

The Association between Uric Acid and Chronic Kidney Disease in Korean Men: A 4-Year Follow-up Study

Jae-Hong Ryoo,^{1,2} Joong-Myung Choi,¹
Chang-Mo Oh,^{1,3} and Min-Gi Kim⁴

¹Department of Preventive Medicine, School of Medicine, Kyung Hee University, Seoul; ²Department of Occupational Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul; ³The Korea Central Cancer Registry, National Cancer Center, Goyang; ⁴Department of Occupational and Environmental Medicine, Dongguk University, Gyeongju Hospital, Gyeongju, Korea

Received: 16 December 2012
Accepted: 6 April 2013

Address for Correspondence:
Min-Gi Kim, MD
Department of Occupational and Environmental Medicine,
Dongguk University, Gyeongju Hospital, 87 Dongdae-ro,
Gyeongju 780-350, Korea
Tel: +82.10-2481-5422, Fax: +82.54-748-9300
E-mail: searchthing@naver.com

There have been many studies between serum uric acid (UA) and chronic kidney disease (CKD). However, as far as we know, little research has been done to examine the prospective association between serum UA and development of CKD in Korean men. This prospective cohort study was performed using 18,778 men who participated in a health checkup program both on January, 2005 and on December, 2009. CKD was defined as an estimated glomerular filtration rate < 60 mL/min per 1.73 m². The odds ratio (OR) from binary logistic regressions for the development of CKD was determined with respect to the quintiles grouping based on serum UA. During 74,821.4 person-years of follow-up, 110 men were found to develop CKD. The OR for the development of CKD increased as the quintiles for baseline serum UA levels increased from the first to fifth quintiles (1.00 vs 1.22, 1.19, 2.59, and 3.03, respectively, *p* for linear trend < 0.001) after adjusting for covariates. The adjusted OR comparing those participants with hyperuricemia (≥ 7.0 mg/dL) to those with normouricemia (< 7.0 mg/dL) was 1.96 (1.28-2.99). Elevated serum UA levels were independently associated with increased likelihood for the development of CKD in Korean men (IRB number: KBC10034).

Key Words: Uric Acid; Kidney Failure, Chronic

INTRODUCTION

Chronic kidney disease (CKD) is associated with end stage renal disease as well as cardiovascular morbidity and mortality (1-3). CKD is a worldwide public health problem, and thus, identification and management of modifiable CKD risk factors are important to deploy for the prevention of adverse effects. The most important established risk factors for CKD are diabetes and hypertension (4-7). Obesity and metabolic syndrome are also known as independent predictors for the development of CKD (8-10).

Uric acid (UA) is a final byproduct produced by purine metabolism in humans. It is strongly associated with renal failure and cardiovascular disease (11, 12), and it is found at particularly high serum levels in people with hypertension and metabolic syndrome, as well as those suffering UA related metabolic abnormalities (e.g., dyslipidemia or insulin resistance) (13, 14).

Recent concerns relating UA and CKD have been identified with some epidemiologic studies reporting an association between hyperuricemia and CKD (15-18). Despite the existence of these studies, there is scarce longitudinal data available about the relationship between serum UA levels and the development of CKD by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in the Korean population, where the genetic and environmental backgrounds differ from that of west-

ern countries. Therefore, we conducted a prospective cohort study in order to investigate whether or not serum UA is useful as an independent predictor for the development of CKD in apparently healthy Korean men.

MATERIALS AND METHODS

Study participants

All employees of Korean companies participate in an annual health examination, as required by Korea's Industrial Safety and Health law. The participants in this study were composed of individuals who had received a comprehensive health examination at baseline (2005) and were then re-examined 4 yr later (2009), with both examination conducted at Kangbuk Samsung Hospital. Initially, 20,721 individuals were identified as potential participants, and of these, 1,943 (9.4%) were excluded for the following reasons: past history of malignancies (*n* = 101, 0.5%); past history of cardiovascular disease (*n* = 105, 0.5%); administration of medications for lipid-lowering (*n* = 1,356, 6.5%) or kidney diseases (*n* = 171, 0.8%) at the time of examination. Based on the baseline (2005) medical records, 210 (1.0%) subjects were also excluded due to the observation of baseline eGFR < 60 mL/min per 1.73 m². After these exclusions, the total number of eligible study participants was 18,778 (Fig. 1).

