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Relationship between smoking, white blood cell count and metabolic syndrome in Japanese women

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Abstract

We found that cigarette smoking increased white blood cell count, and individuals which increased white blood cell count more likely to have metabolic syndrome in Japanese men. We investigated whether similar relationship can be observed also in women. We analyzed the data from 16,383 Japanese women who underwent general health screening. Age-adjusted logistic regression analysis showed that current smoking was positively associated with a highest white blood cell count quartile with an odds ratio of 2.40 (95% CI: 2.16–2.68, $P < 0.0001$). The white blood cell count showed a graded association with metabolic syndrome. On the other hand, the association between current smoking and metabolic syndrome was no longer significant after subdividing the individuals into groups according to the white blood cell quartile. These data collectively suggested that the association between current smoking and metabolic syndrome is heavily confounded by certain factors that increase the circulating white blood cell count in Japanese women, as in men.

Keywords: Metabolic syndrome; Smoking; White blood cell count

1. Introduction

Many previous studies have demonstrated a positive association between several inflammatory markers, including white blood cell (WBC) count and C-reactive protein, and the prevalence of metabolic syndrome [1–3] or reduced sensitivity to insulin [4]. Cigarette smoking is known to increase the circulating WBC count [5,6] even in individuals who have quit for a substantial period [7]. By analyzing data from individuals who had undergone a general health screening test, we previously demonstrated that cigarette smoking is associated with an increase in the circulating WBC count [8], and with a higher prevalence of metabolic syndrome [9] in men. We also showed that the association between smoking and metabolic syndrome is not significant in those with a high WBC count [10], suggesting that the association between smoking and metabolic syndrome may be confounded by certain factors that increase the circulating WBC count in men. In the current study, we have analyzed the mode of association between smoking status, WBC count, and metabolic syndrome in Japanese women.

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2. Methods

2.1. Study subjects

The study was approved by The Ethical Committee of Mitsui Memorial Hospital. In Japan, regular health check-ups for employees are legally mandated. Therefore, the majority of these subjects did not have serious health problems. Between September 1994 and December 2003, 49,358 subjects, who were older than 20 years old (women 16,877, men 32,481), underwent general health screening including the measurement of hemodynamic and metabolic markers necessary to assess the presence or absence of metabolic syndrome. Subject age and cigarette smoking outcome data were collected in a structured interview. Among 16,877 female subjects, 16,383 answered the questionnaire in full concerning the amount and the duration of smoking, and concerning how long since they had stopped smoking at the time of the general health check when they were former smokers. We were unable to identify any specific reasons why remaining 494 subjects failed to complete the questionnaire about their smoking status. These 16,383 female subjects (14,136 never smokers, 625 former smokers, and 1622 current smokers) were enrolled in the current study. The interquartile cutoff points for the WBC count were 4.2×10^3 cells/μL, 4.9×10^3 cells/μL, and 5.8×10^3 cells/μL.

2.2. Criteria for diagnosing metabolic syndrome

The diagnosis of metabolic syndrome was made by the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) [11] using body mass index (BMI) as a surrogate for waist circumference, because data on this parameter were not available in this study sample. The five thresholds used were as follows: triglyceride (TG) levels ≥150 mg/dL; HDL-cholesterol (HDL-C) levels <50 mg/dL fasting plasma glucose (FPG) ≥110 mg/dL or taking an antidiabetic medication; systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or taking an antihypertensive medication; and BMI >25 kg/m^2. Metabolic syndrome was diagnosed when three or more these components were present.

2.3. Laboratory tests

Blood samples were taken from our subjects after an overnight fasting. Total cholesterol (TC), HDL-C, and TG were determined enzymatically, and haemoglobin A1C was determined using the latex agglutination immunoassay.

2.4. Statistical analysis

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

3. Results

3.1. Baseline characteristics of the enrolled individuals

The age of the subjects enrolled ranged from 20 to 89 years with a median of 52 years. The mean age of the current and former smokers was significantly lower than that of never smokers (Table 1). The WBC count was greater in both current ($P < 0.0001$) and former

Table 1
Baseline characteristics

Variables	All subjects (n = 16,383)	Never smoker (n = 14,136)	Former smoker (n = 625)	Current smoker (n = 1622)	P value
Age (years)	51.5 ± 10.1	52.2 ± 9.9	48.5 ± 10.8	45.8 ± 9.9	<0.0001
Body mass index (kg/m^2)	21.4 ± 2.9	21.5 ± 2.8	21.5 ± 2.9	21.2 ± 3.0	0.0006
Systolic blood pressure (mmHg)	117 ± 19	118 ± 19	116 ± 18	111 ± 17	<0.0001
Blood cell count					
WBC count ($\times 10^3$ μL^{-1})	5.0 ± 1.3	4.9 ± 1.2	5.1 ± 1.3	5.7 ± 1.6	<0.0001
Hemoglobin (g/dL)	13.0 ± 1.1	13.0 ± 1.1	13.0 ± 1.1	13.2 ± 1.1	<0.0001
Platelet count ($\times 10^4$ μL^{-1})	23.7 ± 5.3	23.5 ± 5.3	24.1 ± 5.6	24.6 ± 5.4	<0.0001
Biochemical data					
Total cholesterol (mg/dL)	209 ± 35	203 ± 35	203 ± 35	197 ± 38	<0.0001
Triglycerides (mg/dL)	89 ± 57	88 ± 49	89 ± 54	96 ± 104	<0.0001
HDL-cholesterol (mg/dL)	71 ± 17	71 ± 17	74 ± 18	67 ± 17	<0.0001
Fasting glucose (mg/dL)	91 ± 13	91 ± 13	90 ± 12	88 ± 13	<0.0001
Hemoglobin A1C (%)	5.1 ± 0.5	5.1 ± 0.5	5.1 ± 0.5	5.1 ± 0.5	<0.0001
CRP > 0.4 mg/dL, n (%)	505 (3.1)	440 (3.1)	14 (2.2)	51 (3.1)	0.46
Erythrocyte sedimentation rate (cm)	17.3 ± 11.1	17.8 ± 11.2	15.9 ± 10.5	13.8 ± 8.7	<0.0001

WBC: white blood cell; CRP: C reactive protein.

($P = 0.0019$) smokers than in never smokers ($P < 0.0001$). Pearson's correlation coefficients for the relationship between age and each variable were as follows: BMI, 0.186; systolic blood pressure, 0.34; WBC count, −0.077; TC, 0.392; triglycerides, 0.195; HDL-C, −0.040; fasting glucose, 0.195; HbA1C, 0.357. A value of $P < 0.0001$ was obtained for all of these correlations.

3.2. Association between WBC count and metabolic syndrome

Prevalence of metabolic syndrome in individuals of the first, second, third, and fourth quartiles of WBC count were 1.7, 3.0, 5.2, and 8.0%, respectively. After adjusting for age and TC, logistic regression analysis showed that odds ratios of the first, second, third, and fourth quartiles of WBC count for metabolic syndrome were 1.0 (reference), 1.76 (95% CI: 1.31–2.37), 3.23 (2.46–4.24), 5.38 (4.14–7.00), respectively.

3.3. Association between smoking status and WBC count

Next, we analyzed the association between various smoking conditions (amount and duration of smoking) and the prevalence of the highest WBC count quartile by logistic regression analysis adjusted for age and TC. Odds ratio for the highest WBC count quartile increased with the amount of daily cigarette smoked in the case of current smoker (Fig. 1A). Similarly, the odds ratios for the highest WBC count quartile showed a greater increase according to the duration of cigarette smoking (Fig. 1B). In the case of former smokers, those who had smoked ≥20 cigarettes per day, but not those who had smoked less than that showed an increased prevalence of the highest WBC count quartile. Former smokers who had last smoked less than 5 years ago, as well as those who had smoked ≥5 years, did not have significantly greater prevalence of metabolic syndrome than never smokers (Fig. 1C).

