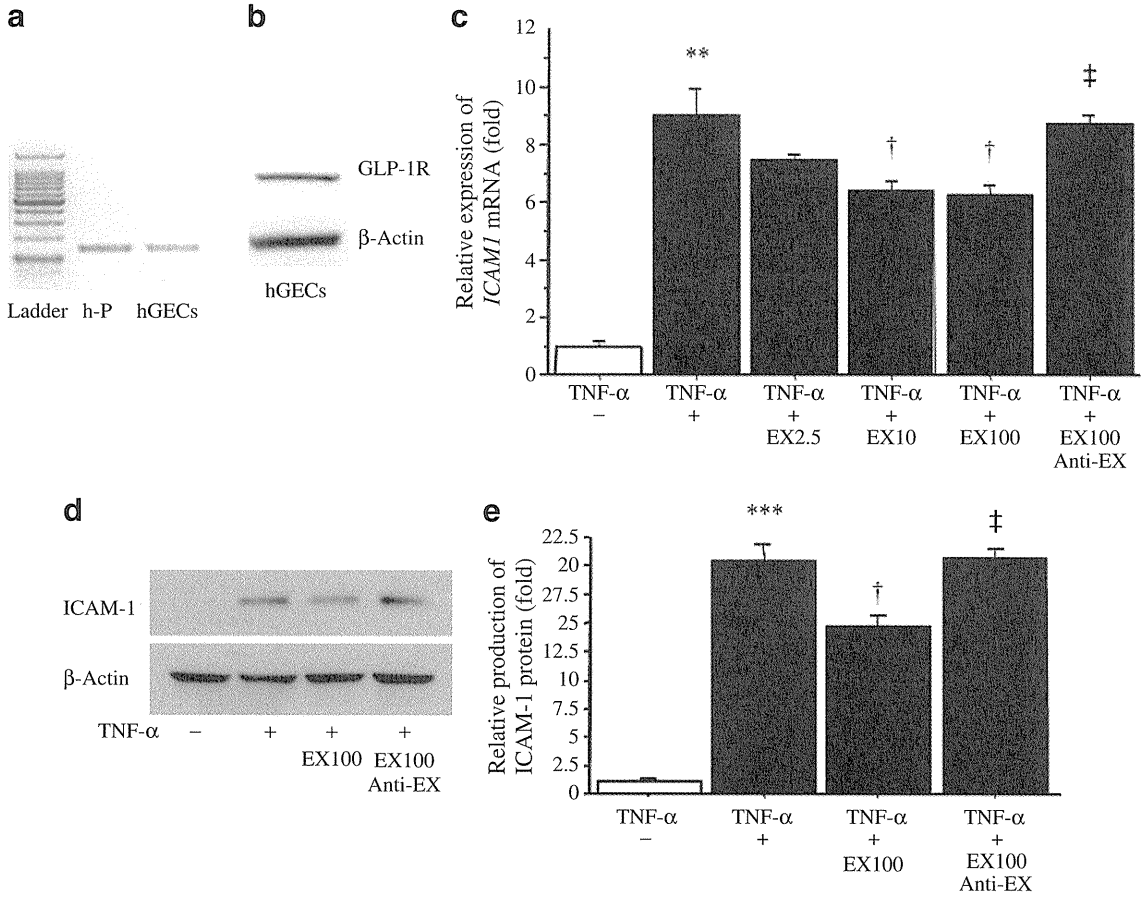

Fig. 6 The direct effects of exendin-4 on hGECs. **a** *GLP1R* gene expression in hGECs. h-P, human positive control (human pancreas). **b** GLP-1R protein production in hGECs by western blotting. **c** Quantification of *ICAM1* expression in hGECs by real-time RT-PCR. hGECs stimulated with TNF-α (100 pg/ml) for 6 h showed significantly enhanced *ICAM1* expression. Exendin-4 (EX) significantly and dose-dependently suppressed *ICAM1* gene expression. GLP-1R antagonist (1,000 nmol/l; anti-EX) significantly inhibited the suppressive effect of 100 nmol/l exendin-4 (EX100) on *ICAM1* expression. Values (means ± SEM) are presented as fold relative to *ACTB* and expressed as 1 in control (no TNF-α stimulation); $n=5$ per group. The experiment was repeated three times. $^{**}p<0.01$ vs control; $^{\dagger}p<0.05$ vs TNF-α stimulation; $^{\ddagger}p<0.05$ vs TNF-α + 100 nmol/l EX (EX100). **d** ICAM-1 production in hGECs by western blotting analysis, with (**e**) quantification. hGECs stimulated with TNF-α (100 pg/ml) for 6 h significantly promoted ICAM-1 production. Exendin-4 significantly suppressed ICAM-1 production. Anti-EX significantly inhibited the suppressive effect of EX100 on ICAM-1 production. Values (means ± SEM) are presented as fold relative to β-actin and expressed as 1 in control (no TNF-α stimulation); $n=5$ per group. The experiment was repeated twice. $^{***}p<0.01$ vs control; $^{\dagger}p<0.05$ vs TNF-α stimulation; $^{\ddagger}p<0.05$ vs TNF-α + EX100. EX2.5, 2.5 nmol/l exendin-4; EX10, 10 nmol/l exendin-4

mation. In HUVECs, treatment with liraglutide, a long-acting GLP-1 analogue, has also been shown to inhibit TNF-α or hyperglycaemia-mediated induction of ICAM-1 gene and protein [30]. These reports support our present findings. In our study, high glucose (15 mmol/l) stimulation for a period of 24 to 72 h did not significantly enhance *ICAM1* gene expression in hGECs (data not shown).

Macrophages play a critical role in the development of diabetic nephropathy. In vitro, the culture supernatant fraction of macrophages has been shown to stimulate mesangial cells to produce fibronectin [31], while macrophages directly secrete TGF-β [32]. Both of these processes play a central role in the enhancement of glomerular extracellular matrix production in diabetic nephropathy [33, 34]. Based on these previous and our present findings, we conclude that the inhibition of macrophage infiltration by exendin-4 has a beneficial effect on suppressing progression of diabetic nephropathy.