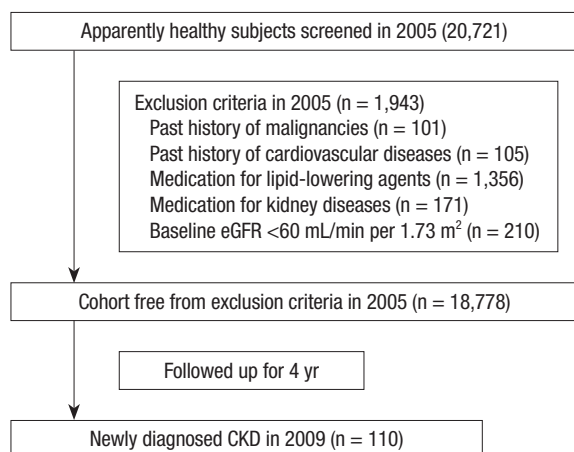


Fig. 1. Selection of study participants.

Measurements

The initial health examinations performed in 2005 included a medical history evaluation, a physical examination, a questionnaire about health-related behavior, and anthropometric and biochemical measurements. The medical and drug prescription history were assessed by the examining physicians as part of the examination. All participants were asked to respond to a health-related behavior questionnaire which included the topics of alcohol consumption, smoking and exercise. The questions about alcohol intake included the frequency of alcohol consumption on a weekly basis and the typical amount consumed on a daily basis (≥ 20 g/day). We considered persons reporting that they smoked at the time of the questionnaire to be current smokers. In addition, the participants were asked about the frequency per week of physical activities they engage in that lasts long enough to produce perspiration such as jogging, bicycling and swimming (≥ 1 time/week). The diagnosis of diabetes mellitus was defined as a fasting blood glucose level of at least 126 mg/dL, or the current use of blood glucose-lowering agents. Hypertension was defined as either the current use of antihypertensive medication or as having a measured blood pressure (BP) $\geq 140/90$ mmHg at the initial examination.

Blood specimens were sampled from an antecubital vein after more than 12 hr of fasting. Serum levels of creatinine, glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and UA were measured using Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Auto Analyzer; Bayer Diagnostics, Leverkusen, Germany). The measurement techniques employed included the hexokinase method for glucose, an enzymatic colorimetric assay for serum lipids, and an immunoradiometric assay for insulin (Biosource, Nivelles, Belgium). The serum UA method was based on the Fossati enzymatic reaction using uricase with a Trinder-like endpoint (Advia 1650 Auto Analyzer). Insulin resistance was calculated using the homeo-

stasis model assessment of insulin resistance (HOMA-IR) as described by Matthews et al. (19): fasting serum insulin (μ U/mL) \times fasting blood glucose (mmol/L)/22.5. Serum creatinine (SCr) was measured using the alkaline picrate (Jaffe) method. Kidney function was estimated using the glomerular filtration rate (GFR) which was calculated using the CKD-EPI equation: $eGFR = 141 \times \min(SCr/K, 1)^a \times \max(SCr/K, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] $\times 1.159$ [if Black], where SCr is serum creatinine, K is 0.7 for females and 0.9 for males, " a " is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/ K or 1 and max indicates the maximum of SCr/ K or 1 (20). CKD was defined as an eGFR of < 60 mL/min per 1.73 m².

Trained nurses obtained sitting BP levels using a standard mercury sphygmomanometer. The first and fifth Korotkoff sounds were utilized in order to estimate the systolic and diastolic BP. Height and weight were measured after an overnight fast with the shoeless participants wearing a lightweight hospital gown.

Statistical analyses

One-way ANOVA and χ^2 -test were used to analyze the statistical differences between the characteristics of the study participants at the time of enrollment in relation to the quintiles of serum UA levels. Categories for serum UA results were comprised of the following quintiles: < 5.1 mg/dL, 5.1 to 5.7 mg/dL, 5.7 to 6.3 mg/dL, 6.3 to 7.0 mg/dL and ≥ 7.0 mg/dL. Age-adjusted and multivariable-adjusted logistic regression analyses (models 1, 2 and 3, with the latter adjusted for age) were performed to include HOMA-IR, triglyceride, BMI, alcohol intake, smoking status, regular exercise, hypertension and diabetes mellitus.

