

42. Savige J, Gregory M, Gross O *et al*. Expert guidelines for the management of Alport syndrome and thin basement membrane nephropathy. *J Am Soc Nephrol* 2013; 24: 364–375
43. Kashtan CE, Ding J, Gregory M *et al*. Clinical practice recommendations for the treatment of Alport syndrome: a statement of the Alport Syndrome Research Collaborative. *Pediatr Nephrol* 2013; 28: 5–11
44. Temme J, Peters F, Lange K *et al*. Incidence of renal failure and nephroprotection by RAAS inhibition in heterozygous carriers of X-chromosomal and autosomal recessive Alport mutations. *Kidney Int* 2012; 81: 779–783
45. Webb NJ, Lam C, Shahinfar S *et al*. Efficacy and safety of losartan in children with Alport syndrome—results from a subgroup analysis of a prospective, randomized, placebo- or amlodipine-controlled trial. *Nephrol Dial Transplant* 2011; 26: 2521–2526
46. Proesmans W, Van Dyck M. Enalapril in children with Alport syndrome. *Pediatr Nephrol* 2004; 19: 271–275
47. Gross O, Licht C, Anders HJ *et al*. Early angiotensin-converting enzyme inhibition in Alport syndrome delays renal failure and improves life expectancy. *Kidney Int* 2012; 81: 494–501
48. Gross O, Friede T, Hilgers R *et al*. Safety and efficacy of the ACE-inhibitor Ramipril in Alport syndrome: the double-blind, randomized, placebo-controlled, multicenter phase III EARLY PRO-TECT Alport Trial in Pediatric Patients. *ISRN Pediatr* 2012; 2012: 436046
49. Shah B, First MR, Mendoza NC *et al*. Alport's syndrome: risk of glomerulonephritis induced by anti-glomerular-basement-membrane antibody after renal transplantation. *Nephron* 1988; 50: 34–38
50. Ding J, Zhou J, Tryggvason K *et al*. COL4A5 deletions in three patients with Alport syndrome and posttransplant antiglomerular basement membrane nephritis. *J Am Soc Nephrol* 1994; 5: 161–168
51. Brosens I, Pijnenborg R, Benagiano G. Risk of obstetrical complications in organ transplant recipient pregnancies. *Transplantation* 2013; 96: 227–233
52. Armenti VT, Constantinescu S, Moritz MJ *et al*. Pregnancy after transplantation. *Transplant Rev (Orlando)* 2008; 22: 223–240
53. Bramham K, Nelson-Piercy C, Gao H *et al*. Pregnancy in renal transplant recipients: a UK national cohort study. *Clin J Am Soc Nephrol* 2013; 8: 290–298
54. Coscia LA, Constantinescu S, Moritz MJ *et al*. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl* 2010; 26: 65–85
55. Luders C, Castro MC, Titan SM *et al*. Obstetric outcome in pregnant women on long-term dialysis: a case series. *Am J Kidney Dis* 2010; 56: 77–85
56. Furaz-Czerpak KR, Fernandez-Juarez G, Moreno-de la Higuera MA *et al*. Pregnancy in women on chronic dialysis: a review. *Nefrologia* 2012; 32: 287–294

Received for publication: 24.2.2014; Accepted in revised form: 27.6.2014

*Nephrol Dial Transplant* (2014) 29: 2286–2292

doi: 10.1093/ndt/gfu256

Advance Access publication 24 July 2014

## A slight increase within the normal range of serum uric acid and the decline in renal function: associations in a community-based population

Keita Kamei<sup>1</sup>, Tsuneo Konta<sup>1,2</sup>, Atsushi Hirayama<sup>1</sup>, Kazuko Suzuki<sup>1</sup>, Kazunobu Ichikawa<sup>1</sup>, Shouichi Fujimoto<sup>2</sup>, Kunitoshi Iseki<sup>2</sup>, Toshiki Moriyama<sup>2</sup>, Kunihiro Yamagata<sup>2</sup>, Kazuhiko Tsuruya<sup>2</sup>, Kenjiro Kimura<sup>2</sup>, Ichiei Narita<sup>2</sup>, Masahide Kondo<sup>2</sup>, Koichi Asahi<sup>2</sup> and Tsuyoshi Watanabe<sup>2</sup>

<sup>1</sup>Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, Yamagata, Japan and <sup>2</sup>Steering Committee of Research on Design of the Comprehensive Health Care System for Chronic Kidney Disease (CKD) Based on the Individual Risk Assessment by Specific Health Checkup, The Ministry of Health, Labour and Welfare of Japan, Fukushima, Japan

Correspondence and offprint requests to: Tsuneo Konta; E-mail: kkonta@med.id.yamagata-u.ac.jp

### ABSTRACT

**Background.** Hyperuricemia is a risk factor for adverse renal outcomes in patients with chronic kidney disease. This study investigated the effect of uric acid on renal function in a community-based population.

