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Association between uric acid level and incidence of albuminuria in patients with type 2 diabetes mellitus

A 4.5-year cohort study

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Abstract

Using animal models and molecular biology researches, hyperuricemia has been shown to instruct renal arteriolopathy, arterial hypertension, and microvascular injury involving the renin-angiotensin system and resulting in renal function impairment. Nevertheless, the association between uric acid levels and the development of albuminuria has been under-investigated in patients with type 2 diabetes mellitus. Patients with type 2 diabetes and regular outpatient visits were recruited from the Puli Branch of the Taichung Veterans General Hospital in Taiwan since January 2014. Demographics, lifestyle features, and medical history were gathered by well-trained interviewers. All participants underwent comprehensive physical examinations, including a biochemical assay of venous blood specimens and urine samples after an 8-hour overnight fast. Participants were followed until June 2018. The primary outcome was the albuminuria incidence. Univariable and multivariable Cox regression analysis were employed to explore the relation between uric acid and incident albuminuria. Uric acid cutoffs for incident albuminuria were determined with the receiver operator characteristic curve. We included 247 qualified subjects (mean age: 64.78 years old [standard deviation = 11.29 years]; 138 [55.87%] men). During a 4.5-year follow-up duration, 20 subjects with incident albuminuria were recognized. Serum uric acid was significantly associated with an increased risk of incident albuminuria (adjusted hazard ratio = 2.39; 95% confidence interval: 1.53–3.75; $P < .001$) with potential confounders adjustment. The uric acid cutoff point was 6.9 mg/dL (area under the curve 0.708, sensitivity 60.0%, specificity 84.58%) for incident albuminuria. Serum uric acid was associated with incident albuminuria among patients with type 2 diabetes.

Abbreviations: AHR = adjusted hazard ratio, BMI = body mass index, CI = confidence interval, HbA1c = hemoglobin A1c, ROC = receiver operator characteristic.

Keywords: albuminuria, cohort study, risk factors, type 2 diabetes mellitus, uric acid

1. Introduction

Diabetic nephropathy is a cardinal source of chronic renal failure, which is a major health concern that results in an increased risk of cardiovascular disease and death worldwide.[1,2] The indicator to identify subjects at risk for glomerular filtration rate declining is albuminuria.[3] Previous studies have confirmed that risk factors associated with diabetic nephropathy included genetic factors, hyperglycemia, hyperlipidemia, hypertension, and smoking.[4]

Recently, several researches suggested that increased uric acid levels may damage renal function. Elevation of uric acid levels not only stimulates the renin-angiotensin system but also reduces endothelial nitric oxide synthetase,[5] leading to damage of

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endothelial and vascular smooth muscle cells, finally cause microvascular disease.[6–8] Animal researches have revealed that elevated serum uric acid levels may induce endothelial dysfunction and promote the kidney function worsening.[9,10]

In humans, recent epidemiologic research has also discovered that elevated uric acid levels were related to chronic kidney disease in community residents and those with type 2 diabetes.[11–14] In east Asia, 2 community-based cohort studies with healthy middle-aged or older participants reported that, after a follow-up duration of 4 years, hyperuricemia at more than 7.0 mg/dL of serum uric acid put people at a significantly higher risk of an insufficient glomerular filtration rate or microalbuminuria with confounding adjustment.[11,12] Similar outcomes were found in individuals with type 2 diabetes regarding the relation between serum uric acid and risk of albuminuria or decreased glomerular filtration rate.[13–16] Overall estimations of the relationship between serum uric acid concentration and poor kidney function were consistently moderate to high.[13–16] However, these researches of the relation between uric acid and diabetic nephropathy had diverse outcome definitions,[13–16] and potential confounders were not fully considered.[14–16] In addition, the cutoff level of uric acid related with an increased risk of albuminuria has not yet been well investigated. Consequently, we intended to investigate the association between uric acid level and the incidence of albuminuria in patients with type 2 diabetes and to estimate the uric acid cutoff levels.

