Elevated Serum Uric Acid Predicts Chronic Kidney Disease

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Abstract: *Introduction:* The question of whether elevated serum uric acid is an independent risk factor for chronic kidney disease in a longitudinal manner was assessed in Japanese subjects undergoing a health checkup. *Methods:* A total of 14,399 participants (8,161 men and 6,238 women) without medication for hyperuremia in both 2000 and 2005 were included. After exclusion of participants taking treatments influencing serum uric acid and having chronic kidney disease defined as estimated glomerular filtration rate <60 mL/min/1.73m^2, in 2000, multiple logistic regression analyses were performed for 6,887 men (48.4 ± 9.9 years) and 5,340 women (49.9 ± 9.0 years) to identify independent factors for newly diagnosed chronic kidney disease in 2005. Adjustment was made for age, body mass index, elevated blood pressure or hypertension, hypertriglyceridemia, impaired fasting glucose, either urinary protein or occult blood, alcohol drinking and smoking. *Results:* The prevalence of chronic kidney disease and the values of body mass index, systolic and diastolic blood pressure and triglyceride were significantly higher in the participants with elevated serum uric acid quartiles. Chronic kidney disease was newly diagnosed in 4.1% of men and 3.7% of women, within the 5-year period. In multivariate models, the higher quartiles of serum uric acid were associated with increased risk of chronic kidney disease in both sexes. The odds ratio and 95% confidence interval for 1 increment of serum uric acid were 1.42 and 1.28 to 1.58 in men and 1.32 and 1.12 to 1.56 in women, respectively. *Conclusions:* Elevated serum uric acid predicts chronic kidney disease in subjects undergoing a health checkup.

Key Indexing Terms: Longitudinal investigation; Multiple logistic regression analysis; Estimated glomerular filtration rate. **[Am J Med Sci 2011;342(6):461–466.]**

Chronic kidney disease (CKD) is an emerging major health problem in many countries.[1–4] The prevalence of CKD, defined as a glomerular filtration rate (GFR) <60 mL/min/1.73m^2 or kidney damage for at least 3 months, is highly prevalent in Japan and other countries.[1–6] It progresses to the end-stage renal disease (ESRD), which is increasing steadily.[3,7] CKD is also known as a risk factor for cardiovascular disease, its mortality and noncardiovascular disease mortality from multiple causes.[3,8–10] Therefore, treatment for CKD is important for preventing CKD and its complications and delaying progression of CKD to ESRD.

Iseki et al[11] demonstrated that uric acid is an independent risk factor for developing high serum creatinine in screened Japanese in a cohort manner. It was further documented that elevated serum uric acid may be the risk for CKD in the general population and the patients. Cross-sectional studies demonstrated that elevated serum uric acid is associated with renal dysfunction assessed by serum creatinine and estimated GFR (eGFR) in the cross-sectional studies in Japan and other countries.[1,2,12–14] Cohort studies also revealed that elevated serum uric acid is an independent risk factor for development and progression of renal disease and ESRD.[15–22] However, other investigations demonstrated a weak correlation and negative results.[23–26] It remains still controversial whether uric acid is a mediator and maker of risk in CKD, specifically CKD assessed by the Modification of Diet in Renal Disease (MDRD) equation or an indicator of other diseases, including hypertension and the metabolic syndrome.[27]

It was reported that CKD in its conservative phase is an epidemiological problem and treatment for CKD is more effective if started as early as possible,[28] suggesting that it is important to diagnose the conservative phase of CKD by assessing eGFR using the MDRD equation.[2–6] However, few studies determined whether serum uric acid is the risk for CKD assessed by this equation. Therefore, in this longitudinal investigation, we assessed risk factors, including serum uric acid assessed in 2000 for newly developing CKD in both sexes of apparently healthy Japanese subjects undergoing a health checkup.

METHODS

Design of the Study

This study included retrospective longitudinal analyses to investigate whether serum uric acid is a risk factor for CKD in apparently healthy Japanese subjects undergoing a health checkup.

Subjects of the Study

The participants voluntarily underwent annual health checkups at Okazaki City Medical Association, Public Health Center, between 2000 and 2005. The numbers of participants undergoing medical checkups and exclusion criteria are listed in Figure 1. After exclusion, 6887 men (48.4 ± 9.9 years) and 5340 women (49.9 ± 9.0 years) were included to identify independent factors for newly diagnosed CKD in 2005.

Questionnaire

Subjects provided data for alcohol drinking habits and smoking status through a self-administered questionnaire, which was checked during individual interview by expert nurses in the center. The participants drinking 1 bottle (500 mL) of beer, 1 gou (180 mL) of Japanese sake or a glass of wine on an occasion were defined as alcohol drinkers. Alcohol drinking habits were classified into occasional (1–6 d/week) and daily (7 d/week) in reference to the previous report.[29] The participants smoking more than 1 cigarette on an occasion were defined as smokers.[29]

Measurements

Age was categorized into 4 categories. Body weight was measured, in light clothing, to the nearest 0.1 kg and height to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kilogram) divided by height (meter) squared and divided into 3 categories according to the criteria determined by the Japan Society for the Study of Obesity (Tokyo, Japan).

