Table 4. Logistic Regression Analysis of the Association between Blood Pressure and Prevalence of Low eGFR in Individuals without Hypertension

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Male						
BP-C1	1.33	0.61–2.87	0.47	1.19	0.53–2.69	0.68
BP-C2	1.00	—	—	1.00	—	—
BP-C3	1.12	0.78–1.62	0.54	1.07	0.73–1.58	0.72
BP-C4	1.17	0.82–1.67	0.37	1.04	0.71–1.51	0.84
BP-C5	1.43	1.00–2.03	0.048	1.10	0.75–1.60	0.64
BP-C6	1.45	1.01–2.08	0.043	1.04	0.70–1.54	0.84
Female						
BP-C1	1.00	—	—	1.00	—	—
BP-C2	1.10	0.67–1.82	0.7	1.05	0.62–1.79	0.86
BP-C3	1.15	0.72–1.86	0.56	0.94	0.57–1.56	0.81
BP-C4	1.27	0.79–2.05	0.33	0.84	0.50–1.40	0.50
BP-C5	1.54	0.94–2.51	0.086	0.82	0.48–1.39	0.45
BP-C6	1.94	1.17–3.22	0.011	0.83	0.48–1.46	0.52

eGFR, estimated glomerular filtration rate; CI, confidence interval; OR, odds ratio. BP-C1, <90/<65 mmHg; BP-C2, 90–100/65–70 mmHg; BP-C3, 100–110/70–75 mmHg; BP-C4, 110–120/75–80 mmHg; BP-C5, 120–130/80–85 mmHg; BP-C6, 130–140/85–90 mmHg.

blood pressure lower than 100–110/70–75 mmHg. On the other hand, such type of association was not present between blood pressure and the risk for low eGFR in our study population.

Hypertension has been shown to be a risk factor for kidney dysfunction as well as cardiovascular diseases (*2–5*). Previous studies have established that, in hypertensives, the lower the blood pressure level, the better the clinical outcomes in regard to cardiovascular diseases and kidney dysfunction (*2, 6–10*). However, the relationship between blood pressure and renal function in apparently healthy Japanese with normal blood pressure or prehypertension has not been fully evaluated. Accordingly, this study was performed to determine whether any intervention is needed to regulate blood pressure in this population.

In the present study, a blood pressure level of ≥110/75 mmHg increased the prevalence of albuminuria in both men and women. Because albuminuria has been shown to be associated with the development of cardiovascular events and deaths (*12, 13*), and because albuminuria is in itself a risk factor for the progression of kidney dysfunction (*14*), the current study suggests that reduction of blood pressure to below 110/75 mmHg might help to prevent atherosclerotic diseases in the Japanese population. This threshold is nearly the same as that shown in the meta-analysis by Lewington *et al.*, in which a "the lower the better" relationship was found between blood pressure and cardiovascular mortality in individuals with blood pressure above 115/75 mmHg (*6*). In the Japanese population, Tozawa *et al.* (*15*) demonstrated that the incidence of ESRD was the lowest in the group with blood pressure below 120/80 mmHg, and it increased along with increases in blood pressure, which may support our present findings.

Furthermore, in both genders in the present study, there was no significant difference in the risk for albuminuria among the different blood pressure categories below 110/75 mmHg after multivariate adjustment. Therefore, when individuals have blood pressure less than 110/75 mmHg, they may not be considered to be at either higher or lower risk for albuminuria or CKD.

We found that the pattern of the relationship between BMI, glucose or lipid profile and blood pressure level showed a similar tendency to that between the prevalence of albuminuria and blood pressure level in both genders. This finding suggests that lifestyle intervention may help in realizing an optimal blood pressure level in apparently healthy Japanese subjects without hypertension.

Interestingly, the pattern of the relationship between blood pressure classes and prevalence of albuminuria seemed to differ slightly between the genders. The risk for albuminuria showed a more abrupt increase in proportion to a blood pressure level above 110/75 mmHg in men than in women. This variation might result from differences in the concentration of sex hormones between men and women. Androgen has been shown to stimulate the renin-angiotensin-aldosterone system (RAAS) and to increase the sensitivity to angiotensin-II through modulation of angiotensin-II receptors (*16*). Therefore, baseline RAAS activity may be higher in men than in women. Because angiotensin-II increases the resistance of mainly efferent arterioles, intraglomerular pressure may be higher in men than in women, even in individuals with the same blood pressure level, and may be more susceptible in men than in women to changes in systemic blood pressure *via*

afferent arterioles. In addition, because aldosterone has been shown to have an adverse effect on the kidneys through inflammatory response and fibrosis as well as on the heart (*17–21*), blood pressure may have a synergic effect on kidney impairment in men.

In this study population, the absolute percentage of the prevalence of albuminuria was slightly higher in women than in men even though the prevalence of hyperglycemia and smoking, the established risk factors for proteinuria, was higher in men than in women (*3*, *22*). This might be because UAER was used as an indicator of albuminuria. Because men tend to have higher skeletal muscle mass than women, the use of UAER might have underestimated the prevalence of albuminuria in men or overestimated it in women, as has been shown in previous studies (*23–25*).

In the current study, we found that blood pressure was significantly associated with albuminuria, but not with low eGFR, in both genders who did not have hypertension. It should be kept in mind, however, that the duration for which an individual maintains a higher blood pressure level may be an important predictor of GFR because blood pressure level has been shown to be associated with rate of decline of eGFR (*26*). Longitudinal observations will be needed, therefore, to further assess the relationship between blood pressure and low eGFR.

Limitations

Our study does have some limitations. First, there may have been some selection bias in terms of the subjects who underwent health check-ups. In Japan, however, regular health check-ups for employees are legally mandated, rather than being due to the decision or recommendation of a physician. Second, as we measured only office blood pressure, masked hypertension could not be detected. Therefore, subjects with masked hypertension might have been enrolled in this study, which could have affected the results. Third, owing to the cross-sectional nature of the current study, we are not able to draw conclusions in regard to a causal relationship between blood pressure and kidney impairment. Longitudinal observations will thus be needed. Fourth, ethnic factors for the Japanese population are not well established when using the abbreviated MDRD formula. Therefore, the eGFR value calculated by the MDRD formula may be inappropriate.

Conclusions

In the present study, we found that blood pressure below 110/75 mmHg was the optimal blood pressure for kidney function in a generally healthy Japanese population. Even individuals without hypertension should be encouraged to lower their blood pressure to this level by lifestyle intervention.

References

1. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Am J Kidney Dis* 2002; **39**: S1–S266.
2. Klag MJ, Whelton PK, Randall BL, *et al*: Blood pressure and end-stage renal disease in men. *N Engl J Med* 1996; **334**: 13–18.
3. Yamagata K, Ishida K, Sairenchi T, *et al*: Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int* 2007; **71**: 159–166.
4. Ramirez SP, McClellan W, Port FK, Hsu SI: Risk factors for proteinuria in a large, multiracial, southeast Asian population. *J Am Soc Nephrol* 2002; **13**: 1907–1917.
5. Cirillo M, Senigalliesi L, Laurenzi M, *et al*: Microalbuminuria in nondiabetic adults: relation of blood pressure, body mass index, plasma cholesterol levels, and smoking: the Gubbio Population Study. *Arch Intern Med* 1998; **158**: 1933–1939.
6. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
7. Hansson L, Zanchetti A, Carruthers SG, *et al*, HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; **351**: 1755–1762.
8. Arima H, Chalmers J, Woodward M, *et al*: Lower target blood pressures are safe and effective for the prevention of recurrent stroke: the PROGRESS trial. *J Hypertens* 2006; **24**: 1201–1208.
9. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker *vs* diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2002; **288**: 2981–2997.
10. Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ, Coresh J: Risk factors for chronic kidney disease: a prospective study of 23,534 men and women in Washington County, Maryland. *J Am Soc Nephrol* 2003; **14**: 2934–2941.
11. Imai E, Horio M, Nitta K, *et al*: Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11**: 41–50.
12. Culleton BF, Larson MG, Parfrey PS, Kannel WB, Levy D: Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. *Am J Med* 2000; **109**: 1–8.
13. Grimm RH Jr, Svendsen KH, Kasiske B, Keane WF, Wahi MM: Proteinuria is a risk factor for mortality over 10 years of follow-up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. *Kidney Int Suppl* 1997; **63**: S10–S14.
14. Iseki K, Ikemiya Y, Iseki C, Takishita S: Proteinuria and the risk of developing end-stage renal disease. *Kidney Int* 2003;

63: 1468–1474.
15. Tozawa M, Iseki K, Iseki C, Kinjo K, Ikemiya Y, Takishita S: Blood pressure predicts risk of developing end-stage renal disease in men and women. *Hypertension* 2003; **41**: 1341–1345.
16. Reckelhoff JF: Gender differences in the regulation of blood pressure. *Hypertension* 2001; **37**: 1199–1208.
17. Pitt B, Remme W, Zannad F, *et al*: Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**: 1309–1321.
18. Aldigier JC, Kanjanbuch T, Ma LJ, Brown NJ, Fogo AB: Regression of existing glomerulosclerosis by inhibition of aldosterone. *J Am Soc Nephrol* 2005; **16**: 3306–3314.
19. Rocha R, Chander PN, Khanna K, Zuckerman A, Stier CT Jr: Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. *Hypertension* 1998; **31**: 451–458.
20. Nagase M, Shibata S, Yoshida S, Nagase T, Gotoda T, Fujita T: Podocyte injury underlies the glomerulopathy of Dahl salt-hypertensive rats and is reversed by aldosterone blocker. *Hypertension* 2006; **47**: 1084–1093.
21. Del Vecchio L, Procaccio M, Vigano S, Cusi D: Mechanisms of disease: the role of aldosterone in kidney damage and clinical benefits of its blockade. *Nat Clin Pract Nephrol* 2007; **3**: 42–49.
22. Tozawa M, Iseki K, Iseki C, Oshiro S, Ikemiya Y, Takishita S: Influence of smoking and obesity on the development of proteinuria. *Kidney Int* 2002; **62**: 956–962.
23. Mattix HJ, Hsu CY, Shaykevich S, Curhan G: Use of the albumin/creatinine ratio to detect microalbuminuria: implications of sex and race. *J Am Soc Nephrol* 2002; **13**: 1034–1039.
24. Warram JH, Gearin G, Laffel L, Krolewski AS: Effect of duration of type I diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 1996; **7**: 930–937.
25. Connell SJ, Hollis S, Tieszen KL, McMurray JR, Dornan TL: Gender and the clinical usefulness of the albumin: creatinine ratio. *Diabet Med* 1994; **11**: 32–36.
26. Bakris GL, Williams M, Dworkin L, *et al*: Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; **36**: 646–661.

Original Article

Association between Cigarette Smoking and Chronic Kidney Disease in Japanese Men

Nobukazu ISHIZAKA[1], Yuko ISHIZAKA[2], Ei-ichi TODA[2], Hiroji SHIMOMURA[2], Kazuhiko KOIKE[3], George SEKI[4], Ryozo NAGAI[1], and Minoru YAMAKADO[2]

Cigarette smoking may affect urinary albumin excretion and the glomerular filtration rate in both diabetic and nondiabetic subjects. Here we investigated the association between smoking and decreased or elevated glomerular filtration rate (GFR) and albuminuria by analyzing data from 7,078 Japanese men who had undergone a general health screening between 2005 and 2006. GFR was estimated with the Modified Diet in Renal Disease (MDRD) equation, and low estimated GFR (eGFR) and elevated eGFR were defined, respectively, as eGFR <60 and >90.7 mL/min/1.73 m². Albuminuria was considered present when the urinary albumin excretion ratio (UAER), expressed as mg/g creatinine, was ≥30 mg/g. Multivariate logistic regression analysis showed that current smoking was associated inversely with low eGFR, and positively with albuminuria and elevated eGFR. The association between current smoking and low or elevated GFR was dependent on the number of cigarettes smoked per day. Former smoking was also significantly inversely associated with low eGFR, but the association between former smoking and albuminuria or elevated eGFR was not significant, even in individuals who had stopped smoking less than 1 year before. These data suggest that cigarette smoking may increase the prevalence of albuminuria and elevated eGFR or hyperfiltration, traits that might be reversed by smoking cessation. Although this concept should be verified by future longitudinal studies, our data suggest that we may need to take into account an individual's smoking status when assessing the presence or absence of chronic kidney disease because cigarette smoking may transiently increase eGFR.
(*Hypertens Res* 2008; 31: 485–492)

Key Words: **smoking, chronic kidney disease, glomerular filtration rate**

Introduction

Recent studies have shown that a mild decline in renal function, designated as chronic kidney disease (CKD), is associated with substantially higher prevalence of cardiovascular disease and premature death (*1–3*). Screening for CKD, which can be detected by a combination of reduced estimated glomerular filtration rate (eGFR) and microalbuminuria, is thus an important issue from the viewpoint of disease prevention (*4*). Cigarette smoking, an established risk factor for atherosclerotic disease, may increase the prevalence of albuminuria in diabetic and/or nondiabetic populations (*5, 6*), whereas the effects of smoking on eGFR are controversial (*7, 8*). In the current study, we investigated whether or not there is an association between cigarette smoking and CKD, its components (low eGFR and albuminuria), or elevated eGFR in Japanese men who had undergone a general health screening.

From the [1]Department of Cardiovascular Medicine, [3]Department of Infectious Diseases, and [4]Department of Nephrology, University of Tokyo Graduate School of Medicine, Tokyo, Japan; and [2]Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital, Tokyo, Japan.
The work was supported in part by a grant from the Smoking Research Foundation, by an Imura Clinical Research Promotion Award, by the Tanita Healthy Weight Community Trust, by the Chiyoda Mutual Life Foundation, and by the St. Luke's Grant for the Epidemiological Research.
Address for Reprints: Nobukazu Ishizaka, M.D., Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Hongo 7–3–1 Bunkyo-ku, Tokyo 113–8655, Japan. E-mail: nobuishizka-tky@umin.ac.jp
Received September 3, 2007; Accepted in revised form October 5, 2007.

Table 1. Clinical Characteristics and Laboratory Data of All Subjects Enrolled

	Never smoker (n=2,669)	Former smoker (n=2,252)	Current smoker (n=2,157)	p value
Age, years	52.8±11.2	56.0±10.0	51.0±9.5	<0.001
Body mass index, kg/m^2	23.5±2.9	23.9±2.7	23.8±3.1	<0.001
Systolic blood pressure, mmHg	125±18	127±18	122±18	<0.001
Diastolic blood pressure, mmHg	79±11	81±11	77±11	<0.001
Antihypertensive medication (n (%))	329 (12)	403 (18)	195 (9)	<0.001
Lipid data				
Total cholesterol, mg/dL	207±32	210±31	206±33	<0.001
HDL-cholesterol, mg/dL	56±13	56±13	52±13	<0.001
LDL-cholesterol, mg/dL	128±29	129±30	126±32	0.002
Triglycerides, mg/dL	101 (73–143)	112 (80–156)	130 (90–189)	<0.001
Glucose metabolism				
Fasting glucose, mg/dL	98±16	101±19	101±24	<0.001
Hemoglobin A1c, %	5.3±0.6	5.4±0.7	5.5±0.9	<0.001
Fasting insulin, μU/mL	5.3 (3.9–7.9)	5.6 (4.0–8.4)	5.4 (3.9–8.4)	0.004
HOMA-IR	1.3 (0.9–1.9)	1.4 (1.0–2.1)	1.3 (0.9–2.1)	<0.001
Diabetes mellitus (n (%))	144 (5.4)	179 (8.0)	219 (10.2)	<0.001
Renal function				
Serum urea nitrogen, mg/dL	15.0±3.4	14.8±3.6	14.0±3.3	<0.001
Serum creatine, mg/dL	0.87±0.13	0.87±0.26	0.83±0.13	<0.001
eGFR, mL/min/1.73 m^2	69.2±9.9	69.2±9.9	73.0±10.3	<0.001
Low eGFR (n (%))	437 (16.4)	369 (16.4)	212 (9.8)	<0.001
Elevated eGFR (n (%))	60 (2.3)	45 (2.0)	99 (4.6)	<0.001
UAER, mg/g	5.2 (3.7–9.5)	6.0 (3.9–12.0)	5.7 (3.9–10.8)	<0.001
Albuminuria (n (%))	200 (7.5)	236 (1,005)	234 (10.8)	<0.001
Uric acid, mg/dL	6.1±1.2	6.2±1.2	6.2±1.3	0.019
Drinking status				
Non-drinkers (n (%))	356 (13.3)	123 (5.5)	167 (7.7)	<0.001
Former drinkers (n (%))	90 (3.4)	228 (10.1)	74 (3.4)	
Current drinkers (n (%))	2,223 (83.3)	1,901 (84.4)	1,916 (88.8)	

Data are means±SD, median (interquartile range), n, or percentage. Diabetes mellitus was diagnosed when the subject had an FPG value of ≥126 mg/dL or current use of anti-diabetic drugs. The Kruskal-Wallis test was used to evaluate differences in triglycerides, fasting insulin, HOMA-IR, and UAER among the different smoking groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment insulin resistance; eGFR, estimated glomerular filtration rate; UAER, urinary albumin excretion rate.

Methods

Study Population

Between April 2005 and August 2006, 8,054 Japanese men underwent such a screening, including the estimation of urinary albumin excretion. Among them, 2,898 were former smokers and 2,487 were current smokers. After 976 subjects were excluded for failing to complete a questionnaire about their smoking habits (the reasons for this failure were unknown), we enrolled a total of 7,078 men, including 2,252 former and 2,157 current smokers. Subjects who had quit smoking for 1 month or less and those who had quit for more than 1 month before the time of the screening were considered to be, respectively, current and former smokers. The mean age of the 8,054 individuals (that is, before exclusion) was 53.7±10.5 years, significantly higher than that of the 7,078 men selected (53.3±10.5 years, p=0.007). Therefore, there may have been some bias in selecting the study subjects; however, this was not the intention of any attending physician. In Japan, regular health check-ups for employees are a legal requirement; all or most of the costs of the screening are paid for either by the employer (accounting for about two-thirds of individuals seen at our institute) or by the subject themselves (the other third). Blood pressure was measured after about 10 min of rest by an automated sphygmomanometer. The study was approved by the Ethics Committee of the Mitsui Memorial Hospital and Faculty of Medicine, University of Tokyo.

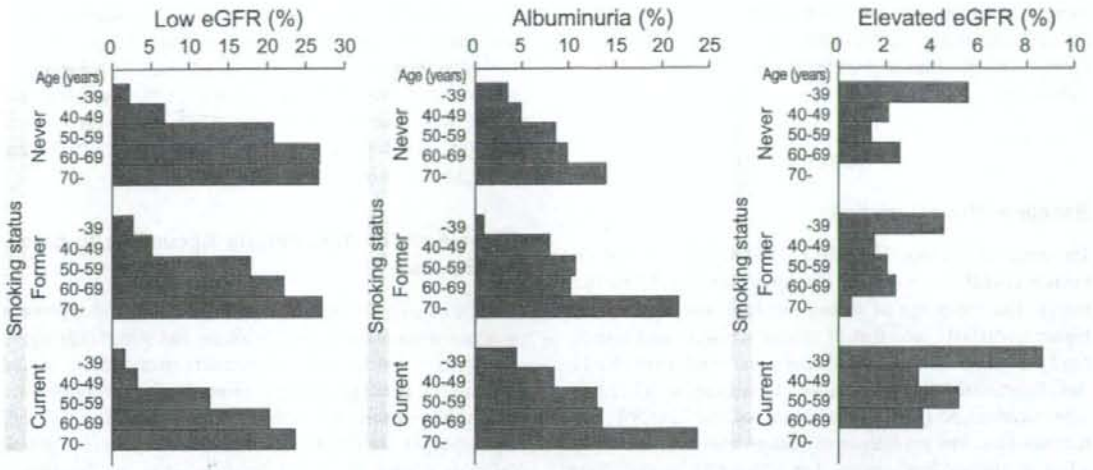

Fig. 1. *Prevalence of low eGFR, albuminuria, and elevated eGFR according to smoking status and age.*

Examination

Blood samples were taken and spot-urine specimens were obtained from the subjects in the morning after an overnight fast. Serum levels of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method, hemoglobin A1c was determined using the latex agglutination immunoassay, and creatinine was determined by the enzymatic method. Plasma glucose was measured by the hexokinase method, and serum insulin was measured by enzyme immunoassay. Homeostasis model assessment insulin resistance (HOMA-IR) was calculated in these individuals according to the following formula: HOMA-IR = [fasting immunoreactive insulin (μU/mL) × fasting plasma glucose (FPG; mg/dL)]/405. Creatinine and urine albumin were measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) and by Accute (Toshiba Medical Systems), respectively, using commercially available kits, Accuras Auto CRE (Shino-test, Tokyo, Japan) and IATRO U-ALB (TIA) (Mitsubishi Kagaku Iatron, Tokyo, Japan) respectively, according to the manufacturers' instructions. Accuracy was monitored every day by constructing X-bar and R charts using commercially available standards. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by an automated sphygmomanometer, BP-203RVIII (Omron Colin, Tokyo, Japan). Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg or current treatment with any antihypertensive drug.