2. Materials and methods

2.1. Setting and participants

This was a cohort study accomplished at the Puli Branch of Taichung Veterans General Hospital, which is a local community hospital in the Puli Township of Nantou County in Taiwan. Since January 2014, patients with type 2 diabetes having regular outpatient visits at the Division of Endocrinology and Metabolism were included in the study. All patients signed written informed consent forms. Patients with disabilities, those who were bedridden, and those who were unable to answer the questionnaire were excluded from the study. Those with albuminuria, which was defined as a urine albumin–creatinine ratio of more than 300 mg/g on a spot sample, were excluded. Participants were under regular outpatient follow-up every 3 months until June 2018. Laboratory data were collected every 3 months. This research was permitted by the ethics committee of the Taichung Veterans General Hospital.

2.2. General assessment

Demographic and anthropometric measurements were obtained during the outpatient visits. Blood pressure, body height, and weight were measured using standardized processes and recorded by interviewers. The definitions of overweight (body mass index [BMI] $\geq$24 kg/m^2) and obesity (BMI $\geq$27 kg/m^2) were recommended by the Taiwan Health Promotion Administration, Ministry of Health and Welfare.[17] Information regarding baseline characteristics, such as education levels, marital status, and smoking, betel nut chewing, and drinking habits were gathered by standardized face-to-face interviews. Since January 2014, all the study subjects underwent a comprehensive health examination, including blood pressure measurement and the collection of serum and urine specimens for a biochemical assay after fasting overnight for 8 hours at first visit. Measurements of fasting glucose, hemoglobin A1c (HbA1c), serum uric acid, creatinine, lipid profiles, and albumin–creatinine ratio in spot urine samples were obtained. Devices used for measuring the values of plasma glucose, serum uric acid, creatinine, and all lipid profiles were based on an enzymatic analysis (SIEMENS Dimension EXL 200, Germany). The HbA1c value was measured by high-performance liquid chromatography, using the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8. The urine albumin was measured by the Roche Cobas Integra, C501.

2.3. Outcome covariates

Microalbuminuria is defined as a urine albumin–creatinine ratio of 30 to 300 mg/g in a spot sample. The outcome of interest in this analysis was albuminuria, which is identified as a urine albumin–creatinine ratio of more than 300 mg/g on a spot sample.[18]

2.4. Statistical analysis

First, a univariable Cox regression analysis was used to access the baseline demographics of the study participants. A multivariable Cox regression analysis was used to explore the association of serum uric acid levels with incident albuminuria. Adjusted hazard ratios (AHR) with 95% confidence intervals (CI) were stated to demonstrate the intensity and direction of these associations. Uric acid cutoffs for the incidence of albuminuria were calculated with the receiver operator characteristic (ROC) curve analysis. The sensitivity, specificity, positive and negative predictive values, area under the curve, and Youden index were calculated at all uric acid cutoff values. Statistical analysis was performed by the SAS software version 9.4 (SAS Institute, Cary, NC). The statistical significance level (alpha level) was considered as 0.05.

3. Results

A total of 279 patients with diabetes were interviewed since January 2014. Individuals with albuminuria (n = 32) were excluded. Finally, the data of 247 patients with diabetes were analyzed in this research. The mean (standard deviation) age of the study subjects was 64.74 (11.29) years, and 138 (55.87%) participants were men. Participants were followed until June 2018. During the 3.32±1.23 years of follow-up, 20 individuals had new-onset albuminuria.

Table 1 reveals the results of the univariable Cox regression model. Those with higher uric acid levels had an increased risk of incident albuminuria (HR, 1.73; 95% CI 1.29–2.32, $P < .001$). Another variate associated with the development of albuminuria was never married (HR: 3.81, 95% CI: 1.09–13.41, $P = .04$).

A multivariable Cox proportional hazard model was used to investigate the factors associated with incident albuminuria (Table 2). After adjusting for age, sex, BMI, cigarette smoking, drinking habit, systolic blood pressure, HbA1c levels, and lipid profiles, serum uric acid was significantly associated with increased risks of incident albuminuria (AHR, 2.39, 95% CI 1.53–3.75, $P < .001$). Other factors significantly associated with the development of albuminuria were triglyceride levels (AHR, 1.01, 95% CI 1.00–1.01, $P = .03$), high-density lipoprotein levels (AHR, 1.07, 95% CI 1.01–1.13, $P = .02$), and HbA1c (AHR, 1.43, 95% CI 1.10–1.86, $P = .01$). Increased total cholesterol level was significantly associated with a decreased risk of incident albuminuria (AHR, 0.97, 95% CI 0.94–1.00, $P = .047$).

