Vol.3, No.8, 498-503 (2011)
doi:10.4236/health.2011.38082

Decreasing serum uric acid levels might be associated with improving estimated glomerular filtration rate (eGFR) in Japanese men

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Received 8 June 2011; revised 20 July; accepted 31 July 2011.

ABSTRACT

The link between changes in a subject's serum uric acid levels and his estimated glomerular filtration rate (eGFR) was evaluated in Japanese men. We used data for 108 Japanese men (45.3 ± 8.0 years) with a 1-year follow up. eGFR was defined by a new equation developed for Japan. eGFR was weakly correlated with serum uric acid levels (r = –0.287, *p* = 0.0026) at baseline. Subjects were given advice for dietary and lifestyle improvement. At the 1-year follow up, almost metabolic syndrome components were significantly improved. However, blood sugar and uric acid did not change and eGFR was significantly decreased. The changes in eGFR were weakly correlated with abdominal circumference (r = –0.249, *p* = 0.0094) and uric acid (r = –0.340, *p* = 0.0003). A decrease in serum uric acid levels may be associated with improving eGFR in Japanese men.

Keywords: Abdominal Circumference; Uric Acid; Estimated Glomerular Filtration Rate (eGFR); Metabolic Syndrome; Lifestyle Modification

1. INTRODUCTION

Chronic kidney disease (CKD) has become a public health challenge and is a common disorder [1]. For example, about 20% of adults have CKD, which is defined as kidney damage or a glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 for at least three months regardless of cause [2]. We have also previously reported in a cross-sectional study that the estimated glomerular filtration rate (eGFR) [3] in men with abdominal obesity and in women with hypertension was significantly lower than that in subjects without these components of metabolic syndrome [4]. In addition, we also showed that decreasing abdominal circumference in men and decreasing systolic blood pressure in women were associated with improving eGFR with lifestyle modification [5, 6]. In turn, there some reports according to the link between serum uric acid levels and CKD in foreign countries [7-12]. However, whether decreases in serum uric acid levels are beneficial for improving eGFR, and what affects this has on eGFR remain to be investigated in a longitudinal study in Japanese men.

In this study, we evaluate the link between changes in eGFR and changes in serum uric acid levels in Japanese men with a 1-year follow up.

2. SUBJECTS AND METHODS

2.1. Subjects

We used data for 108 Japanese men, aged 45.3 ± 8.0 years, who met the following criteria: 1) received a health check-up including special health guidance and a follow-up check-up 1-year later, 2) received anthropometric measurements, fasting blood examination including serum uric acid levels and blood pressure measurements as part of the annual health check-up, 3) received no medications for diabetes, hypertension, and/or dyslipidemia, and 4) provided written informed consent (**Table 1**).

At the first health check-up, all subjects were given instructions by well-trained medical staff on how to change their lifestyle as special health guidance. Nutritional instruction was provided with a well-trained nutritionist, who planned a diet for each subject based on their data and provided simple instructions (*i.e.* not to eat

Table 1. Clinical characteristics and changes in parameters with 1-year follow up.

	Baseline	Follow up	*p*
Number of Subjects	108		
Age	45.3 ± 8.0		
Height (cm)	168.9 ± 5.3		
Body weight (kg)	76.5 ± 11.5	74.9 ± 10.8	<0.0001
Body mass index (kg/m^2)	26.8 ± 3.5	26.2 ± 3.3	0.0001
Abdominal circumference (cm)	89.1 ± 9.9	86.9 ± 9.3	<0.0001
Systolic blood pressure (mmHg)	131.4 ± 14.5	123.6 ± 12.1	<0.0001
Diastolic blood pressure (mmHg)	82.4 ± 11.4	77.0 ± 8.9	<0.0001
Triglyceride (mg/dl)	158.1 ± 114.4	126.4 ± 83.0	0.0029
HDL cholesterol (mg/dl)	53.3 ± 14.5	55.6 ± 14.7	0.0260
Blood sugar (mg/dl)	103.4 ± 18.4	104.7 ± 29.6	0.4731
Uric acid (mg/dl)	6.1 ± 1.3	6.0 ± 1.3	0.3862
Cr (mg/dl)	0.80 ± 0.11	0.83 ± 13.3	0.0002
eGFR (ml/min/1.73 m^2)	85.0 ± 14.0	806. ± 13.3	<0.0001
		Mean ± SD	

too much and to consider balance when they eat). Exercise instruction was also provided by a well-trained physical therapist, who encouraged each subject to increase their daily amount of steps walked.