Estimated GFR, Albuminuria, and Definition of CKD

Serum creatinine was calibrated by using the following formula: serum creatinine (Jaffe method) = 0.2 + serum creatinine (enzyme method). Serum creatinine was measured in mg/dL and age in years; glomerular filtration rate (GFR) was estimated by using the following equation from a simplified version of the Modification of Diet in Renal Disease (MDRD) (*9*): eGFR (mL/min/1.73 m^2) = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 0.881 (× 0.742 if female). In this MDRD formula, 0.881 is a coefficient for eGFR specific to the Japanese population (*10*). An eGFR of <60 mL/min/1.73 m^2 was designated as low eGFR. For the diagnosis of albuminuria, spot urine samples were collected and analyzed; albuminuria was considered present when the urinary albumin excretion ratio (UAER) expressed in mg/g creatinine, was ≥30 mg/g. Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as UAER of <30 mg/g, 30–299 mg/g, and ≥300 mg/g, respectively (*11*). Individuals were said to have CKD when they had low eGFR and/or albuminuria (*12*). Elevated eGFR was defined as an eGFR value that exceeded twice the SD of the mean eGFR value in the individuals enrolled, which was an eGFR value of >90.73 mL/min/1.73 m^2.

Statistical Analysis

Skewed variables, such as TG, fasting serum insulin, HOMA-IR, and UAER, are presented as medians (interquartile range). Other data are expressed as means±SD unless stated otherwise. Analyses of variance with Bonferroni post-hoc test, Kruskal-Wallis test, or χ^2-test were conducted as appropriate to assess the statistical significance of differences between groups. The association of smoking with CKD components (low eGFR and albuminuria) or with elevated eGFR was analyzed with a logistic regression model adjusted for all or some of the following variables: age, body mass index (BMI), SBP, FPG, HDL-C, TG, fasting serum insulin, and

current use of antihypertensive medication. Statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, USA). A value of $p<0.05$ was taken to be statistically significant.

Results

Baseline Characteristics

The mean eGFR was 70.4±10.2 mL/min/1.73 m^2, and the median UAER was 5.6 mg/g (interquartile range 3.8 to 10.6 mg/g). The mean age of former smokers was significantly higher ($p<0.001$), and that of current smokers was significantly lower ($p<0.001$), than that of never smokers (Table 1). Antidiabetic treatment was being administered to 47 (1.8%) never smokers, 85 (3.8%) former smokers, and 72 (3.3%) current smokers. The prevalence of diabetes mellitus, defined as a fasting glucose level greater than 126 mg/dL and/or taking antidiabetic medication, was significantly greater in both current and former smokers ($p<0.001$) than in never smokers. The prevalence of low eGFR was significantly lower and that of elevated eGFR was significantly higher in current than in never smokers ($p<0.001$). The prevalence of albuminuria in both former and current smokers was greater than that in never smokers ($p<0.001$).

Prevalence of Low eGFR, Albuminuria, and Elevated eGFR According to Smoking Status after Stratification by Age

As mean age differed significantly among the three groups, we plotted the prevalence of the components of CDK and elevated eGFR after stratification by age (Fig. 1). The number of individuals in the age categories of <39, 40–49, 50–59, 60–69, and ≥70 years were 7, 52, 170 155, and 53, respectively, in never smokers; 3, 24, 158, 129, and 55 in former smokers; and 4, 22, 104, 69, and 13 in current smokers. The prevalence of low eGFR and albuminuria both increased with age irrespective of smoking status.

Prevalence of Low eGFR According to Smoking Status

After adjusting for age, SBP, and FPG, logistic regression analysis revealed that current smoking showed a dose-dependent inverse association with the prevalence of low eGFR (Table 2). The prevalence of low eGFR was found to be significantly lower in current smokers who had been smoking for 10 years or longer and former smokers who had smoked for 20 years or longer. An inverse association between former smoking and low eGFR was observed in those individuals who had stopped smoking <1 year ago, but not in those who had stopped ≥1 year ago. Similar results were obtained after further adjustment for BMI, TG, HDL-C, serum insulin, and use of antihypertensive drugs; however, the association between former smoking and low eGFR was statistically significant in individuals who had stopped smoking ≥1 year ago as well as in those who had stopped <1 year ago. After adjusting for these variables, current and former smoking as a whole was associated with low eGFR, with odds ratios of 0.60 (95% confidence interval [CI] 0.50–0.73, $p<0.001$) and 0.80 (0.68–0.94, $p=0.005$), respectively.

Prevalence of Albuminuria According to Smoking Status

After adjusting for age, SBP, and FPG, logistic regression analysis showed that current smoking was statistically significantly associated with albuminuria irrespective of the amount of smoking, although the association just missed statistical significance when the amount of smoking was ≥20 cigarettes per day (Table 3). The association was also statistically significant in current smokers when the duration of smoking was ≥10 years. Former smoking tended to be associated with albuminuria when the duration of smoking was ≥10 years. Similar results were obtained after further adjustment for BMI, TG, HDL-C, serum insulin, and use of antihypertensive drugs. After adjusting for these variables, current smoking as a whole was associated with albuminuria, with an odds ratio of 1.63 (95% CI 1.34–2.03, $p<0.001$), although former smoking as a whole was not (odds ratio 1.16, 95% CI 0.94–1.44, $p=0.155$).

Prevalence of Elevated eGFR According to Smoking Status

After adjusting for age, SBP, and FPG, logistic regression analysis revealed that current smoking had a dose-dependent positive association with elevated eGFR (Table 4). In contrast, former smoking was not significantly associated with elevated eGFR irrespective of the amount or duration of smoking, or even when the cessation period was <1 year. Similar results were obtained after further adjustment for BMI, TG, HDL-C, serum insulin, and use of antihypertensive drugs. After adjusting for these variables, current smoking as a whole was associated with albuminuria with an odds ratio of 1.98 (95% CI 1.41–2.78, $p<0.001$), although former smoking as a whole was not (odds ratio 0.97, 95% CI 0.65–1.44, $p=0.878$).

Discussion

This study showed that current smoking was inversely associated with low eGFR when the amount smoked was ≥10 cigarettes per day. This association remained statistically significant after adjustment for age, SBP, and other metabolic parameters related to metabolic syndrome (BMI, HDL-C, TG, FPG, serum insulin, antihypertensive treatment) (Table 2). After adjusting for these variables, current smoking also showed a graded positive association with elevated eGFR

Table 2. Logistic Regression Analysis for Low eGFR as a Dependent Variable and Smoking Status as Independent Variables

Smoking status	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Amount of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (cigarettes/day)						
<10	0.78 (0.55–1.11)	0.171	0.78 (0.55–1.11)	0.164	0.77 (0.54–1.09)	0.143
10–19	0.93 (0.75–1.14)	0.478	0.93 (0.76–1.14)	0.491	0.90 (0.73–1.11)	0.336
20–39	0.77 (0.61–0.96)	0.020	0.77 (0.61–0.96)	0.023	0.72 (0.57–0.91)	0.005
≥40	0.84 (0.60–1.19)	0.332	0.84 (0.60–1.19)	0.334	0.80 (0.57–1.14)	0.222
Current smoking* (cigarettes/day)						
<10	1.12 (0.81–1.54)	0.499	1.13 (0.82–1.56)	0.465	1.07 (0.77–1.48)	0.708
10–19	0.55 (0.43–0.72)	<0.001	0.56 (0.43–0.73)	<0.001	0.53 (0.40–0.69)	<0.001
20–39	0.61 (0.47–0.80)	<0.001	0.63 (0.49–0.83)	<0.001	0.55 (0.42–0.73)	<0.001
≥40	0.29 (0.12–0.72)	0.008	0.32 (0.13–0.79)	0.014	0.26 (0.10–0.65)	0.004
Duration of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (years)						
<5	0.71 (0.42–1.20)	0.200	0.70 (0.42–1.19)	0.189	0.72 (0.42–1.21)	0.213
5–9	0.87 (0.63–1.20)	0.383	0.86 (0.63–1.19)	0.371	0.82 (0.59–1.14)	0.232
10–19	1.00 (0.79–1.25)	0.965	0.99 (0.79–1.25)	0.947	0.97 (0.77–1.22)	0.789
≥20	0.76 (0.62–0.93)	0.007	0.77 (0.63–0.94)	0.010	0.72 (0.59–0.89)	0.002
Current smoking* (years)						
<5	0.94 (0.31–2.79)	0.904	1.00 (0.33–2.99)	0.999	1.12 (0.37–3.37)	0.837
5–9	1.11 (0.48–2.56)	0.805	1.15 (0.50–2.64)	0.750	1.18 (0.51–2.71)	0.701
10–19	0.53 (0.32–0.89)	0.017	0.54 (0.32–0.91)	0.021	0.50 (0.30–0.84)	0.009
≥20	0.64 (0.53–0.78)	<0.001	0.66 (0.55–0.80)	<0.001	0.60 (0.49–0.73)	<0.001
Years of cessation						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking*						
Last smoked <1 year ago	0.51 (0.29–0.88)	0.015	0.52 (0.30–0.89)	0.018	0.51 (0.29–0.88)	0.015
Last smoked ≥1 year ago	0.87 (0.74–1.02)	0.079	0.87 (0.74–1.02)	0.081	0.83 (0.71–0.98)	0.025

Model 1, adjusted for age; model 2, age, SBP, and FPG; model 3, age, SBP, FPG, BMI, HDL-C, TG, fasting serum insulin, and current use of antihypertensive drug. *Never smoking was used as reference. eGFR, estimated glomerular filtration rate; CI, confidence interval; SBP, systolic blood pressure; FPG, fasting blood glucose; BMI, body mass index; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TG, triglyceride.

(Table 4). On the other hand, former smoking showed a statistically significant inverse association with low eGFR, whereas the association with either albuminuria or elevated eGFR did not reach statistical significance irrespective of the duration of smoking (Tables 3, 4). Interestingly, the association between cigarette smoking and elevated eGFR lost statistical significance even within 1 year after quitting (Table 4). These findings collectively suggest that cigarette smoking decreases the prevalence of low eGFR and increases the prevalence of albuminuria and elevated eGFR—an association that is markedly weakened (for low eGFR and albuminuria) or abolished (for elevated eGFR) after quitting smoking.

Several studies have demonstrated a positive association between smoking and albuminuria, some of which showed statistically significant associations in both current and former smokers (*13*), while others demonstrated only in current smokers (*5*, *6*). In the current study, after adjusting for age and variables related to metabolic syndrome, current smoking as a whole showed a statistically significant inverse association with low eGFR and positive ones with albuminuria and elevated eGFR. On the other hand, former smoking, as a whole, showed a statistically significant inverse association with low eGFR, but the association between former smoking and albuminuria was not significant. These findings are in agreement with the results of the third National Health and Nutrition Examination Survey, which showed that the cessation of smoking weakens or abolishes the increase in albuminuria (*5*).

Table 3. Logistic Regression Analysis for Albuminuria as a Dependent Variable and Smoking Status as Independent Variables

Smoking status	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Amount of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (cigarettes/day)						
<10	0.65 (0.39–1.11)	0.112	0.73 (0.42–1.24)	0.239	0.70 (0.41–1.21)	0.203
10–19	1.49 (1.16–1.91)	0.002	1.46 (1.12–1.90)	0.005	1.45 (1.12–1.89)	0.006
20–39	1.26 (0.96–1.65)	0.102	1.08 (0.81–1.44)	0.601	1.03 (0.77–1.37)	0.857
≥40	1.56 (1.05–2.33)	0.029	1.27 (0.84–1.92)	0.261	1.16 (0.77–1.77)	0.482
Current smoking* (cigarettes/day)						
<10	1.57 (1.08–2.30)	0.019	1.72 (1.15–2.56)	0.008	1.67 (1.12–2.51)	0.012
10–19	1.61 (1.24–2.08)	<0.001	1.64 (0.25–2.16)	<0.001	1.70 (1.28–2.24)	<0.001
20–39	1.66 (1.27–2.18)	<0.001	1.56 (1.17–2.08)	0.002	1.53 (1.14–2.06)	0.005
≥40	2.43 (1.37–4.32)	0.003	1.88 (0.99–3.55)	0.053	1.81 (0.96–3.41)	0.068
Duration of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (years)						
<5	0.52 (0.23–1.20)	0.124	0.57 (0.25–1.31)	0.184	0.55 (0.24–1.29)	0.169
5–9	0.69 (0.43–1.13)	0.137	0.72 (0.44–1.18)	0.193	0.70 (0.42–1.15)	0.159
10–19	1.57 (1.19–2.06)	0.001	1.36 (1.02–1.81)	0.035	1.33 (1.00–1.77)	0.050
≥20	1.45 (1.14–1.84)	0.003	1.33 (1.04–1.71)	0.025	1.27 (0.99–1.64)	0.060
Current smoking* (years)						
<5	1.53 (0.46–5.14)	0.491	1.03 (0.24–4.52)	0.965	1.19 (0.28–5.04)	0.809
5–9	0.88 (0.27–2.88)	0.838	0.84 (0.25–2.81)	0.773	0.89 (0.27–2.96)	0.843
10–19	1.83 (1.21–2.78)	0.004	1.82 (1.17–2.83)	0.008	1.73 (1.10–2.72)	0.017
≥20	1.66 (1.35–2.04)	<0.001	1.64 (1.32–2.05)	<0.001	1.66 (1.32–2.08)	<0.001
Years of cessation						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking*						
Last smoked <1 year ago	1.41 (0.83–2.37)	0.204	1.28 (0.74–2.22)	0.374	1.28 (0.74–2.22)	0.382
Last smoked ≥1 year ago	1.29 (1.05–1.58)	0.014	1.20 (0.97–1.48)	0.097	1.16 (0.93–1.43)	0.184

Models as in Table 2. *Never smoking was used as reference. CI, confidence interval.

We also showed here that current smoking dose-dependently reduced the prevalence of low eGFR. In agreement with our result, some studies have shown that current smoking is associated with higher creatinine clearance or GFR in the general population (*14*) and in type 2 diabetic patients (*7*). On the other hand, however, some other studies have shown that current smoking decreases GFR in community-dwelling subjects (*8*) and type 2 diabetic patients (*15*). What causes these conflicting results has not been fully clarified; however, insulin resistance, which might be enhanced by smoking (*16*), may have a role in these discrepant observations, as it may lead to a decrease (*17*) or an elevation (*18*) of eGFR.

In the current study, current smoking, but not former smoking, was dose-dependently positively associated with elevated eGFR (Table 2). Ekberg *et al.* reported that glomerular hyperfiltration was more prevalent in smokers than in nonsmokers (*19*). In addition, in a substudy of the PREVEND study (Prevention of Renal and Vascular End-stage Disease), Pinto-Sietsma *et al.* reported that current smoking showed a dose-dependent association with elevated eGFR in nondiabetic subjects, which disappeared after smoking ceased (*13*). We cannot conclude the mechanism by which smoking elevates GFR in the Japanese population from this type of cross-sectional study; however, it is possible that pre-glomerular vessels and glomerular obsolescence lead to hypertrophy and hyperfiltration of remnant glomeruli after repeated transient decreases in renal plasma flow and GFR induced by smoking, which eventually result in elevated GFR (*14*, *20*). It is recognized that glomerular hyperfiltration is not a rare occurrence in individuals with impaired glucose metabolism (*21*, *22*) or even in apparently healthy young men (*23*). 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 (*23*). Thus, the increase

Table 4. Logistic Regression Analysis for Elevated eGFR as a Dependent Variable and Smoking Status as Independent Variables

Smoking status	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Amount of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (cigarettes/day)						
<10	0.57 (0.20–1.57)	0.276	0.61 (0.22–1.70)	0.348	0.61 (0.22–1.70)	0.342
10–19	0.81 (0.46–1.44)	0.477	0.77 (0.43–1.38)	0.379	0.78 (0.45–1.40)	0.405
20–39	1.40 (0.93–2.37)	0.207	1.21 (0.71–2.06)	0.477	1.32 (0.77–2.25)	0.310
≥40	1.50 (0.63–3.57)	0.358	1.24 (0.53–3.05)	0.592	1.41 (0.58–3.41)	0.447
Current smoking* (cigarettes/day)						
<10	0.72 (0.31–1.67)	0.438	0.70 (0.30–1.63)	0.403	0.71 (0.30–1.69)	0.440
10–19	2.03 (1.37–3.01)	<0.001	1.87 (1.25–2.81)	0.002	1.93 (1.28–2.90)	0.002
20–39	2.50 (1.67–3.75)	<0.001	2.35 (1.56–3.54)	<0.001	2.56 (1.68–3.91)	<0.001
≥40	3.10 (1.30–7.39)	0.011	2.46 (1.01–6.00)	0.049	2.81 (1.13–6.99)	0.026
Duration of smoking						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking* (years)						
<5	0.95 (0.34–2.66)	0.924	1.02 (0.37–2.87)	0.965	1.01 (0.36–2.83)	0.986
5–9	0.48 (0.17–1.32)	0.154	0.50 (0.18–1.38)	0.181	0.50 (0.18–1.39)	0.183
10–19	1.01 (0.57–1.80)	0.963	0.91 (0.51–1.64)	0.762	0.95 (0.53–1.70)	0.853
≥20	1.36 (0.80–2.29)	0.254	1.18 (0.69–2.00)	0.548	1.28 (0.75–2.19)	0.365
Current smoking* (years)						
<5	2.54 (0.59–11.04)	0.214	2.03 (0.43–0.96)	0.369	1.89 (0.38–9.45)	0.439
5–9	2.06 (0.71–5.97)	0.186	2.05 (0.71–5.96)	0.188	1.97 (0.67–5.77)	0.216
10–19	1.70 (0.99–2.92)	0.053	1.59 (0.92–2.74)	0.097	1.68 (0.97–2.92)	0.065
≥20	2.10 (1.48–2.98)	<0.001	1.94 (1.36–2.78)	<0.001	2.04 (1.42–2.95)	<0.001
Years of cessation						
Never smoking	1.00	—	1.00	—	1.00	—
Former smoking*						
Last smoked <1 year ago	1.49 (0.63–3.50)	0.364	1.32 (0.55–3.15)	0.534	1.37 (0.57–3.29)	0.479
Last smoked ≥1 year ago	0.97 (0.64–1.47)	0.871	0.90 (0.59–1.37)	0.628	0.94 (0.62–1.43)	0.768

Abbreviations and models as in Table 2. *Never smoking was used as reference. CI, confidence interval.

in eGFR caused by cigarette smoking may not simply be a preferable or an innocuous observation. In addition, current smoking may increase the prevalence of both low GFR and elevated GFR in the same population (*13*, *15*), which suggests the possibility that a simple comparison of the eGFR between smokers and nonsmokers may lead to an inappropriate conclusion.

Our study has some limitations. First, we used the MDRD formula with the Japanese coefficient of 0.881 for the estimation of GFR (*10*), and a recent study has shown that this formula may underestimate GFR in the inulin clearance range of over 60 mL/min/1.73 m^2 in the Japanese population. Second, in the MDRD formula used, muscle mass was not taken into consideration for GFR estimation. Because the serum creatinine value is the balance of the release from skeletal muscle and removal by the kidneys, both muscle mass and renal function are important determinants. Recent studies have shown that anthropometric/demographic variables, such as age, gender, height, and weight, may not adequately account for variance in muscle mass, and that measures of muscle mass, which can be clinically obtainable (*24*), may improve the estimation of GFR (*25*). Third, owing to the cross-sectional nature of the current study, we cannot determine whether or not elevation of eGFR in smokers modulates long-term renal prognosis.

