypertension, (BP ≥ 140/90 mmHg or use of antihypertensive medication), than in normotensive patients. Positive correlation was found between serum uric acid concentration and UAE. Multiple regression analysis also demonstrated that serum uric acid concentration was an independent determinant of UAE. This study revealed that age, age at onset, duration of diabetes and microalbumin is correlated with serum uric acid.

Duration of DM and hypertension are important factors in the development of albuminuria.[14-16] Similarly age, diabetes duration, glycemic control, BP, and metabolic syndrome are all associated with albuminuria and decline of glomerular filtration rate.[17-19]

Both elevated serum uric acid concentration and increased UAE rate may be manifestation of a common underlying pathogenesis of insulin resistance. Hyperinsulinemia

Table 4: Comparison of serum uric acid concentration in between groups of different confounding variables

	Uric acid level (mg/dL)	P
Current treatment		
OHA	6.39±1.07	0.130
Insulin	6.99±1.49	
Smoking habit		
None	6.69±1.41	0.749
Past	6.82±1.32	
Alcohol intake		
None	6.50±1.33	0.173
Past	6.96±1.37	
Current	8.15±0.49	
Dietary habit		
Vegetarian	6.16±1.30	0.309
Nonvegetarian	6.82±1.36	
Urinary albumin excretion		
Normo	6.44±1.23	0.009
Micro	7.54±1.39	
Blood pressure		
<140/90	6.10±0.82	0.002
>140/90	7.26±1.48	
Glycemic control (%)		
Good (≤6.5)	6.69±1.12	0.858
Poor (>6.5)	6.77±1.44	

Values are presented as mean±SD. SD – Standard deviation; OHA – Oral hypoglycemic agent

Table 5: Correlation between serum uric acid concentration and other variables (*n*=50)

	r	P
Age	0.337	0.017
Age at onset	0.341	0.015
Duration of diabetes	0.312	0.027
BMI	0.026	0.859
HbA1c	0.093	0.522
Systolic blood pressure	0.104	0.474
Diastolic blood pressure	0.093	0.522
Urinary albumin excretion	0.323	0.022

BMI – Body mass index; HbA1c – Glycated hemoglobin

Table 6: Independent determinants of urinary albumin excretion (*n*=50)

	β	P
Duration of diabetes	0.261	0.0001
HbA1c	0.173	0.005
Systolic blood pressure	0.268	0.005
Uric acid	0.293	0.0001

HbA1c – Glycated hemoglobin

resulting from insulin resistance can decrease the renal excretion, increase the renal reabsorption, and increase the production of uric acid.[20] The main pathophysiologic mechanism by which uric acid causes renal dysfunction involves, an inhibition of endothelial nitric oxide bioavailability,[21] activation of rennin-angiotensin system,[22] and direct actions on endothelial cells and vascular smooth muscle cells.[23] A recent study demonstrated that

lowering uric acid in individuals with hyperuricemia was associated with slower progression of renal disease,[24] which suggests a pathogenic role of uric acid in the renal abnormalities and implies a possible efficacy to lower the degree of UAE in diabetic patients by lowering serum uric acid concentration. It is true that elevated serum uric acid concentration can be a consequence of renal dysfunction.[25]

Hyperuricemia is a risk factor for CVD since several pro-atherogenic properties have been attributed to uric acid, which can lead to activation of endothelial cells,[26] platelet activation, and increased platelet adhesiveness.[27] Uric acid also promotes vascular smooth muscle proliferation and up-regulates the expression of platelet-derived growth factor[28] and monocytes chemoattractant protein 1.[29]

Recently, uric acid was found to have a causal role in the metabolic syndrome that was induced experimentally by fructose.[30] Lowering uric acid in fructose-fed rats ameliorates components of metabolic syndrome, including hypertension, hypertriglyceridemia, hyperinsulinemia, and body weight.[30] In general, we have paid little attention to uric acid as a factor for progression of diabetic nephropathy. However, hyperuricemia is common among diabetic patients; and it is easy to lower serum uric acid concentration with lifestyle modifications and medications.

CONCLUSIONS

Serum, uric acid concentration, is associated with microalbuminuria and HbA1c in a patient with T2DM. Screening for microalbuminuria, to prevent renal impairment and measuring HbA1c level on a regular basis for good glycemic control are important in diabetic patients. Further study in nondiabetic subjects with large sample size may be of clinical significance to clarify the role of uric acid in the development and progression of diabetic nephropathy as well as atherosclerosis.

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Conflicts of interest
There are no conflicts of interest.

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