Ethical approval for the study was obtained from the Ethical Committee of Okayama Health Foundation.

2.2. Anthropometric and Body Composition Measurements

Anthropometric and body compositions were evaluated based on the following parameters: height, body weight and abdominal circumference. Body mass index (BMI) was calculated by weight/[height]^2, in kg/m^2. Abdominal circumference was measured at the umbilical level in standing subjects after normal expiration [13].

2.3. Blood Pressure Measurements at Rest

Resting systolic and diastolic blood pressures were measured indirectly using a mercury sphygmomanometer placed on the right arm of the seated participant after at least 15 min of rest.

2.4. Urine Examination

Urine samples were collected from the second- morning urine (before 10 a.m.) and subjected to examination within 1 h. The urine examination was performed using urine test strips (BAYER, Tokyo, Japan). The reagent strip was dipped directly into the urine sample. Just after dipping, the sample was graded as –: negative, ±: trace positive, +: positive (30 mg/dl), 2+: positive (100 mg/dl), 3+: positive (300 mg/dl) or 4+: positive (1,000 mg/dl) by comparison with a standard color chart found on the container's label.

2.5. Blood Sampling and Assays

We measured overnight fasting serum levels of createnine (Cr) (enzymatic method), uric acid, high-density lipoprotein (HDL) cholesterol, triglycerides (L Type Wako Triglyceride・H, Wako Chemical, Osaka, Japan) and blood sugar. eGFR was calculated using the following equation: eGFR (ml/min/1.73 m^2) = 194 × Cr$^{-1.094}$ × Age$^{-0.287}$ [3]. Reduced eGFR was defined as an eGFR < 60 ml/min/1.73 m^2. Serum uric acid levels were measured by the Uricase-Peroxidase method. The institutional normal range was 2.5 - 7.0 mg/dl.

2.6. Definition of Metabolic Syndrome

Men with an abdominal circumference in excess of 85 cm were defined as having metabolic syndrome if they also had two or more of the following components: 1) Dyslipidemia: triglycerides ≥ 150 mg/dl and/or HDL cholesterol < 40 mg/dl, 2) High blood pressure: blood pressure ≥ 130/85 mmHg, 3) Impaired glucose tolerance: fasting plasma glucose ≥ 110 mg/dl [13].

2.7. Statistical Analysis

Data are expressed as means ± standard deviation (SD). A statistical analysis was performed using a paired *t* test, χ^2 test and covariance analysis: $p < 0.05$ was considered to be statistically significant. Pearson' s correla-

tion coefficients were calculated and used to test the significance of the linear relationship among continuous variables; stepwise multiple regression analysis was also used.

3. RESULTS

The clinical parameters at the baseline and the 1-year follow up are summarized in **Table 1**. Anthropometric, body composition parameters and metabolic syndrome components, except blood sugar, were significantly improved with lifestyle modification after one year. However, serum uric acid levels did not change, and Cr was significantly increased and eGFR was significantly decreased. However, thirty five subjects was diagnosed as having metabolic syndrome at baseline and seventeen subjects was diagnosed as having metabolic syndrome, and subjects with metabolic syndrome were significantly reduced after one year ($p < 0.0001$). One subject was diagnosed with reduced eGFR at baseline and two subjects were diagnosed with reduced eGFR at the 1-year follow up. In addition, four subjects were identified as trace positive, two subjects were identified as positive (+) and one subject was identified as positive (2+) for proteinuria at baseline and five subjects were identified as trace positive, four subjects were identified as positive (+) and two subjects were identified as positive (2+) at the 1-year follow up.

In subjects not taking medications, we also compared eGFR levels between the groups with and without each component of the Japanese definition of metabolic syndrome (**Table 2**). To avoid the influence of age, we used age as a covariate and compared eGFR between men with and those without metabolic syndrome components using covariance analysis. There were no significant differences in eGFR between the groups with or without components of metabolic syndrome. In addition, eGFR in subjects with metabolic syndrome was similar to that in subjects without it, even after adjusting for age. Serum uric acid levels was negatively and weakly correlated with eGFR at baseline (r = –0.287, $p = 0.0026$) (**Figure 1**).