In conclusion, by analyzing the cross-sectional data of Japanese men who underwent a general health screening, we showed that current smoking was dose-dependently associated inversely with low eGFR and positively with albuminuria and elevated eGFR—associations that were weakened or abolished after quitting. We may need to take into account an individual's smoking status when assessing the eGFR and

thus the presence of CKD, especially when urine data are not available, as smoking may increase the prevalence of not only albuminuria but also hyperfiltration. Whether or not elevation of eGFR owing to cigarette smoking acts protectively for renal function in the long term, and whether or not elevation of eGFR by current smoking is an acute and transient phenomenon that does not modulate long-term renal prognosis, need to be investigated in future longitudinal studies.

References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351**: 1296–1305.
2. Hallan SI, Dahl K, Oien CM, *et al*: Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. *BMJ* 2006; **333**: 1047.
3. Briet M, Bozec E, Laurent S, *et al*: Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int* 2006; **69**: 350–357.
4. Brosius FC 3rd, Hostetter TH, Kelepouris E, *et al*: Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney and Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. *Circulation* 2006; **114**: 1083–1087.
5. Hogan SL, Vupputuri S, Guo X, *et al*: Association of cigarette smoking with albuminuria in the United States: the third National Health and Nutrition Examination Survey. *Ren Fail* 2007; **29**: 133–142.
6. Ikeda Y, Suehiro T, Takamatsu K, Yamashita H, Tamura T, Hashimoto K: Effect of smoking on the prevalence of albuminuria in Japanese men with non-insulin-dependent diabetes mellitus. *Diabetes Res Clin Pract* 1997; **36**: 57–61.
7. Baggio B, Budakovic A, Dalla Vestra M, Saller A, Brusegnin M, Fioretto P: Effects of cigarette smoking on glomerular structure and function in type 2 diabetic patients. *J Am Soc Nephrol* 2002; **13**: 2730–2736.
8. Shankar A, Klein R, Klein BE: The association among smoking, heavy drinking, and chronic kidney disease. *Am J Epidemiol* 2006; **164**: 263–271.
9. Manjunath G, Sarnak MJ, Levey AS: Prediction equations to estimate glomerular filtration rate: an update. *Curr Opin Nephrol Hypertens* 2001; **10**: 785–792.
10. Imai E, Horio M, Nitta K, *et al*: Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11**: 41–50.
11. Molitch ME, Rupp D, Carnethon M: Higher levels of HDL cholesterol are associated with a decreased likelihood of albuminuria in patients with long-standing type 1 diabetes. *Diabetes Care* 2006; **29**: 78–82.
12. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1–S266.
13. Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de Zeeuw D, de Jong PE: Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med* 2000; **133**: 585–591.
14. Halimi JM, Giraudeau B, Vol S, *et al*: Effects of current smoking and smoking discontinuation on renal function and proteinuria in the general population. *Kidney Int* 2000; **58**: 1285–1292.
15. De Cosmo S, Lamacchia O, Rauseo A, *et al*: Cigarette smoking is associated with low glomerular filtration rate in male patients with type 2 diabetes. *Diabetes Care* 2006; **29**: 2467–2470.
16. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M: Association between cigarette smoking, metabolic syndrome, and carotid arteriosclerosis in Japanese individuals. *Atherosclerosis* 2005; **181**: 381–388.
17. De Cosmo S, Trevisan R, Minenna A, *et al*: Insulin resistance and the cluster of abnormalities related to the metabolic syndrome are associated with reduced glomerular filtration rate in patients with type 2 diabetes. *Diabetes Care* 2006; **29**: 432–434.
18. Dengel DR, Goldberg AP, Mayuga RS, Kairis GM, Weir MR: Insulin resistance, elevated glomerular filtration fraction, and renal injury. *Hypertension* 1996; **28**: 127–132.
19. Ekberg G, Grefberg N, Larsson LO, Vaara I: Cigarette smoking and glomerular filtration rate in insulin-treated diabetics without manifest nephropathy. *J Intern Med* 1990; **228**: 211–217.
20. Remuzzi G: Cigarette smoking and renal function impairment. *Am J Kidney Dis* 1999; **33**: 807–813.
21. Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy—an 8-year prospective study. *Kidney Int* 1992; **41**: 822–828.
22. Chen LK, Lin MH, Chen ZJ, Hwang SJ, Tsai ST, Chiou ST: Metabolic characteristics and insulin resistance of impaired fasting glucose among the middle-aged and elderly Taiwanese. *Diabetes Res Clin Pract* 2006; **71**: 170–176.
23. Tomaszewski M, Charchar FJ, Maric C, *et al*: Glomerular hyperfiltration: a new marker of metabolic risk. *Kidney Int* 2007; **71**: 816–821.
24. Macdonald JH, Marcora SM, Kumwenda MJ, *et al*: The relationship between estimated glomerular filtration rate, demographic and anthropometric variables is mediated by muscle mass in non-diabetic patients with chronic kidney disease. *Nephrol Dial Transplant* 2006; **21**: 3488–3494.
25. Macdonald JH, Marcora SM, Jibani M, *et al*: Bioelectrical impedance can be used to predict muscle mass and hence improve estimation of glomerular filtration rate in non-diabetic patients with chronic kidney disease. *Nephrol Dial Transplant* 2006; **21**: 3481–3487.

Hepatology Research 2008; **38**: 775–783 doi: 10.1111/j.1872-034X.2008.00334.x

Original Article

Association between hepatitis B/C viral infection, chronic kidney disease and insulin resistance in individuals undergoing general health screening

Nobukazu Ishizaka,[1] Yuko Ishizaka,[2] George Seki,[3] Ryozo Nagai,[1] Minoru Yamakado[2] and Kazuhiko Koike[4]

Departments of [1]Cardiovascular Medicine, [4]Infectious Diseases and [3]Nephrology, University of Tokyo Graduate School of Medicine, and [2]Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital, Tokyo, Japan

Aim: Previous studies have shown that hepatitis B virus (HBV) and hepatitis C virus (HCV) infection may be associated with glomerulonephritis.

Methods: In the current study, we investigated the possible association between HBV/HCV infection, estimated GFR (eGFR) and albuminuria by analyzing cross-sectional data from individuals undergoing general health screening.

Results: Of 12 535 individuals enrolled, 130 (1.0%) and 72 (0.6%) tested positive for HBV surface antigen and HCV core antigen, respectively. In comparison with hepatitis-negative individuals, the prevalence of low eGFR and albuminuria was significantly greater in individuals with HCV infection, but not in those with HBV infection. Logistic regression analysis adjusted for age, sex, systolic blood pressure and fasting plasma glucose showed that HCV infection was positively associated with low eGFR (odds ratio 1.63 [95% CI 0.95–2.80, $P = 0.077$]) and with albuminuria (odds ratio 2.00 [95% CI 1.06–3.76, $P = 0.003$]). By contrast, prevalence of neither low eGFR nor albuminuria was greater in individuals with HBV infection than in hepatitis-negative subjects. Further adjustment for either HOMA-IR or serum alanine aminotransferase levels abolished the statistical significance in the association between HCV infection and albuminuria.

Conclusion: Our data suggest that although both HCV and HBV infection are associated with increased insulin resistance, the different viruses may have different impacts on chronic kidney disease among Japanese individuals undergoing general health screening.

Key words: aminotransferase, chronic kidney disease, health screening, insulin resistance, viral hepatitis

INTRODUCTION

IN JAPAN, MORE than 1 million people are estimated to be infected with hepatitis B virus (HBV) and over 2 million with hepatitis C virus (HCV);[1] HBV infection has been reported to be found in 0.8% and HCV infection in 0.5% of Japanese workers.[2] Although a major target organ of HBV and HCV infection is the liver, extrahepatic manifestations are also frequently observed in patients with acute and chronic viral hepatitis. In HCV infected patients, even without clinical evidence of liver involvement, renal complications can occur, most commonly membranoproliferative glomerulonephritis (MPGN) and membranous glomerulonephritis (MGN), which are clinically characterized by hematuria, proteinuria and variable grade renal dysfunction. One study has reported that HCV antibody was found to be positive in a large proportion (60%) of Japanese patients with MPGN.[3] El-Serag *et al.* reported that HCV-infected subjects had a sevenfold increase in the odds of MPGN compared with control subjects without HCV infection.[4] HBV infection may also be associated with MGN and MPGN,[5,6] and about 3% of HBV-infected patients were reported to have glomerulonephritis.[7]

Until recently, few data have been available on the prevalence of chronic kidney disease (CKD) and its components in individuals with HBV or HCV infection

Correspondence: Dr Nobukazu Ishizaka, Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Hongo 7-3-1 Bunkyo-ku, Tokyo 113-8655, Japan. Email: nobuishizka-tky@umin.ac.jp

Received 8 August 2007; revision 15 December 2007; accepted 15 January 2008.

in a population-based study. Tsui *et al.* reported that HCV infection was associated with albuminuria, but not with decreased GFR, in a US population.[8] Huang *et al.* reported a significant association between proteinuria and HCV, but not HBV, infection in an HBV/HCV endemic area.

In the present study, we investigated whether HBV infection, diagnosed by HBV surface antigen (HBsAg) positivity, and HCV infection, diagnosed by HCV core antigen (HCcAg) positivity, were associated with CKD components in Japanese individuals who underwent general health screening.

METHODS

Study population

THE STUDY WAS approved by the Ethical Committee of the Mitsui Memorial Hospital. Between April 2004 and August 2006, 12 535 people (4481 women and 8054 men) underwent a general health screen at Mitsui Memorial Hospital, including an estimation of urinary excretion of albumin, and were enrolled in the present study. In Japan, regular health check ups for employees are a legal requirement; all or most of the costs of the screening are paid for either by the employee's company or by the subject himself.

