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 m^2. 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.

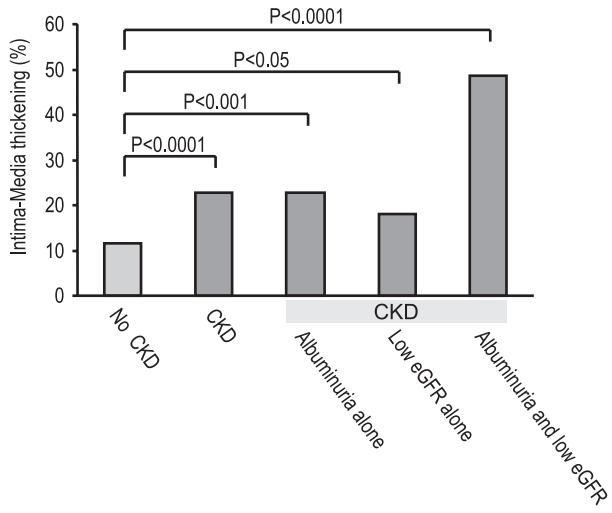

Fig. 1. *Prevalence of intima-media thickening in individuals with or without CKD or its components.*

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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