**Methods.** We used a nationwide database of 165 847 subjects (aged 29–74, male 40%) who participated in the annual ‘Specific Health Check and Guidance in Japan’ checkup between 2008 and 2010; we examined the relationship between serum uric acid levels at baseline and 2-year change in the estimated glomerular filtration rate (eGFR) obtained by using the Japanese equation.

**Results.** After adjusting for possible confounders, the eGFR change was inversely correlated with uric acid at baseline. In the multivariable analysis, the decline in eGFR was significantly more rapid in subjects with the slight increase in uric acid (males  $\geq 5.7$  mg/dL, females  $\geq 4.4$  mg/dL), and the risk for incidental renal insufficiency (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>) was increased at uric acid of  $\geq 6.3$  mg/dL in males and  $\geq 5.5$  mg/dL in females, compared with the lowest quintile. The multiple linear regression analysis revealed that the effect of uric acid on eGFR changes was significant, especially in females, those with proteinuria and diabetes and those without alcohol consumption.

**Conclusion.** This study showed that serum uric acid is independently associated with a more rapid decline of eGFR and incident renal insufficiency, and that a slight increase within the normal range of serum uric acid might be a risk for renal damage in the general population.

**Keywords:** cohort study, renal function, uric acid

## INTRODUCTION

Recent studies have showed that hyperuricemia increases the risk for cardiovascular diseases [1] and mortality [2, 3]. Chronic kidney disease (CKD) is also a risk for cardiovascular events and premature death [4], and the association between uric acid and kidney disease has been previously investigated in the literature [5]. An increase in uric acid was thought to be associated with an increased risk of incidental CKD [6–8], and end-stage kidney disease (ESKD) [9] in the general population. However, studies have reported conflicting results. In the general population, increased uric acid levels were independently associated with ESKD in women but not men [10]. In patients with CKD, hyperuricemia was an incidental factor for all-cause and CVD mortality but not kidney failure [3]. In the elderly population, uric acid levels had a significant but weak association with the progression of kidney disease [11]. Furthermore, previous reports documented that a risk for ESKD was increased at different threshold values for men ( $\geq 7$  mg/dL) and women ( $\geq 6$  mg/dL) [10]. Therefore, the association between an increase in serum uric acid and kidney disease is still unclear.

This inconsistency might be due to several reasons including small sample sizes, differences in the characteristics of the studied populations, the varying classification of serum uric acid levels (hyperuricemia  $\geq 7$  mg/dL, quartiles/quintiles and per the 1 mg/dL increase), the end points [incident CKD, estimated glomerular filtration rate (eGFR)  $< 60$  mL/min/1.73 m<sup>2</sup>; glomerular filtration rate (GFR) decrease and ESKD] and the correction factors used in multivariate analyses. Furthermore, renal insufficiency itself decreases urinary excretion of uric acid, resulting in an increase in serum uric acid levels. This makes it difficult to determine whether hyperuricemia is the cause or result of renal damage. To address this issue, we accessed a nationwide large-scale database and prospectively examined the independent effect of uric acid on the change of renal function, using plural classifications of uric acid levels and end points, and subgroup analyses.

## MATERIALS AND METHODS

### Study population

This study was part of an ongoing ‘Research on design of the comprehensive health care system for CKD based on the individual risk assessment by Specific Health Checkup’ study. The Specific Health Check and Guidance is an annual health checkup for all inhabitants between the ages of 40 and 74 and is covered by Japanese national health insurance. We utilized the nationwide database obtained from 16 prefectures (administrative regions), Hokkaido, Tochigi, Saitama, Chiba, Nagano, Niigata, Ishikawa, Fukui, Gifu, Hyogo, Tokushima, Fukuoka, Saga, Nagasaki, Kumamoto and Okinawa, in keeping with our study aims. We collected data from 87 750 men and 131 485 women (total 219 235, age range 40–74) who took part in the health checkups in both 2008 and 2010. The study was conducted according to the Declaration of Helsinki and was approved by the respective institutional ethics committees. The details of this study have been described elsewhere [12].

Among the 219 235 participants, 53 388 were excluded from this study because the essential data, including serum uric acid and serum creatinine levels, were incomplete. Therefore, data from 66 289 males and 99 558 females (total 165 847, age range 40–74) were included in our statistical analyses. We examined the association between serum uric acid levels at baseline and 2-year change in renal function, as measured by the eGFR. In our analysis of the incidence of renal insufficiency, we used 141 514 subjects (54 152 males and 87 362 females) without renal insufficiency at baseline, after excluding 24 333 subjects who showed renal insufficiency at baseline.