Laboratory analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), HDL-cholesterol (HDL-C) and triglycerides (TG), alanine aminotransferase (ALT) and creatinine were determined by the enzymatic method. Serum uric acid was measured by the uricase–peroxidase method and hemoglobin A1C was determined by latex agglutination immunoassay. The levels of HBsAg and HCcAg in the sera were determined using commercially available enzyme immunoassay kits, AxSYM HBsAg Dynapack (Abbott Japan, Osaka, Japan) and Lumispot "Eiken" HCV antigen (Eiken Chemical, Tokyo, Japan), respectively, according to the manufacturer's instructions. HCcAg of >8.0 pg/mL was considered to be positive. Plasma glucose was measured by the hexokinase method and serum insulin was measured by enzyme immunoassay. Homeostasis model assessment insulin resistance (HOMA-IR) was calculated in these individuals according to the following formula: HOMA-IR = (fasting immunoreactive insulin [μU/mL] × fasting plasma glucose [FPG; mg/dL])/405. The median (range) ALT values in each ALT quartile (IU/mL) were 12 (4–14), 17 (15–19), 23 (20–27) and 37 (28–677).

Estimated glomerular filtration rate, albuminuria and CKD

Serum creatinine was calibrated using the following formula: serum creatinine (Jaffe method) = 0.2 + serum creatinine (measured by enzymatic method). Serum creatinine was measured in mg/dL, and age in years; GFR was estimated using the equation from a simplified version of the Modification of Diet in Renal Disease (MDRD),[9] as follows: estimated GFR (eGFR; mL/min/1.73 m^2) = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 0.881 × 0.742 (if female). In this MDRD formula, 0.881 is a coefficient for eGFR specific to the Japanese population.[10] For the diagnosis of albuminuria, spot urine samples were collected and expressed as urine albumin excretion ratio (UAER), which was expressed per g-creatinine. CKD was diagnosed when individuals had an eGFR of <60 mL/min/1.73 m^2, designated as low eGFR, and/or UAER of ≥30 mg/g, designated as albuminuria.[11]

Diagnosis of metabolic syndrome

Diagnosis of metabolic syndrome was made according to the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III),[12] with body mass index (BMI) used as a surrogate for waist circumference.[13] Metabolic syndrome was said to be present when three or more of the following conditions were met: TG levels ≥150 mg/d; HDL-C levels <40 mg/dL (men), <50 mg/dL (women); FPG levels ≥110 mg/dL or taking antidiabetic medication; systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg or taking an antihypertensive medication; BMI ≥25 kg/m^2.

Statistical analysis

The data in this study were analyzed by one-way ANOVA with Bonferroni post hoc test, χ^2 test and by univariate and multivariate logistic regression analysis using the computer software StatView ver. 5.0 (SAS Institute, Cary, NC, USA). A value of $P < 0.05$ was taken to be statistically significant. Results are expressed as the mean ± standard deviation unless stated otherwise.

RESULTS

Baseline characteristics

THE BASELINE CHARACTERISTICS of the study subjects according to viral hepatitis infection are

Table 1 Clinical characteristics and laboratory data of study subjects

	Hepatitis negative (n = 12 333)	HBsAg positive (n = 130)	HCcAg postive (n = 72)	P-value
Male sex, n (%)	7916 (64)	93 (63)	45 (72)	0.21
Age, years	53.1 ± 10.6	55.3 ± 10.6	59.2 ± 10.5	<0.001
Body mass index, kg/m^2	22.8 ± 3.1	23.9 ± 3.2	22.3 ± 2.8	<0.001
Systolic blood pressure, mmHg	122 ± 19	126 ± 20	123 ± 22	0.024
Diastolic blood pressure, mmHg	77 ± 12	79 ± 11	77 ± 13	0.077
WBC count, ×103 cells/μL	5.3 ± 1.4	5.0 ± 1.2	5.0 ± 1.7	0.025
RBC count, ×104/μL	467 ± 43	473 ± 40	455 ± 48	0.020
Hemoglobin, g/dL	14.6 ± 1.5	14.8 ± 1.4	14.4 ± 1.5	0.17
Platelet count, ×104/μL	23.0 ± 5.1	20.1 ± 4.9	16.9 ± 5.8	<0.001
Serum data				
Total protein, g/dL	7.3 ± 0.4	7.3 ± 0.4	7.6 ± 0.5	<0.001
Albumin, g/dL	4.5 ± 0.2	4.5 ± 0.2	4.4 ± 0.3	<0.001
Total bilirubin, mg/dL	0.90 ± 0.36	0.92 ± 0.35	1.00 ± 0.47	0.040
ALT, IU/L	24 ± 19	27 ± 29	56 ± 46	<0.001
AST, IU/L	22 ± 12	25 ± 13	48 ± 27	<0.001
γ-GTP, IU/L	46 ± 67	38 ± 30	61 ± 57	0.061
Total cholesterol, mg/dL	211 ± 33	205 ± 31	175 ± 32	<0.001
HDL-cholesterol, mg/dL	59 ± 15	58 ± 14	53 ± 11	0.001
Triglycerides, mg/dL	117 ± 84	107 ± 83	89 ± 36	0.006
Fasting glucose, mg/dL	97 ± 19	98 ± 17	96 ± 15	0.82
Hemoglobin A1C, %	5.3 ± 0.7	5.3 ± 0.7	5.2 ± 0.7	0.30
HOMA-IR	1.5 ± 1.5	1.7 ± 1.1	2.4 ± 1.8	<0.001
Renal data				
Serum urea nitrogen, mg/dL	14.3 ± 3.6	14.6 ± 3.1	15.4 ± 6.4	0.031
Serum creatine, mg/dL	0.78 ± 0.26	0.78 ± 0.14	0.81 ± 0.28	0.65
eGFR, mL/min/1.73m2	70 ± 10	70 ± 9	67 ± 13	0.087
Low eGFR, n (%)	1887 (15)	13 (10)	22 (31)	<0.001
UAER, mg/g	21 ± 129	12 ± 20	94 ± 428	<0.001
Albuminuria, n (%)	1157 (9)	8 (6)	14 (19)	0.006
Smoking status				
Never/former/current, %	52/25/23	43/29/28	60/24/17	0.18
Drinking status				
Never/former/current, %	20/5/75	19/5/75	32/17/51	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; γGTP, gamma-glutamyltransferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; UAER, urine albumin excretion ratio; WBC, white blood cells; RBC, red blood cells.

described in Table 1. Of the 12 535 subjects enrolled, 130 (1.0%; 37 women, 93 men) and 72 (0.6%; 27 women, 45 men) were positive for HBsAg and HCcAg, respectively; no subjects were positive for both HBsAg and HCcAg. HCcAg-positive individuals were significantly older than hepatitis-negative individuals ($P < 0.001$), whereas the age between HBsAg-positive and hepatitis-negative individuals did not differ significantly. All hepatitis-positive individuals enrolled in the current study, except one HBsAg-positive subject, underwent abdominal ultrasonography, and none was diagnosed as having advanced cirrhosis. The hematological data and aminotransferase levels of the individual who did not undergo abdominal ultrasonography were as follows: white blood cell count, 4000 (cells/microL); red blood cell count, 524 × 104 (cells/microL); Plt 25.4 × 104 (cells/microL); ALT 19 (IU/L); and AST 19 (IU/L). In the HCcAg-positive group, the mean serum TC level was lower than in the other two groups. Logistic regression analysis adjusted for sex, age, ALT, albumin and total bilirubin levels showed that an odds ratio of HBsAg-positivity and HCcAg-positivity for the lowest TC

Table 2 Logistic regression analysis for HBV/HCV infection as independent variables, and low eGFR and albuminuria as dependent variables

	Dependent variables					
	CKD Odds ratio (95% CI)	*P*-value	Components of CKD			
			Low eGFR Odds ratio (95% CI)	*P*-value	Albuminuria Odds ratio (95% CI)	*P*-value
Unadjusted						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	0.63 (0.39–1.01)	0.056	0.62 (0.35–1.09)	0.098	0.63 (0.31–1.30)	0.21
HCcAg positive	2.46 (1.54–3.94)	0.0002	2.44 (1.47–4.03)	0.0005	2.33 (1.30–4.19)	0.0047
Adjusted for age and sex						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	0.53 (0.32–0.86)	0.011	0.51 (0.28–0.93)	0.027	0.57 (0.28–1.18)	0.13
HCcAg positive	1.77 (1.08–2.92)	0.025	1.64 (0.96–2.82)	0.071	1.86 (1.02–3.37)	0.042
Adjusted for age, sex, SBP and FPG						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	0.49 (0.30–0.81)	0.0057	0.51 (0.28–0.92)	0.026	0.50 (0.23–1.05)	0.066
HCcAg positive	1.83 (1.10–3.05)	0.020	1.63 (0.95–2.80)	0.077	2.00 (1.06–3.76)	0.034

CKD, chronic kidney disease; FPG, fasting plasma glucose; HBV, hepatitis B virus; HCV, hepatitis C virus; SBP, systolic blood pressure.

quartile (TC < 187 mg/dL) was 1.42 (95% CI 0.95–2.12, $P = 0.89$) and 7.30 (95% CI 4.39–12.13, $P < 0.001$), respectively, compared with hepatitis-negative individuals. The finding that HCcAg-positive individuals had lower TC levels than non-hepatitis or HBsAg-positive individuals was in agreement with previous observations of ours and others.[14,15] Neither FPG nor HbA1c differed significantly between individuals positive for HBsAg or HCcAg and hepatitis-negative individuals; however, HOMA-IR was significantly greater in HCcAg-positive individuals than in hepatitis-negative ($P < 0.001$) or HBsAg-positive ($P = 0.003$) individuals. Serum albumin level was statistically significantly lower in HCcAg-positive subjects than in hepatitis-negative subjects, although the difference was very small (Table 1 and 4.4 g/dL vs. 4.5 g/dL). By Bonferroni post hoc analysis, serum bilirubin levels were not statistically significantly different between HCcAg-positive and hepatitis-negative individuals or between HBsAg-positive and hepatitis-negative individuals.

eGFR and urinary albumin excretion

Of the 12 535 subjects enrolled, 1179 (9.4%, 389 women, 790 men) had albuminuria, and 1922 (15.3%, 729 women, 1193 men) had low eGFR. Both of these conditions were present in 278 individuals (2.2%); therefore, 2823 (22.5%) subjects (1023 women, 1800 men) were diagnosed to have CKD. Among the 1179 (9.4%) individuals who had albuminuria, 1062 had an UAER value between 30 and 299 mg/g (microalbuminuria), and the remaining 117 had an UAER value of ≥300 mg/g (macroalbuminuria). The median (interquartile range) of eGFR (mL/min/1.73 m^2) was 69.6 (63.2–75.8) in HBV/HCV-negative individuals, 69.5 (64.3–77.2) in HBsAg-positive individuals, and 65.9 (58.4–76.9) in HCcAg-positive individuals. The median (interquartile range) of UAER (mg/g) was 6.4 (4.2–11.8) in HBV/HCV-negative individuals, 6.4 (4.2–11.6) in HBsAg-positive individuals and 8.0 (4.1–18.6) in HCcAg-positive individuals.