We further evaluated the relationship between changes in eGFR and changes in clinical parameters. Changes in eGFR were weakly correlated with changes in abdominal circumference (r = –0.249, $p = 0.0094$) (**Table 3**). However, changes in eGFR were not significantly correlated with changes in other metabolic components. Changes in eGFR were negatively correlated with changes in serum uric acid levels (r = –0.340, $p = 0.0003$) (**Table 3**, **Figure 2**). We also used stepwise multiple regression analysis to evaluate the effect of changes in clinical parameters, *i.e.* age, abdominal circumference, systolic blood pressure, diastolic blood pressure, triglyceride, HDL cholesterol, blood sugar and serum uric acid levels on the change in eGFR, and found that only change in abdominal circumference and serum uric acid levels were significant [Change in eGFR = –5.296 – 0.330 (change in abdominal circumference) –3.259 (change in uric acid) , $r^2 = 0.149$, $p = 0.0002$].

4. DISCUSSION

Iseki *et al.* [14], Ninomiya T *et al.* [15] and Tanaka *et al.* [16] showed that metabolic syndrome, using the modified ATP III definition [17], was associated with CKD in the Japanese population. Compared with subjects with 0 or 1 component of metabolic syndrome, subjects with 2, 3 and 4 or more components had odds ratios of 1.13, 1.90 and 2.79 for CKD [15]. In this study, thirty five

Table 2. Comparison of eGFR between men with and without metabolic syndrome.

	Abdominal obesity (–)	Abdominal obesity (+)	*p*	*p* (Afrer adjusting for age)
Number of subjects	35	73		
eGFR (ml/min/1.73 m^2)	80.3 ± 14.5	87.2 ± 13.3	0.0168	0.6214
	Impaired glucose torelance (–)	Impaired glucose torelance (+)		
Number of subjects	84	24		
eGFR (ml/min/1.73 m^2)	83.9 ± 13.9	88.8 ± 13.8	0.1246	0.8832
	Hypertension (–)	Hypertension (+)		
Number of subjects	43	65		
eGFR (ml/min/1.73 m^2)	83.8 ± 15.5	85.8 ± 13.0	0.4688	0.8588
	Dyslipidemia (–)	Dyslipidemia (+)		
Number of subjects	60	48		
eGFR (ml/min/1.73 m^2)	84.0 ± 14.3	86.2 ± 13.6	0.4052	0.7367
	Metabolic syndrome (–)	Metabolic syndrome (+)		
Number of subjects	73	35		
eGFR (ml/min/1.73 m^2)	83.7 ± 14.2	87.6 ± 13.4	0.1852	0.3008

Mean ± SD

Table 3. Simple correlation analysis between changes in eGFR and changes in clinical parameters with 1-year follow up.

	r	*p*
Abdominal circumference (cm)	–0.249	**0.0094**
Systolic blood pressre (mmHg)	–0.101	0.2996
Diastolic blood pressure (mmHg)	0.025	0.7946
Triglyceride (mg/dl)	–0.050	0.6071
HDL cholesterol (mg/dl)	–0.044	0.6496
Blood sugar (mg/dl)	–0.037	0.7011
Uric acid (mg/dl)	–0.340	**0.0003**

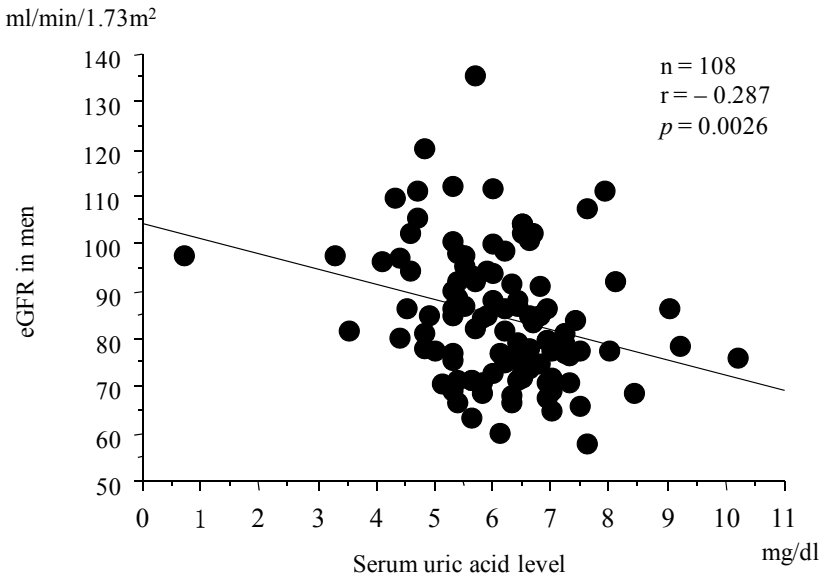

Figure 1. Simple correlation analysis between eGFR and serum uric acid levels at baseline.

