on the extent to which modifications of lifestyle and dietary habits affect the observed changes in general/abdominal obesity[16]. Third, we excluded subjects who were taking lipid-lowering drugs at either visit, and these individuals may, in general, have higher motivation to obtain information on how to improve serum lipid levels effectively as compared with those not taking such drugs. Finally, a longer follow-up should be performed in future studies.

In summary, during a one-year period, percent changes in BMI (%dBMI) were associated positively with percent changes in LDL-C and TG and negatively with those in HDL-C, especially in both genders. Although percent changes in WC (%dWC) also tended to confer adverse changes in lipid parameters, this relationship did not remain significant after controlling for %dBMI.

Acknowledgements

The work was supported in part by a grant from the Smoking Research Foundation, by Chiyoda Mutual Life Foundation, by a St Luke's Grant for the Epidemiological Research, by Daiwa Securities Health Foundation, a Gerontology Research Grant from Kowa Life Science Foundation, the Foundation for Total Health Promotion, and the Gout Research Foundation of Japan.

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Original Paper

Kidney & Blood Pressure Research

Kidney Blood Press Res 2009;32:421–427
DOI: 10.1159/000264233

Received: April 6, 2009
Accepted: October 13, 2009
Published online: December 3, 2009

Impacts of Changes in Obesity Parameters for the Prediction of Blood Pressure Change in Japanese Individuals

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Key Words
Waist circumference · Body mass index · Blood pressure · Health screening

Abstract
Aims and Methods: By analyzing data from 2,861 individuals who underwent general health screening 2 years running, we have investigated the impact of changes in waist circumference (WC) and body mass index (BMI) over a 1-year period on systolic blood pressure (BPs). We termed WC, BMI, and BPs at the first visit as WC1, BMI1, and BPs1, respectively, and those at the second visit as WC2, BMI2, and BPs2, respectively. The %dWC, %dBMI, and %dBPs was defined as (WC2 – WC1)/WC1 × 100, (BMI2 – BMI1)/BMI1 × 100, and (BPs2 – BPs1)/BPs1 × 100, respectively. ***Results:*** In multivariate regression analysis using age, BPs1, WC1, and %dWC as independent variables, %dWC was a significant predictor for %BPs only in men. %dBMI was a significant predictor for %BPs in both genders when age, BPs1, BMI1, and %dBMI were used as independent variables. Compared with individuals with both %dWC <0 and %dBMI <0, age-adjusted %dBPs was significantly greater in those with both %dWC <0 and %dBMI ≥0; however, it did not significantly differ in those with both %dWC ≥0 and %dBMI <0. ***Conclusion:*** Our data suggest that the impact of BMI change might be greater than WC change in terms of BPs change during this short period.

Introduction

Much evidence supports a positive association between obesity parameters and hypertension [1–4], although the strength of such an association may differ according to the parameter used [5]. In addition, a loss or gain in body weight may affect blood pressure levels [6, 7], even in relatively lean or non-obese individuals [8, 9]. Therefore, weight control may be an important target for better blood pressure control, leading to a reduction in mortality from heart and cerebrovascular disease [4]. Compared with weight, or body mass index (BMI), less information seems to be available on whether, or to what extent, a loss (or gain) in waist circumference (WC) would result in a change in blood pressure. We previously reported that a reduction or gain in obesity parameters may affect the status of chronic kidney disease in individuals who underwent general health screening [10]. To this end, here we investigated the mode of association be-

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tween changes in WC or BMI over a 1-year period and changes in blood pressure levels in Japanese individuals. We analyzed the data separately for each gender, because there may be gender differences in the strength of the association between various obesity parameters and blood pressure [11].

Subjects and Methods

Study Population

The study was approved by the Ethical Committees of University of Tokyo and Mitsui Memorial Hospital. Between October 2005 and October 2006, 3,312 (1,203 women, 2,109 men) individuals underwent general health screening (visit 1), and they visited our institute again in the following year (visit 2). Among these 3,312 individuals, 2,861 (1,114 women, 1,747 men) who reported not taking antihypertensive drugs at both visits were enrolled in the present study. After about 10 min of rest, systolic blood pressure (BPs) and diastolic blood pressure (BPd) were measured in the sitting position by automated sphygmomanometer, BP-203RVIII (Omron Colin, Tokyo, Japan). Blood pressure was measured twice and the mean of these data were taken. With the subject standing, WC was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians [12]. After changing into a robe from our institute, height and weight were measured, and the weight of the robe was subtracted from the value indicated by the scales. Age, WC, BMI, and BPs at visit 1 were designated age1, WC1, BMI1, and BPs1, respectively. Similarly, WC, BMI, and BPs at visit 2 were designated WC2, BMI2, and BPs2, respectively. %dWC, %dBMI, and %dBPs were defined as (WC2 – WC1)/WC1 × 100, (BMI2 – BMI1)/BMI1 × 100, and (BPs2 – BPs1)/BPs1 × 100, respectively.

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) were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method, hemoglobin A_{1C} was determined using the latex agglutination immunoassay. Serum creatinine was measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) using commercially available kits, Accuras Auto CRE (Shino-test, Tokyo, Japan), according to the manufacturer's instructions. Accuracy control was performed every day by constructing X-bar and R charts using commercially available standards. Estimated glomerular filtration rate (eGFR) was calculated by the following equation: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ (× 0.739 if female) [13]. 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 (mg/dl)]/405 [14].

Statistical Analysis

Data are expressed as the mean ± SD unless stated otherwise. Analyses of variance with trend analysis, Tukey's post-hoc analysis and multiple regression analysis were conducted as appropriate to assess the statistical significance of differences between groups using computer software Dr. SPSS II (SPSS, Inc., Chicago, Ill., USA). A value of $p < 0.05$ was taken to be statistically significant.

Results

Baseline Characteristics

As described in the Methods section, among the 3,312 individuals who underwent general health screening visited our institute again in the following year; 2,861 (1,114 women, 1,747 men) who reported not taking antihypertensive drugs at both visits were enrolled in the current study (table 1). The mean ± SD of the interval between the two visits of the individuals enrolled was 355 ± 52 days. The mean ± SD age of the enrolled women (51.3 ± 9.9 years) and men (52.5 ± 10.1 years) was significantly smaller than that of the women (60.7 ± 8.3 years) and men (59.0 ± 8.5 years), respectively ($p < 0.001$), who were excluded because of the antihypertensive medication at either or both visits. Similarly, the mean BMI values of enrolled women (21.2 ± 2.9) and men (23.5 ± 2.7) were significantly smaller than those of the excluded women (22.5 ± 3.2) and men (25.0 ± 2.8), respectively ($p < 0.001$).

WC1 ranged between 51.8 and 118.5 cm, and a WC1 ≥90 cm was found in 71/1,114 women (6.4%), and a WC1 ≥85 cm was found in 183/1,114 men (16.4%). BMI1 ranged between 13.1 and 39.4. A BMI1 ≥25 was found in 110/1,114 women (9.9%) and 453/1,747 men (25.9%), and BMI1 ≥30 was found only in 12/1,114 (1.1%) women and 33/1,747 (1.9%) men. The correlation coefficients between %dWC, %dBMI, %dBPs, WC1, BMI1, and BPs1 are described in table 2. The correlation between %dWC and %dBMI was found to be moderate in men (r = 0.476), whereas it was weak in women (r = 0.241). The relationship between %dBMI and %dBPs was found to be statistically significant in the both genders. On the other hand, the relationship between %dWC and %dBPs was statistically significant only in men. Among the study subjects, it was reported that 60 subjects experienced a WC change of –10 cm or less, and 94 subjects experienced a WC change of +10 cm or more. After excluding these 154 individuals from the study population, the results obtained were not essentially changed (data not shown). It was calculated that a 10% weight gain (loss) over a 1-year period was associated with a 3.88 mm Hg BPs gain (loss) in women and a 9.86 mm Hg BPs gain (loss) in men.

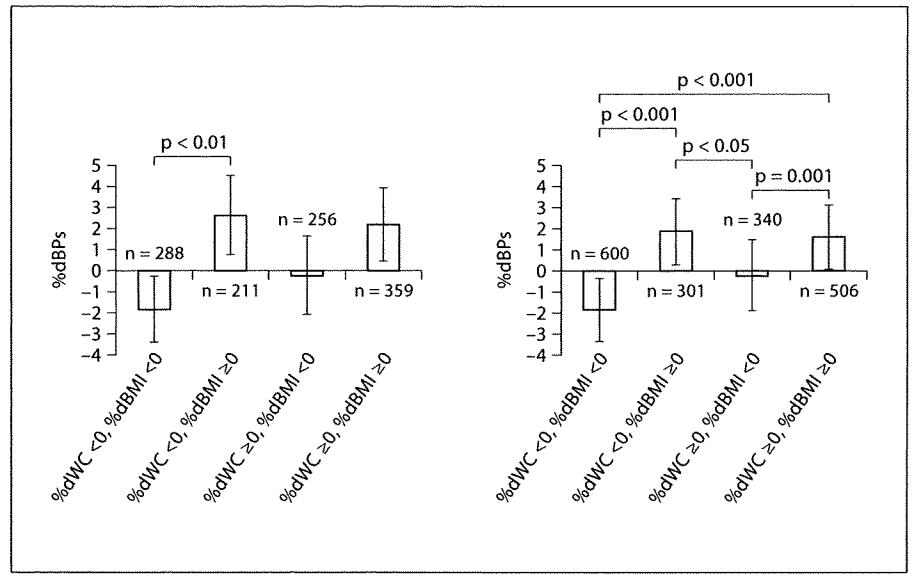

Fig. 1. Comparison of the age-adjusted %dBPs in four subgroups categorized according to the gain or loss of %dWC and %dBMI values. p values were from the result of the Tukey's post-hoc analysis following analyses of variance. Mean ± 95% confidence interval is shown in each group.

Table 1. Clinical characteristics and laboratory data at the first visit

Variables	Whole	%dBPs				p value
		first (range: −40 ~ −7)	second (range: −7 ~ 0)	third (range: +1 ~ +6)	fourth (range: +6 ~ +52)	
Number	2,861	714	809	639	699	
Women/men	1,114/1,747	288/426	314/495	251/388	261/438	0.712
Age, years	52.0 ± 10.1	52.8 ± 10.1	51.4 ± 9.9	51.8 ± 10.0	52.2 ± 10.2	0.047
Height, cm	164.8 ± 8.4	164.5 ± 8.3	165.2 ± 8.5	164.7 ± 8.5	164.7 ± 8.6	0.379
Weight, kg	61.8 ± 11.5	61.8 ± 11.4	62.0 ± 11.6	61.5 ± 11.3	61.8 ± 11.7	0.883
BMI, kg/m^2	22.6 ± 3.0	22.7 ± 3.0	22.6 ± 3.1	22.5 ± 3.0	22.6 ± 3.1	0.781
WC, cm	81.8 ± 9.1	82.0 ± 9.1	81.8 ± 9.3	81.5 ± 9.0	81.9 ± 9.0	0.851
Systolic BP, mm Hg	120.9 ± 18.0	128.7 ± 18.3	121.8 ± 17.0	118.5 ± 16.7	114.2 ± 16.8	<0.001
Diastolic BP, mm Hg	76.4 ± 11.4	79.3 ± 11.3	76.8 ± 10.9	75.5 ± 11.0	73.7 ± 11.5	<0.001
LDL cholesterol, mg/dl	129.2 ± 31.1	131.4 ± 31.5	128.3 ± 29.5	127.1 ± 30.9	130.1 ± 32.4	0.051
HDL cholesterol, mg/dl	61.2 ± 15.3	60.8 ± 15.0	61.8 ± 15.7	61.4 ± 15.6	60.7 ± 15.0	0.465
Triglyceride, mg/dl	109.9 ± 71.4	115.7 ± 69.9	104.7 ± 61.8	109.8 ± 81.0	110.1 ± 73.4	0.030
Uric acid, mg/dl	5.4 ± 1.3	5.4 ± 1.3	5.5 ± 1.3	5.4 ± 1.4	5.5 ± 1.4	0.688
Fasting glucose, mg/dl	95.2 ± 20.0	96.8 ± 20.4	95.1 ± 21.1	94.2 ± 18.0	94.7 ± 20.0	0.072
Hemoglobin A1C, %	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	0.506
HOMA-IR	1.5 ± 1.1	1.6 ± 1.1	1.5 ± 1.1	1.4 ± 1.0	1.5 ± 1.0	0.066
Blood urea nitrogen, mg/dl	14.0 ± 3.4	13.8 ± 3.7	14.0 ± 3.2	14.2 ± 3.4	14.1 ± 3.5	0.245
Serum creatinine, mg/dl	0.8 ± 0.3	0.8 ± 0.4	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.764
Estimated glomerular filtration rate	68.6 ± 11.8	68.3 ± 11.4	69.3 ± 12.0	68.4 ± 11.8	68.1 ± 11.8	0.177
Antidiabetic medication, n (%)	51 (1.8)	12 (1.7)	20 (2.5)	10 (1.6)	9 (1.3)	0.335
Current smoker, n (%)	680 (23.8)	179 (25.0)	184 (22.7)	139 (21.8)	178 (25.5)	0.298

Data are means ± SD, unless stated otherwise. BMI = Body mass index; WC = waist circumference; HOMA-IR = homeostasis model assessment of insulin resistance. %dBPs was calculated by the following equation: (BPs at the second visit − BP1 at the second visit)/(BP1 at the second visit) × 100 (%). p value is for trend.

Table 2. Pearson's correlation coefficient of obesity indices and blood pressure parameters

	%dWC	%dBMI	%dBPs	WC1	BMI1	BPs1
Women						
%dWC						
r	–					
p value	–					
%dBMI						
r	0.241	–				
p value	<0.001	–				
%dBPs						
r	−0.014	0.097	–			
p value	0.635	0.001	–			
WC1						
r	−0.317	−0.053	−0.028	–		
p value	<0.001	0.078	0.350	–		
BMI1						
r	−0.026	−0.087	−0.029	0.787	–	
p value	0.393	0.004	0.331	<0.001	–	
BPs1						
r	−0.025	−0.055	−0.325	0.365	0.409	–
p value	0.396	0.064	<0.001	<0.001	<0.001	–
Men						
%dWC						
r	–					
p value	–					
%dBMI						
r	0.476	–				
p value	<0.001	–				
%dBPs						
r	0.116	0.232	–			
p value	<0.001	<0.001	–			
WC1						
r	−0.268	−0.089	−0.031	–		
p value	<0.001	<0.001	0.189	–		
BMI1						
r	−0.054	−0.071	−0.026	0.830	–	
p value	0.023	0.003	0.286	<0.001	–	
BPs1						
r	−0.090	−0.077	−0.327	0.308	0.322	–
p value	<0.001	0.001	<0.001	<0.001	<0.001	–

BPs = Systolic blood pressure; WC = waist circumference; BMI = body mass index. BPs at visit 1 and visit 2 were designated BPs1 and BPs2, respectively. BMI at visit 1 and visit 2 were designated BMI1 and BMI2, respectively, and WC at visit 1 and visit 2 were designated WC1 and WC2, respectively. %dBMI, %dWC, and %dBPs were calculated by the equation (BMI2 − BMI1)/BMI1 × 100 (%), (WC2 − WC1)/WC1 × 100 (%), and (BPs2 − BPs1)/BPs1 × 100 (%), respectively.

Table 3. Multiple regression analysis between %dBPs and age1, WC1, BMI1, %dWC, and %dBMI

	β	95% CI	Standardized β	p value
Women				
Model 1				
BPs1	−0.23	−0.27 to −0.20	−0.38	<0.001
Age1	0.11	0.05 to 0.18	0.10	0.001
WC1	0.11	0.03 to 0.19	0.09	0.005
%dWC	0.01	−0.06 to 0.09	0.01	0.733
Model 2				
BPs1	−0.24	−0.28 to −0.21	−0.40	<0.001
BMI1	0.47	0.25 to 0.70	0.13	<0.001
Age1	0.13	0.07 to 0.19	0.12	<0.001
%dBMI	0.34	0.15 to 0.53	0.10	0.001
Model 3				
BPs1	−0.24	−0.28 to −0.21	−0.40	<0.001
BMI1	0.65	0.28 to 1.03	0.17	0.001
Age1	0.14	0.07 to 0.20	0.13	<0.001
%dBMI	0.39	0.19 to 0.60	0.11	<0.001
WC1	−0.08	−0.21 to 0.05	−0.06	0.244
%dWC	−0.08	−0.17 to 0.01	−0.06	0.071
Men				
Model 1				
BPs1	−0.22	−0.25 to −0.19	−0.35	<0.001
WC1	0.15	0.08 to 0.22	0.11	<0.001
%dWC	0.28	0.17 to 0.39	0.11	<0.001
Age1	0.02	−0.03 to 0.07	0.02	0.467
Model 2				
BPs1	−0.22	−0.25 to −0.19	−0.35	<0.001
%dBMI	0.80	0.64 to 0.96	0.22	<0.001
BMI1	0.41	0.23 to 0.59	0.10	<0.001
Age1	0.05	0.00 to 0.10	0.05	0.035
Model 3				
BPs1	−0.22	−0.25 to −0.19	−0.35	<0.001
%dBMI	0.82	0.63 to 1.00	0.22	<0.001
BMI1	0.38	0.04 to 0.72	0.10	0.027
Age1	0.05	0.00 to 0.10	0.05	0.046
WC1	0.01	−0.11 to 0.14	0.01	0.845
%dWC	−0.03	−0.16 to 0.11	−0.01	0.705

BPs = Systolic blood pressure; WC = waist circumference; BMI = body mass index. Standardized β values are the estimates resulting from an analysis performed on variables that were standardized. BPs at visit 1 and visit 2 were designated BPs1 and BPs2, respectively. BMI at visit 1 and visit 2 were designated BMI1 and BMI2, respectively, and WC at visit 1 and visit 2 were designated WC1 and WC2, respectively. %dBMI, %dWC, and %dBPs were calculated by the equation of (BMI2 − BMI1)/BMI1 × 100 (%), (WC2 − WC1)/WC1 × 100 (%), and (BPs2 − BPs1)/BPs1 × 100 (%), respectively.

Model 1 = Independent variables include age, BPs1, WC1, and %dWC; model 2 = independent variables include age, BPs1, BMI1, and %dBMI; model 3 = independent variables include model 1 + BMI1, and %dBMI.

Multiple Linear Regression Analysis

In multiple regression analysis, in which age1, WC1, BPs1, and %dWC were used as independent variables (model 1), %dWC was found to be an independent predictive value for %dBPs in men, but not in women (table 3). In a model where age1, BMI1, BPs1, and %dBMI were used as independent variables (model 2), %dBMI was found to be an independent predictive value for %dBPs in the both genders. After including all of the age1, BPs1, WC1, BMI1, %dWC, and %dBMI in a model as independent variables (model 3), %dBMI remained to be a predictor for %dBPs in both genders. In model 3, the variance inflation factor scores of all applied independent variables were <10 (data not shown)

Comparison between Individuals with BMI Gain or Loss together with WC Gain or Loss

We then compared the %BPS values between individuals with both WC loss (%dWC <0) and BMI loss (%dBMI <0), those with both WC loss and BMI gain (%dBMI ≥0), both WC gain and BMI loss, and those with both WC gain and BMI gain during a 1-year period (fig. 1). Age-adjusted %dBPs was significantly greater in individuals with both WC loss and BMI gain compared with those with both WC loss and BMI loss. On the other hand, age-adjusted %dBPs did not significantly differ between individuals with both WC loss and BMI loss and those with WC gain and BMI loss in both genders. When the same analysis was performed after excluding 154 subjects who experienced WC change of –10 cm or less or +10 cm or more, the results obtained were not essentially changed (data not shown).

Discussion

By analyzing data from individuals who underwent general health screening for 2 consecutive years, we showed that a percent difference in BMI (%dBMI) was a statistically significant predictor for a percent difference in BPs (%dBPs) in both genders. A percent difference in WC (%dWC) was also found to be a predictor for %dBPs in men; however, it lost statistical significance after further adjustment for BMI at the first visit and %dBMI, and it was not significant in women before and after such further adjustment.

A body of evidence indicates an association between obesity parameters and blood pressure levels [15, 16]. A reduction in body weight may result in a lowering of blood pressure in overweight or obese subjects [17, 18], although the results may not be always uniform. Moore et al. [19] showed that modest weight loss over a 4-year period substantially lowered the long-term risk of hypertension in overweight adults in Framingham. Haung et al. [20] showed that weight loss occurring after 18 years of age was related to a significantly lower risk, whereas weight gain was related to greater risk of hypertension in middle-aged women. In addition, Yang et al. [21] showed that in men aged between 40 and 74 years, weight gain occurring after 20 years of age was significantly associated with prehypertension. Most of the reports studying the potential association between changes in obesity parameters and changes in blood pressure were carried over a follow-up period longer than that in the current study. Furthermore, Truesdale et al. [22] have more recently shown that weight change over a 3-year period resulted in change in blood pressure levels; men who had experienced a 10% weight gain over the previous 3 years had BPs that was 2.6 mm Hg higher. They found, however, that the impact of weight change was, albeit present, less prominent in women. Women who had experienced a 10% weight gain over the previous 3 years had BPs that was only 0.9 mm Hg higher, suggesting the presence of gender difference in the extent of association between weight change and blood pressure change. We also showed here that the magnitude of the effect of changes in obesity parameters on blood pressure changes may vary by gender (table 3).

As compared to changes in weight, and thus in BMI, fewer analyses have focused on the relationship between changes in WC and blood pressure alterations. Considering that reductions in WC have been recommended more strongly than before for the purpose of prophylaxis and/or resolution of metabolic syndrome by the government in our country [23], the impact of WC reduction (gain) in terms of alterations of atherogenic risk factors, including blood pressure and levels of glucose and lipids, is becoming a more important issue to be investigated. Therefore, we also assessed whether changes in WC were reflected by the BPs change, and whether this relationship, if present, was independent of BMI change. We found that WC change was predictive of BPs change in men but not in women. In addition, the association between %dWC and %dBPs in men lost statistical significance after controlling for BMI1 and %dBMI (table 3). In contrast, %dBMI was a predictor for %dBPs in both genders regardless of the control of %dWC, suggesting that a reduction in BMI may represent a more essential target than WC reduction in terms of blood pressure control. This concept may be further supported by our finding that mean %dBPs did

not differ significantly between individuals with %dWC <0 and those with %dWC ≥0 among individuals with %dBMI <0. In reverse, %dBPs reduction was significantly greater in individuals with %dBMI <0 than in those with %dBMI ≥0 among individuals with %dWC <0 (fig. 1).

It has been reported that, in individuals with a mean BMI of 31, change in BMI was significantly correlated with change in BPs in both genders, even after adjusting for change in waist-hip ratio [24]. In the same study, it was reported that change in waist-hip ratio was not significantly correlated with change in BPs after adjusting for BMI change in men, and that the relationship between change in waist-hip ratio and BPs change was not significant before any adjustment in women. The results of Wing et al. [24] can be said to be similar to our current observation although there is a difference between WC and waist-hip ratio.

The current study has several limitations. First, we retrospectively analyzed data on individuals who underwent general health screening at our institute for 2 consecutive years; as a result, individuals who did not visit our institute the second year for unknown reasons were not enrolled in the current study, which may cause some biases. Second, we could not specify the reasons for weight gain or loss in individuals, however, very few individuals would have been taking antiobesity medications because only one individual in each gender had a BMI of 35 kg/m^2 or more at the first visit. Third, this study population included many non-obese subjects; a BMI1 ≥30 was found only in 1.1% of women and 1.9% of men. Fourth, we excluded those subjects who were taking antihypertensive drugs at either visit. We found that BMI was significantly greater in these excluded subjects than in the study population for both genders. Lastly, although change in BMI may seem to be superior for predicting BPs change than changes in abdominal obesity, abdominal fat volume should be measured by more reliable methods, such as computed tomography, before conclusion. In addition, we have to follow the subjects for a longer period, as a recent study has shown that surrogate measures of abdominal obesity are stronger predictors of all-cause and cardiovascular death than BMI in the general population [25].

In conclusion, in individuals who underwent general health screening for consecutive years, percent change in WC was significantly associated with percent change in BPs in men, but not in women; although this association in men lost statistical significance after controlling for percent change in BMI. By contrast, percent change in BMI was significantly associated with percent change in BPs regardless of controlling for percent change in WC. Our data suggest that controlling BMI, and thus controlling body weight, may represent a more essential goal than a reduction in WC in terms of blood pressure lowering among Japanese individuals who are not taking antihypertensive medication.

Acknowledgements

The work was supported in part by a grant from Chiyoda Mutual Life Foundation, by the St. Luke's Grant for the Epidemiological Research, a grant from Daiwa Securities Health Foundation, by the Foundation for Total Health Promotion, by the Gout Research Foundation of Japan, and by the Kurozumi Medical Foundation, a Gerontology Research Grant from Kowa Life Science Foundation, and Grant-in-Aid from the Ministry of Health, Labour, and Welfare, Japan. We are highly appreciative of Kyoko Furuta for her excellent technical assistance.

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Atherosclerosis 204 (2009) 619–623

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Association between metabolic syndrome and carotid atherosclerosis in individuals without diabetes based on the oral glucose tolerance test

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ARTICLE INFO

Article history:
Received 31 July 2008
Received in revised form 20 October 2008
Accepted 21 October 2008
Available online 30 October 2008

Keywords:
Metabolic syndrome
Carotid artery
Atherosclerosis
Risk factors
Glucose metabolism

ABSTRACT

Introduction: Whether or not metabolic syndrome is predictive of atherosclerotic disorders may depend on the population studied. We investigated whether metabolic syndrome is associated with carotid atherosclerosis in individuals who were shown not to have diabetes mellitus based on results of the 75-g oral glucose tolerance test (OGTT).
Methods and results: Between 1994 and 2003, 3904 individuals underwent general health screening that included the OGTT. Among these 3904 individuals, 3679 had a fasting plasma glucose of <126 mg/dL (subgroup 1), and 3488 had a 2-h post-OGTT glucose value of <200 mg/dL (subgroup 2). In both subgroups, metabolic syndrome was found to be a risk factor for carotid plaque and for carotid intima-media thickening in men, and tended to be a risk factor for carotid plaque in women after adjustment for age. Among 3473 individuals who had both a fasting plasma glucose value of <126 mg/dL and a 2-h post-OGTT glucose of <200 mg/dL, 2440 did not have hypertension, which was defined as systolic and diastolic blood pressure of <140/90 mmHg and absence of use of anti-hypertensive medication. In these non-diabetic non-hypertensive individuals, the association between metabolic syndrome and carotid plaque or carotid intima-media thickening was not statistically significant even with adjustment only for age.
Conclusions: In men who did not have impaired fasting glycemia and/or in those without impaired glucose tolerance, metabolic syndrome was a predictor of carotid atherosclerosis after age adjustment, although metabolic syndrome was not found to be a predictor of carotid atherosclerosis when hypertensive individuals were excluded from the study population.

1. Introduction

Metabolic syndrome (MetS) is a cluster of metabolic and hemodynamic abnormalities linked with insulin resistance. Since components of MetS also represent risk factors for atherosclerotic disorders, it is natural that individuals with this syndrome have an increased risk for ischemic heart disease [1] and stroke [2,3]. On the other hand, the clinical utility of MetS may depend on whether the risk conveyed by this syndrome is higher than the sum of each component utilized as diagnostic criteria for MetS [4,5].

Carotid artery intima-media thickness has been reported to be a discriminator as a surrogate of cardiovascular mortality in community-dwelling Japanese people [6] and, conversely, aggregation of established major coronary risk factors has been reported to strongly influence the presence of carotid atherogenesis in the general Japanese population [7]. Previously, we reported that the presence of MetS may not increase the risk for carotid atherosclerosis in individuals without hypertension, with hypertension defined as systolic blood pressure (SBP) of ≥140 mmHg, diastolic blood pressure (DBP) of ≥90 mmHg, or the use of anti-hypertensive medication [8]. This observation suggested that the properties of MetS that present a risk for atherosclerotic diseases may differ according to the populations selected. Consistent with this idea, it was reported that MetS was not found to be associated with cardiovascular mortality in non-diabetic non-hypertensive Chinese individuals [9], and that MetS did not significantly increase the risk of mortality from cardiovascular disease in non-diabetic Mexican Americans and non-Hispanic whites [10]. In the current study, we investigated whether MetS was associated with carotid atherosclerosis in Japanese individuals who did not have diabetes mellitus based on results of the 75-g oral glucose tolerance test (OGTT).

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doi:10.1016/j.atherosclerosis.2008.10.022

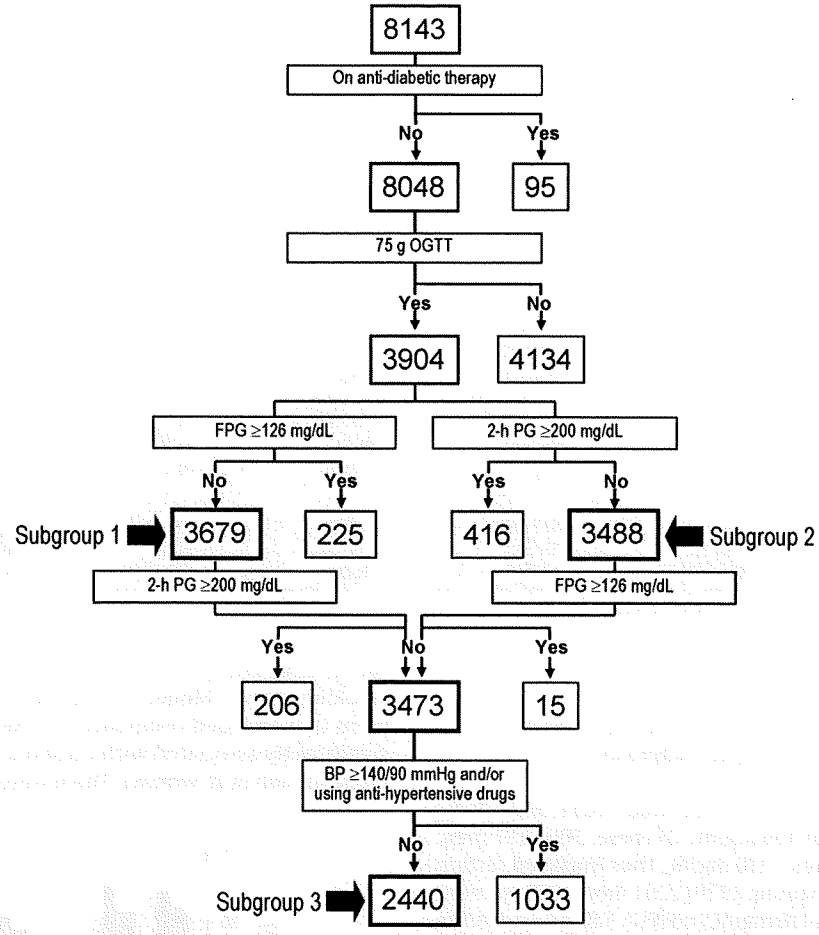

Fig. 1. Flow chart showing selection of the four subgroups.

2. Methods

2.1. Study subjects and selection of subgroups

The study was approved by The Ethical Committee of Mitsui Memorial Hospital and University of Tokyo, Faculty of Medicine. Between September 1994 and December 2003, 8143 subjects underwent general health screening including carotid ultrasonography at the Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital. Of the 8143 subjects, 95 were treated as having diabetes, and of the remaining 8048 individuals, 3904 underwent an OGTT. Among these 3904 individuals, three subgroups were sequentially selected based on various parameters (Fig. 1). Those with a fasting plasma glucose (FPG) value of <126 mg/dL were designated as subgroup 1, and those with a 2-h post-OGTT plasma glucose (2-h PG) value of <200 mg/dL were designated as subgroup 2. Subgroup 3 was comprised of subjects who met all the following conditions: FPG of <126 mg/dL, 2-h PG of <200 mg/dL, and not having hypertension. Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, or the use of anti-hypertensive medication. We also selected individuals without impaired glucose tolerance (IGT), i.e., individuals with a 2-h PG value of <140 mg/dL.

At our institute, several types of health screening programs are available, and some general health screening programs include carotid ultrasonography and/or OGTT, while others do not. However, the decision on the type of health screening was made by the individuals and/or their companies and was not decided upon or recommended by any attending physician.

2.2. Definition of MetS

MetS was defined as the presence of three or more of the following: (1) fasting glucose ≥110 mg/dL; (2) SBP/DBP ≥130/85 mmHg or taking anti-hypertensive medication; (3) triglycerides ≥150 mg/dL mmol/L; (4) HDL cholesterol <40 mg/dL in men and <50 mg/dL in women; and (5) body mass index ≥25 kg/m^2 [11].

2.3. Carotid ultrasonography

Carotid artery status was studied using high resolution B-mode ultrasonography (Sonolayer SSA270A, Toshiba, Japan) equipped with a 7.5 MHz transducer as described previously [12]. Plaque was defined to be present when there is one or more clearly isolated focal thickening(s) of the intima-media layer with thickness of ≥1.3 mm at the common or internal carotid artery or the carotid bulb. Carotid wall intima-media thickening was said to be present when intima-media thickness which was measured at the far wall of the distal 10 mm of the common carotid artery was ≥1.0 mm [12].

2.4. Statistical analysis

Logistic regression analysis was used to obtain adjusted odds ratios and their 95% confidence intervals (CIs) to predict the presence of carotid plaque or carotid intima-media thickening. Statistical analyses were carried out by using Dr. SPSS II (SPSS Inc., Chicago, IL). Results are expressed as the mean ± standard deviation (SD). A value of $p < 0.05$ was taken to be statistically significant.

Table 1
Baseline characteristics.