In the diabetic state, many factors contribute to elevated NF-κB activation [35]. NF-κB is also the most important transcription factor regulating ICAM-1 production [36]. Arakawa et al. [37] reported that exendin-4 suppressed NF-κB activation of lipopolysaccharide-induced macrophages, suggesting that exendin-4 reduced direct NF-κB activation in macrophages. The reduction of NF-κB activity by exendin-4 may lead to inhibition of ICAM-1 levels and suppression of pro-inflammatory cytokines derived from macrophages.

Oxidative stress and inflammation are closely related to each other and create a vicious cycle in the diabetic state. Gorin et al. [38] showed that NADPH oxidase, and especially the NOX4 component of NADPH in the kidney, is important as the major source of oxidative stress in streptozotocin-induced diabetic nephropathy. Although many stimuli activate NOX4 production, cytokines and shear stress are important factors in the diabetic state [39]. NOX4 has been reported to be produced on epithelial cells [40] and mesangial cells [27], and was confirmed to be produced on endothelial cells in this study. In our study, exendin-4 suppressed NOX4 levels in the kidney. We speculate that reducing the release of pro-inflammatory cytokines from macrophages and normalising hyperfiltration by exendin-4 treatment may have contributed to the suppression of NOX4 production. Etoh et al. [27] reported that localisation and levels of NOX4 were in parallel with those of 8-OHdG. Therefore, the reduction of NOX4 level by exendin-4 treatment would contribute to a decrease in 8-OHdG production in glomeruli. Park et al. [25] also reported similar results in regard to 8-OHdG reduction by exendin-4 in a mouse model of type 2 diabetes. We speculate that exendin-4 contributes to an attenuation of oxidative stress and that this helps ameliorate diabetic vascular complications.

It is well known that GLP-1 signalling through GLP-1R enhances cyclic AMP as a second messenger [41]. Previous reports have revealed that an increase in activity of the cyclic AMP/protein kinase A pathway suppresses NF-κB activity in THP-1 cells and HUVECs [42], and inhibits NADPH oxidase [43]. These findings support our finding that exendin-4 modulated the inflammatory vicious cycle in the kidney.