In addition, we compared the development of CKD in hyperuricemic participants (serum UA ≥ 7.0 mg/dL) vs normouricemic participants. Statistical analyses were performed using SPSS 17.0 for Windows software package (SPSS, Chicago, IL, USA). All reported P values were two-tailed and those with results < 0.05 were considered to be statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine in Seoul, Korea (IRB number: KBC10034). All participants gave their written informed consent.

RESULTS

The metabolic characteristics of the participants, arranged according to serum UA quintiles, are shown in Table 1. Overall, the mean \pm S.D age of the participants was 41.8 ± 6.3 yr.

During 74,821.4 person-years of follow-up, 110 cases of CKD had developed by 2009. At baseline, a graded increasing trend in relation to serum UA quintiles was observed for systolic and diastolic BP, BMI, total cholesterol, triglyceride, LDL-cholester-

Table 1. Baseline characteristics of participants relative to quintile grouped by UA levels (n = 18,778)

Characteristic	Total	Uric acid (UA) (mg/dL)					P for trend*
		Q1 (< 5.1)	Q2 (≥ 5.1, < 5.7)	Q3 (≥ 5.7, < 6.3)	Q4 (≥ 6.3, < 7.0)	Q5 (≥ 7.0)	
Person-year (average)	3.98 ± (0.26)	3.99 ± (0.27)	3.98 ± (0.27)	3.99 ± (0.26)	3.98 ± (0.26)	3.98 ± (0.26)	
Age (yr)	41.8 ± (6.3)	43.2 ± (7.3)	42.3 ± (6.7)	41.6 ± (6.1)	41.1 ± (5.5)	40.9 ± (5.3)	< 0.001
BMI (kg/m ²)	24.2 ± (2.8)	23.4 ± (2.7)	23.6 ± (2.6)	24.1 ± (2.6)	24.6 ± (2.7)	25.3 ± (2.8)	< 0.001
Systolic BP (mmHg)	114.6 ± (14.0)	113.7 ± (14.1)	113.5 ± (13.8)	114.3 ± (13.8)	115.0 ± (13.8)	116.4 ± (14.3)	< 0.001
Diastolic BP (mmHg)	77.0 ± (9.4)	76.2 ± (9.3)	76.2 ± (9.2)	76.7 ± (9.3)	77.5 ± (9.3)	78.4 ± (9.6)	< 0.001
Total cholesterol (mg/dL)	192.0 ± (31.4)	187.2 ± (30.7)	187.5 ± (30.5)	190.9 ± (30.2)	194.3 ± (31.6)	199.9 ± (32.0)	< 0.001
Triglyceride (mg/dL)	141.8 ± (81.9)	123.3 ± (67.6)	128.8 ± (78.9)	137.7 ± (76.8)	149.3 ± (82.1)	169.0 ± (93.4)	< 0.001
HDL-cholesterol (mg/dL)	50.0 ± (10.2)	51.8 ± (10.9)	50.8 ± (10.4)	49.9 ± (9.9)	49.2 ± (9.9)	48.4 ± (9.5)	< 0.001
LDL-cholesterol (mg/dL)	112.9 ± (26.4)	109.1 ± (26.0)	109.5 ± (25.5)	112.5 ± (25.6)	114.9 ± (26.9)	118.4 ± (27.0)	< 0.001
Fasting serum glucose (mg/dL)	96.9 ± (14.4)	98.5 ± (21.4)	96.7 ± (14.5)	96.2 ± (12.1)	96.3 ± (10.5)	96.9 ± (10.7)	< 0.001
HOMA-IR	2.1 ± (0.9)	2.0 ± (0.9)	2.0 ± (0.8)	2.1 ± (0.9)	2.2 ± (0.9)	2.4 ± (1.0)	< 0.001
Insulin (μU/dL)	8.9 ± (3.4)	8.2 ± (3.0)	8.3 ± (3.1)	8.8 ± (3.2)	9.2 ± (3.5)	9.8 ± (3.8)	< 0.001
eGFR (mL/min per 1.73 m ²)	81.5 ± (9.4)	83.5 ± (9.8)	82.6 ± (9.4)	81.5 ± (9.2)	81.0 ± (9.3)	79.0 ± (8.9)	< 0.001
SCr (mg/dL)	1.12 ± (0.10)	1.09 ± (0.09)	1.10 ± (0.09)	1.12 ± (0.09)	1.13 ± (0.10)	1.16 ± (0.10)	< 0.001
BUN (mg/dL)	14.1 ± (3.2)	14.0 ± (3.3)	14.0 ± (3.2)	14.1 ± (3.1)	14.2 ± (3.1)	14.5 ± (3.1)	< 0.001
Current smoker (%)	7,806 (41.9)	1,552 (42.5)	1,462 (40.6)	1,695 (41.3)	1,423 (42.0)	1,674 (43.1)	0.310
Alcohol intake (%)	1,937 (10.4)	407 (11.1)	347 (9.6)	435 (10.6)	329 (9.7)	419 (10.8)	0.724
Regular exercise (%)	2,691 (14.5)	588 (16.1)	541 (15.0)	562 (13.7)	436 (12.9)	564 (14.6)	0.005
Diabetes mellitus (%)	572 (3.1)	213 (5.8)	121 (3.3)	97 (2.4)	66 (1.9)	75 (1.9)	< 0.001
Hypertension (%)	2,977 (15.9)	518 (14.1)	504 (13.9)	623 (15.1)	565 (16.5)	767 (19.6)	< 0.001
Development of CKD (%)	110 (0.6)	13 (0.4)	13 (0.4)	15 (0.4)	25 (0.7)	44 (1.1)	< 0.001