### Measurements

Subjects used a self-reporting questionnaire to document their medical history, current medications, smoking habits (smoker or non-smoker) and alcohol consumption (drinker or non-drinker). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by trained staff by using a standard sphygmomanometer or an automated device, with subjects in the sitting position for at least 5 min prior to measurement. Hypertension was defined as a SBP  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg, or being on antihypertensive medication. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height (m<sup>2</sup>). For both men and women, obesity was defined as BMI  $\geq 25.0$  kg/m<sup>2</sup> [13]. Plasma glucose levels were measured by using the hexokinase enzymatic reference method. Subjects with diabetes were identified either by a fasting plasma glucose concentration of  $\geq 126$  mg/dL, an HbA1c value of  $\geq 6.5\%$  or on antidiabetic medication. Triglyceride and low-density lipoprotein cholesterol (LDL-C) concentrations were measured by using enzymatic methods, and high-density lipoprotein cholesterol (HDL-C) concentration was measured directly. Dyslipidemia was defined as triglycerides  $\geq 150$  mg/dL, HDL-C  $< 40$  mg/dL, LDL-C  $\geq 140$  mg/dL or being on lipid-lowering medication. Serum uric acid was measured by using an enzymatic method, and hyperuricemia was defined as serum uric acid  $\geq 7$  mg/dL in males and  $\geq 6$  mg/dL in females, according to the previous report [10].

Urinalysis was performed with a single spot urine specimen collected in the early morning after overnight fasting and measured by using a dipstick. The results of the urinalysis were recorded as negative (–), trace, 1+, 2+ and 3+. Positive proteinuria was defined as  $\geq 1+$ . Serum creatinine was measured by using an enzymatic method, and the eGFR was obtained by using the Japanese equation [14]. According to the universal definition, CKD was defined as the presence of proteinuria and/or renal insufficiency (eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>). Incidental renal insufficiency was defined as the new development of renal insufficiency at a 2-year follow-up examination among the subjects who had no renal insufficiency at baseline.

### Statistical analysis

We divided the subjects into gender-specific quintiles [Q1: males (M)  $\leq 4.9$ , females (F)  $\leq 3.7$ ; Q2: M 5.0–5.6, F 3.8–4.3; Q3: M 5.7–6.2, F 4.4–4.8; Q4: M 6.3–7.0, F 4.9–5.4 and Q5: M  $\geq 7.1$ , F  $\geq 5.5$  mg/dL] by their serum uric acid level at baseline. The  $\chi^2$ -test was used to evaluate differences in proportions. To compare the mean values in the unadjusted model and regression coefficients in the adjusted model among the quintile groups, we used a one-factor analysis of variance (ANOVA) test and the least squares analyses. We adjusted for possible confounders that showed significant correlation across the quintiles of uric acid levels, such as age, gender, BMI, SBP, DBP, eGFR, HbA1c, triglyceride levels, LDL-C, HDL-C, smoking habits, alcohol consumption and proteinuria. Additionally, we performed *post hoc* analyses by using the Dunnett–Hsu test using the quintile with the lowest values as a reference. To examine the factors relating to the 2-year changes in eGFR, we performed a multivariate linear regression analysis and adjusted for the abovementioned confounding factors. To examine the factors related to incidental renal insufficiency, we performed a multivariate logistic regression

analysis and adjusted for possible confounding factors such as age, gender, obesity, hypertension, diabetes, dyslipidemia, smoking habits, alcohol consumption, eGFR and proteinuria. Continuous data are expressed as the mean  $\pm$  SD. All statistical analyses were performed by using JMP version 10 software (SAS Institute Inc., Cary, NC). A P-value of  $< 0.05$  was used to define statistical significance.

## RESULTS

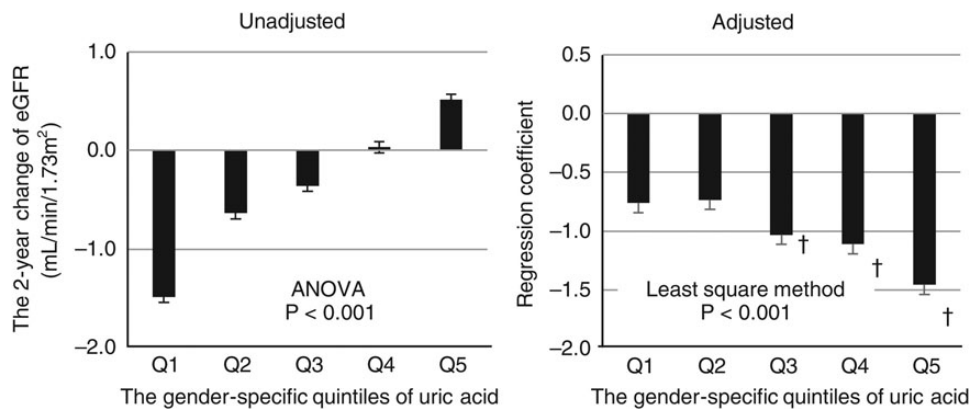
The mean age of the total subjects was 63.3 years, and the prevalence of obesity, hypertension, diabetes, dyslipidemia and hyperuricemia was 25.5, 44.3, 6.4, 55.1 and 12.0%, respectively. Subjects were divided into the quintiles (Q1–Q5) by their serum uric acid levels at baseline, and their baseline characteristics are described in Table 1. Along with an increase in serum uric acid levels, the prevalence of alcohol drinkers, obesity, proteinuria, hypertension and dyslipidemia and the mean values of BMI, SBP, DBP, triglycerides and LDL-C increased significantly. In contrast, the mean values of eGFR and HDL-C significantly decreased. The correlation between these parameters and uric acid at baseline was similar in both males and females (data not shown).

