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# High-normal serum uric acid predicts the development of chronic kidney disease in patients with type 2 diabetes mellitus and preserved kidney function ☆

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ABSTRACT

*Aims:* We evaluated whether high-normal serum uric acid (SUA) levels can predict the development of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus and preserved kidney function at baseline.

*Methods:* This was a retrospective observational longitudinal study of patients presenting at the Department of Endocrinology and Metabolism, Pusan National University Hospital. A total of 512 patients with type 2 diabetes mellitus and preserved kidney function (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 $m^2$) and normouricemia were included. The main outcome was development of CKD of stage 3 or greater. The patients were divided into four groups according to quartiles of SUA levels.

*Results:* During the follow-up period, 62 (12.1%) patients had progressed to CKD 3 or greater. The group with the highest-normal range of SUA (Q4) showed a higher cumulative incidence of CKD stage 3 or greater than that of the other lower quartiles (Q4 vs. Q3; $P = 0.037$, Q4 vs. Q2; $P < 0.001$, Q4 vs. Q1; $P < 0.001$). In a univariate analysis, Q4 was significantly associated with the development of CKD 3 or greater (log-rank statistic, 31.93; $P < 0.001$). In a multivariate analysis, Q4 (hazard ratio, 2.97; 95% confidence interval, 1.15–7.71; $P = 0.025$) showed a significant association with CKD 3 or greater.

*Conclusions:* High-normal SUA may predict the occurrence of CKD stage 3 or greater in patients with type 2 diabetes mellitus and preserved kidney function.



## 1. Introduction

Diabetic nephropathy is the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide (Collins et al., 2012). Diabetic nephropathy is also one of the leading causes of a requirement for renal replacement (Rosolowsky et al., 2008). With the increasing number of patients with type 2 diabetes mellitus, the increase in the number of patients with CKD and ESRD has become a social burden.

Uric acid is the main urinary metabolite of purines in humans (Mene & Punzo, 2008). Previous studies have shown an association between hyperuricemia and hypertension, cardiovascular mortality, and renal injuries in both nondiabetic and diabetic patients (Fang & Alderman, 2000; Johnson et al., 2003; Zoppini et al., 2009). Debate continues about whether SUA is a marker or a mediator of the progression of diabetic nephropathy. Several large observational prospective studies have shown that hyperuricemia has a pathogenic role in the development and progression of CKD (Jalal, Chonchol, Chen, & Targher, 2013; Zoppini et al., 2012). Studies considering the normal SUA range in patients with type 2 diabetes mellitus are limited. One study suggested that high-normal SUA is associated with impaired renal function in patients with type 1 diabetes mellitus (Rosolowsky et al., 2008). However, there are pathophysiological differences between type 1 and type 2 diabetes mellitus.

The aim of this study was to determine whether high-normal SUA levels can predict the development of CKD in patients with type 2 diabetes mellitus and preserved kidney function at baseline.

☆ Disclosures: The authors have nothing to disclose.

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## 2. Materials and methods

### 2.1. Patients

This was a retrospective longitudinal observational study of patients presenting to the Department of Endocrinology and Metabolism, Pusan National University Hospital. This study protocol was approved by the Institutional Research Board of Pusan National University Hospital (E-2013033). A total of 1016 outpatients with type 2 diabetes mellitus were enrolled between January 2008 and December 2009. The patients were followed up until April 2013. Of the 1016 patients, 802 fulfilled the following inclusion criteria: estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 $m^2$ and SUA ≤ 8 mg/dL. Of the 802 patients, 130 were excluded because of a lack of at least 1 year of follow-up data. Among the 672 patients remaining, 102 were excluded because of underlying malignancy (n = 49) and previous history of cerebrovascular disease (n = 53). Of the 570, 58 were excluded due to a newly diagnosed neoplasm (n = 31), newly diagnosed cerebrovascular disease (n = 21), acute and chronic disease requiring admission (hyperglycemic hyperosmolar syndrome, n = 1, hemoptysis, n = 1, cholangitis, n = 1, melena, n = 1, iatrogenic Cushing's syndrome, n = 1, nontuberculous mycobacteria, n = 1), and death (n = 1). Finally, 512 patients with type 2 diabetes mellitus, preserved kidney function (eGFR ≥ 60 mL/min/1.73 $m^2$), and normouricemia were included.

### 2.2. Measurements

eGFR was estimated by the Modification of Diet in Renal Disease (MDRD) Study formula: MDRD = 175 × (serum creatinine [mg/dL])$^{-1.154}$ × age$^{-0.203}$ (Stevens, Coresh, Greene, & Levey, 2006). A correction factor of 0.742 was used for females. CKD stage 3 or greater was defined as GFR < 60 mL/min/1.73 $m^2$. The annual decline in eGFR was calculated by dividing the change in eGFR by follow-up duration.

Hyperuricemia was defined as SUA level > 8 mg/dL. This is the cutoff value used in our clinic. The reference range of SUA was determined using 90 percentile of 40 healthy people from our clinic. Normal range SUA levels were divided into quartiles (in mg/dL: ≤ 3.8, 3.9–4.5, 4.6–5.5, and > 5.5).

