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

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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**

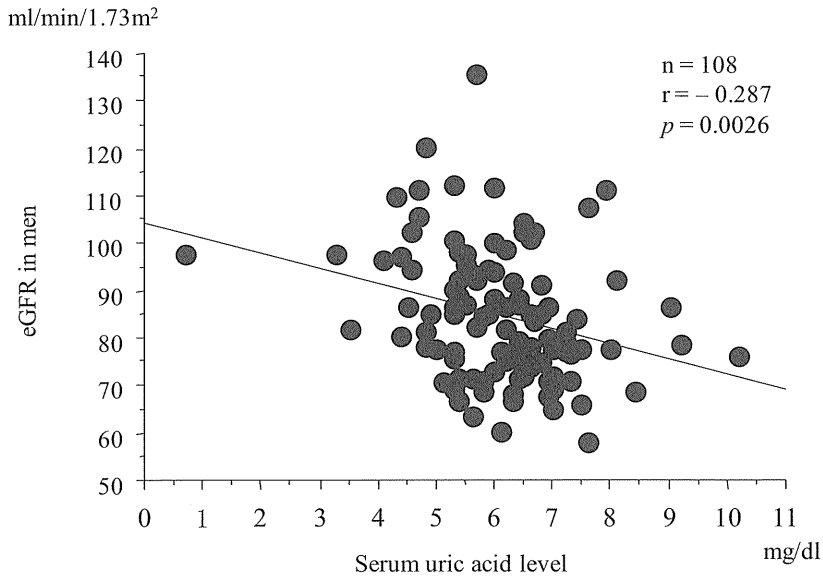

Figure 1. Simple correlation analysis between eGFR and serum uric acid levels at baseline.

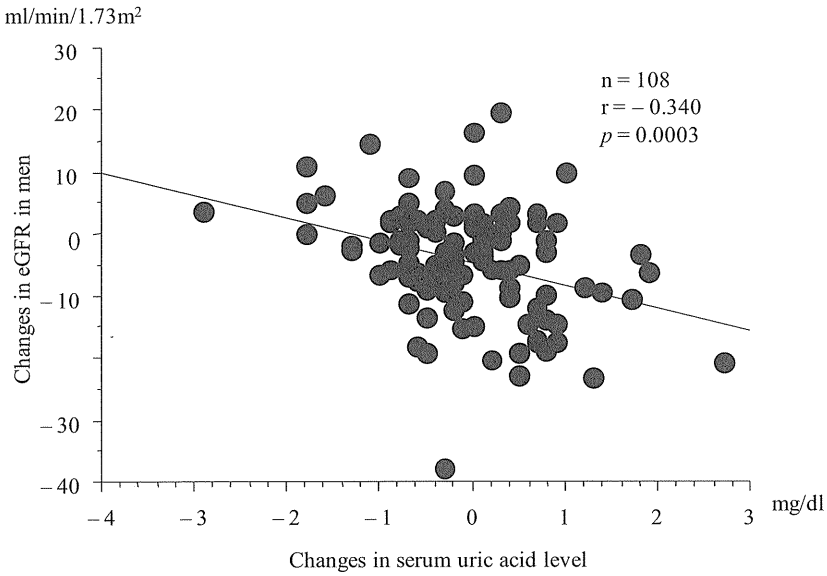

Figure 2. Simple correlation analysis between changes in eGFR and changes in serum uric acid levels at 1-year follow up.

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.

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REFERENCES

[1] National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney disease outcome quality initiative. *American Journal of Kidney Diseases*, **39**, S1-S266.

[2] Imai, E., Horio, M., Iseki, K., *et al.* (2007) Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clinical and Experimental Nephrology*, **11**, 156-163. doi:10.1007/s10157-007-0463-x

[3] Matsuo, S., Imai, E., Horio, M., *et al.* (2009) Revised equations for estimated GFR from serum creatinine in Japan. *American Journal of Kidney Diseases*, **53**, 982-992. doi:10.1053/j.ajkd.2008.12.034

[4] Miyatake, N., Shikata, K., Makino, H. and Numata, T. (2010) Relationship between estimated glomerular filtration rate (eGFR) and metabolic syndrome in the Japanese population. *Acta Medica Okayama*, **64**, 203-208.

[5] Miyatake, N., Shikata, K., Makino, H. and Numata, T. (2011) Decreasing abdominal circumference is associated with improving estimated glomerular filtration rate (eGFR) with lifestyle modification in Japanese men: A pilot study. *Acta Medica Okayama*, in press.

[6] Miyatake, N., Shikata, K., Makino, H. and Numata, T. (2010) Decreasing systolic blood pressure is associated with improving estimated glomerular filtration rate (eGFR) with lifestyle modification in healthy Japanese women. *Acta Medica Okayama*, **64**, 253-258.

[7] Satirapoj, B., Supasyndh, O., Chaiprasert, A., *et al.* (2010) Relationship between serum uric acid levels with chronic kidney disease in a Southeaset Asian population. *Nephrology* (*Carlton*), **15**, 253-258. doi:10.1111/j.1440-1797.2009.01179.x

[8] See, L.C., Kuo, C.F., Chang, F.H., *et al.* (2011) Hyperuricemia and metabolic syndrome: Associations with chronic kidney disease. *Clinical Rheumatology*, **30**, 323-330. doi:10.1007/s10067-010-1461-z

[9] Yen, C.J., Chiang, C.K., Ho, L.C., *et al.* (2009) Hyperuricemia associated with rapid renal function decline in elderly Taiwanese subjects. *Journal of the Formosan Medical Association*, **108**, 921-928. doi:10.1016/S0929-6646(10)60004-6

[10] Cain, L., Shankar, A., Ducatman, A.M. and Steenland, K. (2010) The relationship between serum uric acid and chronic kidney disease among Appalachian adults. *Nephrology Dialysis Transplantation*, **25**, 3593-3599. doi:10.1093/ndt/gfq262

[11] Madero, M., Sarnak, M.J., Wang, X., *et al.* (2009) Uric acid and long-term outcomes in CKD. *American Journal of Kidney Diseases*, **53**, 796-803. doi:10.1053/j.ajkd.2008.12.021

[12] Sturm, G., Kollerits, B., Neyer, U., *et al.* (2008) 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. *Experimental Gerontology*, **43**, 347-352. doi:10.1016/j.exger.2008.01.006

[13] Anonym (2005) Definition and the diagnostic standard

for metabolic syndrome—Committee to evaluate diagnostic standards for metabolic syndrome (in Japanese). *Nippon Naika Gakkai Zasshi*, **94**, 794-809.

[14] Iseki, K., Kohagura, K., Sakime, A., *et al.* (2007) Changes in the demographics and prevalence of chronic kidney disease in Okinawa, Japan (1993 to 2003). *Hypertension Research*, **30**, 55-62. doi:10.1291/hypres.30.55

[15] Ninomiya, T., Kiyohara, Y., Kubo, M., *et al.* (2006) Metabolic syndrome and CKD in a general Japanese population: The Hisayama Study. *American Journal of Kidney Diseases*, **48**, 383-391. doi:10.1053/j.ajkd.2006.06.003

[16] Tanaka, H., Shiohira, Y., Uezu, Y., *et al.* (2006) Metabolic syndrome and chronic kidney disease in Okinawa, Japan. *Kidney International*, **69**, 369-374. doi:10.1038/sj.ki.5000050

[17] Anonym (2001) Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (adult treatment panel III). *Journal of the American Medical Association*, **285**, 2486-2497.