Table 1

Characteristics and results of univariate Cox regression analysis of the study population (n = 247; 20 albuminuria cases).

Demographics	Total participants (% in column)	Participants with albuminuria (% in row)	Hazard ratio	(95% CI)	*P*-value
Uric acid (mg/dL)	5.54 ± 1.45	6.56 ± 1.54	1.73	(1.29–2.32)	<.001
Age (yr)	64.78 ± 11.29	65.40 ± 13.18	1.01	(0.97–1.05)	.56
Gender					
Female	109 (44.13%)	7 (6.42%)	Ref		
Male	138 (55.87%)	13 (9.42%)	1.59	(0.63–4.01)	.32
Marriage status					
Married/cohabiting	194 (79.18%)	16 (8.25%)	Ref		
Never married	13 (5.31%)	3 (23.08%)	3.81	(1.09–13.41)	.04
Widowed/divorced/separated	38 (15.51%)	1 (2.63%)	0.35	(0.05–2.63)	.31
Education					
Low (elementary or below)	81 (37.67%)	6 (7.41%)	Ref		
Moderate (junior/senior high)	98 (45.58%)	8 (8.16%)	1.28	(0.44–3.73)	.65
High (college or above)	36 (16.74%)	1 (2.78%)	0.39	(0.05–3.28)	.39
Body mass index (kg/m^2)					
<24	77 (31.56%)	9 (11.69%)	Ref		
24 ≤ BMI < 27	88 (36.07%)	5 (5.68%)	0.45	(0.15–1.36)	.16
≥27	79 (32.38%)	5 (6.33%)	0.44	(0.15–1.33)	.15
Smoking status					
Never	172 (69.64%)	14 (8.14%)	Ref		
Current	58 (23.48%)	5 (8.62%)	0.93	(0.33–2.58)	.89
Former	17 (6.88%)	1 (5.88%)	0.90	(0.12–6.87)	.92
Drinking					
Never	190 (76.92%)	16 (8.42%)	Ref		
Current	45 (18.22%)	3 (6.67%)	0.86	(0.25–2.94)	.80
Former	12 (4.86%)	1 (8.33%)	0.90	(0.12–6.85)	.92
Betel nut					
Never	219 (88.66%)	17 (7.76%)	Ref		
Current	16 (6.48%)	2 (12.50%)	1.69	(0.39–7.37)	.49
Former	12 (4.86%)	1 (8.33%)	1.61	(0.21–12.35)	.65
Blood pressure (mm Hg)					
Systolic blood pressure	133.91 ± 16.20	134.80 ± 15.77	1.01	(0.98–1.04)	.40
Diastolic blood pressure	77.57 ± 10.85	76.45 ± 11.06	0.99	(0.96–1.04)	.72
HbA1c (%)	7.58 ± 1.95	7.84 ± 1.80	1.15	(0.92–1.44)	.23
Lipid profiles (mg/dL)					
Total cholesterol	171.91 ± 35.97	168.35 ± 32.32	1.00	(0.99–1.01)	.98
Triglyceride	163.69 ± 134.50	221.95 ± 187.65	1.002	(1.000–1.004)	.08
High-density lipoprotein	44.00 ± 14.31	44.40 ± 20.28	1.01	(0.98–1.05)	.45
Low-density lipoprotein	106.98 ± 30.84	100.50 ± 29.59	0.997	(0.98–1.01)	.68

BMI = body mass index, CI = confidence interval.

Figure 1 shows the ROC curve with the sensitivity and specificity of the equation to detect the incidence of albuminuria. The uric acid cutoff point was 6.9 mg/dL (area under the curve 0.708, sensitivity 60.0%, and specificity 84.58%) for the incidence of albuminuria.