3.4. Association between smoking status and metabolic syndrome

Logistic regression analysis adjusting for age and TC showed that the odds ratios for metabolic syndrome increased according to the daily number of cigarettes smoked in both former and current smokers (Fig. 2A). Unlike the relationship between smoking duration and high WBC count, the association between current smoking and metabolic syndrome did not seem to be

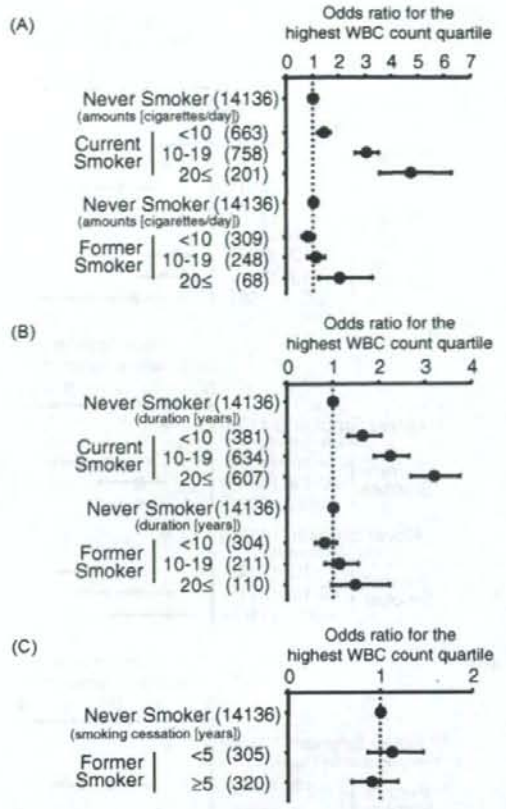

Fig. 1. Multivariate analysis assessing relationship between smoking status and the highest white blood cell count quartile. Data were adjusted for age. (A) Amount of smoking vs. high white blood cell count. (B) Duration of smoking vs. high white blood cell count. (C) Years of smoking cessation vs. high white blood cell count.

increased according to the smoking duration (Fig. 2B). When the former smokers were subdivided into two groups according to the duration of smoking cessation, the prevalence of metabolic syndrome was significantly greater in individuals who had quit smoking <5 years ago, but not in those who had stopped smoking ≥5 years ago (Fig. 2C).

3.5. Association between current smoking and metabolic syndrome after subdivision into WBC quartile groups

When the analysis was done for each WBC quartile separately, logistic regression analysis showed that the current smoking was not statistically significantly associated with metabolic syndrome; the odds ratios

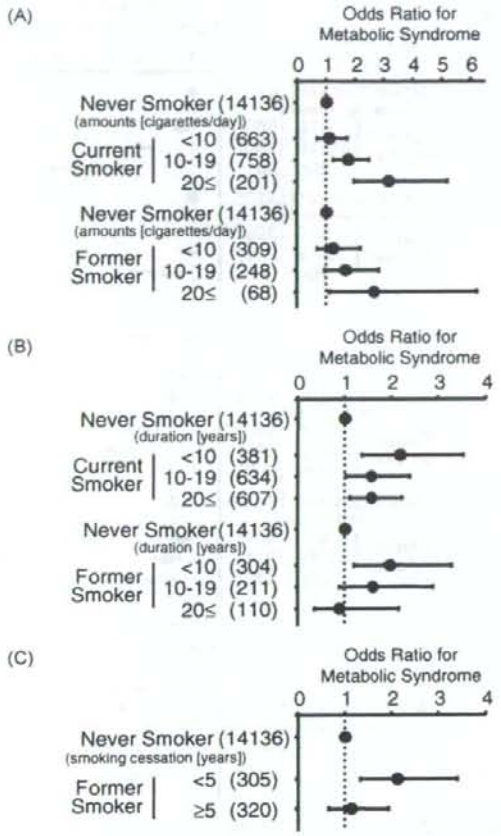

Fig. 2. Multivariate analysis assessing relationship between smoking status and metabolic syndrome. Data were adjusted for age and total cholesterol levels. (A) Amount of smoking vs. metabolic syndrome. (B) Duration of smoking vs. metabolic syndrome. (C) Years of smoking cessation vs. metabolic syndrome. The numbers of subjects with various smoking status are described in the parenthesis.

was 0.87 (95% CI: 0.21–3.61, $P = 0.84$) in the first WBC quartile, 1.85 (95% CI: 0.91–3.77, $P = 0088$) in the second WBC quartile, 0.92 (95% CI: 0.53–1.59, $P = 0.75$) in the third WBC quartile, and 1.30 (95% CI: 0.94–1.79, $P = 0.12$) in the fourth WBC quartile.

4. Discussion

In the current study, we found that current smoking is associated with an increase in the WBC count according to the amount of cigarettes smoked and the duration of smoking, and that the WBC count showed a graded association with the prevalence of metabolic syndrome. In addition, current smoking was not statistically associated with metabolic syndrome after subdividing individuals according to WBC count quartiles. These data collectively indicate that association between current smoking and metabolic syndrome might be heavily confounded certain factors that also increase the circulating WBC count in Japanese women.

In previous studies, we have reported that cigarette smoking shows a graded association with metabolic syndrome according to the amount and duration of smoking in Japanese men [9]. We have also shown that current smoking is associated with an increased WBC count in men [8,10]. In the current study, we aimed to extend these investigations to a female population. In essence, the observations of the current study were similar to those of our previous studies targeted to the male population, although there were several differences. For example, in women, current smoking, but not former smoking, was significantly associated with an increased prevalence of metabolic syndrome. In addition, the prevalence of metabolic syndrome was greater in individuals with longer smoking history in men [9], but this mode of association was not present in women (current study). Some of the different observations between the women and men may be due to the relatively small numbers of women smokers, which may weaken the power of the statistical assessment.

Several previous studies have shown a possible relationship between WBC count and individual components of metabolic syndrome or subsets of these components. For example, Nieto et al. have reported in the ARIC study that the WBC count is associated positively with blood pressure, fasting insulin, and triglycerides and inversely with HDL cholesterol [5]. Similarly, Targher et al. have reported that the WBC count correlates positively with BMI blood pressure and plasma triglycerides, and negatively with HDL cholesterol [12]. Vozarova et al. showed an association between high WBC count and worsening insulin sensitivity [13]. Together with the current study, these studies suggest that increased circulating WBC count, presumably reflecting the chronic inflammation, may exacerbate insulin resistance, leading to metabolic syndrome. Potential candidates for factors that increase WBC count and exacerbate insulin resistance may include proinflammatory cytokines [14–17] and adipocytokines [18–21]. Level of such proinflammatory cytokines and/or adipocytokines in smokers with or without metabolic syndrome should be investigated in health screening participants in future studies. We may also have to investigate why either former or current smoking was not associated with increased CRP value in the current study population.

In summary, in Japanese women, there are positive dose-dependent associations between current smoking and WBC count, and between current smoking and metabolic syndrome. The finding that current smoking was no more statistically significant predictor for metabolic syndrome after subdivision of the individuals according to the WBC quartiles collectively suggests that certain factors that increases circulating WBC count may be one of the factors that promotes development of metabolic syndrome in current smokers. Our data also suggest that increased levels of circulating WBC count might help identify the subjects at higher risk for metabolic syndrome in Japanese women who currently smoke.

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Letter to the Editor

Comparison of several metabolic syndrome definitions with relation to early carotid atherosclerosis in Japanese men

Keywords: Metabolic syndrome; Diagnostic criteria; Carotid atherosclerosis; Japanese; General health screening

To the Editor,

We have read with great interest the recent article by Skilton et al. [1], in which they compared several different definitions of metabolic syndrome in terms of prevalence and strength in predicting increased carotid intima-media thickness, a marker of early atherosclerotic lesions. They found, among the definitions tested, that the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definition may be more strongly associated with carotid atherosclerosis in men than the other definitions.

We sought to investigate the prevalence of metabolic syndrome as defined by several different diagnostic criteria and their association with carotid atherosclerosis in Japanese individuals. Between October 2005 and August 2006, 1106 males who underwent general health screening that included measurement of waist circumference (WC) and carotid ultrasonography, and were enrolled in the current study. Metabolic syndrome was diagnosed by five different definitions:

- NCEP-ATPIII definition [2]: Presence of three or more of the following: (1) fasting plasma glucose (FPG) $\geq$110 mg/dL; (2) systolic blood pressure (SBP)/diastolic blood pressure (DBP) $\geq$130/85 mmHg; (3) triglycerides (TG) $\geq$150 mg/dL; (4) HDL cholesterol (HDL-C) <40 mg/dL; (5) WC $\geq$102 cm.
- Modified-NCEP-ATPIII definition: The same as NCEP-ATPIII except that body mass index $\geq$25 kg/m^2 is a surrogate for WC.
- Japan definition [3]: WC $\geq$85 cm plus 2 or more of the following: (1) FPG $\geq$110 mg/dL; (2) SBP/DBP $\geq$130/85 mmHg; (3) HDL-C < 40 mg/dL or TG $\geq$150 mg/dL.
- IDF definition [4]: WC $\geq$85 cm plus 2 or more of the following: (1) FPG $\geq$100 mg/dL; (2) SBP/DBP $\geq$130/85 mmHg; (3) TG $\geq$150 mg/dL; (4) HDL-C <40 mg/dL.
- AHA/NHLBI definition [5]: Presence of three or more of the following: (1) FPG $\geq$100 mg/dL; (2) SBP/DBP $\geq$130/85 mmHg; (3) TG $\geq$150 mg/dL; (4) HDL-C <40 mg/dL; (5) WC $\geq$102 cm. In each of these definitions, individuals who were taking anti-hypertensive and anti-diabetic medications were considered to fulfill the blood pressure and glucose criteria. Carotid plaque was defined as a portion of the artery with an intima-media complex thickness of $\geq$1.1 mm [6] with a focal protrusion or point(s) of inflexion.

The prevalence of metabolic syndrome defined by each criterion was as follows: NCEP-ATPIII 108/1106 (9.8%), modified NCEP-ATPIII 211/1106 (19.1%), Japan 223/1106 (21.1%), IDF 321/1106 (29.0%) and AHA/NHLBI 161/1106 (14.6%). The odds ratio of each criterion-defined metabolic syndrome for carotid plaque in logistic regression analysis adjusted for age and smoking status was as follows: NCEP-ATPIII, 1.89 (95% CI 1.17–3.05, $P=0.0088$); modified NCEP-ATPIII, 1.76 (95% CI 1.23–2.51, $P=0.0018$); Japan, 1.74 (95% CI 1.23–2.45, $P=0.0015$); IDF, 1.35 (95% CI 1.00–1.83, $P=0.048$); AHA/NHLBI, 1.66 (95% CI 1.21–2.45, $P=0.011$). Therefore, except for the AHA/NHLBI definition, the higher the prevalence of diagnosis of metabolic syndrome according to a definition, the lower the odds ratio for carotid plaque. The prevalence of metabolic syndrome defined by AHA/NHLBI was lower than that of modified NCEP-ATPIII-defined metabolic syndrome, however, the former was found to be less strongly associated with carotid atherosclerosis than the latter one.

Together with the recent article by Skilton et al. [1], our data suggest that the optimal definition for metabolic syndrome, in terms of the combination of components and the cutoff values, may differ among various racial groups and ethnicities from the viewpoint of predicting early atherosclerosis. It might also differ according to gender and the target population, such as hypertensive and non-hypertensive sub-

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jects. These points should be investigated further in future studies.

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Original Article

Association between Chronic Kidney Disease and Carotid Intima-Media Thickening in Individuals with Hypertension and Impaired Glucose Metabolism

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We investigated whether chronic kidney disease (CKD) was associated with carotid intima-media thickening in 1,351 male individuals undergoing general health screening. Glomerular filtration rate (GFR) was estimated by the Modification of Diet in Renal Disease equations using 0.881 as a coefficient for Japanese, and low estimated GFR (eGFR) was defined as an eGFR value of <60 mL/min/1.73 m². Albuminuria was defined as a urine albumin–to–urine creatinine ratio of ≥30 mg/g, and CKD was defined when low eGFR and/or albuminuria was present. After adjusting for age, CKD was associated with carotid intima-media thickening with an odds ratio of 1.47 (95% confidence interval [CI] 1.05–2.06, p=0.0024). After adjusting for age, fasting plasma glucose, and smoking status, both albuminuria and low eGFR were significantly associated with intima-media thickening in individuals with hypertension with an odds ratio of 1.85 (95% CI 1.13–3.03, p=0.015) and 1.79 (95% CI 1.09–2.94, p=0.022), respectively. On the other hand, neither of them was associated with carotid intima-media thickening in individuals without hypertension. Similarly, after adjusting for age, systolic blood pressure, and smoking status, both albuminuria and low eGFR were significantly associated with intima-media thickening in individuals with high fasting glucose (defined as fasting plasma glucose levels of ≥110 mg/dL or current use of anti-diabetic medication), but not in those without. Our data indicate that CKD or its components (low eGFR and albuminuria) may be associated with early carotid atherosclerosis in low-risk individuals, such as those undergoing general health screening, who have hypertension and/or impaired glucose metabolism. (*Hypertens Res* 2007; 30: 1035–1041)

***Key Words*: chronic kidney disease, carotid intima-media thickening, hypertension, risk factors, cross-sectional study**

Introduction

An increasing prevalence of end-stage renal disease that may require hemodialysis is a worldwide public health problem owing to poor outcomes and high costs. A mild decline in renal function may already be associated with a substantially higher prevalence of renal failure, coronary artery disease, arteriosclerosis, and premature death (*1*, *2*), and thus mild renal dysfunction has gathered more attention recently (*3*, *4*).

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Table 1. Clinical Characteristics and Laboratory Data

	No CKD (n=973)	Albuminuria (n=166)	Low eGFR (n=251)
Age (years)	56.0±10.3	61.8±10.5	62.5±9.3
Body mass index (kg/m^2)	24.1±2.9	24.8±3.1	24.1±2.6
Systolic blood pressure (mmHg)	130±18	139±20	130±19
Diastolic blood pressure (mmHg)	80±11	87±13	82±11
Laboratory data			
Serum urea nitrogen (mg/dL)	14.6±3.4	15.5±4.5	17.2±4.0
Serum creatinine (mg/dL)	0.8±0.1	0.9±0.2	1.1±0.1
Median (interquarilte range) of serum creatinine (mg/dL)	0.8 (0.8–0.9)	0.8 (0.8–1.0)	1.0 (1.0–1.1)
eGFR (mL/min/1.73 m^2)	72±8	68±13	55±5
Median (interquarilte range) of eGFR (mL/min/1.73 m^2)	71 (65–76)	68 (60–75)	56 (53–58)
Uric acid (mg/dL)	6.1±1.1	6.3±1.2	6.6±1.2
γ-GTP (IU/L)	57±52	73±84	54±47
Total cholesterol (mg/dL)	209±31	216±35	209±31
HDL-cholesterol (mg/dL)	55±13	54±14	54±12
Triglycerides (mg/dL)	138±99	151±122	133±95
Fasting glucose (mg/dL)	102±19	111±29	100±16
Haemoglobin A1c (%)	5.4±0.7	5.8±1.1	5.4±0.6
HOMA-IR	1.8±1.4	2.7±7.0	1.9±1.3
Smoking status			
Never/former/current (%)	30/43/27	25/52/23	37/47/16
Drinking status			
Never/former/current (%)	10/6/84	7/13/81	15/11/74

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GTP, glutamyl transpeptidase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance.

According to the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) criteria, chronic kidney disease (CKD) is defined as the presence of either of the following two conditions for three months or more: a glomerular filtration rate (GFR) of <60 mL/min/1.73 m^2; or kidney damage, as ascertained by the presence of proteinuria (*5*). The purpose of the current study was to investigate whether CKD or its components (decreased GFR and albuminuria) are associated with carotid atherosclerosis in Japanese men.

Methods

Study Subjects

The study was approved by the Ethical Committee of Mitsui Memorial Hospital. Between April 2005 and May 2006 at Mitsui Memorial Hospital, 6,351 men underwent a general health screen and fully responded a questionnaire concerning alcohol drinking and cigarette smoking. Of these 6,351 subjects, 1,351 underwent carotid ultrasonography as a part of the health screening, and were enrolled in the present study.

In Japan, regular health check-ups for employees are legally mandated, and all or most of the costs of the screening are usually paid either by the company to which a subject belongs or by the subject themselves. At our institute, several types of health screening programs are available, the choice of which is dependent on the decision of individuals and/or the companies to which they belong. Some courses of general health screening include carotid ultrasonography, while others do not. Therefore, it should be noted that the subjects enrolled may not be a random selection of all health screening participants. Indeed, among individuals who underwent general health screening during the study period, individuals who underwent carotid ultrasonography (n=1,351; *i.e.*, study subjects) were significantly older than those who did not (n=5,000) (58±10 and 53±10 years old, respectively, p<0.0001). Therefore, it could be said that there might have been some selection bias for participants planning carotid ultrasound. However, this was never the decision or the recommendation of any attending physician.

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method, haemoglobin A1c was determined using the latex agglutination immunoas-

say, 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 of 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. An increased insulin resistance was defined as a HOMA-IR of ≥2.5. Metabolic syndrome was defined as described previously (*6*).

Serum creatinine was calibrated using the following formula: serum creatinine (Jaffe method) = 0.2 + serum creatinine (enzyme method). GFR was estimated by equations from the simplified version of the Modification of Diet in Renal Disease (MDRD) (*7*), in which 0.881 is a coefficient for eGFR specific to the Japanese population (*8*): eGFR = 186.3 × (serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ × 0.881. Individuals were classified as having low eGFR when their eGFR values were <60 mL/min/1.73 m^2 (*5*). For the diagnosis of albuminuria, spot urine samples were collected and analyzed; albuminuria was expressed as the ratio of urinary albumin to urinary creatinine, designated as the albumin excretion index (AEI). Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as AEI <30 mg/g, 30–300 mg/g, and >300 mg/g, respectively. An eGFR of <60 mL/min/1.73 m^2 was designated as low eGFR, and an AEI ≥30 mg/g was designated as albuminuria. Individuals were said to have CKD when they had either or both of a low eGFR and albuminuria (*5*).

Carotid Ultrasonography

Carotid artery status was studied and analyzed as described previously (*9*). In brief, carotid artery status was assessed by high resolution B-mode ultrasonography, using a machine (Sonolayer SSA270A; Toshiba, Tokyo, Japan) equipped with a 7.5 MHz transducer (PLF-703ST; Toshiba). The carotid arteries were examined bilaterally at the levels of the common carotid, the bifurcation, and the internal carotid arteries from transverse and longitudinal orientations by trained sonographers. The intima-media thickness was measured using a computer-assisted method by experienced sonographers who were unaware of the subjects' clinical and laboratory findings. Carotid intima-media wall thickening was said to have occurred when the intima-media thickness measured at the far wall of the distal 10 mm of the common carotid artery was ≥1.0 mm. Carotid plaque was considered to be present when there was a portion of the artery for which the thickness of the intima-media complex was ≥1.1 mm (*10*) with a focal protrusion or point(s) of inflexion. The difference in the prevalence of carotid plaque in health screening participants between the current and previous studies (*9*) was likely due to the difference in diagnostic criteria for carotid plaque.

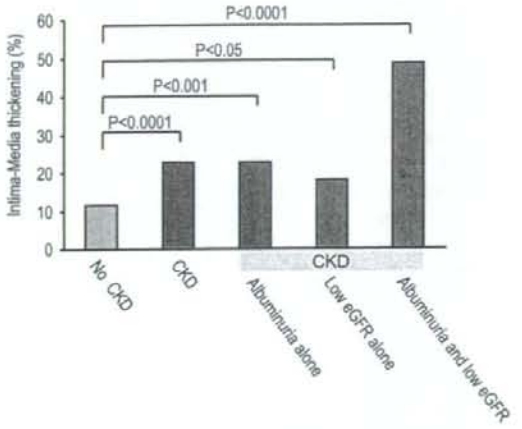

Fig. 1. *Prevalence of intima-media thickening in individuals with or without CKD or its components.*

Statistical Analysis

The data in this study were analyzed by the χ^2 test, ANOVA, and univariate and multivariate logistic regression analysis using computer software StatView ver. 5.0 (SAS Institute, Cary, USA). A value of $p<0.05$ was taken to be statistically significant. Results are expressed as the means±SD unless stated otherwise.

Results

Baseline Characteristics

The mean age±SD of the individuals enrolled was 57.7±10.5 years (Table 1). Of the 1,351 individuals examined, 166 (12%) had albuminuria: 142 (11%) had microalbuminuria and the remaining 24 (2%) had macroalbuminuria. Low eGFR was found in 251 individuals (19%), and 39 (3%) had both albuminuria and low eGFR. Therefore, 378 subjects (28%) were said to have CKD in our study population. If the coefficient for eGFR specific to the Japanese population (0.881) was not used for the calculation of eGFR, only 4.9% (66/1,351) of subjects were judged to have an eGFR of <60 mL/min/1.73 m^2. Individuals with albuminuria had a greater HOMA-IR value than those without CKD (Table 1). After adjusting for age and smoking status, logistic regression analysis showed that albuminuria was significantly associated with increased insulin resistance (*i.e.*, HOMA-IR of ≥2.5): the odds ratio was 2.18 (95% CI 1.52–3.13, $p<0.0001$) for all enrolled subjects, and 1.91 (95% CI 1.16–3.14, $p=0.011$) for individuals who had an FPG level of <126 mg/dL and were not taking antidiabetic medication ($n=1,096$). A positive association between low eGFR and increased insulin resistance was also observed; however, it did not reach statistical

Table 2. Logistic Regression Analysis for CKD or Its Components as Independent Variables and Carotid Intima-Media Thickening as a Dependent Variable According to Hypertension Status

	Odds ratio (95% CI) of CKD	*p* value	Odds ratio (95% CI) of albuminruia	*p* value	Odds ratio (95% CI) of low eGFR	*p* value
Whole (n=1,351)						
Unadjsted	2.26 (1.66–3.09)	<0.0001	2.81 (1.93–4.09)	<0.0001	2.00 (1.42–2.82)	<0.0001
Adjusted for age	1.47 (1.05–2.06)	0.024	2.07 (1.38–3.11)	0.0005	1.30 (0.90–1.88)	0.17
Adjusted for age, SBP, and smoking status	1.39 (0.99–1.95)	0.058	1.74 (1.14–2.65)	0.0098	1.34 (0.92–1.96)	0.13
Adjusted for age, SBP, FPG, and smoking status	1.38 (0.98–1.94)	0.065	1.64 (1.07–2.52)	0.023	1.40 (0.96–2.04)	0.085
Subjects with hypertension (n=563)						
Unadjsted	2.24 (1.47–3.42)	0.0002	2.56 (1.61–4.04)	<0.0001	2.13 (1.34–3.39)	0.0014
Adjusted for age	1.75 (1.13–2.72)	0.013	2.06 (1.27–3.34)	0.0034	1.67 (1.03–2.72)	0.038
Adjusted for age, FPG, and smoking status	1.71 (1.09–2.66)	0.019	1.85 (1.13–3.03)	0.015	1.79 (1.09–2.94)	0.022
Subjects without hypertension (n=788)						
Unadjsted	1.84 (1.13–2.99)	0.014	1.93 (0.90–4.14)	0.089	1.70 (1.00–2.90)	0.050
Adjusted for age	0.97 (0.57–1.67)	0.92	1.40 (0.61–3.23)	0.43	0.90 (0.50–1.62)	0.72
Adjusted for age, FPG, and smoking status	0.99 (0.57–1.70)	0.96	1.31 (0.56–3.05)	0.53	1.01 (0.49–2.11)	0.97

CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; FPG, fasting plasma glucose.

significance (odds ratio 1.45 [95% CI 0.97–2.25, p=0.068] for individuals who had an FPG level of <126 mg/dL and were not taking antidiabetic medication). After adjusting for age and smoking habits, albuminuria and low eGFR were each associated with metabolic syndrome with an odds ratio of 2.63 (95% CI 1.81–3.83, p<0.0001) and 1.54 (95% CI 1.07–2.20, p=0.020), respectively.

Association between CKD and Carotid Atherosclerosis

Intima-media thickening was more frequently found in the individuals with CKD than in those without (Fig. 1). The prevalence of intima-media thickening was more than two times greater in individuals with CKD than in those without. Age-adjusted logistic regression analysis showed that the odds ratios of no-CKD (n=973), low eGFR alone (n=212), albuminuria alone (n=127), and both low eGFR and albuminuria (n=39) were 1 (reference), 1.07 (95% CI 0.69–1.64, p=0.77), 1.60 (0.98–2.61, p=0.060), and 4.38 (2.13–8.99, p<0.0001), respectively. After adjusting for age, CKD was found to be associated with intima-media thickening. After adjustment for age, systolic blood pressure (SBP), FPG, and smoking status, albuminuria, but not low eGFR, was positively associated with intima-media thickening (Table 2). Neither CKD, albuminuria nor low eGFR was significantly associated with carotid plaque after adjusting for age (data not shown).

Association between CKD and Carotid Intima-Media Thickening According to Hypertension Status

Next, we assessed the association between CKD and carotid intima-media thickening after subdividing individuals according to their hypertension status. For this analysis, hypertension was defined as SBP ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of an antihypertensive medication. Of the 1,351 enrolled subjects, 563 were considered to have hypertension. After adjusting for age, logistic regression analysis showed that CKD was associated with intima-media thickening in individuals with hypertension, but not in those without (Table 2). Similar results were obtained after further adjustment for FPG and smoking status; both albuminuria and low eGFR were significantly associated with intima-media thickening in individuals with hypertension, but, again, not in those without after adjusting for age, FPG, and smoking status,

Association between CKD and Intima-Media Thickening According to Glucose Metabolism

We then assessed the association between CKD and carotid intima-media thickening after subdividing individuals according to their fasting glucose levels. For this analysis, high fasting glucose was defined as FPG ≥110 mg/dL or current use of an antidiabetic medication. Of the 1,351 enrolled subjects, 251 had FPG ≥110 mg/dL, 50 were taking an antidiabetic medication, and 46 fell into both categories; therefore, 255 were considered to have high fasting glucose. Logistic regression analysis after adjusting for age, SBP, and smoking

Table 3. Logistic Regression Analysis for CKD or Its Components as Independent Variables and Carotid Intima-Media Thickening as a Dependent Variable According to Fasting Glucose Status

	Odds ratio (95% CI) of CKD	*p* value	Odds ratio (95% CI) of albuminruia	*p* value	Odds ratio (95% CI) of low eGFR	*p* value
Subjects with high fasting glucose (n=255)						
Unadjsted	2.55 (1.41–4.61)	0.0021	2.65 (1.40–5.02)	0.0029	2.82 (1.39–5.71)	0.0040
Adjusted for age	2.12 (1.15–3.92)	0.017	2.30 (1.19–4.46)	0.013	2.15 (1.03–4.49)	0.042
Adjusted for age, SBP, and smoking status	1.99 (1.06–3.72)	0.031	2.00 (1.01–3.95)	0.046	2.39 (1.11–5.14)	0.026
Subjects without high fasting glucose (n=1,096)						
Unadjsted	2.08 (1.44–3.01)	0.0001	2.45 (1.51–3.97)	0.0003	1.89 (1.26–2.83)	0.019
Adjusted for age	1.22 (0.82–1.84)	0.33	1.66 (0.97–2.83)	0.063	1.16 (0.75–1.81)	0.50
Adjusted for age, SBP, and smoking status	1.16 (0.77–1.75)	0.48	1.41 (0.81–2.43)	0.23	1.17 (0.75–1.83)	0.48

CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

status showed that CKD, albuminuria, and low eGFR were each significantly associated with intima-media thickening in individuals with high fasting glucose, but not in those without (Table 3).

Association between CKD and Intima-Media Thickening According to Smoking Status

Logistic regression analysis after adjusting for age, SBP, and FPG showed that CKD was significantly associated with intima-media thickening in current smokers (n=337) with an odds ratio of 2.67 (95% CI 1.26–5.68, p=0.011) but not in former smokers (n=596, odds ratio 1.04 [95% CI 0.64–1.69, p=0.87]) or in never smokers (n=418, odds ratio 1.27 [95% CI 0.67–2.42, p=0.47]).

Discussion

We found that 28% of the male individuals undergoing general health screening in the present series had CKD (albuminuria, 12%: low eGFR, 19%: both, 3%). Several previous studies have reported on the prevalence of CKD in the general population in Japan. Ninomiya *et al.* reported that 11% (324/2,736) of subjects had an eGFR of less than 60 mL/min/1.73 m^2 at the beginning of their study, although the number of each gender was not specified (*11*). Nakamura *et al.* reported that the prevalence of CKD was 4.7% (146/3,047) in a randomly selected Japanese men (*12*). In these two studies, CKD was defined solely by the eGFR criterion. The greater prevalence of CKD in the current study is in part due to the fact that we included the albuminuria criterion for the diagnosis of CKD. Nevertheless, the prevalence of low eGFR itself seems to have been greater in the current study than in the previous reports. This is, at least in part, because we used 0.881 as a coefficient for Japanese to calculate an eGFR value specific to the Japanese population (*8*). Tanaka *et al.* have diagnosed CKD considering both albuminuria and low eGFR and reported that the prevalence of CKD in individuals included in a hospital-based registry was 13.7% (*13*); however, the coefficient for Japanese may not be used to estimate eGFR in their study. In the present study, when we estimated GFR without using the coefficient for Japanese, the prevalence of CKD was calculated to be 16.0%. Micro- and macroalbuminuria were found in 10.5% and 1.8%, respectively, of individuals in the current study. These values are comparable to those found in the general population in Japan by Konta *et al.* (13.7% and 1.7%, respectively) (*14*).