[18] Miyatake, N., Kawasaki, Y., Nishikawa, H., Takenami, S. and Numata, T. (2006) Prevalence of metabolic syndrome in Okayama prefecture, Japan. *Internal Medicine*, **45**, 107-108. doi:10.2169/internalmedicine.45.1509

[19] Endo, M., Kumakura, H., Kanai, H., *et al.* (2010) Prevalence and risk factors for renal artery stenosis and chronic kidney disease in Japanese patients with peripheral arterial disease. *Hypertension Research*, **33**, 911-915. doi:10.1038/hr.2010.93

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The relation between estimated glomerular filtration rate (eGFR) and coffee consumption in the Japanese

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ABSTRACT

We investigated the link between estimated glomerular filtration rate (eGFR) and coffee consumption in Japanese. We used data of 376 men and 794 women who were not taking any medications, aged 20 - 78 years, in this cross-sectional investigation study. eGFR was calculated using serum creatinine (Cr), age and sex. Habitual coffee consumption was defined as drinking one or more cups of coffee per day. Two hundred thirty three men (62.0%) and 400 women (50.4%) were subjects with habitual coffee consumption (coffee consumption 1 cup/day ≥). eGFR was negatively correlated with age (men: r = –0.533, women: r = –624). eGFR in subjects with coffee consumers was not significantly different from that in subjects without coffee consumers after adjusting for age in both sexes (men: p = 0.1375, women: p = 0.2069). Among Japanese not taking medications, coffee consumption was not associated with eGFR in the Japanese population.

Keywords: Estimated Glomerular Filtration Rate (eGFR); Coffee Consumption; Creatinine; Japanese

1. INTRODUCTION

Coffee is one of the most common frequently consumed beverages and 10.6 coffee cups per week are reported to be consumed [1] and about 50% of Japanese drinks coffee daily [2]. Some studies showed that habitual coffee consumption may improve insulin resistance and abdominal glucose metabolism [3-5]. However, Tofovic *et al.* [6] have reported that prolonged consumption of caffeine has adverse effects on renal function, in high-renin hypertension.

Chronic kidney disease (CKD) has become a public health challenge and is a common disorder [7]. 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 [8]. We have also previously reported in a cross-sectional study that the estimated glomerular filtration rate (eGFR) [9] in men with abdominal obesity and in women with hypertension was significantly lower than that in subjects without these components of metabolic syndrome [10]. Therefore, the effect of coffee consumption on renal function may be required and it still remains to be investigated in Japanese.

In this study, we investigated renal function evaluated by eGFR in Japanese and evaluated the clinical impact of coffee consumption on eGFR in subjects not taking medications.

2. SUBJECTS AND METHODS

2.1. Subjects

We used all data on 1170 Japanese (376 men and 794 women) aged 20-78 years in a cross-sectional study. All subjects met the following criteria: 1) they had wanted to change their lifestyle *i.e.* diet and exercise habits, and had received an annual health checkup from April 2006 to December 2010 at Okayama Southern Institute of Health; 2) they had received creatinine (Cr), anthropometric measurements and evaluation of coffee consumption as part of their annual health checkups; and 3) they provided informed consent (**Table 1**).

The study was approved by the Ethics Committee of Okayama Health Foundation.

Table 1. Clinical profiles of enrolled subjects.

	Men			Women		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Number of subjects	376			794		
Age	42.7 ± 13.2	20	74	40.6 ± 14.5	20	78
Height (cm)	170.3 ± 6.1	143.7	186.7	157.4 ± 5.3	140.5	172.9
Body weight (kg)	71.3 ± 11.7	42.0	120.3	54.4 ± 8.5	29.3	113.9
Body mass index (kg/m^2)	24.6 ± 3.6	14.6	41.8	22.0 ± 3.3	14.1	44.9
Abdominal circumference (cm)	85.3 ± 10.1	60.5	122.0	75.7 ± 9.8	55.1	120.0
Hip circumference (cm)	95.7 ± 8.4	74.5	193.4	92.0 ± 7.0	70.0	196.5
Systolic blood pressure (mmHg)	127.4 ± 13.8	94.0	191.0	114.7 ± 15.6	85.0	192.0
Diastolic blood pressure (mmHg)	75.9 ± 10.9	50.0	112.0	67.0 ± 10.9	40.0	111.0
Creatinine (mg/dl)	0.84 ± 0.12	0.51	1.34	0.62 ± 0.09	0.29	1.00
eGFR (ml/min/1.73 m^2)	83.2 ± 15.5	41.0	139.7	88.8 ± 18.2	42.5	172.9
Coffee consumption (cup/week)	9.5 ± 8.5	0	40	7.5 ± 7.9	0	50

2.2. Anthropometric Measurements

The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, and hip circumference. BMI was calculated by weight/[height]^2 (kg/m^2). The abdominal circumference was measured at the umbilical level and the hip was measured at the widest circumference over the trochanter in standing subjects after normal expiration [11].

2.3. Blood Pressure Measurements

Each participant's blood pressure was measured after resting at least 15 minutes in the sitting position.

2.4. Blood Sampling and Assays

The level of Cr was measured with an automated biochemical analyzer (model 7700; HITACHI, Tokyo, Japan) and Accuras Auto CRE (Shino-Test Corporation, Tokyo, Japan) at the Okayama Southern Institute of Health, Okayama Health Foundation. eGFR was calculated using the following equation: eGFR (ml/min/1.73 m^2) = 194 × Cr$^{-1.094}$ × Age$^{-0.287}$ (for men) and eGFR (ml/min/1.73 m^2) = 194 × Cr$^{-1.094}$× Age$^{-0.287}$ × 0.739 (for women) [9]. Reduced eGFR was defined as an eGFR < 60 ml/min/1.73 m^2.

2.5. Coffee Consumption

Subjects were asked how many cups of coffee per week. They were dichotomized into coffee consumers who drink one or more cups of coffee per day, and non-coffee consumers who seldom drink coffee. The way of drinking was not asked.

2.6. Statistical Analysis

Data are expressed as means ± standard deviation (SD) values. A comparison of parameters between the two groups was made using the unpaired *t*-test and covariance analysis. Simple correlation analysis was performed as well to test for the significance of the linear relationship among continuous variables: $p < 0.05$ was considered statistically significant.

3. RESULTS

The mean eGFR was 83.2 ± 15.5 ml/min/1.73 m^2 in men and 88.8 ± 18.2 ml/min/1.73 m^2 in women (**Table 1**). The mean coffee consumption was 9.5 ± 8.5 cups/week/person in men and 7.5 ± 7.9 cups/week/person. A diagnosis of reduced eGFR was made for 19 men (5.1%) and 27 women (3.4%). eGFR was negatively correlated with age in either sex (**Figure 1**).

We clarified the prevalence of subjects with coffee consumers among subjects who were not taking without medications (**Table 2**). Among the 1,170 Japanese subjects, 233 men (62.0%) and 400 women (50.4%) were coffee consumers (coffee consumption 1 cup/day ≥). The prevalence of coffee consumers was the highest in 50's in men and 70's in women.

In subjects not taking medications, we also compared eGFR levels between the groups with and without coffee

consumers of the Japanese (**Table 3**). To avoid the influence of age, we used age as a covariate and compared eGFR between Japanese with and without coffee consumers using covariance analysis. The significant difference of eGFR was not noted between subjects with and without coffee consumers, even after adjusting for age.

4. DISCUSSION

We firstly evaluated the link between eGFR using newly developed in Japan and coffee consumption in Japanese without taking any medications. The difference of eGFR was not noted between subjects with and without coffee consumers.

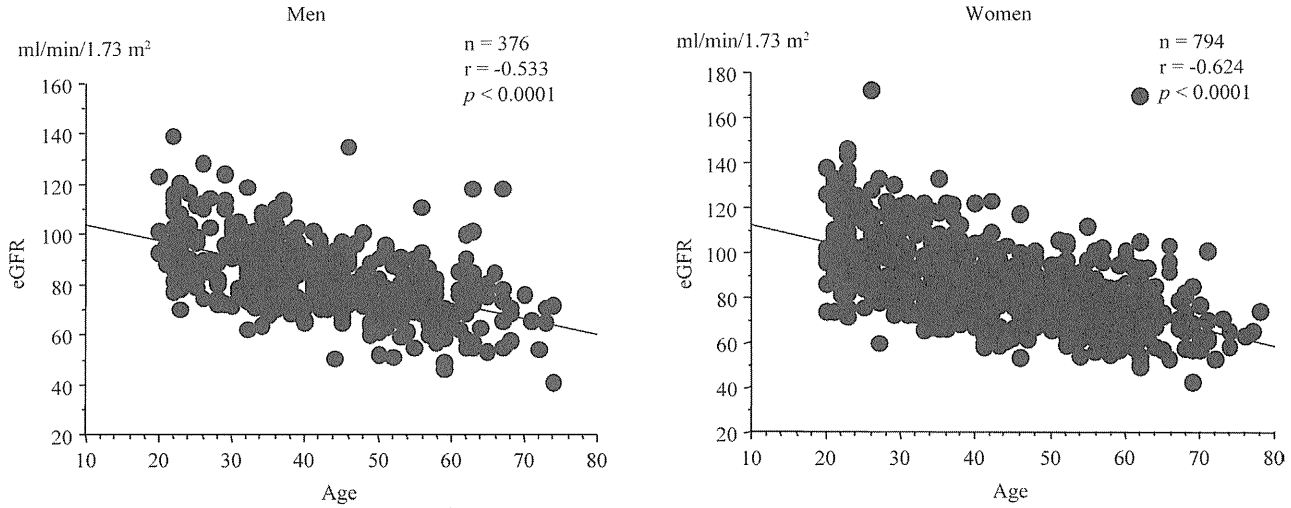

Figure 1. Simple correlation analysis between estimated glomerular filtration rate (eGFR) and age.

Table 2. Coffee consumption as classified by age groups.

	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70-	Total
Men							
Coffee consumption 1 cup/day <	44 (65.7)	37 (35.9)	32 (37.6)	16 (21.6)	12 (30.0)	2 (28.6)	143 (38.0)
Coffee consumption 1 cup/day ≥	23 (34.3)	66 (64.1)	53 (62.4)	58 (78.4)	28 (70.0)	5 (71.4)	233 (62.0)
Men							
Coffee consumption 1 cup/day <	206 (85.4)	73 (48.0)	37 (23.0)	45 (32.4)	29 (33.7)	4 (26.7)	394 (49.6)
Coffee consumption 1 cup/day ≥	35 (14.5)	79 (52.0)	124 (77.0)	94 (67.6)	57 (66.3)	11 (73.3)	400 (50.4)

Number of subjects (%).

Table 3. Comparison of eGFR between subjects as classified by coffee consumption.

	Coffee consumption 1 cup/day <	Coffee consumption 1 cup/day ≥	*p*	*p* (After adjusting for age)
Men				
Number of subjects	143	233		
Age	38.8 ± 13.7	45.1 ± 12.4	**<0.0001**	
eGFR (ml/min/1.73 m²)	86.5 ± 16.5	81.1 ± 14.4	**0.0009**	0.1375
Women				
Number of subjects	394	400		
Age	34.5 ± 14.3	46.6 ± 12.1	**<0.0001**	
eGFR (ml/min/1.73 m²)	94.1 ± 19.0	83.6 ± 15.9	**<0.0001**	0.2069

Mean ± SD.

Iso *et al.* [2] reported that consumption of green tea, coffee, and total caffeine was associated with a risk for type 2 diabetes in 17,413 subjects with 5-year follow-up. Multivariable odds ratio for diabetes among participants who frequently drank coffee (3 cups of coffee per day ≥) was 0.58, respectively, compared with those who drank less than 1 cup per week. According to the link between habitual coffee consumption and eGFR in Japanese, Nakajima *et al.* [12] reported that eGFR in coffee consumers (n = 182) was significantly higher than that in non-coffee consumers (n = 160), which was not attenuated even after adjustment for age, sex and considerable factors. Kotani *et al.* [13] also reported that coffee drinkers had higher eGFR values than non-coffee drinkers in 114 Japanese. The difference remained significant, independently of clinical variables. However, in this study, we could not found the significant difference of eGFR between subjects with and without habitual coffee consumption. Compared the previous studies, the age enrolled in this study was younger. In addition, the age in subjects with habitual coffee consumption was significantly higher than that in subjects without in this study. Enrolled subjects in this study were taking no medications, suggesting apparently healthy subjects. Prolonged caffeine consumption has adverse effects on renal function in rats [6]. Therefore, the results may not be similar to previous reports.

Potential limitations remain in this study. First, our study was a cross sectional and not a longitudinal study. Second, the 1170 subjects, all of whom wanted to change their lifestyle, underwent measurements for this study: they were therefore more health-conscious than the average person. Second, we could not clarify the mechanism the link between eGFR and coffee consumption. Third, the coffee consumption was reported to be 10.6 cups/week/person in 2008, and it is the highest between 40 and 59 (men: 13.5 cups/week/person, women: 14.2 cups/week/person) in Japanese by All Japan Coffee Association [1]. The coffee consumption was gradually increasing [1]. In this study, the mean of the coffee consumption was lower than that in the previous report. Further prospective studies are needed in Japanese subjects using the new Japanese criteria.

5. ACKNOWLEDGEMENTS

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REFERENCES

[1] All Japan Coffee Association (2011). http://coffee.ajca.or.jp/data/pdf/2010-04.pdf

[2] Iso, H., Date, C., Wakai, K., Fukui, M., Tamakoshi, A., JACC Study Group. (2006) The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. *Annals of Internal Medicine*, **144**, 554-562.

[3] Van Dam, R.M. (2008) Coffee consumption and risk of type 2 diabetes, cardiovascular diseases, and cancer. *Applied Physiology, Nutrition, and Metabolism*, **33**, 1269-1283. doi:10.1139/H08-120

[4] Greenberg, J.A., Boozer, C.N. and Geliebter, A. (2006) Coffee, diabetes, and weight control. *The American Journal of Clinical Nutrition*, **84**, 682-693.

[5] Tunnicliffe, J.M. and Shearer, J. (2008) Coffee, glucose homeostasis, and insulin resistance: Physiological mechanisms and mediators. *Applied Physiology, Nutrition, and Metabolism*, **33**, 1290-1300. doi:10.1139/H08-123

[6] Tofovic, S.P. and Jackson, E.K. (1999) Effects of long-term caffeine consumption on renal function in spontaneously hypertensive heart failure prone rats. *Journal of Cardiovascular Pharmacology*, **33**, 360-366. doi:10.1097/00005344-199903000-00003

[7] National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *American Journal of Kidney Diseases*, **39**, S1-S266.