In our model, exendin-4 did not affect blood glucose levels, blood pressure, food intake or body weight as it has been shown to do in models of type 2 diabetes. To determine that the effects of exendin-4 occurred without lowering of blood glucose, we started exendin-4 treatment at 1 week after the streptozotocin injections and confirmed that exendin-4 did not restore insulin secretion in our model. A much higher dose than that used in our study would have been necessary to reduce blood pressure in diabetic rats [26]. GLP-1 inhibits food intake and results in weight loss [18, 20, 21]. In the present study, the non-diabetic group treated with exendin-4 had decreased food intake and weight loss compared with the control group, but there were no significant differences. It is difficult to differentiate the effect of exendin-4 from the significant weight reduction that is generally seen in the model of type 1 diabetes.

In this study, the ratio of kidney weight to body weight in the diabetic groups was significantly increased in diabetic rats compared with the non-diabetic groups. However, exendin-4 treatment did not affect them. As periodic acid–Schiff's reagent staining revealed, exendin-4 did not ameliorate tubular hypertrophy. Tubular hypertrophy may be the main factor contributing to kidney weight, and we need to investigate a longer period to appreciate the effect of exendin-4 on tubular hypertrophy and interstitial fibrosis. Additionally, exendin-4 prevented diabetes-induced hyperfiltration. Previous reports have revealed that hyperfiltration was improved by exendin-4 treatment in obese diabetic patients [44] and the *db/db* mouse model [25]. There has been no report that exendin-4 affects creatinine clearance in a later stage of diabetic nephropathy.

The inflammatory process is involved in the mechanism of obesity-related insulin resistance [45] and in the pathogenesis of atherosclerosis [46]. Moreover, there is also a close relationship between chronic renal insufficiency and the cardiorenal syndrome, through several pathways including inflammation [47, 48]. GLP-1R agonists might be beneficial for these diseases through their anti-inflammatory effects. Recently, Arakawa et al. [37] reported an anti-inflammatory effect of exendin-4 in an animal model of atherosclerosis. Their report also pointed out the importance of exendin-4 as a potential therapeutic agent for cardiovascular disease in diabetes.

In conclusion, we have shown that exendin-4 exerts renoprotective effects through anti-inflammatory actions without lowering blood glucose in a streptozotocin-induced rat model of type 1 diabetes. Furthermore, exendin-4 directly acted on GLP-1R and suppressed production of pro-inflammatory cytokines and ICAM-1. This study may provide the first evidence that GLP-1R agonists directly contribute to the prevention of diabetic nephropathy via an anti-inflammatory effect.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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Original Article

Decreasing Abdominal Circumference Is Associated with Improving Estimated Glomerular Filtration Rate (eGFR) with Lifestyle Modification in Japanese Men: A Pilot Study

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The link between changes in a subject's metabolic syndrome components and his estimated glomerular filtration rate (eGFR) was evaluated in healthy Japanese men. We used data from 120 Japanese men (45.5 ± 8.4 years) with a 1-year follow up. eGFR was defined by a new equation developed for Japan. There were no significant differences in eGFR between men with and without metabolic syndrome components at baseline. Subjects were given advice for dietary and lifestyle improvement. At the 1-year follow up, almost all metabolic syndrome components were significantly improved. However, eGFR was significantly decreased. The changes in eGFR were weakly correlated with abdominal circumference ($r = -0.232$, $p = 0.0106$). A decrease in abdominal circumference may be associated with improving eGFR in Japanese men.

Key words: abdominal circumference, estimated glomerular filtration rate (eGFR), metabolic syndrome, lifestyle modification

Chronic kidney disease (CKD) has become a public health challenge and is a common disorder [1]. For example, approximately 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 3 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 have shown that decreasing systolic blood pressure is associated with improving eGFR with lifestyle modification in healthy Japanese women [5]. However, whether decreases in metabolic syndrome components are beneficial for improving eGFR, and what effect this has on eGFR remain to be investigated in a longitudinal study in Japanese men.

In this study, we evaluated the link between changes in eGFR and changes in metabolic syndrome components in Japanese men with a 1-year follow up.

Subjects and Methods

Subjects. We used data for 120 Japanese men from a data-base of 16,383 people at the Okayama Southern Institute of Health in Okayama prefecture, Japan, aged 45.5 ± 8.4 years, who met the following criteria: (1) received a health check-up, including

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special health guidance and a follow-up check-up 1-year later; (2) received anthropometric measurements, fasting blood examination, 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 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 number of steps walked.

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

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 [6].

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.

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.

Blood sampling and assays. We measured overnight fasting serum levels of creatinine (Cr) (enzymatic method), 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) = $194 \times \mathrm{Cr}^{-1.094} \times \mathrm{Age}^{-0.287}$ [3]. Reduced eGFR was defined as an eGFR < 60 ml/min/1.73 m^2.

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 $\geq$ 150 mg/dl and/or HDL cholesterol $<$ 40 mg/dl, 2) High blood pressure: blood pressure $\geq$ 130/85 mmHg, 3) Impaired glucose tolerance: fasting plasma glucose $\geq$ 110 mg/dl [6].

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

	Baseline	Follow up	*p*
Number of Subjects	120		
Age	45.5 ± 8.4		
Height (cm)	169.0 ± 5.3		
Body weight (kg)	75.6 ± 11.3	74.0 ± 10.7	**<0.0001**
Body mass index (kg/m^2)	26.5 ± 3.6	25.9 ± 3.4	**<0.0001**
Abdominal circumference (cm)	88.5 ± 9.8	86.3 ± 9.2	**<0.0001**
Systolic blood pressre (mmHg)	131.5 ± 14.6	123.9 ± 12.5	**<0.0001**
Diastolic blood pressure (mmHg)	82.6 ± 11.5	77.0 ± 9.2	**<0.0001**
Triglyceride (mg/dl)	153.3 ± 110.2	121.7 ± 80.3	**0.0011**
HDL cholesterol (mg/dl)	54.2 ± 14.6	56.2 ± 14.9	**0.0390**
Blood sugar (mg/dl)	102.7 ± 18.1	104.2 ± 28.3	0.3710
Cr (mg/dl)	0.81 ± 0.12	0.84 ± 0.12	**0.0012**
eGFR (ml/min/1.73 m^2)	84.0 ± 13.9	80.1 ± 13.1	**<0.0001**
		Mean ± SD	

Statistical analysis. Data are expressed as means ± standard deviation (SD). A statistical analysis was performed using a paired t test and χ^2 test: $p < 0.05$ was considered to be statistically significant. Pearson's correlation coefficients were calculated and used to test the significance of the linear relationship among continuous variables.

Results

The clinical parameters at the baseline and the 1-year follow up are summarized in Table 1. Anthropometric and body composition parameters such as body weight, BMI, and abdominal circumference were significantly reduced with lifestyle modification after 1 year. Cr was significantly increased, and eGFR was decreased. Thirty-six subjects were diagnosed as having metabolic syndrome at baseline, and 18 subjects were diagnosed as having metabolic syndrome after 1 year, which was a significant reduction ($p < 0.0001$). Two subjects were diagnosed with reduced eGFR at baseline, and 3 subjects were diagnosed with reduced eGFR at the 1-year follow up. In addition, four subjects were identified as trace positive, 2 were identified as positive (+), and one was identified as positive (2+) for proteinuria at baseline, while 5 were identified as trace positive, 4 as positive (+), and 2 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). eGFR in men with abdominal obesity was significantly higher than that in men without abdominal obesity. However, there were no significant differences of eGFR between the groups with or without other components of metabolic syndrome. In addition, eGFR in subjects with metabolic syndrome was similar to that in subjects without it.

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 ($r = -0.232$, $p = 0.0106$) (Table 3, Fig. 1). After we excluded one subject with abnormal changes in eGFR (-37.7 ml/min/1.73 m^2), changes in eGFR were still weakly correlated with changes in abdominal circumference ($n = 119$, $r = -0.203$, $p = 0.0265$). However, changes in eGFR were not significantly correlated with changes in other metabolic components.