After adjusting for age, SBP, FPG, and smoking status, albuminuria was found to be associated with carotid intima-media thickening in the current study. An association between albuminuria and atherosclerotic diseases has been reported in a number of previous papers; albuminuria is known to be a predictor of cardiovascular mortality, although its capabilities may differ according to gender, race, and ethnicities (*15*, *16*), and albuminuria is an independent predictor for carotid intima-media thickness in diabetic (*17*) as well as non-diabetic (*18*) subjects. There have also been several studies that have assessed the possible association of low eGFR with carotid atherosclerosis in individuals who had only a mild decline in renal function, and in the general population. Preston *et al.* reported that common carotid artery intima-media thickness was greater in CKD patients. In their study, the mean GFR was 29.6±18.4 mL/min/1.73 m^2, which is much lower than that in the current study (*19*). Taniwaki *et al.* reported that decreasing GFR was significantly correlated with carotid intima-media thickness in diabetic patients (*20*), and this correlation may be independent of albuminuria status. In their study, the decrease in GFR was much milder than that in the study of Preston *et al.* (*19*): the mean GFR values were 127±26 mL/min/1.48 m^2 and 119±27 mL/min/1.48 m^2, respectively, in patients with and without microalbuminuria. In addition, by analyzing the data from a population-based survey, Rodondi *et al.* showed that carotid intima-media thickness increased with decreasing eGFR, although this association did not retain its statistical significance after adjusting for age (*21*).

Interestingly, albuminuria was associated with carotid intima-media thickening in individuals with hypertension, but not in those without. Similarly, the association between albuminuria and carotid intima-media thickening was statistically significant in individuals with high fasting glucose, but not in those without. In addition, in individuals with hypertension or high fasting glucose, not only albuminuria, but also low eGFR was significantly associated with intima-media thickening after multivariate adjustment. Previous studies showed that reduced GFR was an independent risk factor for worse cardiovascular outcomes in patients with hypertension (*22*, *23*) and diabetes (*24*). Our data suggest that a mild decline in GFR may also be a risk factor for early atherosclerosis in Japanese men with relatively low risk profiles, especially when individuals have hypertension and diabetes, which is agreement with the previous findings (*25*). As CKD was associated with carotid intima-media thickening in current smokers but not in former smokers or nonsmokers in the current study, it is possible that the presence of CKD might increase the prevalence of early carotid atherosclerosis when some atherogenic risk factors are present.

We also showed that CKD was associated with metabolic syndrome, although we cannot determine a causal or resultant relationship. Ninomiya *et al.* have reported in their Hisayama Study that metabolic syndrome was an independent risk factor for CKD based on the 5-year cumulative data for the disease (*11*), suggesting that the clustering of hemodynamic/metabolic syndrome may be a reason for the increase in CKD in the general population. Whether the clustering of the hemodynamic/metabolic risk factors can explain the observed association between CKD and carotid intima-media thickening should be analyzed in future studies.

In conclusion, albuminuria, low eGFR, and CKD were found in 12%, 19%, and 28%, respectively, of male individuals undergoing general health screening in the present study. CKD was found to be a risk factor for carotid intima-media thickening after the adjustment for age, SBP, FPG, and smoking status. Both albuminuria and low eGFR were significantly associated with carotid intima-media thickening in individuals with hypertension and in those with high fasting glucose, but not in those without either condition. To what extent maintaining blood pressure and/or plasma glucose levels within a preferable range suppresses the future development of carotid atherosclerosis in CKD patients would be a meaningful question to be addressed in future longitudinal studies.

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Original Article

Association between Obesity and Chronic Kidney Disease in Japanese: Differences in Gender and Hypertensive Status?

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Obesity is a known risk factor for hypertension and diabetes, both of which ultimately promote renal dysfunction. In the current study, we investigated the association between body mass index (BMI) and chronic kidney disease (CKD) in 8,168 Japanese individuals (2,924 women, 5,244 men) who underwent general health screening. CKD was diagnosed if the estimated glomerular filtration rate (eGFR) was less than 60 mL/min/1.73 m^2 (designated as low eGFR) and/or if the urinary albumin/creatinine value was equal to or greater than 30 mg/g (designated as albuminuria). Logistic regression analysis adjusted for age, systolic blood pressure, fasting glucose, and smoking habits showed that, in men, both overweight (BMI 25–29 kg/m^2) and obesity (BMI ≥30 kg/m^2) were associated with increased prevalence of low eGFR and albuminuria, whereas, in women, obesity was associated with albuminuria, but neither overweight nor obesity was associated with low eGFR. After multivariate adjustment, logistic regression analysis showed that BMI had a graded association with both low eGFR and albuminuria in men. On the other hand, in women, the second and third BMI quartiles were associated with a lower prevalence of albuminuria in comparison with the first BMI quartile. Essentially the same results were obtained when the subjects were subdivided according to the presence and absence of hypertension. Our data showed that overweight and obesity were associated with increased risk for CKD in Japanese individuals undergoing a general health screening, irrespective of the presence or absence of hypertension, although there was a gender difference in these associations. (*Hypertens Res* 2007; 30: 1059–1064)

***Key Words*: obesity, chronic kidney disease, gender difference, hypertension**

Introduction

As in Western countries (*1*, *2*), the prevalence of obesity among Japanese is increasing, especially in men and women older than 40 years of age (*3*). Several cross-sectional and longitudinal epidemiological studies have shown that obesity may increase the prevalence and incidence of chronic kidney disease (CKD) (*4–8*). Care must be taken in interpreting these data, since several of the studies have diagnosed CKD based on an estimated glomerular filtration rate (eGFR) lower than a certain cutoff value, while others have defined CKD based on either low eGFR or the presence of albuminuria/proteinuria. Nevertheless, it is of note that one study found a gender-related difference in the association between obesity and CKD (*9*), whereas other reports did not (*4*, *5*). Obesity

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increases renal sodium reabsorption, which results in an elevation of blood pressure (*6*, *10*, *11*) and may explain the observed link between obesity and CKD, as hypertension is one of the most important factors associated with the progression of both diabetic and nondiabetic CKD (*7*). On the other hand, Kramer *et al.* noted a significant association between obesity and the risk for CKD, defined as ≥1 + proteinuria and/or eGFR <60 mL/min/1.73 m^2, in a cohort of hypertensive adults, which was statistically significant after adjustment for blood pressure and diabetes (*8*). This finding suggested that obesity and overweight increase the incidence of CKD independent of the degree of hypertension.

In the current study, we sought to investigate whether body mass index (BMI) was associated with CKD and its components, which are low eGFR and albuminuria, in Japanese individuals who underwent general health screening, and whether the mode of this association, if present, differed according to gender and hypertensive status.

Methods

Study Population

The study was approved by the Ethical Committee of the Mitsui Memorial Hospital. Between April 2004 and August 2006, 12,535 individuals (4,481 women and 8,054 men) undergoing a general health screen at this institute, including an estimation of urinary excretion of albumin, and who completed a questionnaire concerning the amount and duration of their alcohol consumption, 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 place of employment or by the subjects themselves. Ideal BMI, overweight, and obesity were defined as BMI <25 kg/m^2, BMI 25–29 kg/m^2, and BMI ≥30 kg/m^2, respectively.

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol (HDL-C), and triglycerides (TG) were determined enzymatically. Serum uric acid (UA) 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 of 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. Metabolic syndrome was said to be present when three or more of the following conditions were met: TG levels ≥150 mg/dL; HDL-C levels <40 mg/dL; FPG levels ≥110 mg/dL or current use of antidiabetic medication; systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg or current use of antihypertensive medication; BMI ≥25 kg/m^2.

Table 1. Baseline Characteristics

	Women (n=2,924)	Men (n=5,244)
Age (years)	52.0±10.7	53.8±10.5
Waist circumferrence (cm)	76.8±9.0	85.8±7.8
Body mass index (kg/m^2)	21.2±3.0	23.7±2.9
Systolic blood pressure (mmHg)	117±19	125±19
Diastolic blood pressure (mmHg)	73±12	79±11
Lipid data		
LDL-cholesterol (mg/dL)	127±33	129±31
HDL-cholesterol (mg/dL)	68±15	55±13
Triglycerides (mg/dL)	85±47	133±89
Glucose metabolism		
Fasting glucose (mg/dL)	90±15	100±21
Hemoglobin A1c (%)	5.2±0.5	5.4±0.8
HOMA-IR	1.2±0.9	1.7±1.3
Metabolic syndrome (n (%))	103 (3.5)	744 (14.2)
Renal data		
Serum urea nitrogen (mg/dL)	13.6±3.5	14.6±3.5
Serum creatine (mg/dL)	0.63±0.24	0.86±0.20
eGFR (mL/min/1.73 m^2)	69±10	70±10
Urinary albumin/creatinine ratio (mg/g)	18±68	26±182
Smoking status		
Non-smokers (n (%))	2,510 (86)	1,743 (33)
Former smokers (n (%))	177 (6)	1,893 (36)
Current smokers (n (%))	243 (8)	1,608 (31)

LDL, low-density lipoprotein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate.