[8] Imai, E., Horio, M., Iseki, K., Yamagata, K., Watanabe, T., Hara, S., Ura, N., Kiyohara, Y., Hirakata, H., Moriyama, T., Ando, Y., Nitta, K., Inaguma, D., Narita, I., Iso, H., Wakai, K., Yasuda, Y., Tsukamoto, Y., Ito, S., Makino, H., Hishida, A. and Matsuo, S. (2007) Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clinical and Experimental Nephrology*, **11**, 156-163. doi:10.1007/s10157-007-0463-x

[9] Matsuo, S., Imai, E., Horio, M., Yasuda, Y., Tomita, K., Nitta, K., Yamagata, K., Tomino, Y., Yokoyama, H. and Hishida, A. (2009) Revised equations for estimated GFR from serum creatinine in Japan. *American Journal of Kidney Diseases*, **53**, 982-992. doi:10.1053/j.ajkd.2008.12.034

[10] Miyatake, N., Shikata, K., Makino, H. and Numata, T. (2010) Relationship between Estimated Glomerular Filtration Rate (eGFR) and Metabolic Syndrome in the Japanese Population. *Acta Medica Okayama*, **64**, 203-208.

[11] Anonym (2005) Definition and the diagnostic standard for metabolic syndrome—Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. *Nippon Naika Gakkai Zasshi*, **94**, 794-809. doi:10.2169/naika.94.794

[12] Nakajima, K., Hirose, K., Ebata, M., Morita, K. and Munakata, H. (2009) Association between habitual coffee consumption and normal or increased estimated glomerular filtration rate in apparently healthy adults. *British Journal of Nutrition*, **103**, 149-152. doi:10.1017/S0007114509991681

[13] Kotani, K., Sakane, N., Yamada, T. and Taniguchi, N. (2010) Association between coffee consumption and the estimated glomerular filtration rate in the general Japanese population: Preliminary data regarding C-reactive protein concentration. *Clinical Chemistry and Laboratory Medicine*, **48**, 1773-1776. doi:10.1515/CCLM.2010.347

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Comparison of muscle strength between subjects with and without proteinuria

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ABSTRACT

We compared the levels of muscle strength between subjects with and without proteinuria. We used data of 721 men and 1063 women, aged 20 - 79 years, in this cross-sectional investtigation study. Parameters at muscle strength *i.e.* grip strength, leg strength and leg strength per body weight were evaluated. Proteinuria was measured by urine strip devices. Thirty five men (4.9%) and 27 women (2.5%) were diagnosed as having the proteinuria (+: 30 mg/dl) ≦). Leg strength and leg strength per body weight in men with proteinuria was significantly lower than that in men without proteinuria after adjusting for age. Grip strength in men with proteinuria was also lower than that in men without, but not at a significant level. However such link was not noted in women after adjusting for age. Among Japanese, proteinuria might be a modifiable factor of muscle strength in Japanese men.

Keywords: Proteinruia; Grip Strength; Leg Strength; Leg Strength per Body Weight

1. INTRODUCTION

Chronic kidney disease (CKD) has become a public health problem in Japan and it is a major risk factor for the end stage renal disease, cardiovascular disease and premature death [1,2]. 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 [3]. We have previously showed in a cross-sectional study that the estimated glomerular filtration rate (eGFR) [4] in men with abdominal obesity and in women with hypertension was significantly lower than that in subjects without these components of metabolic syndrome [5]. In addition, we have also reported that proteinuria was closely linked to lower cardiorespilatory fitness evaluated by ventilatory threshold (VT) [6].

It is also well known that low and declining muscle strength is associated with increased mortality, independent of physical activity and muscle mass [7]. In 2006 in Japan, levels of maximal oxygen uptake and muscle strength were recommended as exercise and physical activity reference quantity for health promotion 2006 (EPARQ2006) by the Ministry of Health, Labor and Welfare [8]. Although resistance training has been advocated as the most suitable exercise for increasing muscle strength [9,10], the link between proteinuria and muscle strength in a large sample of Japanese has not yet been investigated.

In this study, we investigated muscle strength evaluated by grip strength, leg strength and leg strength per body weight between subjects with and without proteinuria in Japanese.

2. SUBJECTS AND METHODS

2.1. Subjects

We used all data on 1,784 Japanese (721 men and 1063 women) aged 20 - 79 years in a cross-sectional study. All subjects met the following criteria: 1) they had wanted to change their lifestyle *i.e.* diet and exercise habits, and had received an annual health checkup at Okayama Southern Institute of Health; 2) they had received muscle strength, urine examination and anthropometric measurements as part of their annual health checkups; and 3) they provided informed consent (**Table 1**).

Table 1. Clinical profiles of enrolled subjects.

	Men			Women		
	Mean ± SD	Minimum	Maximum	Mean ± SD	Minimum	Maximum
Number of subjects	721			1063		
Age	47.9 ± 15.1	20	78	44.7 ± 13.9	20	79
Height (cm)	169.7 ± 6.0	143.7	186.7	156.9 ± 5.3	140.4	172.9
Body weight (kg)	71.3 ± 11.8	39.1	146.5	55.8 ± 9.6	29.3	118.0
Body mass index (kg/m^2)	24.7 ± 3.7	13.6	43.1	22.7 ± 3.8	14.1	44.9
Abdominal circumference (cm)	86.5 ± 10.3	62.4	135.0	78.3 ± 10.9	55.1	127.0
Right grip strength (kg)	42.4 ± 7.7	3.4	70.2	25.6 ± 5.1	7.1	45.1
Left grip strength (kg)	40.4 ± 7.6	4.6	63.1	24.3 ± 4.9	4.5	43.5
Leg strength (kg)	67.1 ± 17.5	19.0	140.0	41.5 ± 11.2	11.0	79.0
Leg strength per body weight	0.95 ± 0.22	0.28	1.65	0.75 ± 0.19	0.17	1.46

The study was approved by the Ethics Committee of Okayama Health Foundation.

2.2. Anthropometric Measurements

The anthropometric parameters were evaluated by using the following respective parameters such as height, body weight, body mass index (BMI), abdominal circumference, and hip circumference. BMI was calculated by weight/[height]^2 (kg/m^2). The abdominal circumference was measured at the umbilical level in standing subjects after normal expiration [11].

2.3. Muscle Strength

To assess muscle strength, grip and leg strength were measured [12]. Grip strength was measured using THP-10 (SAKAI, Tokyo, Japan), while leg strength was measured by COMBIT CB-1 (MINATO, Osaka, Japan). Isometric leg strength was measured as follows: the subject sat in a chair, grasping the armrest in order to fix the body position. A dynamometer was then attached to the subject's one ankle joint by a strap. The subject extended his or her leg to 60 degrees as described in previous reports [12,13] which have also demonstrated good accuracy for this measurement [13]. All muscle strength measurements were recorded in 2 trials, and the better one was employed for analysis. In addition, to standardize the influence of body weight, we calculated the ratio of leg strength to body weight; a ratio of 1.0 in leg strength per body weight has been a standard in past studies [13].

2.4. Urine Examination

Urine samples were collected from the second-morning urine (before 10 a.m.) and examined within 1 hour. The urine examination was performed using urine strip tests (BAYER, Tokyo, Japan). The reagent strip was dipped directly into the urine sample. Just after dipping, the sample is graded as −: negative, ±: trace positive, +: positive (30 mg/dl), 2+: positive (100 mg/dl), 3+: positive (300 mg/dl) or 4+: positive (1000 mg/dl) by comparison with a standard color chart found on the container's label [14].