First, we compared the changes seen at the 2-year follow-ups in the eGFR among the quintiles at baseline. The ANOVA showed that the eGFR declined significantly more rapidly in subjects with low uric acid levels in the unadjusted model ( $P < 0.001$ ) (Figure 1). It is well known that factors such as gender, age and renal function affect serum uric acid levels; therefore, to avoid the confounding effect of such factors, we performed a least squares analysis with an adjustment for gender, age, baseline eGFR, BMI, SBP, DBP, eGFR, HbA1c, triglyceride, LDL-C, HDL-C, smoking habits, alcohol consumption and

**Table 1. Baseline characteristics of the study population**

	Total subjects	Gender-specific quintiles of serum uric acid (mg/dL)					P-value
		Q1 (M $\leq 4.9$ , F $\leq 3.7$ )	Q2 (M 5.0–5.6, F 3.8–4.3)	Q3 (M 5.7–6.2, F 4.4–4.8)	Q4 (M 6.3–7.0, F 4.9–5.4)	Q5 (M $\geq 7.1$ , F $\geq 5.5$ )	
Number	165 847	32 630	34 870	32 558	32 918	32 871	
Age (years)	63.3 $\pm$ 7.4	63.1 $\pm$ 7.7	63.2 $\pm$ 7.5	63.4 $\pm$ 7.3	63.5 $\pm$ 7.3	63.5 $\pm$ 7.3	<0.001
Male (%)	40.0	40.6	37.6	39.1	43.2	39.6	<0.001
Smoker (%)	13.2	13.4	12.5	12.7	13.4	13.8	<0.001
Alcohol consumption (%)	44.0	40.2	40.8	44.1	47.2	47.9	<0.001
Obesity (%)	25.5	16.5	18.9	23.2	23.1	39.3	<0.001
BMI (kg/m <sup>2</sup> )	23.1 $\pm$ 3.2	22.2 $\pm$ 3.0	22.5 $\pm$ 3.0	23.0 $\pm$ 3.0	23.6 $\pm$ 3.1	24.4 $\pm$ 3.4	<0.001
SBP (mmHg)	128.9 $\pm$ 17.3	126.6 $\pm$ 17.4	127.4 $\pm$ 17.3	128.5 $\pm$ 17.1	129.9 $\pm$ 17.1	131.9 $\pm$ 17.0	<0.001
DBP (mmHg)	76.2 $\pm$ 10.5	74.6 $\pm$ 10.5	75.3 $\pm$ 10.4	76.1 $\pm$ 10.4	76.9 $\pm$ 10.5	78.0 $\pm$ 10.5	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	74.5 $\pm$ 15.2	80.6 $\pm$ 15.8	77.1 $\pm$ 14.5	74.4 $\pm$ 14.1	72.0 $\pm$ 14.0	68.1 $\pm$ 14.7	<0.001
Triglyceride (mg/dL)	119.4 $\pm$ 77.3	103.5 $\pm$ 62.5	108.8 $\pm$ 65.8	116.0 $\pm$ 70.7	125.4 $\pm$ 78.6	144.0 $\pm$ 96.7	<0.001
LDL-C (mg/dL)	125.9 $\pm$ 29.8	122.0 $\pm$ 28.6	125.0 $\pm$ 29.1	126.5 $\pm$ 29.2	127.3 $\pm$ 29.9	129.0 $\pm$ 31.6	<0.001
HDL-C (mg/dL)	62.1 $\pm$ 15.9	64.3 $\pm$ 16.1	63.5 $\pm$ 16.0	62.3 $\pm$ 15.8	60.9 $\pm$ 15.8	59.2 $\pm$ 15.6	<0.001
HbA1c (%)	5.3 $\pm$ 0.6	5.4 $\pm$ 0.8	5.3 $\pm$ 0.6	5.3 $\pm$ 0.6	5.3 $\pm$ 0.5	5.4 $\pm$ 0.5	<0.001
Proteinuria ( $\geq 1+$ ) (%)	4.7	3.8	3.6	4.0	4.8	7.1	<0.001
Hypertension (%)	44.3	36.4	38.7	42.8	48.1	55.6	<0.001
Diabetes (%)	6.4	8.4	6.0	6.0	5.7	6.1	<0.001
Dyslipidemia (%)	55.1	46.1	50.4	54.9	58.5	66.0	<0.001

M, males; F, females; BP, blood pressure; eGFR, estimated glomerular filtration rate. Mean  $\pm$  SD.