Variables	Subgroup 1		Subgroup 2		Subgroup 3	
	Men	Women	Men	Women	Men	Women
Number	2548	1131	2386	1102	1588	852
Age, years	58.2 ± 10.6	57.9 ± 10.4	58.0 ± 10.7	57.8 ± 10.3	56.7 ± 10.9	56.6 ± 10.5
Body mass index, kg/m^2	24.0 ± 2.8	22.2 ± 3.1	23.9 ± 2.7	22.1 ± 3.1	23.6 ± 2.6	21.7 ± 2.8
Systolic BP, mmHg	127 ± 19	121 ± 21	128 ± 19	120 ± 20	119 ± 12	123 ± 14
Diastolic BP, mmHg	79 ± 12	73 ± 12	79 ± 12	73 ± 12	73 ± 8	69 ± 9
Total cholesterol, mg/dL	206 ± 32	219 ± 35	205 ± 32	219 ± 35	205 ± 32	216 ± 35
HDL-cholesterol, mg/dL	55 ± 16	70 ± 17	55 ± 16	70 ± 17	56 ± 16	71 ± 17
Triglycerides, mg/dL	144 ± 117	96 ± 56	142 ± 98	95 ± 54	141 ± 98	95 ± 54
Uric acid, mg/dL	6.2 ± 1.2	4.7 ± 1.0	6.2 ± 1.2	4.7 ± 1.0	6.2 ± 1.2	4.6 ± 1.0
Fasting glucose, mg/dL	96 ± 10	90 ± 10	95 ± 10	90 ± 9	94 ± 9	88 ± 9
2-h OGTT glucose, mg/dL	132 ± 41	118 ± 32	125 ± 29	115 ± 26	121 ± 29	112 ± 25
Haemoglobin A1C, %	5.2 ± 0.4	5.1 ± 0.4	5.2 ± 0.4	5.1 ± 0.4	5.2 ± 0.4	5.1 ± 0.4
Hypertension, *n* (%)	863 (34)	263 (23)	788 (33)	248 (23)	0	0
Anti-hypertensive drugs, *n* (%)	336(13)	99(9)	307(13)	95(9)	0	0
Metabolic syndrome, *n* (%)	439(17)	84(7)	372(16)	72(7)	131 (8)	25(3)
Smoking status						
Never, *n* (%)	764 (30)	933 (82)	714(30)	909 (82)	465 (29)	689(81)
Former, *n* (%)	799(31)	53(5)	753 (32)	50(5)	464 (29)	44(5)
Current, *n* (%)	985 (39)	145(13)	919(39)	143(13)	659(41)	119(14)

BP indicates blood pressure, OGTT indicates oral glucose tolerance test.

3. Results

3.1. Association between MetS and carotid atherosclerosis in individuals with FPG value of <126 mg/dL (subgroup 1)

Among the 3904 individuals who underwent OGTT, 3679 (94%) had an FPG value of less than 126 mg/dL. Of these, 300 (257 men, 43 women), the FPG value was ≥110 mg/dL, thus impaired fasting glycemia (IFG), and in the remaining 3379 (2291 men, 1088 women) had an FPG value of less than 110 mg/dL (no IFG). Table 1 shows the baseline characteristics of this group according to gender. Carotid plaque was found in 823 (32%) men and 191 (17%) women and carotid intima-media thickening was found in 422 (17%) men and 122 (11%) women (Fig. 2). Age-adjusted logistic regression analysis (Model 2) showed that, in men, MetS was statistically significantly associated with carotid plaque (Table 1) and intima-media thickening (Table 2). In women, MetS tended to be associated with carotid plaque, but not with intima-media thickening after age adjustment. Similar patterns of relationships could be observed after further adjustment for total cholesterol (TC) and smoking status (Model 3). On the other hand, after full adjustment including that for components of MetS (Model 4), MetS was not significantly associated with carotid plaque or intima-media thickening in either men or women.

3.2. Association between metabolic syndrome and carotid atherosclerosis in individuals with 2-h PG value of <200 mg/dL (subgroup 2)

Among 3904 individuals who underwent OGTT, 3488 (89%) had a 2-h PG value of less than 200 mg/dL. Of these 3488 individuals 2644 (1717 men, 927 women) had a 2-h PG value of less than 140 mg/dL (no IGT) and the remaining 844 (669 men, 175 women) had a 2-h PG FPG value of ≥140 mg/dL, and thus IGT. Carotid plaque was found in 761 (32%) men and 182 (17%) women and carotid intima-media thickening was found in 378 (16%) men and 116 (11%) women. Age-adjusted logistic regression analysis (Model 2) showed that, in men, MetS was statistically significantly associated with carotid plaque (Table 2) and intima-media thickening (Table 3). In women, MetS tended to be associated with carotid plaque but not with intima-media thickening. Similar patterns of relationship could be observed after further adjustment for TC and smoking status (Model 3). On the other hand, after full adjustment that included components of MetS (Model 4), MetS was not significantly associated with carotid plaque or intima-media thickening in men or in women. There were only 15 (13 men, 2 women)

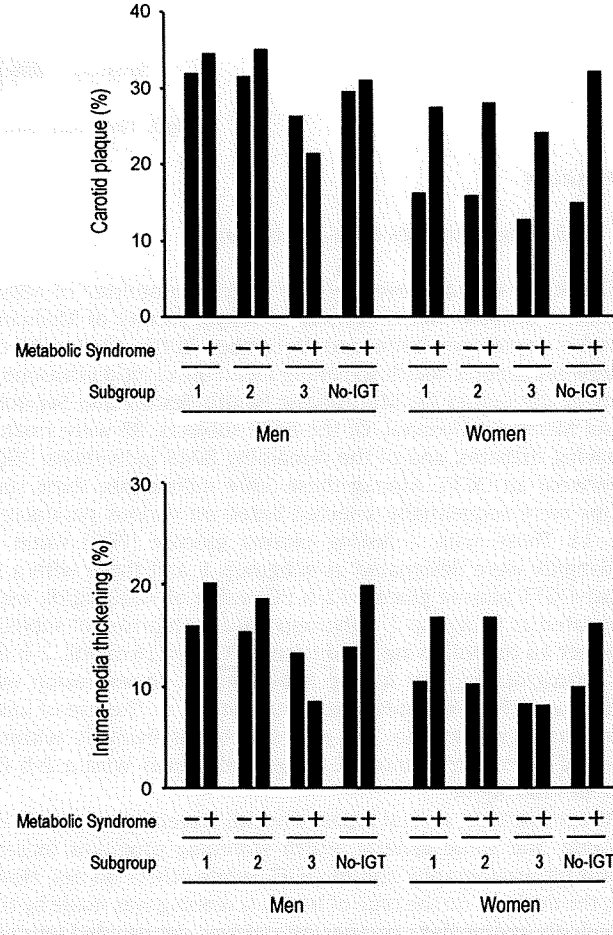

Fig. 2. Prevalence of carotid plaque and carotid intima-media thickening according to the presence or absence of metabolic syndrome in subgroups.

Table 2
Logistic regression analysis with metabolic syndrome as an independent variable and carotid plaque as a dependent variable.

Variables	Odds ratio for carotid plaque			
	Men		Women	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Subgroup 1				
Model 1	1.12(0.90–1.39)	0.302	1.97(1.19–3.28)	0.009
Model 2	1.41(1.11–1.79)	0.005	1.68(0.96–2.95)	0.072
Model 3	1.30(1.03–1.67)	0.030	1.63(0.93–2.88)	0.091
Model 4	1.21(0.90–1.63)	0.209	1.61(0.79–3.29)	0.188
Subgroup 2				
Model 1	1.18(0.93–1.49)	0.170	2.06(1.20–3.55)	0.009
Model 2	1.47(1.14–1.90)	0.003	1.78(0.98–3.24)	0.058
Model 3	1.38(1.07–1.78)	0.014	1.72(0.95–3.14)	0.076
Model 4	1.23(0.90–1.69)	0.202	1.73(0.82–3.63)	0.151
Subgroup 3				
Model 1	0.77(0.50–1.19)	0.232	2.20(0.86–5.62)	0.101
Model 2	0.99(0.62–1.58)	0.971	1.89(0.66–5.43)	0.235
Model 3	0.94(0.59–1.50)	0.796	1.85(0.64–5.33)	0.254
Model 4	0.82(0.48–1.41)	0.479	2.44(0.72–8.29)	0.152

Model 1, unadjusted; Model 2, adjusted for age; Model 3, adjusted for age, total cholesterol and smoking status; Model 4, adjusted for age, body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose, and smoking status.

individuals among the 3488 in subgroup 2 who had an FPG value of <126 mg/dL in addition to a 2-h PG value of <200 mg/dL, and, thus, the mode of association between MetS, carotid plaque, and intima-media thickening in this subgroup was essentially the same as that observed in total population of subgroup 2.

We also investigated the association between MetS and carotid atherosclerosis in individuals without IGT. There were 2644 individuals who did not have IGT, and among them, 61 had FPG value of ≥110 mg/dL (Fig. 2, Supplementary Tables 1 and 2). The obtained results in these subgroups were similar to those in the subgroup 2; however, association between MetS and carotid intima-media thickening was statistically significant even after multivariate adjustment in women.

Table 3
Logistic regression analysis with metabolic syndrome as an independent variable and carotid intima-media thickening as a dependent variable.