2.5. Statistical Analysis

All data are expressed as mean ± standard deviation (SD) values. A statistical analysis was performed using an unpaired t test and covariance analysis, where $p < 0.05$ was considered to be statistically significant.

3. RESULTS

Clinical profiles are summarized in **Table 1**. Leg strength was 67.1 ± 17.5 kg in men and 41.5 ± 11.2 in women. Prevalence of proteinuria in enrolled subjects is also summarized in **Table 2**. A total of 35 men (4.9%) and 27 women (2.5%) was diagnosed as having the proteinuria (+: 30 mg/dl ≦).

We compared muscle strength between subjects with and without proteinuria (**Table 3**). In men, leg strength and leg strength per body weight in subjects with proteinuria was significantly lower than those in subjects without proteinuria even after adjusting for age by using covariance analysis (leg strength: $p = 0.0017$, leg strength per body weight: $p = 0.0495$). The significant differences of grip strength were not noted in men at a significant level (right grip strength: $p = 0.3691$, left grip strength: $p = 0.0670$). In women, parameters of muscle strength in subjects with proteinuria were not significant different from those in subjects without proteinuria (**Table 3**).

Table 2. Prevalence of proteinuria in enrolled subjects.

Proteinuria	20's	30's	40's	50's	60's	70's	Total	%
Men								
−	72	120	132	138	124	25	611	84.7
±	7	18	13	12	18	7	75	10.4
+	4	3	3	6	4	3	23	3.2
2+	0	3	2	1	3	1	10	1.4
3+	0	0	0	0	1	0	1	0.1
4+	0	0	0	0	1	0	1	0.1
Total	83	144	150	157	151	36	721	
Women								
−	165	224	202	207	144	30	972	91.4
±	13	15	10	18	8	0	64	6.0
+	5	1	3	5	2	0	16	1.5
2+	2	1	3	0	0	2	8	0.8
3+	1	2	0	0	0	0	3	0.3
Total	186	243	218	230	154	32	1063	

Table 3. Comparison of muscle strength between subjects with and without proteinuria.

	Proteinuria (− or ±)	Proteinuria (+≦)	*p*	*p* After adjusting for age
Men				
Number of subjects	686	35		
Age	47.8 ± 14.1	51.3 ± 16.2	0.1553	
Right grip strength (kg)	42.6 ± 7.6	39.6 ± 9.9	**0.0284**	0.3691
Left grip strength (kg)	40.5 ± 7.5	37.8 ± 8.9	**0.0379**	0.0670
Leg strength (kg)	67.3 ± 17.2	62.9 ± 21.7	0.1509	**0.0017**
Leg strength per body weight	0.95 ± 0.22	0.83 ± 0.26	**0.0017**	**0.0495**
Women				
Number of subjects	1036	27		
Age	44.8 ± 13.9	42.3 ± 16.3	0.3519	
Right grip strength (kg)	25.7 ± 5.1	23.5 ± 5.0	**0.0294**	0.7149
Left grip strength (kg)	24.3 ± 4.9	22.7 ± 4.4	0.0877	0.6094
Leg strength (kg)	41.5 ± 11.2	40.9 ± 11.5	0.7804	0.4926
Leg strength per body weight	0.75 ± 0.19	0.71 ± 0.18	0.2672	0.8468

4. DISCUSSION

In this study, we firstly evaluated the link between proteinuria and muscle strength *i.e.* grip strength, leg strength and leg strength per body weight in Japanese. Proteinuria might be a modifiable factor of muscle strength, especially in Japanese men.

Proteinuria and/or reduced renal function have been reported to be closely linked to cardio vascular disease (CVD) [15,16]. Anavekar *et al.* showed that even mild renal disease was considered a major risk factor for CVD after myocardial infarction in 14527 patients with acute myocardial infarction [15]. Irie *et al.* reported that they evaluated 30,764 men and 60,668 women aged 40 - 79 years for 10 years, and proteinuria and hypercreatinemia or reduced GFR and their combination were sig-

nificant predictors of CVD and all-cause mortality [16]. We have also reported that proteinuria was a modifiable factor for cardiorespilatory fitness evaluated by VT [6]. However, according to the link between proteinuria and muscle strength, there were few studies especially in Japan. Protein-energy wasting is the term proposed to describe the reduction in the stores of energy and protein in patients CKD [17]. Muscle wasting is one of the best markers of protein-energy wasting in these patients [18]. Leal *et al.* reported that handgrip strength is a useful tool for continuous and systematic assessment of muscle mass related to nutritional status in patients on dialysis [19]. Takhreen reviewed that relationship between exercise intervention and quality of life (QOL) in CKD patients. Exercising patients have shown improvements in physical fitness, psychological function, reaction times and lower extremity muscle strength, and these factors help improve QOL [20]. In this study, we solely evaluated the relationship between proteinuria and muscle strength *i.e.* grip strength, leg strength and leg strength per body weight in the Japanese. The significant differences of leg strength and leg strength per body weight between men with and without proteinuria even after adjusting for age. However, muscle strength in women with proteinuria was not significantly lower than that in women without.

Potential limitations still remain in this study. First, our study was a cross sectional and not a longitudinal study. Second, 721 men and 1063 women in our study voluntarily underwent measurements: they were therefore more likely to be health-conscious compared with the average person. Second, we could not show clear mechanism between proteinuria and muscle strength. We have previously reported that brachial-ankle pulse wave velocity (baPWV) in subjects with reduced eGFR was significantly higher than that in subjects without [21]. In addition to protein-energy wasting, arterial stiffness might affect the results. Third, significant difference of muscle strength was not noted in women in this study. Low prevalence of proteinuria also affected the results, especially in women. To show this, further prospective studies are needed in the Japanese.

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REFERENCES

[1] Foley, R.N., Parfrey, P.S. and Sarnak, M.J. (1998) Clinical epidemiology of cardiovascular disease in choronic renal disease. *American Journal of Kidney Diseases*, **32**, S112-S119. doi:10.1053/ajkd.1998.v32.pm9820470

[2] National Kidney Foundation K/DOQI clinical practice guidelines for chronic kidney disease, evaluation, classification, and stratification. (2002) Kidney Disease Outcome Quality Initiative. *American Journal of Kidney Diseases*, **39**, S1-S266.

[3] Imai, E., Horio, M., Iseki, K., Yamagata, K., Watanabe, T., Hara, S., Ura, N., Kiyohara, Y., Hirakata, H., Moriyama, T., Ando, Y., Nitta, K., Inaguma, D., Narita, I., Iso, H., Wakai, K., Yasuda, Y., Tsukamoto, Y., Ito, S., Makino, H., Hishida, A. and Matsuo, S. (2007) Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. *Clinical and Experimental Nephrology*, **11**, 156-163. doi:10.1007/s10157-007-0463-x

[4] Matsuo, S., Imai, E., Horio, M., Yasuda, Y., Tomita, K., Nitta, K., Yamagata, K., Tomino, Y., Yokoyama, H. and Hishida, A. (2009) Revised equations for estimated GFR from serum creatinine in Japan. *American Journal of Kidney Diseases*, **53**, 982-992. doi:10.1053/j.ajkd.2008.12.034

[5] Miyatake, N., Shikata, K., Makino, H. and Numata, T. (2010) Relationship between Estimated Glomerular Filatration Rate (eGFR) and Metabolic Syndrome in the Japanese Population. *Acta Medica Okayama*, **64**, 203-208.