**FIGURE 1:** Serum uric acid at baseline and the 2-year change in eGFR. eGFR, estimated glomerular filtration rate. The gender-specific quintiles of uric acid (mg/dL), Q1: males (M)  $\leq 4.9$ , females (F)  $\leq 3.7$ ; Q2: M 5.0–5.6, F 3.8–4.3; Q3: M 5.7–6.2, F 4.4–4.8; Q4: M 6.3–7.0, F 4.9–5.4 and Q5: M  $\geq 7.1$ , F  $\geq 5.5$ . Adjusted for gender, age, BMI, SBP, DBP, eGFR, HbA1c, triglyceride, LDL-C, HDL-C, smoking, alcohol consumption and proteinuria. †P < 0.05 versus Q1. Mean  $\pm$  SE.

proteinuria. The adjusted analysis showed that the change in eGFR observed at the 2-year follow-up was inversely correlated with serum uric acid levels at baseline ( $P < 0.001$ ) and the decline was significantly more rapid in subjects with high uric acid (Q3–Q5: M  $\geq 5.7$  mg/dL, F  $\geq 4.4$  mg/dL), as compared with those with low uric acid levels (Q1: M  $\leq 4.9$  mg/dL, F  $\leq 3.7$  mg/dL) (Figure 1). We performed a sensitivity analysis in the subjects without renal insufficiency at baseline. It showed similar results as presented in total population that the subjects with high uric acid at baseline showed a slow decline of eGFR in the unadjusted analysis and, in contrast, a faster decline of eGFR in the adjusted analysis (Supplementary Data, Figure S1). Furthermore, the adjusted analysis was performed in males and females separately, and it showed that the eGFR decline was significantly more rapid in subjects with high uric acid (Q3–Q5) in both males and females (Supplementary Data, Figure S2).

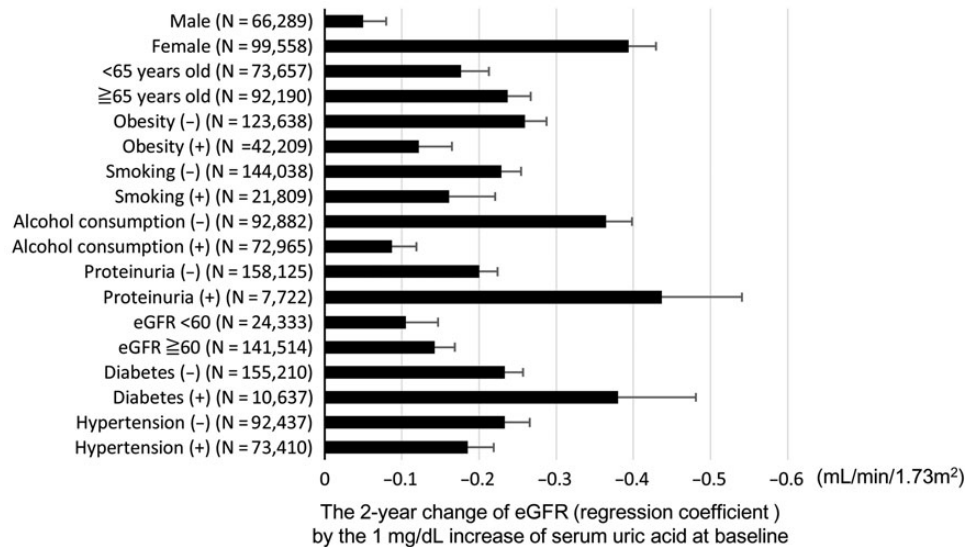
Second, we evaluated the independent effect of the increase in serum uric acid per 1 mg/dL on the changes in renal function. In the unadjusted model of linear regression analysis, the uric acid levels at baseline were positively correlated with the changes in eGFR (regression coefficient of the 1 mg/dL increase of uric acid, 0.355; SE 0.019;  $P < 0.001$ ). The baseline GFR shows a significant negative correlation with uric acid at baseline (regression coefficient  $-0.024$ , SE 0.001,  $P < 0.001$ ) and GFR change (regression coefficient  $-0.237$ , SE 0.001,  $P < 0.001$ ). Therefore, we performed a further analysis with the adjustment for baseline eGFR. It showed that the increase of serum uric acid was inversely correlated with change in eGFR (regression coefficient  $-0.362$ , SE 0.019,  $P < 0.001$ ). In the multiple linear regression analysis fully adjusted for the confounders, the regression coefficient of the 1 mg/dL increase of uric acid was  $-0.213$  (SE 0.023,  $P < 0.001$ ). There was a significant interaction between uric acid and other baseline parameters such as gender, age, eGFR, BMI, triglycerides, HDL-C, presence of proteinuria and alcohol consumption ( $P < 0.05$ ). The subgroup analyses, divided by the characteristics of the participants at baseline, showed that the effect of the increase in serum uric acid on eGFR was statistically significant in all

subgroups except in males and was especially prominent in females, those with diabetes and proteinuria and those who did not drink alcohol (Figure 2).