Variables	Odds ratio for carotid intima-media thickening			
	Men		Women	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Subgroup 1				
Model 1	1.33(1.03–1.73)	0.031	1.74(0.95–3.19)	0.074
Model 2	1.74(1.31–2.30)	<0.001	1.40(0.72–2.73)	0.324
Model 3	1.65(1.24–2.19)	<0.001	1.38(0.70–2.70)	0.349
Model 4	0.97(0.67–1.39)	0.851	0.70(0.31–1.60)	0.398
Subgroup 2				
Model 1	1.26(0.94–1.68)	0.120	1.78(0.93–3.42)	0.083
Model 2	1.63(1.20–2.22)	0.002	1.47(0.73–2.98)	0.285
Model 3	1.55(1.13–2.11)	0.006	1.44(0.71–2.93)	0.317
Model 4	1.00(0.68–1.48)	0.993	0.71(0.30–1.67)	0.435
Subgroup 3				
Model 1	0.61(0.32–1.15)	0.125	0.99(0.23–4.28)	0.985
Model 2	0.83(0.43–1.61)	0.586	0.71(0.15–3.41)	0.673
Model 3	0.77(0.40–1.50)	0.443	0.70(0.15–3.39)	0.660
Model 4	0.52(0.24–1.11)	0.092	0.56(0.05–1.45)	0.123

Model 1, unadjusted; Model 2, adjusted for age; Model 3, adjusted for age, total cholesterol and smoking status; Model 4, adjusted for age, body mass index, systolic blood pressure, total cholesterol, HDL cholesterol, triglycerides, fasting plasma glucose, and smoking status.

3.3. Association between metabolic syndrome and carotid atherosclerosis in individuals with FPG value of <126 mg/dL, 2-h PG value of <200 mg/dL, and no hypertension (subgroup 3)

Among 3904 individuals who underwent OGTT, 2440 (63%) could be assigned to subgroups 3. Their baseline characteristics according to gender are shown in Table 1. Carotid plaque was found in 409 (26%) men and 110 (13%) women and carotid intima-media thickening was found in 202 (13%) men and 69 (8%) women. Unlike subgroups 1 and 2, MetS was not significantly associated with either carotid plaque or intima-media thickening after age adjustment, or even before any adjustment in either gender (Tables 2 and 3).

4. Discussion

Here, we have assessed whether MetS is a risk factor for carotid atherosclerosis in individuals who were determined not to have diabetes mellitus based on results of OGTT. MetS was found to be associated with carotid atherosclerosis especially in men; however, when individuals with hypertension, defined as those having SBP/DBP ≥140/90 mmHg or using anti-hypertensive medication, were excluded, the presence of MetS no longer conferred excess risk when adjustments were made only for age or even when no adjustments were made.

It is known that clustering of certain metabolic abnormalities and hypertension increases the incidence of atherosclerotic diseases [13]. However, whether such clustering of atherogenic risk factors should be separately designated as MetS has been controversial. Whether MetS is independently associated with carotid atherosclerosis has been analyzed in various populations. By analyzing data on a multi-ethnic cohort of apparently healthy individuals in Canada, Paras et al. reported that although MetS was significantly associated with measures of sub-clinical carotid atherosclerosis, this association is mediated entirely through the components of MetS that have been considered as risk factors [14]. Similarly, by analyzing data on individuals recruited from a local community in Italy, Fadini et al. demonstrated that the clustering of MetS components led to a no-more-than additive increase in carotid intima-media thickness [4]. In addition, Vaidya et al. reported that MetS did not have supra-additive association with carotid intima-media thickening [15].

In our previous study that analyzed data on subjects who underwent general health screening, we found that MetS may not be associated with carotid atherosclerosis even after adjustment only for age when individuals did not have hypertension (SBP/DBP <140/90 mmHg and not using anti-hypertensive medication) [8]. In the current study, we expanded this theme to investigate whether MetS increases the risk for carotid atherosclerosis in individuals who had no or only mild (i.e., not in the diabetic range) abnormalities in glucose metabolism. We found that in individuals with FPG values of <126 mg/dL (subgroup 1) or in those with 2-h PG values of <200 mg/dL (subgroup 2), MetS was positively associated with carotid plaque after adjustment for only age (Model 2), although the relationship was only borderline positive in women. In men, the association between MetS and carotid intima-media thickening was also statistically significantly positive after adjustment for only age. These associations lost statistical significance after adjustment for TC, smoking status, and components of MetS (Model 4), suggesting that these associations may not be independent of these factors. Attention should be given to the fact that after excluding individuals with hypertension from the analysis, the association between MetS and carotid plaque or carotid intima-media thickening was no longer statistically significant even after adjustment for only age (subgroup 3), which is in agreement with our previous finding [8].

Several previous cross-sectional and longitudinal studies have investigated whether MetS increases the risk for atherosclerotic diseases in subjects without apparent impairment in glucose metabolism. A prospective population-based study of Finnish men showed that MetS was associated with higher mortality from coronary heart disease in men without impaired fasting glycemia [16]. Wilson et al. reported that MetS was associated with increased risk for cardiovascular disease in those without diabetes [17]. Leoncini et al. reported that MetS was associated with carotid atherosclerosis in non-diabetic hypertensive individuals who attended an outpatient clinic in Italy [18]. Kawamoto et al. analyzed Japanese inpatients and found that MetS increased the risk for carotid intima-media thickening in non-diabetic subjects [19]. Tzou et al. reported that the presence of MetS increased the composite of carotid intima-media thickness of ≥75th percentile of enrolled subjects in non-diabetic young adults [20]. These results support the notion that the presence of MetS will increase the risk for carotid atherosclerosis even in non-diabetic populations; however, caution should be paid in interpreting these results, as these results were not always adjusted for each component of MetS. The present results showed that MetS was associated with carotid plaque and intima-media thickening in men in subgroups 1, and 2 after adjustment for age, TC, and smoking status, although statistically significance would be lost after further adjustment for MetS components.

We found that in the absence of hypertension (subgroup 3), the association between MetS and carotid plaque or intima-media thickening was no more statistically significant after adjustment for only age, or even when no adjustments were made. These data collectively suggested that the presence or absence of hypertension, but not an abnormality in glucose metabolism, is crucial to determine whether the presence of MetS would increase the risk for carotid atherosclerosis. A recent study showed that MetS significantly increased all-cause mortality in hypertensive community-based French individuals with a hazard ratio of 1.40 (95% CI 1.13–1.74), but not in non-hypertensive individuals, during a mean follow-up period of 4.7 years [21], which was consistent with the idea of major role played by hypertension.

This study has several limitations. First, due to the cross-sectional nature of the study, we cannot determine whether there is a causal or resultant relationship between the MetS and presence of atherosclerosis. Second, among 8048 individuals who were not taking anti-diabetic medication, we excluded 4144 individuals who did not undergo OGTT. The mean age of the 3904 individuals who underwent OGTT and those 4144 who did not were significantly different (55 ± 10 years versus 58 ± 10 years, respectively, $P < 0.001$); therefore, it could be said that there had been some selection bias, though, again, the type of health screening was not decided or recommended by the physicians.

In conclusion, we showed that MetS was associated with carotid plaque and carotid intima-media thickening in non-diabetic individuals; although, this relationship did not remain statistically significant after adjustment for MetS components. In non-diabetic non-hypertensive individuals, the association between MetS and carotid plaque or carotid intima-media thickening was not statistically significant when adjustment was made for only age or even when no adjustment were made. These data collectively indicate that presence or absence of hypertension, but not an abnormality in glucose metabolism, is crucial to determine the relationship between MetS and carotid atherosclerosis.

Acknowledgements

The work was supported in part by a grant from the Smoking Research Foundation, that from Chiyoda Mutual Life Foundation, from the St. Luke's Grant for the Epidemiological Research, and that from Daiwa Securities Health Foundation. We are highly appreciative of Kyoko Furuta for her excellent technical assistance.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.atherosclerosis.2008.10.022.

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Advance Publication by J-STAGE

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Relationship Between Renal Dysfunction and Severity of Coronary Artery Disease in Japanese Patients

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Background: The relationship between renal dysfunction and the severity of coronary artery disease (CAD) was examined.

Methods and Results: The severity of CAD in 572 patients was graded according to the number of stenotic coronary arteries, and the estimated glomerular filtration rate (eGFR) was monitored for 3 years. Patients were stratified into 3 eGFR groups: normal (>75 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$), mild reduction (60–75) and chronic kidney disease (CKD: <60). There were 161 patients in the CKD group. The average number of stenotic coronary arteries was larger in the CKD group than in the other groups (normal vs mild reduction vs CKD=1.35±0.07 (SE) vs 1.22±0.08 vs 1.69±0.08 vessel disease (VD), P<0.001). During the 3-year follow-up, the renal function of 13.8% of the patients worsened. Those who showed more deterioration of eGFR had more severe CAD than those who did not (1.20±0.06 vs 1.61±0.06 VD, P<0.001). Multivariate analysis revealed that the severity of CAD was independently and significantly associated with the deterioration of eGFR.