[6] Miyatake, N., Shikata, K., Makino, H. and Numata, T. (2011) Comparison of ventilatory threshold between subjects with and without proteinuria in Japanese. *Health*, **6**, 394-399. doi:10.4236/health.2011.36066

[7] Metter, E.J., Talbot, L.A., Schrager, M. and Conwit, R. (2002) Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *The Journals of Gerontology, Series A*, **57**, B359-B365. doi:10.1093/gerona/57.10.B359

[8] Ministry of Health, Labor and Welfare (2010) http://www.nih.go.jp/eiken/programs/pdf/guidelines2006.pdf.

[9] Rhodes, E.C., Martin, A.D., Taunton, J.E., Donnelly, M., Warren, J. and Elliot, J. (2000) Effect of one year of resistance training on the relation between musclar strength and bone density in elderly women. *British Journal of Sports Medicine*, **34**, 18-22. doi:10.1136/bjsm.34.1.18

[10] Geliebter, A., Mahaer, M.M., Gerace, L., Gutin, B., Heymsfield, S.B. and Hashim, S.A. (1997) Effects of strength or aerobic training on body composition, resting metabolic rate, and peak oxygen consumption in obese dieting subjects. *American Journal of Clinical Nutrition*, **66**, 557-563.

[11] (2005) Definition and the diagnostic standard for metabolic syndrome—Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. *Nippon Naika Gakkai Zasshi*, **94**, 794-809 (in Japanese). doi:10.2169/naika.94.794

[12] Miyatake, N., Wada, J., Nishikawa, H., Saito, T., Takenami, S., Miyachi, M., Makino, H. and Numata, T. (2007) Comparison of muscle strength between Japanese men with and without metabolic syndrome. *Acta Medica Okayama*, **66**, 99-102.

[13] Kigawa, A., Yamamoto, T., Koyama, Y., Kageyama, S. and Arima, K. (1987) Evaluation of knee extensor

strength for prevention of sports injury. *Japanese Orthopaedic Society of Sports Medicine*, **6**, 141-145 (in Japanese).

[14] Wallace, J.F., Pugia, M.J., Lott, J.A., Luke, K.E., Shihabi, Z.K., Sheehan, M. and Bucksa, J.M. (2001) Multisite evaluation of a new dipstick for albumin, protein and creatinine. *Journal of Clinical Laboratory Analysis*, **15**, 231-235. doi:10.1002/jcla.1032

[15] Anavekar, N.S., McMurray, J.J., Velazquez, E.J., Solomon, S.D., Kober, L., Rouleau, J.L., White, H.D., Nordlander, R., Maggioni, A., Dickstein, K., Zelenkofske, S., Leimberger, J.D., Califf, R.M. and Pfeffer, M.A. (2004) Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *The New England Journal of Medicine*, **351**, 1285-1295. doi:10.1056/NEJMoa041365

[16] Irie, F., Iso, H., Sairenchi, T., Fukasawa, N., Yamagishi, K., Ikehara, S., Kanasahiki, M., Saito, Y., Ota, H. and Nose, T. (2006) The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. *Kidney International*, **69**, 1264-1271. doi:10.1038/sj.ki.5000284

[17] Fouque, D., Kalantar-Zadeh, K., Kopple, J., Cano, N., Chauveau, P., Cuppari, L., Franch, H., Guarnieri, G., Ikizler, T.A., Kaysen, G., Lindholm, B., Massy, Z., Mitch, W., Pineda, E., Stenvinkel, P., Trevino-Becerra, A. and Wanner, C. (2008) A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney International*, **73**, 391-398. doi:10.1038/sj.ki.5002585

[18] Carrero, J.J., Chmielewski, M., Axelsson, J., Sanedal, S., Heimburger, O., Baraby, P., Suliman, M.E., Lindholm, B., Stenvinkel, P. and Qureshi, A.R. (2008) Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clinical Nutrition*, **27**, 557-564. doi:10.1016/j.clnu.2008.04.007

[19] Leal, V.O., Mafra, D., Fouque, D. and Anjos, L.A. (2011) Use of handgrip strength in the assessment of the muscle function of chronic kidney disease patients on dialysis: a systematic review. *Nephrology Dialysis Transplantation*, **26**, 1354-1360. doi:10.1093/ndt/gfq487

[20] Takhreem, M. (2008) The effectiveness of intradialytic exercise prescription on quality of life in patients with chronic kidney disease. *The Medscape Journal of Medicine*, **10**, 226.

[21] Miyatake, N., Shikata, K., Makino, H. and Numata, T. (2010) Relation between the estimated glomerular filtration rate and pulse wave velocity in Japanese. *Internal Medicine*, **49**, 1315-1320. doi:10.2169/internalmedicine.49.3085

である．特に，IFNには，IFN自体による腎障害の惹起およびHCV腎症以外の潜在性腎炎の活性化を生じる可能性があることを考慮する必要がある．

糖尿病性腎症
diabetic nephropathy

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病態と診断

糖尿病性腎症（腎症）は新規透析導入の原因疾患の第1位であり，高血糖による細小血管障害によって生じる．腎症は微量アルブミン尿により診断され，持続性蛋白尿から腎不全に至る進行性の病態をとる例が典型である．未治療であれば，10－15年後に尿蛋白陽性の顕性腎症に移行する．

腎症は，主としてアルブミン尿/蛋白尿を用いて病期分類がされる．尿中アルブミン排泄量が正常である第1期（腎症前期），微量アルブミン尿を呈する第2期（早期腎症期），持続性蛋白尿（顕性蛋白尿）がみられる第3期（顕性腎症期），第4期（腎不全期），第5期（透析療法期）に分類される．微量アルブミン尿は午前中の随時尿を用いて，3回測定して2回以上30－299 mg/g・Crで診断する．この際，糖尿病罹病期間，網膜症などの合併症の有無も参考になる．一方，アルブミン尿/蛋白尿のない腎機能低下例も存在する．

治療方針

腎症の治療は生活習慣の修正に加えて，高血糖，全身血圧ならびに糸球体高血圧のコントロールが基本であり，血清脂質の管理など寛解と退縮を目指して集約的に行われる．実際，早期腎症，顕性腎症において，正常アルブミン尿への改善例が報告されている．以下に糖尿病性腎症の病期分類による治療法を記す．

Ⓐ 第1期（腎症前期）－第2期（早期腎症期）

正常アルブミン尿－微量アルブミン尿であり，一般的には腎機能は正常の時期である．腎症の発症，進展予防には血糖コントロールが重要である．食事療法，運動などの生活習慣修正，薬物療法によりHbA1c（JDS値）6.5%未満を目標とする．さらに，高血圧合併例では，生活習慣の修正とともにレニン・アンジオテンシン系阻害薬を第1選択薬とし130/80 mmHg未満を目標とする．

Ⓑ 第3期（顕性腎症期）

顕性蛋白尿がみられる時期であり，尿蛋白量低下，腎機能低下，腎不全への進展抑制が治療目標で

ある．厳格な血糖ならびに血圧コントロールが重要である．一方，顕性腎症後期以降は経口糖尿病薬・インスリン治療の際に低血糖に注意する．目標血圧130/80 mmHg未満とし，尿蛋白が1 g/日以上では125/75 mmHg未満とする．食事療法では，蛋白制限食（0.8 g/kg標準体重/日）が必要となる．なお，病期にかかわらず高血圧合併例では減塩（6 g/日未満）が必要である．