Categorical data presented as (%); continuous data presented as mean (standard deviation). *P value by ANOVA for continuous variables and chi square test for categorical variables. UA, uric acid; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CKD, chronic kidney disease.

Table 2. Baseline characteristics of participants relative to development of chronic kidney disease (CKD) during the 4-yr follow-up period.

Characteristic	Total participants (n = 18,778)		P value*
	CKD (n = 110)	Non-CKD (n = 18,668)	
Age (yr)	48.4 ± (8.5)	41.8 ± (6.3)	< 0.001
BMI (kg/m ²)	24.9 ± (2.5)	24.2 ± (2.8)	0.013
Systolic BP (mmHg)	119.6 ± (17.5)	114.6 ± (14.0)	0.004
Diastolic BP (mmHg)	80.6 ± (10.4)	77.0 ± (9.4)	< 0.001
Total cholesterol (mg/dL)	193.9 ± (33.5)	192.0 ± (31.4)	0.529
Triglyceride (mg/dL)	147.5 ± (101.2)	141.7 ± (80.7)	0.459
HDL-cholesterol (mg/dL)	48.4 ± (9.2)	50.0 ± (10.2)	0.106
LDL-cholesterol (mg/dL)	114.2 ± (31.4)	112.9 ± (26.4)	0.678
Fasting serum glucose (mg/dL)	100.2 ± (17.3)	96.9 ± (14.4)	0.050
HOMA-IR	2.2 ± (1.0)	2.1 ± (0.9)	0.414
Insulin (μU/dL)	8.9 ± (4.7)	8.9 ± (3.4)	0.966
eGFR (mL/min per 1.73 m ²)	67.4 ± (5.9)	81.6 ± (9.4)	< 0.001
SCr (mg/dL)	1.26 ± (0.10)	1.12 ± (0.10)	< 0.001
BUN (mg/dL)	15.8 ± (3.4)	14.1 ± (3.2)	< 0.001
UA (mg/dL)	6.7 ± (1.5)	6.0 ± (1.2)	0.002
Current smoker (%)	36 (33.0)	7,771 (42.0)	0.059
Alcohol intake (%)	7 (6.2)	1,930 (10.4)	0.175
Regular exercise (%)	30 (27.5)	2,661 (14.4)	< 0.001
Diabetes mellitus (%)	7 (6.4)	565 (3.0)	0.042
Hypertension (%)	33 (30.0)	2,945 (15.8)	< 0.001

*P value by t-test for continuous variables and chi square test for categorical variables. UA, uric acid; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CKD, chronic kidney disease.

ol, HOMA-IR, blood creatinine, insulin, BUN and percentage of Hypertension. Age, HDL-cholesterol, fasting serum glucose, eGFR, percentage of regular exercise, and diabetes mellitus showed a graded decreasing trend in relation to serum UA quintiles.