Finally, we investigated the changes in eGFR amongst men with different levels of increased abdominal circumference [Group I: Delta (delta represents positive changes in abdominal circumference) abdominal circumference ≧ 0 cm, Group D: Delta abdominal circumference < 0 cm]. After the 1-year follow up, changes in eGFR in Group I (-6.0 ± 10.2ml/min/1.73 m^2) were lower than those in Group D (-2.7 ± 8.2 ml/min/1.73 m^2), but not at a significant level ($p = 0.0599$).

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

	Abdominal obesity (−)	Abdominal obesity (+)	p
Number of subjects	42	78	
eGFR (ml/min/1.73 m^2)	79.1 ± 13.9	86.6 ± 13.2	**0.0042**
	Impaired glucose torelance (−)	Impaired glucose torelance (+)	
Number of subjects	96	24	
eGFR (ml/min/1.73 m^2)	82.7 ± 13.7	88.8 ± 13.8	0.0535
	Hypertension (−)	Hypertension (+)	
Number of subjects	48	72	
eGFR (ml/min/1.73 m^2)	83.2 ± 14.8	84.5 ± 13.3	0.6326
	Dyslipidemia (−)	Dyslipidemia (+)	
Number of subjects	71	49	
eGFR (ml/min/1.73 m^2)	82.3 ± 14.1	86.2 ± 13.5	0.1348
	Metabolic syndrome (−)	Metabolic syndrome (+)	
Number of subjects	84	36	
eGFR (ml/min/1.73 m^2)	82.4 ± 14.0	87.5 ± 13.2	0.0644

Mean ± SD

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

	r	p
Abdominal circumference (cm)	−0.232	**0.0106**
Systolic blood pressre (mmHg)	0.094	0.3068
Diastolic blood pressure (mmHg)	−0.009	0.9227
Triglyceride (mg/dl)	−0.055	0.5521
HDL cholesterol (mg/dl)	−0.016	0.8616
Blood sugar (mg/dl)	−0.030	0.7458

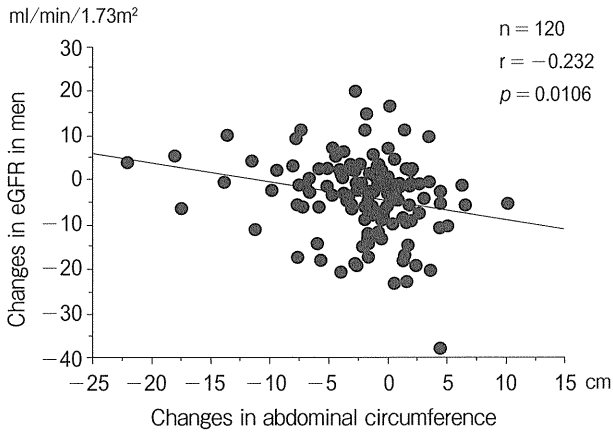

Fig. 1 Simple correlation analysis between changes in eGFR and changes in systolic blood pressure at the 1-year follow up.

Discussion

The main objective of this study was to explore the link between changes in eGFR and changes in metabolic syndrome components in Japanese men with a 1-year follow up.

Ninomiya T *et al.* [7], Tanaka *et al.* [8] and Iseki *et al.* [9] reported that metabolic syndrome, using the modified ATP III definition [10], was associated with CKD in the Japanese population. Compared with subjects with 0 or 1 components 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 [7]. In this study, 36 subjects was diagnosed as having metabolic syndrome, using the Japanese criteria, at baseline, and 18 were diagnosed as having metabolic syndrome at the 1-year follow up. We have previously reported a prevalence of 30.7% for metabolic syndrome in Japanese men [11]. In this study, with lifestyle modification after the initial health check-up, metabolic components were significantly improved in men without medications at the 1-year follow-up. Although eGFR was not increased after 1 year, changes in eGFR were negatively correlated with changes in abdominal circumference. Taken together, lifestyle modification targeting reducing abdominal circumference may be a useful method for improving eGFR in Japanese men.