Third, we examined the association between uric acid and renal damage by using incidental renal insufficiency as the end point. We analyzed 141 514 subjects without renal insufficiency at baseline; the characteristics of these subjects were similar to those of the total population (Supplementary Data, Table S1). At the 2-year follow-up, there were 9169 cases (6.5%) of incidental renal insufficiency. The incidence of renal insufficiency increased along with the increase in uric acid levels at baseline (Q1: 4.2%, Q2: 5.2%, Q3: 6.5%, Q4: 7.8% and Q5: 9.6%, respectively,  $P < 0.001$ ). In the multivariable logistic regression analysis adjusted for confounders (age, gender, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, eGFR and proteinuria), the odds ratio (OR) significantly increased along with the increase of uric acid [OR: 1.104, 95% confidence interval (CI): 1.024–1.191 in Q4, OR: 1.203, 95% CI: 1.115–1.299 in Q5, using Q1 as a reference] (Table 2). The adjusted analysis was performed in males and females separately and revealed that the risk for incidental renal insufficiency was increased at uric acid of Q4–Q5 ( $\geq 6.3$  mg/dL) in males and Q5 ( $\geq 5.5$  mg/dL) in females, compared with the lowest quintile Q1 (Table 3). The OR for hyperuricemia and the 1 mg/dL increase in serum uric acid for incidental renal insufficiency were 1.117 (95% CI: 1.051–1.187) and 1.056 (95% CI: 1.035–1.078), respectively, after adjustment for confounders (Table 2).

## DISCUSSION

In this longitudinal nationwide cohort study, our results showed that an increase in serum uric acid levels is independently associated with a more rapid decline in eGFR and incidental renal insufficiency and showed that a slight increase within the normal range of serum uric acid levels might be a risk for renal damage in the general population. Furthermore, the association between uric acid and a decline in renal



**FIGURE 2:** The 2-year change in eGFR by the 1 mg/dL increase of serum uric acid at baseline. eGFR, estimated glomerular filtration rate. Adjusted for gender, age, BMI, SBP, DBP, eGFR, HbA1c, triglyceride, LDL-C, HDL-C, smoking, alcohol consumption and proteinuria. Mean ± SE.

**Table 2. OR of serum uric acid level categories for incidental renal insufficiency**

Category	Unadjusted			Adjusted <sup>a</sup>		
	OR	95% CI	P-value	OR	95% CI	P-value
Q1 (M ≤ 4.9, F ≤ 3.7)	Reference			Reference		
Q2 (M 5.0–5.6, F 3.8–4.3)	1.229	1.141–1.324	<0.001	0.995	0.920–1.077	0.909
Q3 (M 5.7–6.2, F 4.4–4.8)	1.576	1.466–1.696	<0.001	1.048	0.971–1.132	0.231
Q4 (M 6.3–7.0, F 4.9–5.4)	1.921	1.789–2.063	<0.001	1.104	1.024–1.191	0.010
Q5 (M ≥ 7.1, F ≥ 5.5)	2.399	2.236–2.575	<0.001	1.203	1.115–1.299	<0.001
Uric acid (M < 7.0, F < 6.0 mg/dL)	Reference			Reference		
Hyperuricemia (M ≥ 7.0, F ≥ 6.0 mg/dL)	1.739	1.645–1.837	<0.001	1.117	1.051–1.187	<0.001
Uric acid (per 1 mg/dL increase)	1.280	1.260–1.300	<0.001	1.056	1.035–1.078	<0.001

OR, odds ratio; CI, confidence interval; M, males; F, females.

<sup>a</sup>Adjusted for gender, age, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, eGFR and proteinuria.

**Table 3. Adjusted OR of serum uric acid level categories for incidental renal insufficiency by gender.**

Category	Males			Females		
	OR	95% CI	P-value	OR	95% CI	P-value
Q1 (M ≤ 4.9, F ≤ 3.7)	Reference			Reference		
Q2 (M 5.0–5.6, F 3.8–4.3)	1.007	0.896–1.133	0.904	0.985	0.886–1.096	0.784
Q3 (M 5.7–6.2, F 4.4–4.8)	1.113	0.992–1.248	0.067	1.013	0.913–1.125	0.806
Q4 (M 6.3–7.0, F 4.9–5.4)	1.183	1.059–1.323	0.003	1.065	0.960–1.182	0.237
Q5 (M ≥ 7.1, F ≥ 5.5)	1.243	1.107–1.397	<0.001	1.216	1.098–1.348	<0.001
Uric acid (M < 7.0, F < 6.0 mg/dL)	Reference			Reference		
Hyperuricemia (M ≥ 7.0, F ≥ 6.0 mg/dL)	1.134	1.045–1.230	0.003	1.136	1.036–1.245	0.007
Uric acid (per 1 mg/dL increase)	1.056	1.027–1.087	<0.001	1.076	1.043–1.109	<0.001

Adjusted for gender, age, obesity, hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, proteinuria and eGFR.

OR, odds ratio; CI, confidence interval; M, males; F, females.

function could be modulated by the characteristics of the studied population.