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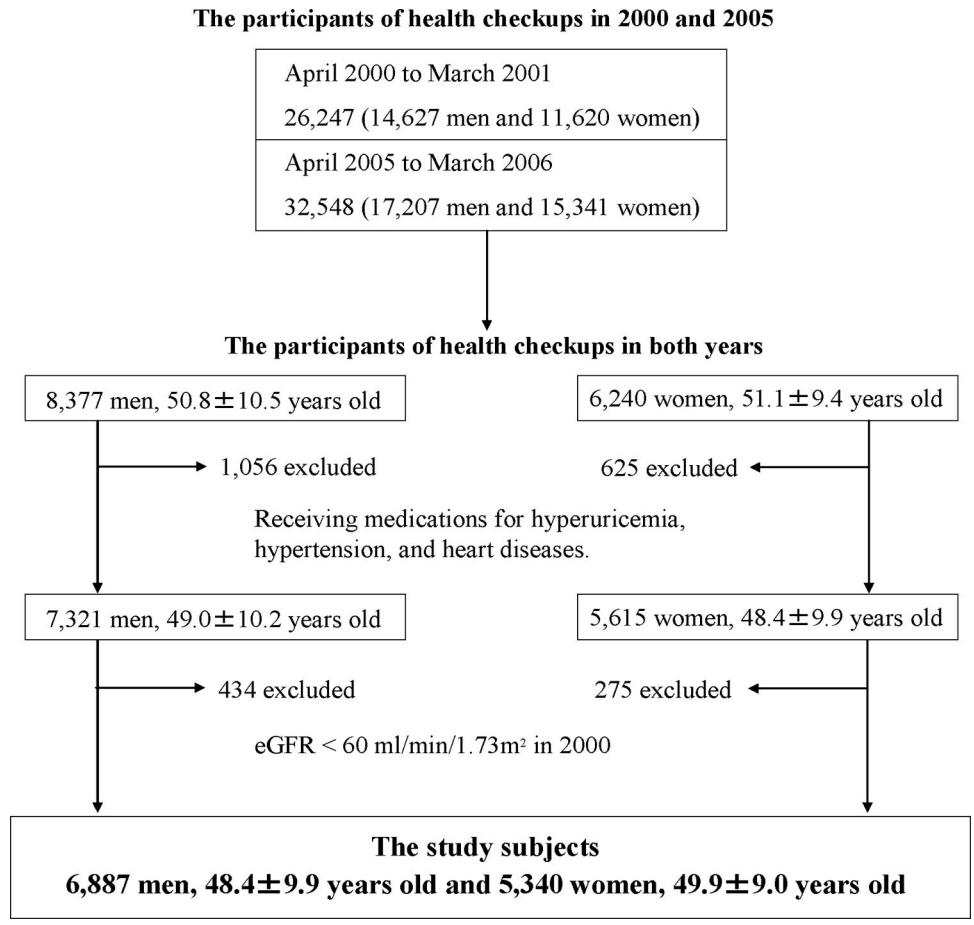

FIGURE 1. Study population.

Blood samples were taken from each participant after overnight fasting. Fasting blood glucose (FBG), creatinine, uric acid and triglyceride (TG) were measured with Hitachi autoanalyzer model 7700 (Hitachi Medical, Tokyo, Japan), which has been annually approved by the Precision Management Committee at Japan Medical Association (Tokyo, Japan). Impaired fasting glucose was defined if serum FBG was ≥110 mg/dL and hypertriglyceridemia was defined if serum TG was ≥150 mg/dL as determined by the Japan Medical Association (Tokyo, Japan) in 2005.

Blood pressure was measured to the nearest 1 mm Hg by an automatic sphygmomanometry (BP-203 RV III B; Nippon COLIN, Komaki, Japan). Elevated blood pressure or hypertension was diagnosed if resting blood pressures was ≥130/85 mm Hg as determined by the Japan Medical Association in 2005 or if the participants had a history of hypertension.

Kidney function was assessed by eGFR, which was calculated by using the revised MDRD equation for Japanese: $eGFR = 194 \times Cr^{-0.1094} \times Age^{-0.287} \times 0.739$ (if female).[5,30] CKD was defined as an eGFR <60 mL/min/1.73 m^2 as reported previously.[1–6,31]

Dipstick urinalysis was performed on midstream urine. Urinary occult blood and protein was measured semiquantitatively by an Uropaper III Eiken (Eikenkagaku, Tokyo, Japan).

Because the mean serum uric acid significantly differed between men and women, sex-specific quartiles of uric acid were determined as reported previously.[32] Quartiles 1 to 4 for men were <5.20 mg/dL, 5.20 to 5.89 mg/dL, 5.90 to 6.69 mg/dL and ≥6.70 mg/dL. For women, they were <3.70 mg/dL, 3.70 to 4.19 mg/dL, 4.20 to 4.79 mg/dL and ≥4.80 mg/dL. The numbers in these groups were 1825, 1920, 1810 and 1766 for men and 1345, 1547, 1370 and 1353 for women.

Statistical Analyses

Logistic regression analyses were respectively performed to determine the risk of serum uric acid in both men and women separately. We evaluated 2 models in both sexes: an age-adjusted and a multivariate model with adjustment for age (<40, 40–49, 50–59 and ≥60 years), BMI (<20, 20.0–24.9, 25.0–27.9 and ≥28 kg/m^2), elevated blood pressure or hypertension (yes or no), hypertriglyceridemia (yes or no), impaired fasting glucose (yes or no), alcohol drinking (none, occasional, daily or unknown), urinary analysis (urinary occult blood, urinary protein or both) and smoking (never, ever or unknown), which were assessed in 2000.

Statistical differences among groups were identified using 1-way analysis of variance, followed by multiple comparisons using Bonferroni's method. The m × n χ^2 test and the Fisher's test were used for comparison of prevalence. Logistic regression analyses were performed using computer software (SPSS version 13.0 for Windows; SPPS, Chicago, IL). *P* values less than 0.05 were considered significant.

Informed Consent

Informed consent was obtained from all participants.