Estimated Glomerular Filtration Rate, Albuminuria, and Definition of CKD

Serum creatinine was calibrated 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; GFR was estimated using the equation from a simplified version of the Modification of Diet in Renal Disease (MDRD) (*12*) as follows: eGFR (mL/min/1.73 m^2) = $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.881$ (× 0.742 if female). In this MDRD formula, 0.881 is a coefficient for eGFR specific to the Japanese population (*13*). 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 to be present when the urinary albumin excretion ratio (UAER) was ≥30 mg/g-creatinine. Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as an UAER of <30 mg/g, 30–

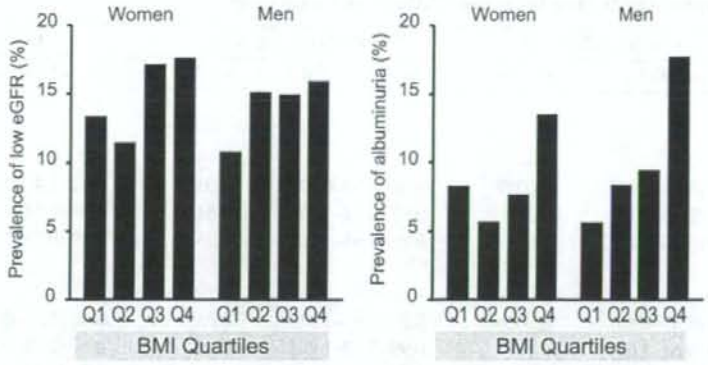

Fig. 1. *Prevalence of low eGFR and albuminuria according to BMI quartiles.*

299 mg/g, and 300 mg/g, respectively (*14*). Individuals were said to have CKD when they had either or both of low eGFR and albuminuria (*15*).

Statistical Analysis

The data in this study were analyzed by multivariate logistic regression analysis using computer software, StatView ver. 5.0 (SAS Institute, Cary, USA). A value of $p<0.05$ was taken to be statistically significant. Results are expressed as the means±SD unless stated otherwise.

Results

Baseline Characteristics

Characteristics of the enrolled subjects are shown in Table 1. The numbers of women with overweight and obesity were 254 (8.7%) and 32 (1.1%), respectively, and the numbers in men were 1,361 (26.0%) and 147 (2.8%), respectively.

Among women, 432 (14.8%) had low eGFR, 254 (8.7%) had albuminuria, and 55 (1.9%) had both low eGFR and albuminuria. Therefore, 631 (21.6%) women were considered to have CKD. In men, low eGFR was found in 739 (14.1%) and albuminuria in 535 (10.2%), and both low eGFR and albuminuria were present in 122 (2.3%). Therefore, 1,152 men (22.0%) were considered to have CKD. Micro- and macroalbuminuria were found in 236 (8.1%) and 18 (0.6%) women, respectively, and in 467 (8.9%) and 68 (1.3%) men, respectively. Pearson's correlation coefficients for the relationship between BMI and UA were 0.29 ($p<0.0001$) in women and 0.23 ($p<0.0001$) in men.

The interquartile cutoff values for BMI were 19.2, 20.7, and 22.8 kg/m^2 in women and 21.9, 22.5, and 25.3 kg/m^2 in men. The correlation coefficient between WC and BMI was 0.79 in women and 0.84 in men.

Association among BMI, Overweight, Obesity and CKD

In both genders, the prevalence of low eGFR and that of albuminuria was greatest in the highest BMI quartile (Fig. 1). Age-adjusted logistic regression analysis showed that women in the second and third BMI quartiles had a lower prevalence of CKD and albuminuria after adjustment for age, SBP, FPG, and smoking status. On the other hand, in men, the prevalence of CKD and albuminuria was increased according to BMI in the multivariate adjusted model. BMI showed a graded association with low eGFR in men (Table 2). When data on only male never smokers ($n=1,743$) were analyzed, the first, second, third, and fourth BMI quartiles were associated with low eGFR with an odds ratio of 1 (referent), 1.21 (95% confidence interval [CI] 0.83–1.77, $p=0.33$), 1.18 (95% CI 0.80–1.74, $p=0.41$), and 1.76 (95% CI 1.16–2.67, $p=0.0077$), respectively.

We then analyzed the association between overweight and obesity and CKD components in a logistic regression analysis after adjusting for age, SBP, FPG, and smoking status; the ideal BMI was used as the reference (Table 3). Both overweight and obesity were associated with low eGFR in men, but again not in women. Obesity in women and both overweight and obesity in men were associated with albuminuria.

Association between BMI and CKD Components in Hypertensive and Non-Hypertensive Subjects

We next evaluated whether hypertension modified the association between BMI and CKD. Hypertension was found in 502 (17.2%) of the women and 1,658 (31.6%) of the men. The mode of association between BMI and CKD (and its components) was similar between hypertensive and non-hypertensive individuals (Table 4). In women without hypertension, individuals in the second BMI quartile had significantly lower prevalence of low eGFR when compared with those in the

Table 2. Association between Body Mass Index and CKD and Its Components

	Odds raio (95% CI)		Odds raio (95% CI)		Odds raio (95% CI)	
	For CKD	*p* value	For low eGFR	*p* value	For albuminuria	*p* value
Women						
Model 1						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.63 (0.48–0.84)	0.0017	0.69 (0.50–0.97)	0.032	0.61 (0.40–0.92)	0.020
BMI-Q3	0.86 (0.66–1.13)	0.28	0.93 (0.68–1.27)	0.64	0.76 (0.51–1.11)	0.16
BMI-Q4	0.99 (0.76–1.29)	0.96	0.86 (0.63–1.18)	0.36	1.39 (0.98–1.96)	0.065
Model 2						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.60 (0.45–0.80)	0.0004	0.72 (0.51–1.01)	0.055	0.48 (0.32–0.74)	0.0009
BMI-Q3	0.80 (0.61–1.05)	0.10	0.99 (0.72–1.36)	0.94	0.57 (0.38–0.85)	0.0062
BMI-Q4	0.82 (0.62–1.09)	0.17	1.01 (0.72–1.41)	0.97	0.73 (0.50–1.07)	0.11
Men						
Model 1						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.50 (1.22–1.85)	0.0001	1.40 (1.11–1.78)	0.0055	1.45 (1.06–1.98)	0.019
BMI-Q3	1.56 (1.27–1.92)	<0.0001	1.44 (1.13–1.83)	0.0028	1.71 (1.27–2.32)	0.0005
BMI-Q4	2.66 (2.18–3.25)	<0.0001	1.71 (1.35–2.17)	<0.0001	3.81 (2.88–5.03)	<0.0001
Model 2						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.41 (1.14–1.74)	0.0016	1.43 (1.12–1.82)	0.040	1.27 (0.92–1.75)	0.16
BMI-Q3	1.38 (1.11–1.70)	0.0032	1.47 (1.15–1.88)	0.0019	1.32 (0.96–1.82)	0.088
BMI-Q4	2.05 (1.66–2.54)	<0.0001	1.82 (1.42–2.34)	<0.0001	2.26 (1.68–3.06)	<0.0001

Model 1: adjusted for age. Model 2: adjusted for age, systolic blood pressure, fasting glucose and smoking habits. BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate.

first BMI quartile, and individuals in the second or third BMI quartiles had significantly lower prevalence of albuminuria when compared with those in the first BMI quartile.