Conclusions: Patients with CKD had more severe CAD, which may explain the high rate of cardiovascular events in these patients. Moreover, the prognosis of renal function was poor in patients with severe CAD, and CAD was found to be an independent risk factor for worsening of renal dysfunction.

Key Words: Chronic kidney disease; Coronary artery disease; Glomerular filtration rate; Renal function

It is well established that decreased renal function is associated with an increased frequency of cardiovascular disease, so patients with end-stage renal disease have a very high risk for cardiovascular events. However, this is the case even in patients with mildly reduced renal function. In fact, Go et al reported that among the American population patients with mild chronic kidney disease (CKD), such as those whose glomerular filtration rate (GFR) is between 45 and 59 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$, already showed substantial increases in the frequency of cardiovascular events.[1] This has been confirmed not only in population-based epidemiological studies, but also in clinical trials.[2–6] However, the mechanisms of the involvement of renal dysfunction in the occurrence of cardiovascular events remain unclear, although several possibilities have been suggested. It is also unclear which cardiovascular events are likely to occur in patients with renal damage. According to previous reports, coronary artery disease (CAD), including acute myocardial infarction (AMI), is the most frequent type of cardiovascular event in patients with CKD.[3–6] Furthermore, the prognosis of such patients is worse than in those without CKD.[1,2] A Japanese population study recently showed that the risk of cardiovascular events increased as renal function decreased.[7] In that study the leading etiology of the cardiovascular events was cerebral vascular accidents rather than CAD. In Asian countries, particularly in Japan, the occurrence of stroke is twice that of CAD.[8] Nonetheless, the prevalence of AMI is higher in patients with decreased renal function.[7]

In the present study, we explored the relationship between renal dysfunction and the severity of CAD by counting the number of stenotic coronary arteries in Japanese patients. Furthermore, as cardiovascular damage has been suggested to aggravate renal dysfunction,[9–11] we followed patients with CAD for 3 years to examine the influence of CAD on renal function.

Methods

For this study, data from 572 consecutive Japanese patients who underwent scheduled coronary angiography (CAG) at the University of Tokyo Hospital under the suspected diagnosis of CAD from August 1999 to February 2004 were analyzed retrospectively.

Scheduled CAG was performed using a transradial, trans-

Received September 28, 2009; accepted December 14, 2009; released online February 17, 2010 Time for primary review: 36 days
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ISSN-1346-9843 doi:10.1253/circj.CJ-09-0715

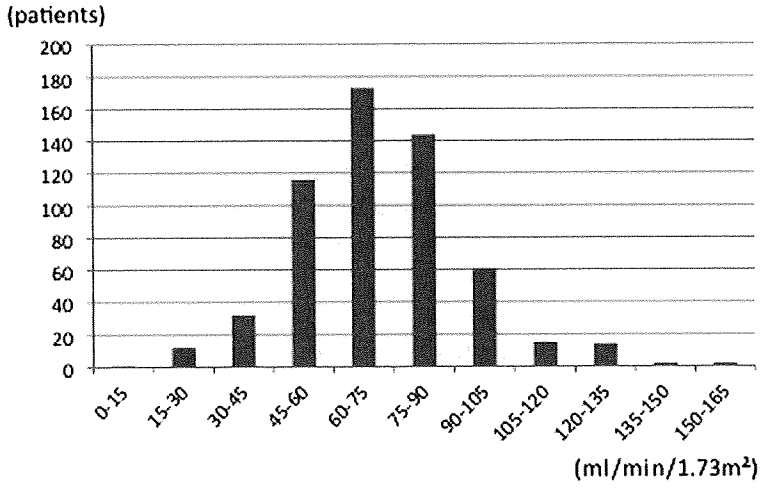

Figure 1. Distribution of the estimated glomerular filtration rate.

Table 1. Clinical Profile of the Patients in Each Renal Function Group

	Total (eGFR)	Normal (>75)	Mild reduction (60–75)	CKD (<60)	P value ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)
n	572	238	173	161	
Sex, M/F	412/160	174/64	127/46	111/50	0.589
Age (years)	66.4±0.4	63.1±0.6	67.1±0.7	70.7±0.7	<0.001
BMI	23.9±0.1	24.0±0.2	23.5±0.2	24.2±0.3	0.151
Coexisting coronary risk factors					
Hypertension, %	92.7	91.6	92.5	94.4	0.570
Diastolic BP, mmHg	77.0±12.9	77.5±13.5	77.8±13.1	75.4±11.7	0.178
Systolic BP, mmHg	135.6±20.7	134.9±20.5	135.9±20.9	136.2±20.9	0.824
Diabetes mellitus, %	36.1	37.0	35.0	36.0	0.852
Dyslipidemia, %	63.1	63.4	64.2	61.0	0.872
Smoking habit, %	61.2	61.3	62.4	60.0	0.870
No. of coronary risk factors/patient	2.53±0.04	2.54±0.06	2.54±0.07	2.52±0.07	0.967
Serum Cr, mg/dl	0.84±0.01	0.64±0.01	0.82±0.01	1.14±0.03	<0.001
eGFR, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$	72.1±0.9	91.1±1.0	68.0±0.3	48.5±0.8	<0.001
LVEF, %	66.0±12.1	66.4±12.2	66.7±12.1	64.7±11.8	0.294
Plasma BNP, pg/ml	85±205	67±142	59±92	140±328	<0.001

Data are mean±SE or percentage.
eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; Cr, creatinine; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide.

brachial or transfemoral approach. All angiographic reports were reviewed by at least 2 operators. The severity of coronary artery stenosis was assessed in the worst view projection and the percentage of luminal narrowing was recorded according to the American Heart Association criteria.[12] Luminal narrowing >51% was considered as significant stenosis. The left anterior descending, left circumflex and right coronary arteries were evaluated, and the number of stenotic arteries was recorded (0 to 3-vessel disease (VD)). A significant stenosis in the left main trunk was scored as 2VD.

Patients were admitted 1–3 days before the day CAG was to be performed. Body weight and blood pressure were measured in the morning of the day of admission. Blood samples were obtained from the antecubital vein, while the patient was supine, in the morning after an overnight fast. The plasma B-type natriuretic peptide (BNP) concentration was measured by enzymatic immunoassay,[13] and that of serum creatinine (Cr) by an enzymatic method using a standard autoanalyzer. Echocardiographic parameters were measured within 1 month after diagnostic CAG. The left ventricular (LV) dimension was measured on the long-axis view of the left ventricle taken with the patient in the left lateral position. LV ejection fraction (LVEF) was obtained by the following formula: LVEF=(LV end-diastolic volume−end-systolic volume)/LV end-diastolic volume. To evaluate cardiovascular risk factors, the numbers of smokers and patients with hypertension, diabetes mellitus or dyslipidemia were determined. Hypertension was defined as blood pressure >140/90 mmHg or use of antihypertensive agents; diabetes mellitus by fasting blood glucose ≥126 mg/dl or use of hypoglycemic agents or insulin; dyslipidemia by low-density lipoprotein cholesterol level ≥140 mg/dl, high-density lipoprotein cholesterol level ≤40 mg/dl or use of lipid lowering agents; and smoking by present or past smoking.

The patients were divided into 3 groups according to their estimated GFR (eGFR) calculated by the Modification of

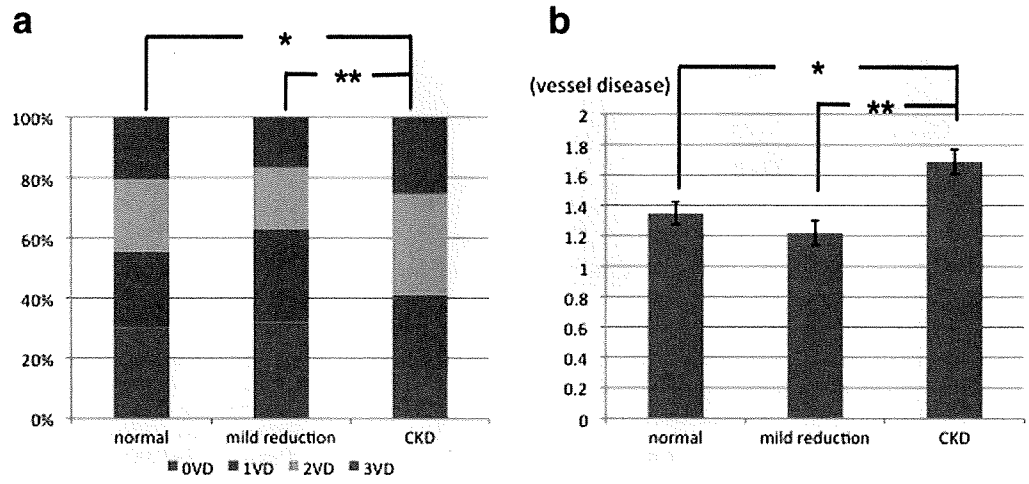

Figure 2. (a) Percentages of patients with 0 to 3-vessel disease (VD) in each group. (b) Number of stenotic coronary arteries in each group. Each column represents the mean±SE. The percentages of patients with multivessel stenosis (2VD+3VD) were significantly greater in the chronic kidney disease (CKD) group (*P<0.01, **P<0.001).