The metabolic characteristics of the participants relative to the development of CKD during the 4 yr follow-up period are shown in Table 2. During the follow-up period, CKD occurred in 110 of the total participants. Table 3 presents the odds ratio (OR) and 95% confidence intervals (CI) for the likelihood of development of CKD relative to the quintile groups established for serum UA level. In the categorical analyses, the likelihood of developing CKD increased with increasing serum UA quintile (*P* for trend < 0.001). In unadjusted analyses whereby Q1 was utilized as a reference, the Q4 and Q5 groups were found to be significantly associated with a greater likelihood for the development of CKD. This difference remained significant even after further adjustments for covariates in models 1, 2, and 3. After adjusting for age, baseline eGFR, systolic BP, HOMA-IR, triglyceride, BMI, alcohol intake, smoking status, regular exercise, hypertension and diabetes mellitus, the OR and 95% CI associated with the likelihood for development of CKD with respect to groups Q2, Q3, Q4, and Q5 were 1.22 (0.54-2.75), 1.19 (0.54-2.65), 2.59 (1.22-5.51), and 3.03 (1.48-6.19), respectively.

Table 4 presents the multivariate-adjusted OR and 95% CI for the development of CKD by comparing the hyperuricemic (≥ 7.0 mg/dL) vs normouricemic (< 7.0 mg/dL) participants.

Table 3. Odds ratio (OR) and 95% confidence intervals (CI) for the likelihood of development of chronic kidney disease (CKD) relative to quintile groups established for serum uric acid (UA) levels

Characteristics	Odds ratio (95% confidence interval)				
	Unadjusted	Age-adjusted	Model 1	Model 2	Model 3
UA (mg/dL)					
Q1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	1.02 (0.47-2.19)	1.32 (0.60-2.88)	1.11 (0.50-2.45)	1.20 (0.53-2.70)	1.22 (0.54-2.75)
Q3	1.03 (0.49-2.16)	1.70 (0.79-3.64)	1.05 (0.48-2.28)	1.15 (0.52-2.56)	1.19 (0.54-2.65)
Q4	2.08 (1.06-4.07)	4.19 (2.06-8.51)	2.29 (1.10-4.75)	2.50 (1.18-5.30)	2.59 (1.22-5.51)
Q5	3.21 (1.73-5.97)	6.64 (3.43-12.87)	2.64 (1.33-5.24)	2.92 (1.43-5.93)	3.03 (1.48-6.19)
<i>P</i> for linear trend	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Age		1.15 (1.12-1.17)	1.05 (1.03-1.08)	1.06 (1.03-1.09)	1.06 (1.03-1.09)
Baseline eGFR			0.79 (0.76-0.82)	0.79 (0.76-0.82)	0.79 (0.76-0.82)
HOMA-IR			0.95 (0.76-1.18)	0.94 (0.75-1.18)	0.91 (0.72-1.15)
BMI			1.02 (0.93-1.11)	1.02 (0.93-1.11)	1.02 (0.93-1.12)
Systolic BP			1.02 (1.00-1.03)	1.02 (1.01-1.03)	1.02 (1.01-1.04)
Triglyceride			1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.99-1.00)
Alcohol intake				2.58 (1.16-5.73)	2.58 (1.16-5.70)
Smoking status				1.15 (0.75-1.76)	1.15 (0.75-1.76)
Regular exercise				0.88 (0.55-1.39)	0.88 (0.56-1.39)
Hypertension					1.18 (0.67-3.71)
Diabetes mellitus					1.57 (0.66-2.02)

Model 1: adjusted for age, baseline eGFR, systolic BP, HOMA-IR, triglyceride and BMI. Model 2: adjusted for Model 1 plus alcohol intake, smoking status and regular exercise. Model 3: adjusted for Model 2 plus hypertension and diabetes mellitus. Q1, quintile 1; Q2, quintile 2; Q3, quintile 3; Q4, quintile 4; Q5, quintile 5; UA, uric acid; BP, blood pressure; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; CKD, chronic kidney disease.