4. Discussion

The current study revealed that an elevated serum uric acid level is associated with an increased risk of incident albuminuria in patients with type 2 diabetes. In addition to albuminuria, several novel markers were investigated as markers of diabetic nephropathy, including urinary level of cyclophilin A, periostin, and netrin-1.[19,20] This study used albuminuria for detection of diabetic nephropathy. Previous research in animal models has suggested potential biological mechanisms for how hyperuricemia causes chronic renal dysfunction. Uric acid may impair nitric oxide production to induce endothelial cell dysfunction.[10] Moreover, hyperuricemia has been shown to trigger the renin-angiotensin system and damage vascular smooth muscle cells,[6–8] leading to the development of renal arteriolopathy, arterial hypertension, and then microvascular injury.[5,9,21] Another probable mechanism is the elevation of serum uric acid inducing inflammatory cytokine production, including tumor necrosis factor-α, C-reactive protein, interleukin-1β, and interleukin-6.[22]

Previous studies in different settings with various study designs have reported similar findings in individuals with type 2 diabetes.[13–16] In both cross-sectional and cohort researches, uric acid was reported to be related to diabetic nephropathy. In cross-sectional studies, serum uric level was related with microalbuminuria in Korean, Taiwanese, and Chinese patients with type 2 diabetes.[13,23,24] A cohort study in Japan reported that diabetic patients with increased serum uric acid levels had increased risk of deterioration of diabetic nephropathy defined as shifting from microalbuminuria to albuminuria. However, this study also showed that uric acid was not associated with the risk of shifting from normoalbuminuria to microalbuminuria or

Table 2

Multivariate Cox regression analysis of the incidence of albuminuria.

Demographics	Adjusted hazard ratio	(95% CI)	*P*-value
Uric acid (mg/dL)	2.39	(1.53–3.75)	<.001
Age (yr)	1.00	(0.94–1.06)	.95
Gender			
Female	Ref		
Male	0.83	(0.19–3.65)	.80
Smoking status			
Never	Ref		
Current	1.53	(0.36–6.58)	.57
Former	1.38	(0.12–16.57)	.80
Drinking			
Never	Ref		
Current	1.23	(0.21–6.89)	.83
Former	1.01	(0.08–13.17)	.99
Body mass index (kg/m^2)			
<24	Ref		
24 ≤ BMI < 27	0.47	(0.11–2.01)	.31
≥27	0.31	(0.07–1.36)	.12
Systolic blood pressure (mm Hg)	1.01	(0.98–1.05)	.56
HbA1c (%)	1.43	(1.10–1.86)	.01
Total cholesterol (mg/dL)	0.97	(0.94–1.00)	.047
Triglyceride (mg/dL)	1.01	(1.00–1.01)	.03
High-density lipoprotein (mg/dL)	1.07	(1.01–1.13)	.02
Low-density lipoprotein (mg/dL)	1.03	(1.00–1.06)	.11

BMI = body mass index, CI = confidence interval.

albuminuria.[25] This may be because the follow-up period of the study was only 2 years, which was too short for the occurrence of diabetic nephropathy. A cohort study with a 4-year follow-up duration in Italy revealed that serum uric acid was significantly associated with risk of incident albuminuria only if the estimated glomerular filtration rate <60 mL/min per 1.73 m^2.[16] Another cohort study with a follow-up duration of 5 years reported that uric acid was related to risk of incident diabetic nephropathy defined as an estimated glomerular filtration rate less than 60 mL/min per 1.73 m^2 or an albumin–creatinine ratio greater 30 mg/mmol.[15] However, most of the study subjects were white, and race has some impact on the risk of kidney function progression.[26]

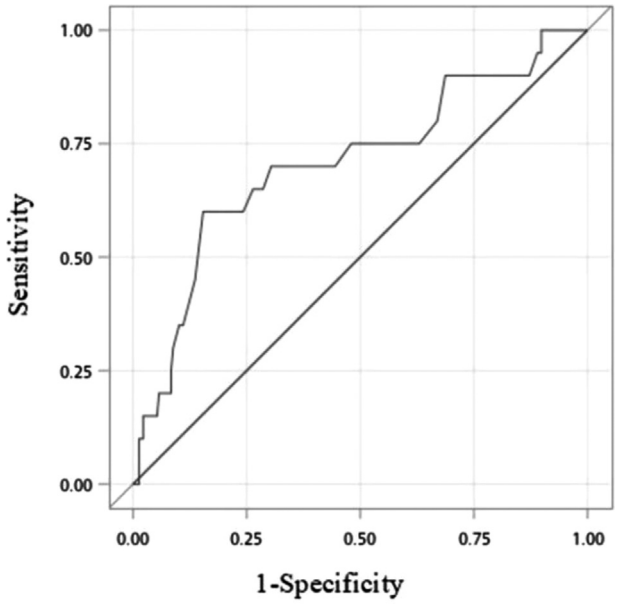

Figure 1. Receiver operating characteristic curve showing the sensitivity and specificity of the equation to detect the incidence of albuminuria.