© 第4期（腎不全期）

腎機能低下がみられ，血糖コントロールは内服薬よりインスリン療法が推奨される．血圧コントロールは重要であるが，難渋することも多い．高カリウム血症に注意してレニン・アンジオテンシン系阻害薬を投与することに加えて，症例によりカルシウム拮抗薬，少量の利尿薬を併用する．なお，食事療法（蛋白制限食0.8/kg標準体重/日以下を含む），腎性貧血や電解質異常に対する対処も必要である．

Ⓓ 高血圧を示す糖尿病例に対する処方例

1. 第1選択薬

Ⓡ 処方例　下記の1）-8）のいずれかを用いる．

（ACE阻害薬）

1）タナトリル錠（5 mg）　1-2錠　分1　食後 24
2）プレラン錠（1 mg）　1-2錠　分1　食後

（アンジオテンシンII受容体拮抗薬）

3）ニューロタン錠（50 mg）　1-2錠　分1-2　食後
4）ミカルディス錠（40 mg）　1-2錠　分1　食後 25
5）ディオバン錠（80 mg）　1-2錠　分1　食後 25
6）ブロプレス錠（4・8・12 mg）　1錠　分1　食後 24
7）オルメテック錠（10・20 mg）　1-2錠　分1　食後 25
8）アバプロ錠またはイルベタン錠（100 mg）　1-2錠　分1　食後

2. 第2選択薬　上記薬剤で効果不十分，もしくは副作用があるときは以下の薬剤を併用する．

Ⓡ 処方例　下記の1）-6）のいずれかを用いる．

（カルシウム拮抗薬）

1）アテレック錠（10 mg）　1-2錠　分1-2　食後
2）アダラートCR錠（20 mg）　1-4錠　分1-2　食後 19
3）ノルバスク錠（5 mg）　1錠　分1　食後 19
4）レザルタスHD配合錠　1錠　分1　食後

（少量の利尿薬）

5）フルイトラン錠（2 mg）　1/4-1/2錠　食後 22
6）プレミネント配合錠　1錠　分1　食後

3. 虚血性心血管系合併症や浮腫があるときの投与を追加する．

Ⓡ 処方例　下記の薬剤を症状に応じて選択する．

1）アーチスト錠（10 mg）　1-2錠　分1　食後（虚血性心血管系） 18
2）ラシックス錠（40 mg）　1-2錠　分1　食後（浮腫） 22

4. 腎機能低下に対して

Ⓡ 処方例

クレメジンカプセル（200 mg）・細粒（2 g）　分3　食間

5. 高カリウム血症に対して

Ⓡ 処方例

アーガメイトゼリー（製剤量として5 g）　1-3個　分1-3

6. 腎性貧血に対して

Ⓡ 処方例　下記のいずれかを用いる．

1）エポジン注　1回6,000-12,000 IU　週3回　皮下注
2）ネスプ注　1回30-120 μg　2週に1回　皮下または静注
3）ミルセラ注　1回25-250 μg　4週に1回　皮下注または静注

服薬指導・薬剤情報

・ACE阻害薬・ARBは糖尿病性腎症抑制作用を有して降圧効果以外に抗蛋白尿作用などによる腎保護効果を有し，末期腎不全への進展を抑制する．この点にも触れ，服薬遵守を促す．また，腎不全への進展に伴うCa拮抗薬や利尿薬などとの併用時には，併用の意義と必要性について説明し，アドヒアランスを良好に維持するよう努める．

・外来処方に際しては，ACE阻害薬で高頻度に起こる乾性咳，レニン・アンジオテンシン・アルドステロン系抑制薬に共通する初回投与量時にまれに発現する一過性の急激な血圧低下によるめまい・立ちくらみ・失神，血管浮腫の初期症状（顔面，口唇，咽頭・喉頭，舌の腫脹），低血糖（特に糖尿病治療中の患者）などに注意し，気づいた場合はすぐに医師に相談するよう指導する．

・クレメジンは他の薬を吸着して効力を低下させるので，他の薬とは30分以上時間をずらす．

また，本剤は炭素の粒なので便が黒くなる場合があることを患者に説明する．

ゼリーは服薬しにくい主薬（陽イオン交換樹脂の微細粒）をゼリーに混ぜて食品化した製剤であり，そのまま噛まずに飲み込むように指導する．冷蔵庫で冷やすと服用しやすい．また，お菓子状なので子どもが誤って食べないよう保管に注意する．

慶應義塾大学医学部腎臓内分泌代謝内科学講師・腎・免疫・内分泌代謝内科学

痛風とは，狭義には痛風に合併する腎障害と定義され，高尿酸血症が長期間持続することで，尿酸塩結晶が腎の尿細管腔や間質に析出・沈着し，腎機能低下をきたす末期腎不全に至る病態である．病理組織学的には慢性間質性腎炎を呈し，腎実質に尿酸塩結晶が沈着するとされているが，実際に尿酸塩沈着を認めることは少ない．

高尿酸血症の長期罹患歴を有することに加えて，尿沈渣で尿酸結晶，軽度腎機能低下，酸性尿，尿浸透圧低下を呈し，超音波検査では腎髄質が腎皮質よりも高エコーレベルに描出される．腎機能障害の早期診断には，血清Crのほかシスタチン Cや推算糸球体濾過量（eGFR）が有用である．

治療の最正

腎障害を進行させないためには，血清尿酸値のコントロールが重要である．「高尿酸血症・痛風の治療ガイドライン第2版」（日本痛風・核酸代謝学会）では，血清尿酸値6 mg/dL以下に保つことを目標とし，食事療法（プリン体摂取制限，アルコール制限），生活指導（適度な運動，十分な飲水）でも十分な効果が得られない場合には，薬物療法を考慮する．

痛風における薬物療法は，尿酸生成抑制薬であるアロプリノール（ザイロリック）が中心となる．腎機能が低下した症例においては，アロプリノールによる副作用（骨髄抑制など）が生じやすく，腎機能に応じて減量が必要である．また，クレアチニンクリアランス（Ccr）が30 mL/分以下の腎不全例では，アロプリノールと尿酸排泄薬であるベンズブロマロン（ユリノーム）の少量併用療法も有効である．

℞ 処方例　以下の薬剤を腎機能に応じて投与．

ザイロリック錠（100 mg）⑦
Ccr＞50 mL/分：1－3錠　分2－3
30 mL/分＜Ccr≦50 mL/分：1錠　分1
Ccr≦30 mL/分：0.5錠　分1

Ccr≦30 mL/分であれば，ユリノーム錠（25 mg）1－2錠　分1の併用も可能．

Ⓑ 尿路管理

尿路への尿酸塩の析出を予防するために，尿量の増加と尿のアルカリ化が重要である．尿pHは6.0－7.0に保つことが推奨されている．飲水を励行し，尿量を1日2,000 mL以上に保つ．また，食事療法（海藻類や野菜などアルカリ性食品の摂取）により，尿のアルカリ化をはかる．それでも改善を認めない場合は，薬物療法を考慮する．