Abdominal obesity contributes to the development of renal injury and end-stage renal disease [12–14]. Bonnet *et al.* have reported that abdominal obesity is related to the development of elevated albuminuria in both sexes, suggesting that the measurement of abdominal circumference might improve the identification of non-diabetic individuals at risk of developing microalbuminuria [12]. In addition, a greater waist-to-hip ratio is associated with a greater risk of diminished filtration, even when corrected for BMI [13]. Yamagata *et al.* have reported that the baseline-adjusted predictor of developing CKD included age, GFR, hematuria, hypertension, diabetes, serum lipids, obesity, smoking status, and consumption of alcohol with a 10-year follow up [14]. In the present study, there were significant differences in eGFR between subjects with and without abdominal obesity at baseline. However, we revealed that, with lifestyle modification, changes in abdominal circumference were weakly correlated with changes in eGFR in men without medications. Changes in other metabolic components were not linked to changes in eGFR. Therefore, the clinical impact of adnominal circumference on eGFR was noted in Japanese men.

Potential limitations remain in our study. First, the 16,383 subjects in our study voluntarily underwent the annual health check-up; they were, therefore, probably more health-conscious than the average person. The selected 120 men underwent an annual health check-up every year with a follow-up duration of 1-year and received no medication; they were, therefore, probably even more health-conscious than most of the subjects in the database, and the small sample size may make it difficult to infer causality between eGFR and abdominal circumference. At baseline, in contrast to our previous report regarding a large sample (n = 11,711) from a cross-sectional study [4], eGFR in men with abdominal obesity was higher than that in men without abdominal obesity. eGFR was not increased with lifestyle modification after 1 year

($-3.9\,ml/min/1.73\,m^2$/year). A link has previously been found between eGFR and age, based on a large sample from a Japanese cohort, with an average decline rate of eGFR of $0.36\,ml/min/1.73\,m^2$/year [15]. Therefore, the decline rate of eGFR in our study was higher than that previously reported. Second, we could not identify the mechanism of the linkage between eGFR and abdominal circumference. Third, most of the enrolled subjects were not diagnosed as CKD at baseline. Therefore, the results in this study may not apply to patients with CKD. Further prospective studies are needed in Japanese subjects.

In conclusion, a decrease in abdominal circumference with lifestyle modification might induce an improvement in eGFR. Therefore, lifestyle modification may be a necessary and useful measure for the prevention of CKD in Japanese men.

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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**

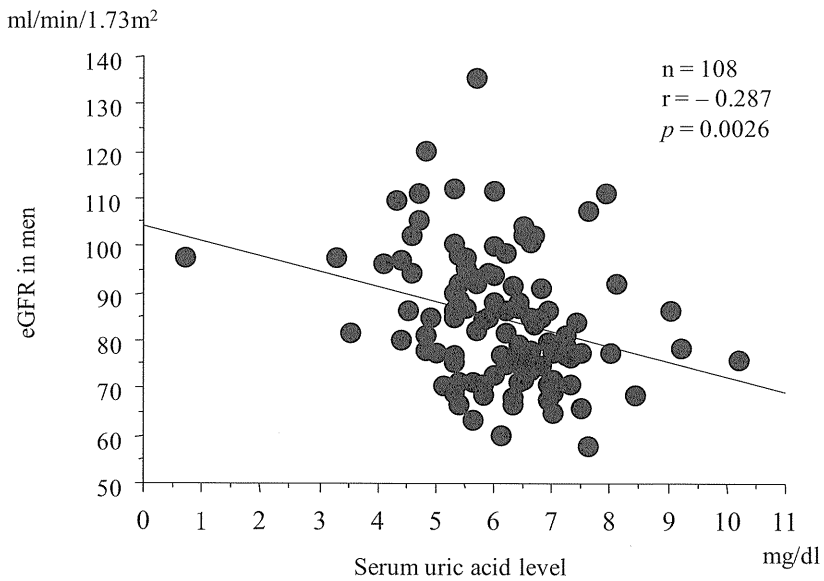

Figure 1. Simple correlation analysis between eGFR and serum uric acid levels at baseline.