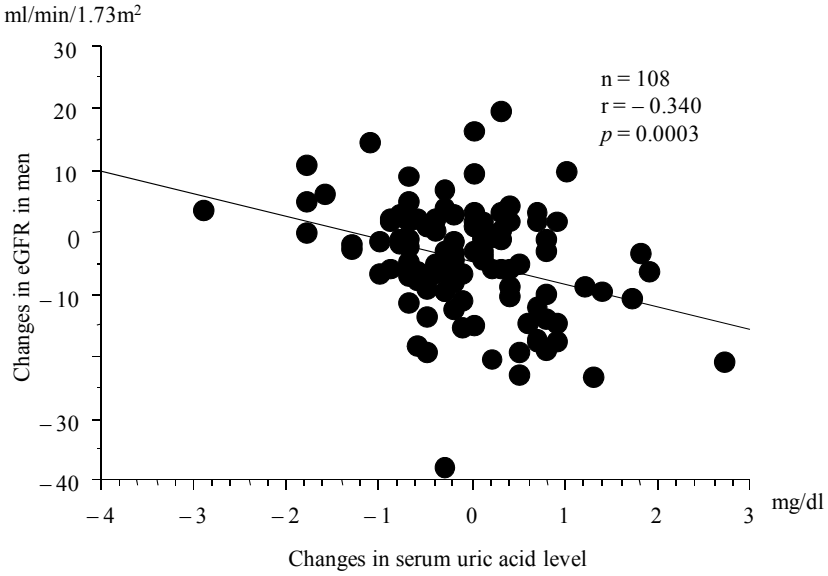

Figure 2. Simple correlation analysis between changes in eGFR and changes in serum uric acid levels at 1-year follow up.

subjects was diagnosed as having metabolic syndrome, using the Japanese criteria, at baseline and seventeen subjects were diagnosed as having metabolic syndrome at the 1-year follow up. We have previously reported that the prevalence of metabolic syndrome was 30.7% in Japanese men [18]. In this study, with lifestyle modification after the initial health check-up, metabolic components were significantly improved in men without medications at the one year follow-up. Although eGFR and serum uric acid levels were not improved after one year, changes in eGFR were negatively correlated with changes in serum uric acid levels. Taken together, reducing serum uric acid levels such as medications may be useful for improving eGFR in Japanese men.

Higher serum uric acid levels contribute to the development of renal injury and end-stage renal disease [7-12]. Satirapoj B *et al.* reported in a cross-sectional study that high serum uric acid level was independently associated with increased prevalence of CKD in 5546 Southeast Asian population [7]. The age-adjusted odds ration for CKD, with subjects with no hyperuricemia and no metabolic syndrome, was 5.85 for subjects with both hyperuricemia and metabolic syndrome [8]. Yen CJ *et al.* also showed that serum uric acid levels were associated with eGFR and decline in renal function in elderly Taiwanese subjects by longitudinal analysis [9]. In Japanese, hyperuricemia, hypercholesterolemia and diabetes are risk factors for CKD in peripheral arterial disease [19]. In the present study, there was weak relationship between eGFR and serum uric acid levels at baseline. In addition, we revealed that, changes in serum uric acid levels were correlated with changes in eGFR in men without medications. Changes in other metabolic components, except abdominal circumference, were not linked to changes in eGFR. Therefore, the clinical impact of serum uric acid levels on eGFR was noted in Japanese men.

Potential limitations remain in our study. First, the small sample size in our study makes it difficult to infer causality between eGFR and serum uric acid levels. In addition, eGFR and serum uric acid levels were not increased with lifestyle modification after one year. Second, we also could not reveal the mechanism of the linkage between eGFR and serum uric acid levels. Third, most of the enrolled subjects were not diagnosed as CKD at baseline. Therefore, the results in this study may not apply for patients with CKD. Further prospective studies using medications are needed in Japanese subjects.

5. ACKNOWLEDGEMENTS

This research was supported in part by Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare, Japan.

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