Table 4. Odds ratio (OR) and 95% confidence intervals (CI) for the likelihood of the development of chronic kidney disease (CKD) relative to elevated serum uric acid (UA) levels

Model of CKD	OR (CI) in hyperuricemia (≥ 7.0 mg/dL)		
	No (n = 14,868)	Yes (n = 3,910)	<i>P</i> value
No. of the development of CKD	66 (0.4)	44 (1.1)	< 0.001
Unadjusted	1.00 (reference)	2.55 (1.74-3.74)	< 0.001
Model 1	1.00 (reference)	1.89 (1.25-2.87)	< 0.001
Model 2	1.00 (reference)	1.95 (1.27-2.95)	< 0.001
Model 3	1.00 (reference)	1.96 (1.28-2.99)	< 0.001

Model 1: adjusted for age, baseline eGFR, systolic BP, HOMA-IR, triglyceride and BMI. Model 2: adjusted for Model 1 plus alcohol intake, smoking status and regular exercise. Model 3: adjusted for Model 2 plus hypertension and diabetes mellitus.

With the normouricemic participants set as the reference, the OR and 95% CI for the development of CKD with respect to the hyperuricemic participants was 1.96 (1.28-2.99).

DISCUSSION

The major finding of our study was that high serum UA levels increased the risk for the development of CKD, independent of confounding variables. Thus, serum UA levels are useful as a predictor of disease susceptibility in apparently healthy Korean men. Our findings provide significant evidence that hyperuricemia is associated with the development of CKD, regardless of other well-known risk factors such as aging, alcohol intake, smoking, hypertension and diabetes mellitus.

In this study, only men were considered eligible study participants. The application of the CKD-EPI equation is not the same

for men and women, and pre-menopausal women have lower serum UA levels than men or post-menopausal women, as estrogen stimulates urinary urate excretion (21).

The importance of serum UA as an independent predictor for CKD progression remains a topic of ongoing debate. A number of studies have reported that hyperuricemia is associated with the development of CKD (15-18), while others have produced contrary results (22, 23). In a population-based study including epidemiological follow-up data from 13,338 participants in two community-based cohorts, the Atherosclerosis Risks in Communities and the Cardiovascular Health Study (Weiner et al.) evaluated the association between elevated serum UA and increased risk of incident kidney disease in a general US population over an extended follow-up period. They reported that each 1 mg/dL increase in UA increased the risk of developing CKD by 7%-11% (15). Obermayr et al. evaluated the prospective cohort of the Vienna Health Screening Project and found that elevated levels of serum UA independently increased the risk for developing new-onset kidney disease (16). On the other hand, Sturm et al. reported that serum UA was not an independent predictor for CKD progression as evidenced by a 7-yr follow-up study, The Mild to Moderate Kidney Disease (MMKD) Study (22).

There are a number of mechanisms by which hyperuricemia increases the risk for the development of CKD. Clinical evidence exists indicating that hyperuricemia raises BP due to endothelial dysfunction caused by UA (24). Another study in rats suggests that hyperuricemic conditions alter glomerular hemodynamics and cause cortical renal vasoconstriction as evidenced by a sig-

nificant increase of afferent and efferent arteriolar resistances. A decrease in the glomerular plasma flow and ultrafiltration coefficient resulted in a 35% decrease in single nephron GFR but an increase in glomerular pressure (25).

The major strengths of this study include the large sample size and the prospective study design. Furthermore, estimating eGFR using the recently developed CKD-EPI equation is known to be more accurate in the eGFR range > 60 mL/min per 1.73 m². Participants with baseline eGFR < 60 mL/min per 1.73 m² were excluded. Nevertheless, some limitations should be considered. First, the study participants were recruited from individuals who actively sought to evaluate their health status at a health promotion center; thus, this study may show a participant selection bias. Second, the participant's serum creatinine levels were measured only once a year. Third, we used an eGFR instead of a directly measured GFR in order to define CKD. A recent review article reported that current eGFR had greater inaccuracy in populations without known CKD than in those with the disease (26). Nevertheless, current eGFR facilitates the detection, evaluation and management of CKD, and many organizations recommend the use of equations that estimate GFR in epidemiologic studies and in clinical evaluation of renal function (26). Therefore, our findings are applicable to clinical and public health practice settings. In addition, ethnic factors characteristic of Asian populations are not well-established for the use of equations that estimate GFR. Therefore, these equations need to be validated with additional studies including large Asian cohorts.