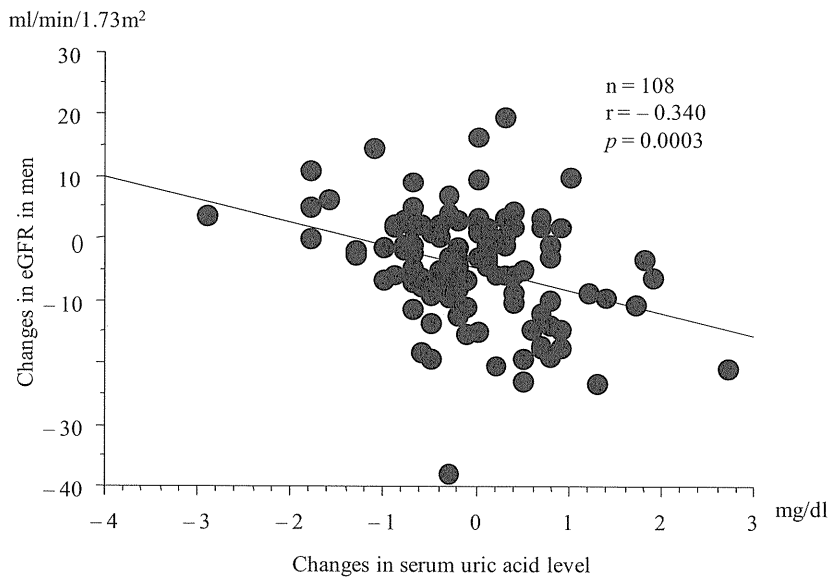

Figure 2. Simple correlation analysis between changes in eGFR and changes in serum uric acid levels at 1-year follow up.

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.

5. ACKNOWLEDGEMENTS

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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.

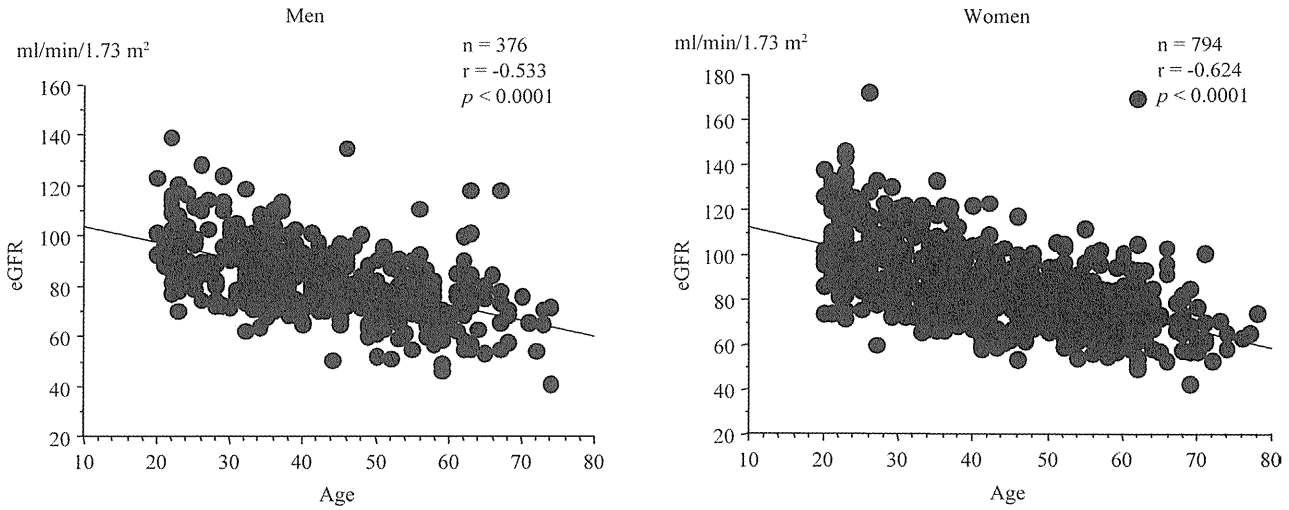

Figure 1. Simple correlation analysis between estimated glomerular filtration rate (eGFR) and age.

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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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**).