Discussion

In this cross-sectional study, we investigated the association between BMI and CKD components in individuals who underwent general health screening. BMI had a graded association with CKD, low eGFR, and albuminuria in men, whereas women in the second and the third BMI quartiles had a significantly lower prevalence of CKD and albuminuria. Modes of association between BMI and CKD (and its components) were similar between hypertensive and non-hypertensive individuals, especially in men.

Several previous studies have examined the association between BMI and CKD. In a community-based longitudinal cohort study in the U.S., BMI was found to be related to the development of kidney disease (*16*). Kramer *et al.* reported that overweight (BMI 25–29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2) were associated with CKD, defined as the presence of 1+ or greater proteinuria and/or eGFR <60 mL/min/1.73 m^2, in hypertensive subjects, and that this association remained statistically significant even after adjustment for blood pressure and diabetes (*8*). Gelber *et al.* reported that BMI was associated with low eGFR in a 14-year follow-up of apparently healthy men (*17*).

In the current study, we found a gender difference in the association between BMI and low eGFR: an increased BMI was a risk factor for low eGFR only in men, but not in women. Iseki *et al.* reported in their 17-year cohort study that elevations in BMI had a graded association with the cumulative incidence of end-stage renal disease (ESRD) compared with individuals with a baseline BMI of <21 kg/m^2 (*9*); however, this association was only found in men. In the same study, Iseki *et al.* suggested that this gender difference might be partly attributable to a difference in the prevalence of cigarette smoking (*9*). This was because cigarette smoking, prevalence of which is higher in men, is a risk factor for the ESRD and proteinuria (*18, 19*).

It is possible that the difference in the mode of association between BMI and low eGFR (or albuminuria) between genders was attributable to the usage of sex-specific quartiles, which resulted in different cutoff values between genders. And in fact, when we used the same cutoff values, the association between obesity and albuminuria was observed in both genders with similar odds ratios (Table 4). It should be noted, however, that overweight and obesity were associated with low eGFR in men, but again, not in women (Table 4). Thus, this concept could not explain the gender difference in the

Table 3. Association between Overweight, Obesity, and CKD and Its Components

	Odds ratio (95% CI)		Odds ratio (95% CI)		Odds ratio (95% CI)	
	For CKD	*p* value	For low eGFR	*p* value	For albuminuria	*p* value
Women						
Ideal BMI	1	—	1	—	1	—
Overweight	1.00 (0.72–1.39)	>0.99	1.06 (0.72–1.55)	0.78	1.07 (0.71–1.61)	0.74
Obesity	2.20 (0.98–4.96)	0.056	0.27 (0.03–2.09)	0.21	2.74 (1.20–6.27)	0.017
Men						
Ideal BMI	1	—	1	—	1	—
Overweight	1.56 (1.33–1.82)	<0.0001	1.44 (1.20–1.73)	0.0001	1.70 (1.38–2.08)	<0.0001
Obesity	2.77 (1.91–4.02)	<0.0001	2.14 (1.32–3.47)	0.0021	2.72 (1.77–4.17)	<0.0001

Odds ratios were obtained after adjusting for age, systolic blood pressure, fasting glucose and smoking habits. CKD, chronic kidney disease; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate.

Table 4. Association between Body Mass Index and CKD and Its Components According to Hypertensive Status

	Odds raio (95% CI)		Odds raio (95% CI)		Odds raio (95% CI)	
	For CKD	*p* value	For low eGFR	*p* value	For albuminuria	*p* value
Women						
HT (+)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.73 (0.32–1.63)	0.44	1.17 (0.43–3.18)	0.75	0.75 (0.30–1.87)	0.53
BMI-Q3	0.82 (0.38–1.78)	0.61	1.13 (0.43–2.94)	0.81	0.79 (0.33–1.92)	0.61
BMI-Q4	1.08 (0.53–2.22)	0.83	1.34 (0.55–3.26)	0.52	1.16 (0.53–2.57)	0.71
HT (–)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	0.60 (0.44–0.81)	0.0011	0.67 (0.47–0.97)	0.033	0.45 (0.27–0.74)	0.0017
BMI-Q3	0.85 (0.63–1.14)	0.28	1.01 (0.72–1.41)	0.97	0.57 (0.36–0.91)	0.018
BMI-Q4	0.80 (0.57–1.10)	0.17	1.00 (0.69–1.46)	1.00	0.61 (0.38–1.00)	0.052
Men						
HT (+)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.36 (0.91–2.01)	0.13	1.45 (0.90–2.35)	0.13	1.19 (0.72–1.96)	0.49
BMI-Q3	1.56 (1.06–2.28)	0.023	1.78 (1.13–2.82)	0.014	1.28 (0.79–2.07)	0.32
BMI-Q4	1.90 (1.32–2.74)	0.0006	1.81 (1.15–2.83)	0.0097	1.86 (1.18–2.91)	0.0071
HT (–)						
BMI-Q1	1	—	1	—	1	—
BMI-Q2	1.43 (0.11–1.85)	0.0053	1.45 (0.19–1.93)	0.010	1.19 (0.77–1.83)	0.44
BMI-Q3	1.25 (0.96–1.64)	0.099	1.32 (0.98–1.79)	0.070	1.14 (0.74–1.78)	0.55
BMI-Q4	2.13 (1.61–2.81)	<0.0001	1.87 (1.35–2.61)	0.0002	2.20 (1.44–3.34)	0.0002

Odds ratios were obtained after adjusting for age, systolic blood pressure, fasting glucose and smoking habits. BMI, body mass index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HT (+), hypertensive; HT (–), non-hypertensive.

association between obesity and low eGFR in both genders. A study in the U.S. showed a relationship between obesity and nephrosclerosis in women only (*20*), and a study in Norway showed an association between obesity (BMI ≥30 kg/m^2) and decreased eGFR (eGFR <45 mL/min/1.73 m^2) in both genders. Together with these previous findings, our data suggested that the gender difference in the mode of association between BMI and CKD might differ according to racial groups and ethnicities. On the other hand, recent studies analyzing the data of Japanese hypertensive patients showed that the mode of association between UA and left ventricular hypertrophy (LVH) (*21*), and that between insulin resistance and LVH (*22*) differed according to gender. Considering the possible association between CKD and LVH (*23*), it is possible that the gender difference in the association between BMI and CKD components that was observed in the current study

might be attributed to certain variables that may also underlie the gender difference in the association between insulin resistance, UA, and LVH. This possibility should be investigated in future studies.

We also showed that the pattern of association between BMI and low eGFR was not significantly affected by the hypertension status. Together with the finding that the association between BMI and CKD was only slightly altered when SBP was used as a covariate (Model 2 in Tables 2 and 3), this result indicates that the effect of blood pressure on the association between obesity and CKD may not be as pronounced as previously thought.

In conclusion, we analyzed cross-sectional data on 8,168 individuals (2,924 women, 5,244 men) who underwent general health screening and found that BMI showed a graded association with both low eGFR and albuminuria in men. In women, on the other hand, the second and third quartiles of WC and BMI were associated with lower prevalence of albuminuria when compared with the first BMI quartile. Obesity (BMI $\geq$30 kg/m^2) was associated with albuminuria in both genders, whereas the association between obesity and low eGFR was observed only in men. Modes of association between BMI and CKD (or its components) were similar in hypertensive and non-hypertensive individuals, especially in men. Our data showed that overweight and obesity have already become associated with an increased risk of CKD in low risk Japanese individuals, such as general health screening participants, although there is a slight gender difference.

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