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Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus

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Abstract

Hyperuricemia has been reported to be associated with increased risk of renal insufficiency as well as cardiovascular events. The aim of this study was to evaluate the relationships between serum uric acid concentration and degree of urinary albumin excretion as well as markers of subclinical atherosclerosis in men with type 2 diabetes mellitus. Serum uric acid concentrations were measured in 343 men with type 2 diabetes mellitus. We then evaluated relationships of serum uric acid concentrations to degree of urinary albumin excretion as well as to major cardiovascular risk factors, including age, blood pressure, serum lipid concentration, and glycemic control (hemoglobin A_{1c}). The relationships between serum uric acid concentration and pulse wave velocity or ankle-brachial index (n = 236) and between serum uric acid concentration and carotid intima-media thickness or plaque score (n = 125) were investigated additionally in a subgroup of patients. Serum uric acid concentration correlated positively with logarithm of urinary albumin excretion ($r = 0.302$, $P < .0001$). Positive correlation was found between serum uric acid concentration and intima-media thickness ($r = 0.233$, $P = .0087$), whereas inverse correlation was found between serum uric acid concentration and ankle-brachial index ($r = -0.150$, $P = .0207$). Multiple regression analysis demonstrated that serum uric acid concentration ($\beta = .281$, $P < .0001$), duration of diabetes ($\beta = .253$, $P < .0001$), hemoglobin A_{1c} ($\beta = .166$, $P = .0034$), serum triglyceride concentration ($\beta = .125$, $P = .0472$), and systolic blood pressure ($\beta = .275$, $P = .0013$) were independent determinants of logarithm of urinary albumin excretion. In conclusion, serum uric acid concentration is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus.

1. Introduction

Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in patients with type 2 diabetes mellitus; and several risk factors, including smoking, hypertension, and dyslipidemia, have been shown to accelerate the progression of CVD [1,2]. Male sex is also an independent risk factor for CVD [3]. Furthermore, elevated urinary albumin excretion has been reported to be associated with increased risk of CVD [4].

Uric acid is a product of purine metabolism; and elevated serum uric acid concentration can result from increased generation, caused by ingesting a purine-rich diet or alcohol, or decreased elimination. Several large epidemiologic studies have reported that elevated serum uric acid concentration is associated with CVD [5-7]. Some investigators have suggested that uric acid plays a causal role in the development of CVD [8], whereas others have concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, or dyslipidemia [9]. Hyperuricemia has been reported to be associated with increased risk of renal insufficiency as well as cardiovascular events. Epidemiologic studies have found that hyperuricemia is an independent risk factor for renal dysfunction in a general population [10], in patients with hypertension [11], and in patients with diabetes [12].

Although several studies have previously shown the association between hyperuricemia and microalbuminuria in hypertensive patients [13], there are few studies concerning the association between hyperuricemia and

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microalbuminuria in patients with type 2 diabetes mellitus [12]. To the best of our knowledge, no previous reports have examined a linear association between serum uric acid concentration and degree of urinary albumin excretion as well as markers of subclinical atherosclerosis in men with type 2 diabetes mellitus. Afterward, we evaluated the relationships between serum uric acid concentration and degree of urinary albumin excretion as well as markers of subclinical atherosclerosis such as carotid intima-media thickness (IMT), plaque score, pulse wave velocity (PWV), or ankle-brachial index (ABI) in men with type 2 diabetes mellitus.

2. Subjects and methods

2.1. Subjects

Serum uric acid concentrations were measured in 343 consecutive men with type 2 diabetes mellitus recruited from the outpatient clinic at the Kyoto Prefectural University of Medicine. We then evaluated relationships of serum uric acid concentrations to degree of urinary albumin excretion as well as to major cardiovascular risk factors—including age, blood pressure, serum lipid concentration, and glycemic control (hemoglobin A_{1c} [HbA_{1c}])—body mass index (BMI), severity of diabetic retinopathy, severity of diabetic nephropathy, current treatment of diabetes, and presence of CVD. The relationships between serum uric acid concentration and PWV or ABI (n = 236) and between serum uric acid concentration and IMT or plaque score (n = 125) were investigated additionally in a subgroup of patients.

Serum uric acid concentrations (reference range, 2.9-7.6 mg/dL) were measured by enzymatic method (uricase-peroxidase). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were assessed using standard enzymatic methods. The HbA_{1c} was assayed using high-performance liquid chromatography. Urinary albumin and creatinine (Cr) concentrations were determined in an early morning spot urine. Urinary albumin excretion was measured with an immunoturbidimetric assay. A mean value for urinary albumin excretion was determined from 3 urine collections.