In conclusion, this epidemiologic prospective cohort study indicates that high serum UA levels are associated with an increased likelihood for the development of CKD over a 4-yr follow-up period, and these associations are significant after adjusting for age, baseline eGFR, systolic BP, HOMA-IR, triglyceride, BMI, alcohol intake, smoking status, regular exercise, hypertension and diabetes mellitus, all of which are known independent risk factors for development of CKD. These findings highlight the importance of regular surveillance and monitoring of serum UA for the goal of circumventing the manifestation of CKD and its progression into cardiovascular disease and end-stage renal disease.

DISCLOSURE

The authors have no conflicts of interest to disclose.

REFERENCES

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. *Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med* 2004; 351: 1296-305.
2. Kiberd B. *The chronic kidney disease epidemic: stepping back and look-*

- ing forward. J Am Soc Nephrol* 2006; 17: 2967-73.
3. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, Salem DN, Levey AS, Sarnak MJ. *Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol* 2004; 15: 1307-15.
4. Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. *Predictors of new-onset kidney disease in a community-based population. JAMA* 2004; 291: 844-50.
5. National Kidney Foundation. *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis* 2002; 39: S1-266.
6. Nagahama K, Inoue T, Iseki K, Touma T, Kinjo K, Ohya Y, Takishita S. *Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan. Hypertens Res* 2004; 27: 835-41.
7. Sundström J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. *Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence. Hypertension* 2005; 45: 28-33.
8. Ejerblad E, Forel CM, Lindblad P, Fryzek J, McLaughlin JK, Nyrén O. *Obesity and risk for chronic renal failure. J Am Soc Nephrol* 2006; 17: 1695-702.
9. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. *Body mass index and risk for end-stage renal disease. Ann Intern Med* 2006; 144: 21-8.
10. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. *Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int* 2004; 65: 1870-6.
11. Fukui M, Tanaka M, Shiraishi E, Harusato I, Hosoda H, Asano M, Kadono M, Hasegawa G, Yoshikawa T, Nakamura N. *Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. Metabolism* 2008; 57: 625-9.
12. Nakagawa T, Kang DH, Feig D, Sanchez-Lozada LG, Srinivas TR, Sautin Y, Ejaz AA, Segal M, Johnson RJ. *Unearthing uric acid: an ancient factor with recently found significance in renal and cardiovascular disease. Kidney Int* 2006; 69: 1722-5.
13. Liu PW, Chang TY, Chen JD. *Serum uric acid and metabolic syndrome in Taiwanese adults. Metabolism* 2010; 59: 802-7.
14. Klein BE, Klein R, Lee KE. *Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. Diabetes Care* 2002; 25: 1790-4.
15. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. *Uric acid and incident kidney disease in the community. J Am Soc Nephrol* 2008; 19: 1204-11.
16. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. *Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol* 2008; 19: 2407-13.
17. Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. *Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis* 2004; 44: 642-50.
18. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF. *Relationship of uric acid with progression of kidney disease. Am J Kidney Dis* 2007; 50: 239-47.
19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. *Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia* 1985; 28: 412-9.
20. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman

- HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. *A new equation to estimate glomerular filtration rate. Ann Intern Med* 2009; 150: 604–12.
21. Johnson RJ, Rideout BA. *Uric acid and diet: insights into the epidemic of cardiovascular disease. N Engl J Med* 2004; 350: 1071–3.
22. Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F; MMKD Study Group. *Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? the Mild to Moderate Kidney Disease (MMKD) Study. Exp Gerontol* 2008; 43: 347–52.
23. Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, Collins AJ, Levey AS, Menon V. *Uric acid and long-term outcomes in CKD. Am J Kidney Dis* 2009; 53: 796–803.
24. Zoccali C, Maio R, Mallamaci F, Sesti G, Perticone F. *Uric acid and endothelial dysfunction in essential hypertension. J Am Soc Nephrol* 2006; 17: 1466–71.
25. Sánchez-Lozada LG, Tapia E, Santamaría J, Avila-Casado C, Soto V, Nepomuceno T, Rodríguez-Iturbe B, Johnson RJ, Herrera-Acosta J. *Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int* 2005; 67: 237–47.
26. Stevens LA, Coresh J, Greene T, Levey AS. *Assessing kidney function: measured and estimated glomerular filtration rate. N Engl J Med* 2006; 354: 2473–83.