Association between HBsAg/HCcAg positivity and CKD

The prevalence of both low eGFR ($P < 0.001$) and albuminuria ($P = 0.007$) was significantly greater in HCcAg-positive than in HBV/HCV-negative individuals by χ^2 test (Table 1). In contrast, compared with HBV/HCV-negative individuals, the prevalence of either low eGFR ($P = 0.12$) or albuminuria ($P = 0.27$) was not different in HBsAg-positive individuals. After adjusting for age and sex, logistic regression analysis showed that HCcAg was statistically significantly positively associated with albuminuria (Table 2) and that it tended to be positively associated with low eGFR. In contrast, HBsAg positivity was inversely associated with low eGFR, whereas it was not significantly associated with albuminuria. Essentially the same results were obtained after further adjustment for SBP and FPG.

Table 3 Logistic regression analysis for HBV/HCV infection as independent variables, and metabolic syndrome, increased insulin resistance and elevated ALT levels as dependent variables

	Dependent variables					
	Metabolic syndrome Odds ratio (95% CI)	*P*-value	Highest HOMA-IR quartile Odds ratio (95% CI)	*P*-value	Highest ALT quartile Odds ratio (95% CI)	*P*-value
Unadjusted						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	1.21 (0.71–2.04)	0.49	1.60 (1.12–2.31)	0.011	1.42 (0.98–2.06)	0.068
HCcAg positive	0.25 (0.60–1.00)	0.050	3.39 (2.13–5.39)	<0.0001	10.3 (0.60–17.8)	<0.0001
Adjusted for age and sex						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	1.09 (0.34–1.86)	0.75	1.57 (1.09–2.26)	0.016	1.36 (0.92–2.01)	0.12
HCcAg positive	0.23 (0.06–0.95)	0.042	3.18 (1.99–5.05)	<0.0001	16.53 (9.20–29.7)	<0.0001

ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HOMA-IR, homeostasis model assessment-insulin resistance.

HBsAg/HCcAg positivity, metabolic syndrome and insulin resistance

Metabolic syndrome was diagnosed in 1304 individuals (10.4%, 160 women and 1144 men). The mean values of HOMA-IR in individuals with and without metabolic syndrome were 3.1 ± 3.1 and 1.4 ± 1.0, respectively ($P < 0.001$). Age and sex-adjusted logistic regression analysis showed that HCcAg positivity was inversely associated with metabolic syndrome, whereas HBsAg positivity was not (Table 3). On the other hand, after adjusting for the same variables, both HBsAg and HCcAg positivity was positively associated with the highest sex-specific HOMA-IR quartile, which was HOMA-IR of >1.39 in women and >2.06 in men.

Relationship between metabolic syndrome, insulin resistance and CKD components

After adjusting for age and sex, logistic regression analysis showed that metabolic syndrome was positively associated with both low eGFR (odds ratio 1.43 [95% CI 1.23–1.67, $P < 0.001$]) and albuminuria (odds ratio 3.84 [95% CI 3.31–4.47, $P < 0.001$]). After adjusting for the same variables, the highest HOMA-IR quartile was also positively associated with both low eGFR (odds ratio 1.21 [95% CI 1.08–1.35, $P = 0.0012$]) and albuminuria (odds ratio 2.86 [95% CI 2.52–3.23, $P < 0.001$]).

The relationship between HBV/HCV infection and CKD components was analyzed after further adjustment for either metabolic syndrome or HOMA-IR (Table 4). The negative association between HBsAg positivity and low eGFR and the positive association between HCcAg positivity and albuminuria remained statistically significant after further adjustment for metabolic syndrome. However, in the logistic regression analysis further adjusted for HOMA-IR, the association between HCcAg positivity and albuminuria did not remain statistically significant.

Serum alanine aminotransferase activity and CKD components

Logistic regression analysis adjusted for age, sex, SBP and FPG showed that ALT was dose-dependently associated with albuminuria, but not with low eGFR (Table 5). When adjusted for age, sex, SBP, FPG and ALT, the positive association between HCcAg positivity and albuminuria did not remain statistically significant, whereas the negative association between HBsAg positivity and low eGFR remained statistically significant (Table 4).

DISCUSSION

IN THE CURRENT study, by analyzing the data from individuals who underwent general health screening, it was found that HCcAg positivity was associated with a greater prevalence of low eGFR and albuminuria, both of which are components of CKD, than hepatitis-negative individuals. By contrast, the prevalence of neither low eGFR nor albuminuria was not different between HBsAg-positive and hepatitis-negative individuals. After adjusting for age, sex, SBP and FPG, the association of HCcAg with low eGFR (tendency) or with albuminuria (statistically significant) was still present.

Table 4 Logistic regression analysis for HBV/HCV infection as independent variables, and low eGFR and albuminuria as dependent variables after further adjusting for HOMA-IR and ALT

	Dependent variables					
	CKD Odds ratio (95% CI)	*P*-value	Components of CKD			
			low eGFR Odds ratio (95% CI)	*P*-value	Albuminuria Odds ratio (95% CI)	*P*-value
Adjusted for age, sex and metabolic syndrome						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	0.51 (0.31–0.84)	0.0082	0.50 (0.28–0.91)	0.024	0.54 (0.26–1.13)	0.10
HCcAg positive	1.92 (1.17–3.17)	0.010	1.70 (0.99–2.91)	0.055	2.19 (1.21–3.99)	0.010
Adjusted for age, sex, SBP, FPG and HOMA-IR						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	0.49 (0.29–0.80)	0.0046	0.51 (0.28–0.92)	0.025	0.48 (0.23–1.02)	0.056
HCcAg positive	1.63 (0.97–2.74)	0.064	1.58 (0.92–2.72)	0.099	1.67 (0.88–3.19)	0.12
Adjusted for age, sex, SBP, FPG and ALT						
HBV/HCV negative	1.00	–	1.00	–	1.00	–
HBsAg positive	0.49 (0.30–0.81)	0.0050	0.51 (0.28–0.92)	0.025	0.49 (0.23–1.03)	0.060
HCcAg positive	1.55 (0.92–2.59)	0.098	1.49 (0.86–2.57)	0.16	1.59 (0.83–3.02)	0.16

ALT, alanine aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HBV, hepatitis B virus; HCV, hepatitis C virus; HOMA-IR, homeostasis model assessment-insulin resistance; SBP, systolic blood pressure.

Table 5 Logistic regression analysis for ALT quartiles as an independent variable and low eGFR, and albuminuria as dependent variables

	Dependent variables					
	CKD Odds ratio (95% CI)	*P*-value	Components of CKD			
			Low eGFR Odds ratio (95% CI)	*P*-value	Albuminuria Odds ratio (95% CI)	*P*-value
Unadjusted						
ALT-Q1	1.00	–	1.00	–	1.00	–
ALT-Q2	1.21 (1.07–1.36)	0.0020	1.21 (0.16–1.38)	0.0058	1.16 (0.96–1.40)	0.012
ALT-Q3	1.35 (0.20–1.53)	<0.0001	1.21 (1.06–1.39)	0.0057	1.55 (1.29–1.85)	<0.0001
ALT-Q4	1.33 (1.18–1.50)	<0.0001	0.95 (0.82–1.09)	0.45	2.05 (1.73–2.43)	<0.0001
Adjusted for age and sex						
ALT-Q1	1.00	–	1.00	–	1.00	–
ALT-Q2	1.03 (0.91–1.17)	0.63	1.02 (0.88–1.17)	0.80	1.04 (0.86–1.26)	0.66
ALT-Q3	1.27 (1.12–1.45)	0.0003	1.13 (0.97–1.31)	0.11	1.47 (1.22–1.77)	<0.0001
ALT-Q4	1.47 (1.28–1.67)	<0.0001	1.03 (0.88–1.20)	0.70	2.16 (1.80–2.59)	<0.0001
Adjusted for age, sex, SBP and FPG						
ALT-Q1	1.00	–	1.00	–	1.00	–
ALT-Q2	1.00 (0.88–1.14)	0.96	1.03 (0.89–1.19)	0.68	0.97 (0.80–1.18)	0.75
ALT-Q3	1.18 (1.03–1.34)	0.015	1.15 (0.99–1.34)	0.062	1.23 (1.02–1.49)	0.035
ALT-Q4	1.24 (1.08–1.41)	0.0023	1.08 (0.93–1.27)	0.32	1.45 (1.20–1.76)	0.0001

ALT-Q1, ALT-Q2, ALT-Q3 and ALT-Q4 indicate the first, second, third and fourth, respectively, serum alanine aminotransferase activity quartiles.
ALT, alanine aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SBP, systolic blood pressure.

Both HCcAg positivity and HBsAg positivity were positively associated with increased insulin resistance. On the other hand, HCcAg positivity was inversely associated with metabolic syndrome.

Although renal involvement of hepatitis virus infection was first reported more than three decades ago,[16] knowledge of the association between HBV/HCV, proteinuria and low eGFR in the general population remains limited. Huang *et al.* analyzed data from individuals in southern Taiwan, an HBV/HCV-endemic area. They found that HBsAg and anti-HCV were positive in 13% and 7%, respectively, of the study population, and HCV infection, but not HBV infection, was associated with proteinuria.[17] Tsui *et al.* analyzed the data from a general population in the US and reported that HCV infection was associated with albuminuria, but not with low eGFR.[8] Our findings that albuminuria was positively associated with HCcAg positivity, but not with HBsAg, were therefore in agreement with these previous findings.