Type 2 diabetes mellitus was diagnosed according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [14]. Retinopathy was graded as follows: no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), or proliferative diabetic retinopathy (PDR). Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion less than 30 mg/g Cr; microalbuminuria, 30 to 300 mg/g Cr; or macroalbuminuria, more than 300 mg/g Cr. Mean values for biochemical parameters obtained during the previous year in patients with type 2 diabetes mellitus were used for statistical analysis. *Cardiovascular disease* was defined as the presence of previous myocardial infarction or cerebral infarction based on the clinical history or physical examination.

Patients were excluded if they were taking any medications that might affect serum uric acid concentrations (eg, uric acid–lowering agents or diuretics). Patients with advanced renal dysfunction (serum Cr >2.0 mg/dL) or urinary tract infection were also excluded. Approval for the study was obtained from the local Research Ethics Committee, and informed consent was obtained from all participants.

2.2. Measurement of PWV and ABI

Brachial-ankle (ba) PWV and ABI were measured using a Colin Waveform Analyzer (form PWV/ABI; Colin Medical Technology, Komaki, Japan), which simultaneously measures pulse volumes in the brachial and posterior tibial arteries using an oscillometric method together with bilateral arm and ankle blood pressure. Both PWV and ABI were measured after allowing the patient to rest in the supine position for at least 5 minutes. For measuring baPWV, pulse volume waveforms of the brachial and tibial arteries were recorded. Details of the method have been described elsewhere [15]. After bilateral determination of baPWV, the higher value was taken as representative for each subject. The ABI was calculated bilaterally as the ratio of systolic pressure in the ankle to systolic pressure in the arm, with the lower value considered representative for each subject.

2.3. Ultrasonographic measurement of carotid IMT and plaque score

B-mode ultrasonographic imaging of the carotid artery was performed as described previously [16] using a high-resolution, real-time ultrasonograph with a 7.5-MHz transducer. Examination and image analysis were performed by trained sonographers kept unaware of other data. The IMT was measured in the far wall of the vessel as the distance from the leading edge of the lumen-intima interface to the leading edge of the intima-adventitia interface. The average measurement was taken as the mean IMT. We defined a *plaque* as a visually distinct area with an IMT greater than that of neighboring sites. The plaque score was determined as the sum of the maximum thicknesses of all plaques measured in millimeters on the near and far walls of the vessels.

2.4. Statistical analysis

Means and frequencies of potential confounding variables were calculated. Unpaired Student *t* tests or analyses of variance were conducted to assess statistical significance of differences between groups using Stat View software (version 5.0; SAS Institute, Cary, NC). Because urinary albumin excretion showed a skewed distribution, logarithmic transformation was carried out before performing correlation and regression analysis. The relationships between serum uric acid concentrations and logarithm of urinary albumin excretion, PWV, ABI, IMT, or plaque score as well as the relationships between serum uric acid concentrations and age, glycemic control, or other variables were examined by Pearson correlation analyses. The relationship between

serum uric acid concentrations and logarithm of urinary albumin excretion was also examined by adjustment for estimated glomerular filtration rate. To examine the effects of various factors on logarithm of urinary albumin excretion, the following factors, which might affect albuminuria, were considered as independent variables for multiple regression analysis: serum uric acid concentrations, age, duration of diabetes, BMI, HbA_{1c}, systolic blood pressure, diastolic blood pressure, serum total cholesterol, triglyceride, HDL cholesterol concentrations, and smoking status. All continuous variables are presented as the mean ± SD. A P value < .05 was considered statistically significant.