Previous studies showed conflicting results on the association between uric acid levels and kidney disease, and this

could be due to the insufficient statistical power resulting from a small sample size, the difference in characteristics of subjects and the analytical methods used [5]. In this study, we had a very large sample size to allow for subgroup

analyses with sufficient statistical power, different classifications of uric acid levels (hyperuricemia, quintiles and the 1 mg/dL increase in uric acid), to include various correction factors and end points (GFR decrease and incidental renal insufficiency). Therefore, the findings obtained in this study appear to be robust.

Our study showed that the decline of renal function was significantly more rapid with the increased uric acid levels ( $\geq 5.7$  mg/dL in males and  $\geq 4.4$  mg/dL in females), and the OR for incidental renal insufficiency was significantly increased with uric acid levels of  $\geq 6.3$  mg/dL in males and  $\geq 5.5$  mg/dL in females. This indicates that a slight increase within the normal range of serum uric acid might be a risk for renal function deterioration. This is consistent with the previous observation that cardiovascular mortality in females increases with serum uric acid levels of  $\geq 5.5$  mg/dL [1]. Together with previous observations, our finding suggests that the risk for reduced renal function might increase with increased serum uric acid levels, even within the normal range.

Although it is difficult to explain the mechanism of how uric acid causes renal function deterioration, a series of experimental studies provide a possible assumption that mild elevation of uric acid induces oxidative stress and endothelial dysfunction, resulting in the development of glomerular hypertension and arteriosclerosis [15]. This assumption is supported by the clinical observations that uric acid levels are associated with renal arteriopathy in biopsy specimens [16] and that an increase of uric acid ( $\geq 7$  mg/dL for men,  $\geq 6$  mg/dL for women) was independent predictor for the development of albuminuria in a community-based population [17].

There was an interaction between uric acid and several clinical parameters such as eGFR, gender, age, BMI, triglycerides, HDL-C, presence of proteinuria and alcohol consumption. This indicates that the characteristics of the studied population might modulate the association between uric acid levels and renal changes. Its effect seems to be stronger in females, those with diabetes and proteinuria and those who do not drink alcohol. In females, serum uric acid levels are lower than males, because of estrogenic compounds that enhance the renal urate excretion [18], and after menopause serum uric acid is increased [19], suggesting an important role of estrogenic hormones in the regulation of uric acid. The estrogenic compounds are also known to have a vascular protective property. Therefore, it is speculated that the increase in uric acid in females is induced by the combination of the decrease of the protective estrogenic compounds and the overproduction of uric acid. This might enhance the effect of uric acid on renal function in females. Hyperuricemia increases intraglomerular pressure [20] and urinary albumin excretion [21]. Diabetes also develops glomerular hypertension and albuminuria, and massive proteinuria is a risk for ESKD [22]. Therefore, it is speculated that hyperuricemia and diabetes synergistically promote kidney injury by inducing glomerular hypertension and proteinuria. Several studies disclosed that regular light-to-moderate drinking appears to protect against incident hypertension and cardiovascular events [23]. Such protective effect of alcohol consumption might attenuate the aggravating effect of uric acid

on renal function. The precise mechanism of how these factors interact with uric acid warrants a further research.

Interestingly, there was a positive association between uric acid levels and the change in eGFR in the unadjusted model that became inverse in the eGFR- and multivariate-adjusted models. A significant interaction between uric acid levels and renal function was detected. The baseline GFR was reported to be negatively correlated with GFR changes in the diabetic population [24]. Similarly, in this study, the baseline GFR shows a significant negative correlation with uric acid at baseline and GFR change. This indicates that subjects with high eGFR at baseline is likely to show a low uric acid at baseline and a rapid decline of eGFR. This observation suggests that eGFR at baseline should be regarded as a confounding factor to evaluate the independent effect of uric acid on renal function. Some previous studies did not include baseline eGFR in their multivariate-adjusted models, which may explain the conflicting results observed.

The increase in uric acid was associated with a slow decline of eGFR, but a high incidence of renal insufficiency in the unadjusted model. One of the possible explanations for these contrasting results between the eGFR change and incident renal insufficiency is the difference in baseline eGFR among the quartiles. The subjects with high uric acid are likely to show low eGFR at baseline and to fall into a category of renal insufficiency with a small decline of eGFR. On the other hand, the subjects with low uric acid are likely to show high eGFR at baseline and not to develop renal insufficiency even with a relatively large decline of eGFR.

The strength of this study is the large number of nationwide samples that were prospectively followed. This adds reliability to our results, even in the subgroup analyses. However, this study has several limitations. First, the serum uric acid levels were measured only at the baseline. Therefore, the changes in serum uric acid levels during the follow-up period that might have an independent effect on renal outcome [25] were not evaluated. Second, the eGFR was evaluated only twice (at baseline and 2 years). These parameters are known to show day-to-day variations. Measuring them twice only might, therefore, underestimate the association between uric acid levels and renal outcomes. Third, renal function was estimated by using the Japanese equation for eGFR, not inulin clearance. Fourth, we have no information on uric acid-lowering medication use in this population.