Albumin-to-creatinine ratio (ACR) was measured from spot urine. Albuminuria values were defined as follows: normoalbuminuria (ACR, < 30 mg/g), microalbuminuria (ACR, 30–299 mg/g), and macroalbuminuria (ACR ≥ 300 mg/g) (Molitch, DeFronzo, Franz, Keane, & Mogensen, 2003).

### 2.3. Statistical analyses

Statistical analyses were performed using SPSS ver. 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). Data are presented as means ± standard deviation for normally distributed variables and medians (interquartile range) for nonparametric variables. Categorical data are expressed as frequencies and percentages. Analysis of variance was used to evaluate differences among the SUA quartile groups. Cumulative incidence of CKD stage 3 or greater was evaluated with the Kaplan–Meier method and log-rank test. A univariate analysis was performed to determine the relationship between development of CKD stage 3 or greater and the variables. A multivariate analysis, using a enter procedure was conducted including factors with a *P*-value < 0.2 in the univariate analysis. A Cox regression analysis was performed to assess the effect of multiple variables on the development of CKD stage 3 or greater. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). A multiple regression analysis was performed to evaluate the association between SUA level as a continuous variable and annual decline in eGFR. *P* values < 0.05 two-tailed were considered statistically significant.

## 3. Results

Table 1 summarizes the baseline characteristics of the patients according to SUA quartiles. Mean age of the patients was 56 ± 11.3 years (range, 18–86 years). They consisted of 208 males (40.6%) and 304 females (59.4%). Age, duration of diabetes, systolic blood pressure (SBP), total cholesterol, low-density lipoprotein (LDL) cholesterol, urine ACR, presence of diabetic retinopathy, and use of lipid-lowering agents were not significantly different between the groups. The group with the highest SUA level had a greater proportion of males and a higher body mass index (both *P* < 0.001). They had lower glycated hemoglobin (HbA1c), lower high density lipoprotein

**Table 1**
Baseline characteristics of the patients with type 2 diabetes mellitus and preserved kidney function according to uric acid quartile.

| | Q1 (n = 137) | Q2 (n = 120) | Q3 (n = 136) | Q4 (n = 119) | *P*-value |
|---|---|---|---|---|---|
| Sex, male/female | 30/107 | 30/90 | 62/74 | 86/33 | < 0.001 |
| Age, years | 55.9 ± 12.3 | 55.6 ± 10.8 | 56.8 ± 10.6 | 55.7 ± 11.4 | 0.826 |
| BMI, kg/$m^2$ | 23.4 ± 3.3 | 24.5 ± 3.4 | 24.8 ± 3.4 | 25.4 ± 3.3 | < 0.001 |
| Duration of diabetes, years | 9.2 ± 6.8 | 8.1 ± 6.6 | 9.2 ±5.9 | 8.2 ± 6.3 | 0.435 |
| Hypertension, n (%) | 49 (36.3) | 59 (50) | 51 (37.8) | 51 (43.2) | 0.115 |
| SBP, mmHg | 122 ± 15 | 124 ± 14 | 123 ± 14 | 125 ± 14 | 0.652 |
| DBP, mmHg | 73 ± 10 | 75 ±10 | 75 ± 10 | 77 ± 11 | 0.002 |
| HbA1c, % (mmol/mol) | 8.0 ± 1.9 (63.7 ± 20.3) | 7.7 ± 1.5 (60.4 ± 16.7) | 7.5 ± 1.5 (58.1 ± 16.1) | 7.0 ± 1.2 (52.8 ± 12.7) | < 0.001 |
| Total cholesterol, mg/dL | 175 ± 39 | 179 ± 38 | 180 ± 41 | 178 ± 44 | 0.771 |
| LDL cholesterol, mg/dL | 98 ± 32 | 101 ± 31 | 101 ± 33 | 97 ± 33 | 0.684 |
| HDL cholesterol, mg/dL | 51 ± 14 | 49 ± 13 | 48 ± 11 | 45 ± 13 | 0.001 |
| Triglycerides, mg/dL | 117 (83–157) | 123 (80–191) | 138 (95–207) | 154 (102–226) | < 0.001 |
| Serum creatinine, mg/dL | 0.76 ± 0.13 | 0.77 ± 0.14 | 0.85 ± 0.16 | 0.93 ± 0.15 | < 0.001 |
| eGFR, mL/min/1.73 $m^2$ | 93.7 ± 18.9 | 93.4 ± 23.9 | 87.1 ± 16.8 | 85.1 ± 13.9 | < 0.001 |
| Urine ACR, mg/g | 15 (8–34) | 15 (9–32) | 15 (7–41) | 18 (8–53) | 0.455 |
| Serum uric acid, mg/dL | 3.2 ± 0.5 | 4.2 ± 0.2 | 5.0 ± 0.3 | 6.4 ± 0.6 | < 0.001 |
| Diabetic retinopathy, n (%) | 25 (24.5) | 26 (31.7) | 28 (29.8) | 29 (36.3) | 0.383 |
| Aspirin users, n (%) | 31 (22.6) | 21 (17.5) | 30 (22.2) | 41 (34.5) | 0.016 |
| Lipid-lowering agent, n (%) | 70 (51.1) | 66 (55) | 81 (60) | 71 (59.7) | 0.409 |

Data are means ± standard deviation, medians (interquartile range) for continuous variables and frequencies (percentage) for categorical variables. Quartiles of uric acid were ≤ 3.8, 3.9–4.5, 4.6–5.5, and > 5.5.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio.