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Original Article

Influence of Cigarette Smoking on Estimated Glomerular Filtration Rate (eGFR) in Japanese Male Workers

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The link between changes in estimated glomerular filtration rate (eGFR) and cigarette smoking was evaluated in Japanese male workers with a 5-year follow-up. We examined the data of 456 Japanese male workers, aged 22–70 years, who were taking no medications, and from this group, 286 men (43.5 ± 8.2 years) were followed for 5-years. Habits of cigarette smoking were obtained during interviews by well-trained staff. The influence of cigarette smoking on eGFR was evaluated. In the first analysis, there was no significant difference in eGFR between subjects with and without cigarette smoking. In the second analysis, eGFR was significantly reduced after 5 years in all subjects. Changes in eGFR in subjects with cigarette smoking (-1.90 ± 12.31 ml/min/1.73 m^2) were significantly smaller than those in subjects without cigarette smoking (-4.97 ± 12.05 ml/min/1.73 m^2). At follow-up, we found that eGFR was weakly and negatively correlated with the number of cigarettes smoked (/day). The present study indicated that cigarette smoking may be an important modifiable factor for eGFR in Japanese male workers who are not taking any medications.

Key words: cigarette smoking, estimated glomerular filtration rate (eGFR), male worker

Cigarette smoking has become an important public health challenge, and it has been reported that 39.4% of men and 11.0% of women are current smokers in Japan (http://www.mhlw.go.jp/houdou/2008/12/dl/h1225-5j.pdf, accessed on June 7, 2010). Cigarette smoking has been demonstrated to be a strong risk factor for atherosclerosis and cardiovascular disease in a dose-dependent manner [1].

Chronic kidney disease (CKD) has also become an important public health challenge in Japan and it is a major risk factor for end-stage renal disease, cardiovascular disease and premature death [2, 3]. Identifying and treating risk factors for early CKD may be the best approach to prevent and/or delay adverse outcomes [2]. In Japan, clinical practice guidelines established by the Japanese Society of Nephrology estimate that 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 3 months regardless of cause [4], and that about 4% of adults have moderate or severe CKD (GFR < 50 ml/min/1.73 m^2) [5].

Revised equations for estimating GFR from serum creatinine were recently developed in Japan [6]. Although previous studies showed that cigarette smoking was closely linked to CKD and albuminuria

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[7–10], the link between eGFR using the new equations with Japanese subjects and cigarette smoking remains to be investigated.

Therefore, in this study, we investigated the link between eGFR and cigarette smoking in Japanese male workers who were not taking any medications with a 5-year follow-up.

Subjects and Methods

Subjects. Japanese male workers (n = 456), aged 22–70 years (46.4 ± 9.2) were enrolled into this study (Table 1). Subjects were not receiving any medications for diabetes, hypertension and/or dyslipidemia at baseline.

In a longitudinal analysis, we used follow-up data of 286 subjects (43.5 ± 8.2 years) selected from the 456 subjects who met the following criteria: [1] received an annual health check-up at Kagawa Rosai Hospital in 2003 and 2008, [2] received evaluation of cigarette smoking as part of the annual health check-up.

Ethical approval for the study was obtained from the Ethical Committee of Kagawa Rosai Hospital, Japan.

Anthropometric measurements. Anthropometric and body compositions were evaluated based on the subjects' height and body weight. Body mass index (BMI) was calculated by weight /[height]^2 (kg/m^2) [11].

Cigarette smoking. The data on cigarette smoking was obtained at interviews by well-trained staff in a structured way. The subjects were asked if they currently smoked cigarettes. When the answer was "yes", they were classified as current smokers, and at follow-up, further questions were asked regarding the average number (pieces) of cigarettes smoked per day. When the answer was "no", they were classified as non-smokers. However, we did not ask about the average number (pieces) of cigarettes smoked per day at baseline.

Blood pressure measurements. Blood pressure of each participant was measured after the subject rested at least 15 min in the sitting position.

Blood sampling and assays. We measured overnight fasting serum levels of creatinine (enzymatic method), high-density lipoprotein (HDL) cholesterol, triglycerides (L Type Wako Triglyceride·H, Wako Chemical, Osaka) and blood sugar. eGFR was calculated using the following equation: eGFR (ml/min/1.73 m^2) = $194 \times Cr^{-1.094} \times Age^{-0.287}$ [6]. Reduced eGFR was defined as an eGFR < 60 ml/min/1.73 m^2.

Table 1 Clinical profiles of 456 men

Number of subjects	456
Age	46.4 ± 9.2
Height (cm)	168.7 ± 6.1
Body weight (kg)	67.0 ± 10.5
Body mass index (kg/m^2)	23.5 ± 3.3
Systolic blood pressure (mmHg)	125.9 ± 17.4
Diastolic blood pressure (mmHg)	77.9 ± 17.4
Triglyceride (mg/dl)	120.8 ± 91.7
HDLcholesterol (mg/dl)	59.7 ± 17.2
Blood sugar (mg/dl)	95.3 ± 23.2
Creatinine (mg/dl)	0.79 ± 0.11
eGFR (ml/min/1.73 m^2)	86.3 ± 15.1

Mean ± SD

Statistical analysis. All data are expressed as mean ± standard deviation (SD) values. Statistical analysis was performed using an unpaired t test and covariance analysis; $p < 0.05$ 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 measurements of age and eGFR in subjects with and without cigarette smoking recorded during the first analysis are indicated in Table 2. eGFR was significantly correlated with age at baseline ($r = -0.329$, $p < 0.0001$). A total of 234 men (51.3%) were current smokers and 10 of these men were diagnosed as having reduced eGFR. There was a significant difference of age between subjects with and without cigarette smoking. Therefore, to avoid the influence of age on eGFR, we used age as a covariate and compared eGFR using covariance analysis. eGFR in subjects with cigarette smoking was similar to that in subjects without cigarette smoking after adjusting for age (Table 2).

The clinical parameters at the baseline and the 5-year follow-up recorded during the second analysis are summarized in Table 3. One hundred forty-five men were current smokers at baseline, and 109 men were current smokers after 5 years. eGFR was sig-

Table 2 Comprison of eGFR between men with and without cigarette smoking

	Cigarette somoking (+)	Cigarette smoking (−)	*p*	*p* (After adjusting for age)
Number of subjects	234	222		
Age	45.6 ± 9.4	47.3 ± 8.9	0.0390	
eGFR (ml/min/1.73 m^2)	87.7 ± 14.5	84.9 ± 15.6	0.0503	0.1952

Mean ± SD

Table 3 Changes in clinical prameters in 286 men with a 5 year follow-up

	Baseline	Follow up	*p*
Number of subjects		286	
Age	43.5 ± 8.2		
Height (cm)	169.4 ± 6.1		
Body weight (kg)	67.8 ± 11.0	68.0 ± 11.1	0.3711
Body mass index (kg/m^2)	23.6 ± 3.5	23.7 ± 3.5	0.1935
Systolic blood pressure (mmHg)	124.0 ± 16.4	124.4 ± 16.9	0.6616
Diastolic blood pressure (mmHg)	76.6 ± 11.5	77.8 ± 11.5	0.0625
Triglyceride (mg/dl)	112.0 ± 74.5	126.1 ± 113	0.0093
HDLcholesterol (mg/dl)	61.3 ± 18.3	59.5 ± 16.3	0.0087
Blood sugar (mg/dl)	92.0 ± 14.9	95.8 ± 22.9	0.0010
Creatinine (mg/dl)	0.79 ± 0.11	0.80 ± 0.12	0.1322
eGFR (ml/min/1.73 m^2)	87.9 ± 14.5	84.5 ± 14.5	$<$0.0001

Mean ± SD

nificantly decreased after 5 years and correlated with age at follow-up ($r = -0.264$, $p < 0.0001$). The decline rate of eGFR was −0.68 ml/min/1.73 m^2 per year. One man at baseline and 12 men at follow-up were diagnosed as having reduced eGFR. Triglyceride and blood glucose levels were also significantly increased, and HDL cholesterol was significantly decreased after 5 years. In addition, eGFR was weakly correlated with the number of cigarettes smoked (/day) at follow-up ($r = -0.208$, $p = 0.0310$) (Fig. 1). No significant correlation was noted between number of cigarettes smoked per day and age ($r = 0.182$, $p = 0.0503$) at follow-up.

To evaluate the effect of cigarette smoking on changes in eGFR, we compared changes in eGFR between subjects with (n = 145) and without (n = 141) cigarette smoking at baseline and 5 years later. There were no differences of age or eGFR at baseline. However, changes in eGFR in subjects with cigarette smoking (−1.90 ± 12.31 ml/min/1.73 m^2) were significantly smaller than those in subjects without cigarette smoking (−4.97 ± 12.05 ml/min/1.73 m^2) after 5 years. There were no significant differences in the changes in other clinical parameters between men with and without cigarette smoking at the 5-year follow-up (Table 4).

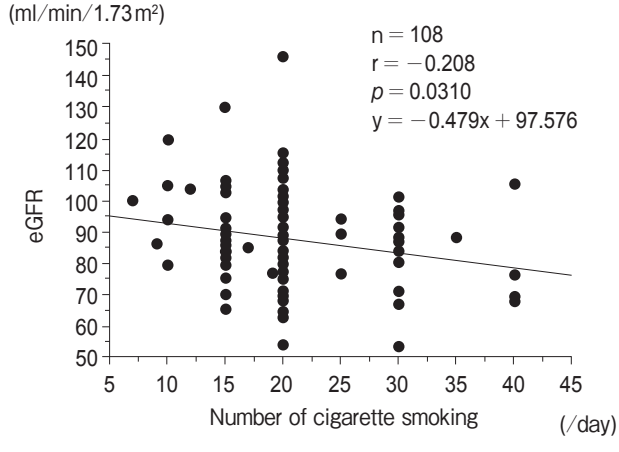

Fig. 1 Simple correlation analysis between eGFR and number of cigarettes smoked (/day) in Japanese male workers who were taking no medications.

Finally, in the current smokers at baseline (n = 145), we further investigated the changes in eGFR

Table 4 Comparison of eGFR and changes in parameters between men with and without cigarette smoking at baseline

	Cigarette smoking (+)	Cigarette smoking (−)	*p*
Number of subjects	145	141	
Age	42.5 ± 8.3	44.4 ± 8.1	0.0526
eGFR (ml/min/1.73 m^2)	88.7 ± 13.2	87.0 ± 15.7	0.3917
Changes in eGFR (ml/min/1.73 m^2)	−1.9 ± 12.3	−5.0 ± 12.1	0.0336
Changes in body weight (kg)	0.4 ± 4.5	0.8 ± 3.5	0.5714
Changes in BMI (kg/m^2)	0.1 ± 1.5	0.1 ± 1.3	0.8970
Changes in systolic blood pressure (mmHg)	1.0 ± 15.8	−0.3 ± 15.0	0.4699
Changes in diastolic blood pressure (mmHg)	2.3 ± 10.9	0.0 ± 9.5	0.0586
Changes in triglyceride (mg/dl)	18.5 ± 110.5	9.6 ± 65.4	0.4069
Changes in HDL cholesterol (mg/dl)	−1.0 ± 10.4	−2.5 ± 11.7	0.2323
Changes in blood sugar (mg/dl)	4.9 ± 18.8	2.7 ± 19.9	0.3542

Mean ± SD

between subjects with (n = 109) and without (n = 39) cigarette smoking at follow-up. There was no significant difference of eGFR between subjects with (89.6 ± 13.2 ml/min/1.73 m^2) and without (86.1 ± 12.9 ml/min/1.73 m^2) cigarette smoking after adjusting for age at baseline, and there was no significant difference in the changes in eGFR between subjects with (−1.92 ± 13.39 ml/min/1.73 m^2) and without (−1.81 ± 8.40 ml/min/1.73 m^2) cigarette smoking after adjusting at the 5-year follow-up.

Discussion

The main goal of this study was to explore the link between eGFR and cigarette smoking in Japanese male workers who were taking no medications, with a 5 year follow-up. eGFR was weakly and negatively correlated with the number of cigarettes smoked per day by cross-sectional analysis. However, longitudinal analysis showed that changes in eGFR in subjects with cigarette smoking were significantly smaller than those in subjects without cigarette smoking.

Previous studies showed that cigarette smoking was associated with CKD. Sawicki *et al.* reported that cigarette smoking increased proteinuria in patients with CKD [12]. Orth *et al.* [13] and Ejerblad *et al.* [14] also reported that cigarette smoking promoted renal dysfunction. In this study, by cross-sectional analysis, eGFR was weakly and negatively correlated with the number of cigarettes smoked per day in Japanese male workers who were taking no medications. In agreement with this result, Ritz *et al.* reported that GFR decreased during smoking, and this was accompanied by a significant decrease of filtration fraction and an increase in renovascular resistance. In addition, these findings were reproduced with nicotine-containing chewing gum [15].

On the other hand, we showed that cigarette smoking was associated with preventing a decline of eGFR in Japanese male workers who were taking no medications, with a 5 year follow-up. There were no significant differences in changes in other clinical parameters between subjects with and without cigarette smoking in the second analysis. Some studies have shown that current smoking is associated with higher creatinine clearance or GFR in the general population [16] and in patients with type 2 diabetes mellitus [17]. Pinto-Sietsma *et al.* also reported that current smoking showed a dose-dependent association with elevated eGFR in nondiabetic subjects, which disappeared after smoking ceased [18]. Although the mechanism of this higher renal function in current smokers is unknown, it is possible that vasodilatory compounds such as nitric oxide and atrial natriuretic peptide repeatedly released after each cigarette smoked eventually cause chronic glomerular hyperfiltration [19, 20]. Hormones such as vasopression or adrenocorticoid hormone may also play a role [21].

Does this prevention of low eGFR in current smokers mean a better renal function? It should be noted that glomerular hyperfiltration represents a new marker of clustering of metabolic risk factors even before overt features of cardiovascular disease are manifest [22]. It was also demonstrated in animal models that hyperfiltration is associated with increased intraglomerular capillary pressure, which

results in proteinuria reflecting glomerulosclerosis lesions [23]. Therefore, an increase in eGFR caused by cigarette smoking may not simply be a preferable outcome or an innocuous observation. In fact, our study showed, in a cross-sectional analysis, that eGFR was weakly and negatively correlated with the number of cigarettes smoked (/day), and some reports show that cigarette smoking was critically involved in CKD [7–10].

This study had a number of potential limitations. First, the 456 male workers who were taking no medications in our study underwent annual health check-ups, indicating that they were probably more health-conscious than the average person. Second, we could not prove the mechanism of the link between eGFR and cigarette smoking. Third, at follow-up we could not obtain the data of the average number of cigarettes smoked per day at baseline or subject' age when they started smoking. Subjects who smoked before the date of the first analysis but who had stopped by then would have therefore been categorized as non-smokers.

In conclusion, cigarette smoking is a modifiable factor for eGFR in Japanese male workers who are taking no medications. We may need to take into account an individual's smoking status when assessing eGFR and the prevalence of CKD. Further long-term analysis by using this cohort is required, and microalbuminuria should be measured to address these issues.

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