℞ 処方例　下記のいずれかを用いる．尿pHを確認しながら投与量を調整する．

1）ウラリット配合錠　6錠　分3，またはウラリット－U配合散　3.0 g（製剤量）　分3
2）炭酸水素ナトリウム末　1.5－3.0 g　分3

Ⓒ 合併する病態の管理

痛風腎，高尿酸血症を呈する患者は，同時に糖尿病，高血圧，脂質異常症などを合併していることが多く，それらの疾患によっても腎機能障害が進行するため，合併する疾患の管理も重要である．

患者説明のポイント

- 食事療法，運動療法，合併疾患（肥満，糖尿病，高血圧，脂質異常症など）の管理が重要であることを理解してもらうことが大切である．
- プリン体が多く含まれる食事（レバー，干物など）を控え，アルカリ性食品（海藻，野菜など）を摂取するように指導する．
- アルコールを制限する（ビール　500 mL/日以下など）．
- 1日2,000 mL以上の尿量を確保するため，飲水を促す．

糖尿病性腎症

和田隆志*

abstract

糖尿病性腎症は最大の慢性腎臓病であり，増加の一途をたどる透析例の新規導入疾患の第一位である．高血糖による細小血管障害により生じ，微量アルブミン尿の出現により診断される．持続性タンパク尿から腎不全に至る進行性の病態を辿る例が典型であり，未治療であれば，10～15年後に尿タンパク陽性の顕性腎症に移行する．糖尿病性腎症の予後改善のうえで予防に勝る治療法はない．糖尿病性腎症の治療は生活習慣の改善，高血糖のコントロール，全身血圧のコントロールが基本となる．最近では，糖尿病性腎症の集約的治療は寛解（remission）と退縮（regression）を目指す治療に変化してきている．今後，糖尿病性腎症の発症予防，予後改善に向けて，疫学，早期診断，病態解明，治療法確立といった総合的な取り組みが一層期待される．

I　はじめに

糖尿病性腎症は糖尿病の主要な臓器合併症であると同時に，本邦の慢性腎臓病（chronic kidney disease：CKD）の原疾患として重要な位置を占める．目下のところ，新規透析導入の原因疾患の第一位であり，2011年6月に日本透析医学会から公表された新規の導入患者数は，全透析療法導入者数のなかで43.5%（16,271人）を占めるに至っている．糖尿病性腎症では臨床的寛解が可能となってきたが，糖尿病性腎症の病態の理解や包括的治療がますます重要となることは論を待たない．そこで本稿では，糖尿病性腎症の疫学，病態，治療について概説する．

II　本邦の糖尿病性腎症の現状

現在，早期糖尿病性腎症は臨床的に微量アルブミン尿の出現した時点で診断される[1]．現在用いられている糖尿病性腎症の病期分類ではアルブミン尿（タンパク尿）を主体として分類がなされている（表1）[2]．この病期分類では，尿タンパク（尿アルブミン）と糸球体濾過量（glomerular filtration rate：GFR）（クレアチニンクリアランス）の2種類の臨床的パラメーターから，腎症の病期を第1期（腎症前期），第2期（早期腎症期），第3期A・B（顕性腎症期），第4期（腎不全期），第5期（透析療法期）と定めている．このうち，本邦の糖尿病データマネジメント研究会（JDDM）から，第2期である早期腎症は全体の32%，腎症全体の76%を占めていると報告されている[3]．したがって，尿アルブミン測定の糖尿病性腎症，ことに早期腎症の診断への重要性が浮き彫りとなる．一方，第3期は7%，第4期は2.6%，第5期は0.4%とされている．さらに，日本腎臓学会が推進している腎臓病総合レジストリーにより，腎生検の有無にかかわらず，糖尿病性腎症の経年的な統計調査が可能となった．これにより本邦における糖尿病性腎症の現状がみえる[4]．2010年12月27日現在

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表1　糖尿病性腎症病期分類

病期	臨床的特徴 タンパク尿（アルブミン）	GFR（Ccr）	病理学的特徴 （糸球体病変）	備考 （主な治療法）
第1期 （腎症前期）	正常	正常 時に高値	びまん性病変： ない～軽度	血糖コントロール
第2期 （早期腎症）	微量アルブミン尿	正常 時に高値	びまん性病変： 軽度～中等度 結節性病変： 時に存在	厳格な血糖コントロール・降圧療法
第3期A （顕性腎症前期）	持続的タンパク尿	ほぼ正常	びまん性病変： 中等度 結節性病変： 多くは存在	厳格な血糖コントロール・降圧療法・ タンパク制限食
第3期B （顕性腎症後期）	持続的タンパク尿	低下	びまん性病変： 高度 結節性病変： 多くは存在	厳格な降圧療法・タンパク制限食
第4期 （腎不全期）	持続的タンパク尿	著明低下 （血清クレアチニン上昇）	荒廃糸球体	厳格な降圧療法・タンパク制限食 透析療法導入
第5期 （透析療法）	透析療法中			移植

において，腎臓病総合レジストリーに11,282例が登録され，解析した10,000例のうち，糖尿病性腎症関連登録例として組織診断確定例は432例（男性307例，女性125例，平均59.4歳）であった．このうち，糖尿病性腎症の臨床診断は，代謝性疾患に伴う腎障害135例（31.3%），ネフローゼ症候群110例（25.5%），ネフローゼ症候群＋代謝性疾患に伴う腎障害58例（13.4%），慢性腎炎症候群62例（14.4%）とその38.9%がネフローゼ症候群を伴う症例であることが判明した．さらに，この腎臓病総合レジストリーの二次研究として，糖尿病性腎症レジストリー（JDNCS）が構築され，糖尿病性腎症の病態解明，予後調査などの基盤が整備されている．

III　糖尿病性腎症の病態

1　糖尿病性腎症における血尿の意義

腎臓病総合レジストリーの運用とその拡充から本邦の糖尿病性腎症の臨床像が改めてみえてきた．このレジストリーの検尿所見では，尿潜血陽性を49.8%に認めることが明らかになってきた[4]．本邦において，糖尿病性腎症例の血尿を詳細に検討した報告は少なく，頻度など尿潜血陽性例の疫学にはさらなる検討が必要である．この際，ほかの糸球体疾患との鑑別が必要となるため腎生検による評価が重要である．実際，病理学的に糖尿病性腎症の確定診断が行われた本邦の34例において，尿潜血陽性が14例（41.2%）に認められた[5]．尿潜血陰性例と比較して，ネフローゼ症候群と糖尿病性網膜症の合併も高率であり，尿潜血陽性例の腎機能低下が高度であることならびにネフローゼ症候群と糖尿病罹病期間が血尿の予測因子であることが示されている[5]．今後，腎臓病総合レジストリーへの腎生検例の登録が進むことにより，糖尿病性腎症における血尿の頻度，病態とその臨床病理学的意義について，本邦の実態がより鮮明になると考えられる．また，組織診断は行われていないが尿タンパク1＋以上の糖尿病患者542例を対象とした報告がある[6]．この研究では，タンパク尿が同程度であっても，潜血陽性例は血清尿素窒素，血清クレアチニン値，白血球数，高感度CRP値が高値であることが示されている．

2　糖尿病性腎症の予後におけるアルブミン尿（タンパク尿），腎機能の意義

糖尿病性腎症病期分類はアルブミン尿（タンパク尿）を主体としている（**表1**）．一方，現行のCKDステージ分類は腎機能の評価指標である糸球体濾過量（glomerular filtration rate：GFR）を主体としている[7,8]．そのため，両病期分類での乖離例が存