3. Results

Clinical characteristics of the 343 men with type 2 diabetes mellitus enrolled in this study are shown in Table 1. Mean serum uric acid concentration was 5.7 ± 1.3 mg/dL. Relationships between serum uric acid concentrations and other variables are shown in Table 2. No significant correlations were found between serum uric acid concentration and age, BMI, HbA_{1c}, blood pressure, or serum lipid concentration. Serum uric acid concentration correlated positively with logarithm of urinary albumin excretion (r = 0.302, P < .0001). A positive association between serum uric acid concentration and degree of urinary albumin excretion was also significant even after adjustment for estimated glomerular filtration rate (P = .0298). Positive correlation was found between serum uric acid concentration and IMT (r = 0.233, P = .0087), whereas inverse correlation was found between serum uric acid concentration and ABI (r = −0.150, P = .0207). No significant correlations were found between serum uric acid concentrations and PWV (r = −0.015, P = .8291) or plaque score (r = 0.139, P = .1303). Multiple regression analysis demonstrated that serum uric acid concentration (β = .281, P < .0001), duration of diabetes (β = .253, P < .0001), HbA_{1c} (β = .166, P = .0034), serum triglyceride concentration (β = .125, P = .0472), and systolic blood pressure (β = .275, P = .0013) were independent determinants of logarithm of urinary albumin excretion (Table 3).

Table 1
Clinical characteristics of patients with diabetes

	Mean ± SD
n	343
Age (y)	63.2 ± 11.2
Age at onset (y)	49.7 ± 12.5
Duration of diabetes (y)	13.4 ± 11.6
BMI (kg/m^2)	23.3 ± 3.5
HbA_{1c} (%)	7.2 ± 1.2
Systolic blood pressure (mm Hg)	134 ± 15
Diastolic blood pressure (mm Hg)	78 ± 10
Uric acid (mg/dL)	5.7 ± 1.3
Total cholesterol (mg/dL)	193 ± 33
Triglyceride (mg/dL)	138 ± 96
HDL cholesterol (mg/dL)	51 ± 14
Retinopathy (NDR/SDR/PDR)	246/45/52
Nephropathy (normo-/micro-/macroalbuminuria)	198/106/39
Current treatment (diet/OHA/insulin)	39/224/80
Smoking (none/past/current)	78/161/104
CVD (−/+)	285/58

OHA indicates oral hypoglycemic agent.

Table 2
Correlation between serum uric acid concentration and other variables

	r	P
Age	0.017	.7555
Age at onset	−0.011	.8486
Duration of diabetes	−0.010	.8554
BMI	0.064	.2479
HbA_{1c}	−0.071	.1882
Systolic blood pressure	−0.052	.3440
Diastolic blood pressure	−0.095	.0830
Total cholesterol	−0.010	.8605
Triglyceride	0.064	.2416
HDL cholesterol	−0.053	.3313
PWV	−0.015	.8291
ABI	−0.150	.0207
IMT	0.233	.0087
Plaque score	0.139	.1303
Logarithm of urinary albumin excretion	0.302	<.0001

Serum uric acid concentration did not differ between patients treated with and without insulin (5.7 ± 1.3 vs 5.7 ± 1.4 mg/dL, P = .9493). In addition, serum uric acid concentration did not differ between patients with and without CVD (5.8 ± 1.4 vs 5.6 ± 1.3 mg/dL, P = .4399). Serum uric acid concentration was higher in patients with SDR (6.1 ± 1.4 mg/dL) than in patients with NDR (5.5 ± 1.2 mg/dL, P = .0111), and serum uric acid concentration was also higher in patients with PDR (6.0 ± 1.4 mg/dL) than in patients with NDR (P = .0317). Serum uric acid concentration was higher in patients with macroalbuminuria (6.6 ± 1.6 mg/dL) than in patients with microalbuminuria (5.8 ± 1.4 mg/dL, P = .0011) or normoalbuminuria (5.4 ± 1.2 mg/dL, P < .0001), and serum uric acid concentration was also higher in patients with microalbuminuria than in patients with normoalbuminuria (P = .0086).

4. Discussion

We evaluated relationships between serum uric acid concentration and degree of urinary albumin excretion as well as markers of subclinical atherosclerosis such as PWV,

Table 3
Independent determinants of logarithm of urinary albumin excretion

	β	P
Duration of diabetes	.253	<.0001
HbA_{1c}	.166	.0034
Triglyceride	.125	.0472
Systolic blood pressure	.275	.0013
Uric acid	.281	<.0001

R^2 = 0.252 (P < .0001).

ABI, IMT, or plaque score in men with type 2 diabetes mellitus. Positive correlation was found between serum uric acid concentration and logarithm of urinary albumin excretion. Multiple regression analysis also demonstrated that serum uric acid concentration was an independent determinant of logarithm of urinary albumin excretion. Serum uric acid concentration correlated positively with IMT and correlated inversely with ABI.

Epidemiologic studies have found that hyperuricemia is an independent risk factor for renal dysfunction in a general population [10], in patients with hypertension [11], and in patients with diabetes [12]. It has been shown that hyperuricemia induced endothelial dysfunction [17], glomerular hypertension [18], and renal hypertrophy [19]. The main pathophysiologic mechanism by which uric acid causes renal dysfunction involves an inhibition of endothelial nitric oxide bioavailability [17], activation of the rennin angiotensin system [20], and direct actions on endothelial cells and vascular smooth muscle cells [21]. A recent prospective study demonstrated that lowering uric acid in individuals with hyperuricemia was associated with slower progression of renal disease [22], which suggests a pathogenic role of uric acid in the renal abnormalities and implies a possible efficacy to lower the degree of urinary albumin excretion 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 [23]. However, a positive association between serum uric acid concentration and degree of urinary albumin excretion was also significant even after exclusion of patients with macroalbuminuria (data not shown) or even after adjustment for estimated glomerular filtration rate.

Several proatherogenic properties have been attributed to uric acid including activation of endothelial cells [24], platelet activation, and increased platelet adhesiveness [25]. Uric acid promotes vascular smooth muscle proliferation and up-regulates the expression of platelet-derived growth factor [26] and monocyte chemoattractant protein 1 [27]. Uric acid has also been shown to stimulate production of interleukin 1β, interleukin 6, tumor necrosis factor α by human mononuclear cells, and C-reactive protein by cultured human vascular cells [28]. Our study demonstrated that serum uric acid concentrations are not significantly different between patients with or without CVD. However, serum uric acid concentrations were significantly correlated with ultrasonographically evaluated carotid IMT and ABI, which are early preclinical markers of atherosclerosis. In other words, serum uric acid concentration correlated with the severity of atherosclerosis, regardless of the presence of clinical manifestations.

Both elevated serum uric acid concentration and increased urinary albumin excretion rate may be manifestations of a common underlying pathogenesis of insulin resistance. Hyperinsulinemia resulting from insulin resistance can decrease the renal excretion, increase the renal reabsorption, and increase the production of uric acid [29]. Microalbuminuria is a component of the metabolic syndrome characterized by insulin resistance [1]. 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]. Bo et al [31] reported that hyperuricemia is associated with the insulin-resistant syndrome and with early onset or increased progression to overt nephropathy in patients with type 2 diabetes mellitus.

Some drugs, including losartan, cilnidipine, fenofibrate, and atorvastatin [32], can reduce serum uric acid concentration. However, serum uric acid concentration correlated positively with logarithm of urinary albumin excretion (r = 0.306, $P < .0001$) and with IMT ($r = 0.206$, $P = .0276$) even after exclusion of patients treated with those drugs. No correlation was found between serum uric acid concentration and blood pressure in this study; however, serum uric acid concentration was higher in patients with *hypertension* (5.8 ± 1.4 mg/dL), defined as blood pressure of at least 140/90 mm Hg or use of antihypertensive medication, than in patients without (5.4 ± 1.1 mg/dL, $P = .0118$).

In general, we have paid little attention to uric acid as a factor for progression of diabetic nephropathy as well as atherosclerosis. However, hyperuricemia is common among diabetic patients; and it is easy to lower serum uric acid concentration with lifestyle modifications and medications. Therefore, it is of clinical significance to clarify the role of uric acid in the development and progression of diabetic nephropathy as well as atherosclerosis. Further examination is needed to clarify the validity to extrapolate the relationship between serum uric acid concentration and degree of urinary albumin excretion in nondiabetic subjects. Although several studies have previously shown the association between hyperuricemia and microalbuminuria in hypertensive patients [13], there are few studies concerning the association between hyperuricemia and microalbuminuria in patients with type 2 diabetes mellitus [12]. To the best of our knowledge, the present study is the first to report on a linear association between serum uric acid concentration and degree of urinary albumin excretion in men with type 2 diabetes mellitus.

Limitations of our study include a cross-sectional design and effects of treatment of diabetes, hypertension, and dyslipidemia on the results. However, ongoing treatments necessarily complicate analyses of patients with type 2 diabetes mellitus. Although we are unable to determine whether hyperuricemia has a causative effect, these findings suggest that hyperuricemia combined with diabetes might be associated with an increased risk of progression of diabetic nephropathy and atherosclerosis. Large prospective trials and intervention studies are needed to better assess the effects of uric acid on diabetic nephropathy and atherosclerosis in men with type 2 diabetes mellitus. In

conclusion, serum uric acid concentration is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus.

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