In conclusion, our study showed that serum uric acid levels are an independent factor for a more rapid decline in renal function in a community-based population and that a slight increase in uric acid levels within the normal range might be a risk for a decline in renal function. To understand the effect of serum uric acid levels on the progression of renal disease, clinical trials of uric acid-lowering therapy are required.

#### SUPPLEMENTARY DATA

Supplementary data are available online at <http://ndt.oxfordjournals.org>.

## ACKNOWLEDGEMENTS

This study was supported by the Health and Labor Sciences Research Grant for ‘the Study on the appropriate states of Specific Health Checkups and Specific Health Guidance for prevention of CKD progression and the design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by Specific Health Checkups’ from the Ministry of Health, Labour and Welfare of Japan.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

- Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971–1992. *National Health and Nutrition Examination Survey*. *JAMA* 2000; 283: 2404–2410
- Chen JH, Chuang SY, Chen HJ *et al*. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. *Arthritis Rheum* 2009; 61: 225–232
- Madero M, Sarnak MJ, Wang X *et al*. Uric acid and long-term outcomes in CKD. *Am J Kidney Dis* 2009; 53: 796–803
- Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351: 1296–1305
- Jalal DI, Chonchol M, Chen W *et al*. Uric acid as a target of therapy in CKD. *Am J Kidney Dis* 2013; 61: 134–146
- Obermayr RP, Temml C, Gutjahr G *et al*. Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol* 2008; 19: 2407–2413
- Weiner DE, Tighiouart H, Elsayed EF *et al*. Uric acid and incident kidney disease in the community. *J Am Soc Nephrol* 2008; 19: 1204–1211
- Zhang L, Wang F, Wang X *et al*. The association between plasma uric acid and renal function decline in a Chinese population-based cohort. *Nephrol Dial Transplant* 2012; 27: 1836–1839
- Hsu CY, Iribarren C, McCulloch CE *et al*. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009; 169: 342–350
- Iseki K, Ikemiya Y, Inoue T *et al*. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004; 44: 642–650
- Chonchol M, Shlipak MG, Katz R *et al*. Relationship of uric acid with progression of kidney disease. *Am J Kidney Dis* 2007; 50: 239–247
- Konta T, Ikeda A, Ichikawa K *et al*. Blood pressure control in a Japanese population with chronic kidney disease: a baseline survey of a nationwide cohort. *Am J Hypertens* 2012; 25: 342–347
- WHO/IASO/IOTF. *The Asia-Pacific Perspective: Redefining Obesity and Its Treatment*. Health Communications Australia Pty Ltd, 2000, pp. 15–21
- Matsuo S, Imai E, Horio M *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982–992
- Johnson RJ, Nakagawa T, Jalal D *et al*. Uric acid and chronic kidney disease: which is chasing which? *Nephrol Dial Transplant* 2013; 28: 2221–2228
- Kohagura K, Kochi M, Miyagi T *et al*. An association between uric acid levels and renal arteriopathy in chronic kidney disease: a biopsy-based study. *Hypertens Res* 2013; 36: 43–49
- Suzuki K, Konta T, Kudo K *et al*. The association between serum uric acid and renal damage in a community-based population: the Takahata study. *Clin Exp Nephrol* 2013; 17: 541–548
- Antón FM, García Puig J, Ramos T *et al*. Sex differences in uric acid metabolism in adults: evidence for a lack of influence of estradiol-17 beta (E2) on the renal handling of urate. *Metabolism* 1986; 35: 343–348
- Hak AE, Choi HK. Menopause, postmenopausal hormone use and serum uric acid levels in US women— the Third National Health and Nutrition Examination Survey. *Arthritis Res Ther* 2008; 10: R116
- Mazzali M, Hughes J, Kim YG *et al*. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001; 38: 1101–1106
- Fukui M, Tanaka M, Shiraiishi E *et al*. Serum uric acid is associated with microalbuminuria and subclinical atherosclerosis in men with type 2 diabetes mellitus. *Metabolism* 2008; 57: 625–629
- Yamagata K, Ishida K, Sairenchi T *et al*. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007; 71: 159–166
- Beilin LJ, Puddey IB, Burke V. Alcohol and hypertension— kill or cure? *J Hum Hypertens* 1996; 10(Suppl 2): S1–R115
- Yokoyama H, Kanno S, Takahashi S *et al*. Risks for glomerular filtration rate decline in association with progression of albuminuria in type 2 diabetes. *Nephrol Dial Transplant* 2011; 26: 2924–2930
- Iseki K, Iseki C, Kinjo K. Changes in serum uric acid have a reciprocal effect on eGFR change: a 10-year follow-up study of community-based screening in Okinawa, Japan. *Hypertens Res* 2013; 36: 650–654

Received for publication: 31.3.2014; Accepted in revised form: 27.6.2014