As far as we know, few researches have reported the uric acid cutoff for an increased risk of impaired renal function. A cohort study in Italy reported that hyperuricemia is associated with incident diabetic nephropathy, and the definition of hyperuricemia was a serum uric acid level greater 7.0 mg/dL in men and greater than 6.6 mg/dL in women.[15] These cutoff values were those generally used to define hyperuricemia in their medical laboratory. The current study showed that the uric acid level cutoff for an increased risk of incident diabetic nephropathy was 6.9 mg/dL, which was calculated by the area under the ROC curve.

Previous studies had also reported that reducing the serum uric acid concentration can reduce kidney damage and recover renal function in diabetic mice, which suggested that the nephropathy caused by a high serum uric acid concentration might be reversible.[27] Momeni et al[28] thus conducted a double-blinded randomized controlled trial recruiting patients with diabetic nephropathy, reporting that the serum uric acid concentration decreased after allopurinol management for 4 months, and the 24-hour urine protein excretion also decreased. Another single-blind, randomized, controlled trial showed that allopurinol therapy for 2 years enhanced the estimated glomerular filtration rate and decreased cardiovascular risks.[29,30] However, to date, despite some preliminary pilot studies of randomized clinical trials of allopurinol,[28–30] there is still limited evidence regarding pharmacological intervention to reduce serum uric acid levels and thus prevent the deterioration of renal function.

One strength of the current study is the highly detailed demographic information of the participants collected by well-trained interviewers, including socioeconomic status, smoking habits, and alcohol consumption, which were proven to be potential confounders. Laboratory tests, including fasting blood glucose, HbA1c, uric acid, creatinine, lipid profiles, and urine albumin–creatinine ratio were achieved by standardized processes at the hospital with high accuracy. Moreover, there were few missing values in our dataset. The study was a cohort survey with longitudinal follow-up for 4.5 years, resulting in adequate relationships for causal inference. However, there are also some limitations to be borne in mind. The study was performed at the outpatient department of the Puli Branch of Taichung Veterans Hospital, which is a local hospital. Individuals with disabilities, those who were bedridden, and those who were unable to answer the questionnaire were excluded from the study, which might limit its generalizability. Moreover, recall bias on the self-reported questionnaire might be another concern. Only uric acid levels at baseline were collected, and the change over time was not measured; thus, the influence of uric acid on the incidence of diabetic nephropathy over time was not estimated. Medications, including anti-diabetic drugs, hypertensive drugs, and urate-lowering drugs were not included in the study because we believe that the effect of medication could be estimated by the laboratory data, including HbA1c, uric level, lipid profiles, and blood pressure measurements. However, only baseline laboratory data was analyzed and the change during the follow-up period was not available, which is a major limitation of the study.

5. Conclusions

Integrated treatment policies for diabetic nephropathy consist of intensive glycemic control, appropriate blood pressure management, smoking cessation, and regular screening of the urine albumin–creatinine ratio. Our study revealed an association between increased uric acid levels and the development of albuminuria in patients with type 2 diabetes. Further research with an observational or interventional study design with an adequate sample size and better generalizability will enhance the understanding of causal relation of uric acid in renal function deterioration in patients with diabetes. Physicians should also pay attention to the serum uric levels of patients with type 2 diabetes because it was demonstrated that hyperuricemia is associated with albuminuria. Early intervention to decrease serum uric levels may be benefit for preserving renal function in patients with diabetes.

Author contributions

YFY and YYC contributed considerably to study design and conception. LJC and PWK explored and explained the data and composed the initial version of the manuscript. YFY and YJL obtained the data and conceived of the study project, contributed in the statistics analysis. All authors seriously edited the document and gave final approval.

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