We showed that HCcAg positivity was associated with increased insulin resistance, defined as the highest HOMA-IR quartile. Several previous studies have shown that HCV infection was associated with diabetes as well as insulin resistance.[18,19] We have shown previously that HCV infection induces insulin resistance by the virus itself, which may influence the progression of chronic liver disease.[20,21] Compared to HCV infection, the relationship between HBsAg and insulin resistance has been less extensively studied. Custro *et al.* reported that both HBV and HCV infections increased the incidence of impaired glucose metabolism, and that the impact on glycemic homeostasis evoked by these two infections seemed to be similar.[22] In contrast, by analyzing subjects in Taiwan, where the prevalence of HBV infection is very high, Wang *et al.* showed that HBV carriers were not associated with insulin resistance.[23] We showed here that HBsAg positivity was also associated with increased insulin resistance, although to a lesser extent than HCcAg positivity (Table 3). Serum ALT levels, a marker for the extent of liver injury, is known to affect the degree of insulin resistance.[23] In the current study, the mean ALT levels were greater in HCcAg-positive than in HBsAg-positive individuals. The relative impacts of virus infection per se and liver injury for the development of hepatitis-related insulin resistance in our study population should be investigated further in future studies.

It was of note that the positive association between HCcAg positivity and albuminuria lost its statistical significance after adjusting for HOMA-IR, which suggested that the observed association between HCcAg positivity and albuminuria was confounded by insulin resistance. Insulin resistance is one of the background features of albuminuria,[24] and albuminuria is one of the diagnostic components of metabolic syndrome in WHO criteria.[12] In contrast to the positive association between HCV infection and increased insulin resistance, however, we found an apparent *negative* association between HCcAg positivity and metabolic syndrome (Table 3). Several previous studies also reported that the prevalence of metabolic syndrome was lower in HBV or HCV-infected individuals.[25,26] Together with these reports, our data suggest that increased insulin resistance, which may play a role in the development of albuminuria in HCV infection, may not be recognized as a phenotype of metabolic syndrome in HCcAg-positive individuals. In addition, our data suggest the possibility that increased insulin resistance, but not metabolic syndrome phenotype, enhances the risk for albuminuria and CKD in these individuals.

In the current study, the association between HBsAg and low eGFR or albuminuria was not statistically significant by univariate analysis (Table 1). However, after multivariate adjustment, there was an inverse mode association between HBsAg positivity and low eGFR (statistically significant) or albuminuria (tendency). Whether or not there is truly an inverse relationship between HBsAg positivity and CKD components should be investigated further after increasing the number of HBsAg-positive individuals. Nevertheless, we may be able to conclude from the current study that there is a difference in the mode of association with CKD components between HCcAg positivity and HBsAg positivity in individuals who underwent general health screening, and had, if present, only minor liver damage.

The current study had several limitations. First, GFR was not determined by a direct measurement, but instead by the MDRD formula with the Japanese coefficient of 0.881. A recent study has suggested that estimation of GFR by this method may result in an underestimation of GFR when insulin clearance is over 60 mL/min/1.73 m^2 in Japanese.[10] Second, we could not assess data of anti-HBe positivity, which might affect the prevalence of extrahepatic manifestations in HBV infection.[7] Third, due to the cross-sectional nature of the study, we could not derive the causal and resultant relationship between HBV/HCV infection and CKD components. Fourth, as the liver is the primary organ of insulin clearance, C-peptide concentration may be a better marker of secreted insulin levels and insulin resistance than parameters derived from insulin,[27] such as HOMA-IR; however, serum C-peptide data were not available in

the current study. Finally, interferon therapy may affect albuminuria and renal function, which may be either reversible or irreversible.[28–30] Although information on the history of interferon therapy was not available in the current study, this point should be taken into account in future studies.

CONCLUSION

IN CONCLUSION, BY analyzing the cross-sectional data of 12 535 individuals who underwent general health screening, we have investigated a possible association between viral hepatitis infection and CKD components. There was a positive association between HCcAg positivity, but not HBsAg positivity, and CKD components (low eGFR and albuminuria). The observed associations were confounded by the degree of insulin resistance and serum ALT levels. Although HCcAg positivity was associated with increased insulin resistance, HCcAg positivity was negatively associated with metabolic syndrome. These data collectively indicate that some differences may exist between HCV infection and HBV infection in terms of association with CKD components in Japanese individuals who undergo general health screening.

ACKNOWLEDGMENTS

THIS WORK WAS supported in part by grants from the Smoking Research Foundation, Chiyoda Mutual Life Foundation, St Luke's Grant for the Epidemiological Research and Daiwa Securities Health Foundation.

REFERENCES

1 Higuchi M, Tanaka E, Kiyosawa K. Epidemiology and clinical aspects on hepatitis C. *Jpn J Infect Dis* 2002; **55**: 69–77.
2 Narai R, Oyama T, Ogawa M *et al.* HBV- and HCV- infected workers in the Japanese workplace. *J Occup Health* 2007; **49**: 9–16.
3 Yamabe H, Johnson RJ, Gretch DR *et al.* Hepatitis C virus infection and membranoproliferative glomerulonephritis in Japan. *J Am Soc Nephrol* 1995; **6**: 220–3.
4 El-Serag HB, Hampel H, Yeh C, Rabeneck L. Extrahepatic manifestations of hepatitis C among United States male veterans. *Hepatology* 2002; **36**: 1439–45.
5 Johnson RJ, Couser WG. Hepatitis B infection and renal disease: clinical, immunopathogenetic and therapeutic considerations. *Kidney Int* 1990; **37**: 663–76.
6 Tang S, Lai FM, Lui YH *et al.* Lamivudine in hepatitis B-associated membranous nephropathy. *Kidney Int* 2005; **68**: 1750–8.
7 Cacoub P, Saadoun D, Bourliere M *et al.* Hepatitis B virus genotypes and extrahepatic manifestations. *J Hepatol* 2005; **43**: 764–70.
8 Tsui JI, Vittinghoff E, Shlipak MG, O'Hare AM. Relationship between hepatitis C and chronic kidney disease: results from the Third National Health and Nutrition Examination Survey. *J Am Soc Nephrol* 2006; **17**: 1168–74.
9 Manjunath G, Sarnak MJ, Levey AS. Prediction equations to estimate glomerular filtration rate: an update. *Curr Opin Nephrol Hypertens* 2001; **10**: 785–92.
10 Imai E, Horio M, Nitta K *et al.* Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. *Clin Exp Nephrol* 2007; **11**: 41–50.
11 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1–266.
12 Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539–53.
13 Ishizaka N, Ishizaka Y, Toda E, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. *Arterioscler Thromb Vasc Biol* 2005; **25**: 1038–44.
14 Moriya K, Shintani Y, Fujie H *et al.* Serum lipid profile of patients with genotype 1b hepatitis C viral infection in Japan. *Hepatol Res* 2003; **25**: 371–6.
15 Serfaty L, Andreani T, Giral P, Carbonell N, Chazouilleres O, Poupon R. Hepatitis C virus induced hypobetalipoproteinemia: a possible mechanism for steatosis in chronic hepatitis C. *J Hepatol* 2001; **34**: 428–34.
16 Combes B, Shorey J, Barrera A *et al.* Glomerulonephritis with deposition of Australia antigen-antibody complexes in glomerular basement membrane. *Lancet* 1971; **2**: 234–7.
17 Huang JF, Chuang WL, Dai CY *et al.* Viral hepatitis and proteinuria in an area endemic for hepatitis B and C infections: another chain of link? *J Intern Med* 2006; **260**: 255–62.
18 Tai TY, Lu JY, Chen CL *et al.* Interferon-alpha reduces insulin resistance and beta-cell secretion in responders among patients with chronic hepatitis B and C. *J Endocrinol* 2003; **178**: 457–65.
19 Shaheen M, Echeverry D, Oblad MG, Montoya MI, Teklehaimanot S, Akhtar AJ. Hepatitis C, metabolic syndrome, and inflammatory markers: results from the Third National Health and Nutrition Examination Survey [NHANES III]. *Diabetes Res Clin Pract* 2007; **75**: 320–6.
20 Shintani Y, Fujie H, Miyoshi H *et al.* Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. *Gastroenterology* 2004; **126**: 840–8.

21 Koike K. Hepatitis C virus infection can present with metabolic disease by inducing insulin resistance. *Intervirology* 2006; **49**: 51–7.
22 Custro N, Carroccio A, Ganci A *et al.* Glycemic homeostasis in chronic viral hepatitis and liver cirrhosis. *Diabetes Metab* 2001; **27**: 476–81.
23 Wang CC, Hsu CS, Liu CJ, Kao JH, Chen DS. Association of chronic hepatitis B virus infection with insulin resistance and hepatic steatosis. *J Gastroenterol Hepatol* 2008; (in press).
24 Niskanen L, Laakso M. Insulin resistance is related to albuminuria in patients with type II (non-insulin-dependent) diabetes mellitus. *Metabolism* 1993; **42**: 1541–5.
25 Jan CF, Chen CJ, Chiu YH *et al.* A population-based study investigating the association between metabolic syndrome and hepatitis B/C infection (Keelung Community-based Integrated Screening study, 10). *Int J Obes (Lond)* 2006; **30**: 794–9.
26 Luo B, Wang Y, Wang K. Association of metabolic syndrome and hepatitis B infection in a Chinese population. *Clin Chim Acta* 2007; **380**: 238–40.
27 Bonora E, Coscelli C, Orioli S *et al.* Hyperinsulinemia of chronic active hepatitis: impaired insulin removal rather than pancreatic hypersecretion. *Horm Metab Res* 1984; **16**: 111–14.
28 Jones GJ, Itri LM. Safety and tolerance of recombinant interferon alfa-2a (Roferon-A) in cancer patients. *Cancer* 1986; **57**: 1709–15.
29 Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity of interferons in cancer patients: a review. *J Clin Oncol* 1986; **4**: 234–43.
30 Lederer E, Truong L. Unusual glomerular lesion in a patient receiving long-term interferon alpha. *Am J Kidney Dis* 1992; **20**: 516–18.