Table 2. Clinical Background of Patients Whose Renal Function Remained Unchanged (Upper Half) or Decreased (Lower Half) During Follow-up

	Total	Upper half	Lower half	P value
n	572	286	286	
Age, (years)	66.4±0.4	65.5±0.6	67.3±0.5	0.020
Sex, M/F	412/160	211/75	201/85	0.352
BMI	23.9±0.1	24.0±0.2	23.8±0.2	0.599
Coexisting coronary risk factors				
Hypertension, %	92.7	91.3	94.1	0.200
Systolic BP, mmHg	135.6±0.9	131.6±1.1	139.5±1.3	<0.001
Diastolic BP, mmHg	77.0±0.5	76.0±0.7	78.0±0.8	0.076
Diabetes mellitus, %	36.2	31.1	41.3	0.012
Dyslipidemia, %	63.1	62.2	64.0	0.665
Smoking habit, %	61.2	58.4	64.0	0.170
No. of coronary risk factors/patient	2.53±0.04	2.43±0.05	2.63±0.05	0.008
Baseline serum Cr, mg/dl	0.84±0.01	0.85±0.01	0.82±0.02	0.253
Serum Cr after 3 years, mg/dl	1.01±0.03	0.83±0.01	1.19±0.02	0.001
Baseline GFR, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$	72.1±0.9	69.5±1.0	74.6±1.4	0.003
GFR after 3 years, $ml \cdot min^{-1} \cdot 1.73 m^{-2}$	62.4±0.8	69.9±1.0	54.9±1.2	<0.001
Change in GFR after follow-up, %	−12.8±0.8	1.4±0.7	−27.0±0.8	<0.001
LVEF, %	66.0±0.5	66.4±0.7	65.3±0.7	0.271
Plasma BNP, pg/ml	85.1±8.6	69.3±8.5	100.1±14.7	<0.001
Administration of ACEI or ARB, %	49.8	48.9	51.7	0.358
No. of stenotic coronary arteries, VD	1.41±0.05	1.20±0.06	1.61±0.06	<0.001
No. of CAG and PCI/patient during follow-up	2.81±0.09	2.57±0.12	3.05±0.14	0.012

Data are mean±SE or percentage.
GFR, glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; VD, vessel disease; CAG, coronary angiography; PCI, percutaneous coronary intervention. Other abbreviations see in Table 1.

Diet in Renal Disease (MDRD) equation[14] with coefficients modified for Japanese patients:[15] eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$) = $194 \times Cr^{-1.094} \times age^{-0.287}$ (×0.739 if female). The normal group had an eGFR >75 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$; the mild reduction group had an eGFR between 60 and 75 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$; the CKD group had an eGFR <60 $ml \cdot min^{-1} \cdot 1.73 m^{-2}$. The patients were excluded because of unstable renal function if they had overt congestive heart failure or AMI, or were on hemodialysis.

The study was approved by the institutional ethical committee (No. 2252).

All study subjects visited hospital regularly as outpatients after discharge. eGFR was monitored for 3 years after diagnostic CAG. To evaluate the effect of contrast media admin-

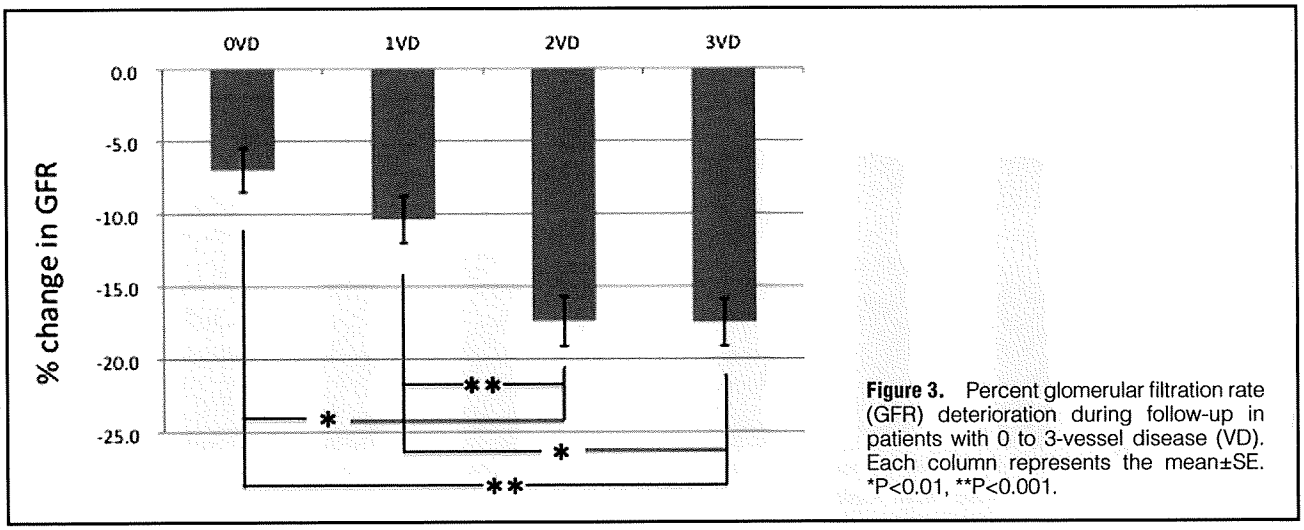

Figure 3. Percent glomerular filtration rate (GFR) deterioration during follow-up in patients with 0 to 3-vessel disease (VD). Each column represents the mean±SE. *P<0.01, **P<0.001.

Table 3. Correlation Between the Percent GFR Deterioration During Follow-up and Clinical Parameters

	Univariate analysis		Multivariate analysis (r^2=0.1417)		
	r^2	P value	β	F value	P value
Age	0.0031	0.1828	0.0739	1.5479	0.1223
Sex	0.0041	0.1244	–	–	–
BMI	0.0001	0.8558	–	–	–
Coexisting coronary risk factors					
Hypertension	0.0001	0.7903	–0.0539	–1.2641	0.2068
Systolic BP	0.0351	<0.0001	0.1542	2.9390	0.0034
Diastolic BP	0.0069	0.0488	0.0265	0.5088	0.6111
Diabetes mellitus	0.0209	0.0005	0.0875	2.0253	0.0434
Hyperlipidemia	0.0021	0.2795	0.0395	0.9055	0.3656
Smoking habit	0.0021	0.2736	–0.0068	–0.1638	0.8700
Baseline eGFR	0.0135	0.0053	0.1812	4.0747	0.0001
LVEF	0.0045	0.1092	–0.0157	–0.3480	0.7280
Plasma BNP	0.0468	<0.0001	0.1953	4.2209	<0.0001
No. of stenotic coronary arteries	0.0399	<0.0001	0.1140	2.4282	0.0155
No. of CAG and PCI/patient during follow-up	0.0118	0.0094	0.0379	0.8365	0.4033

Abbreviations see in Tables 1,2.

istered during CAG or percutaneous coronary intervention (PCI), the frequency of exposure of each patient to contrast media during those 3 years was recorded.

Statistical Analysis

Values are expressed as the mean±SE. Statistical analyses were performed using SPSS version 17.0 (Chicago, IL, USA). Unpaired Student's t-test was used for comparisons between 2 groups. Tukey's multiple comparison of means following ANOVA was used for comparisons among more than 2 groups. A multiple linear regression analysis of independent predictors of renal prognosis was also performed. The level of statistical significance was set at P<0.05.

Results

The baseline eGFR of the 572 patients showed a normal distribution (**Figure 1**), and the mean was 72.1±0.9 ml·min^{-1}·1.73 m^{-2} (median, 71.7; interquartile range, 58.0–84.7). There were 173 (30.2%) patients with a normal eGFR, 238 (41.6%) with a mildly reduced eGFR, and 161 (28.1%) with CKD. The clinical profile of the patients in each group is shown in **Table 1**. Although CKD patients were slightly older than those in the other groups and had decreased renal function, the prevalence of risk factors for CAD was similar among the 3 groups.

As for the severity of CAD, 151 patients (26.4%) had 1VD, 145 (25.3%) had 2VD and 123 (21.5%) had 3VD (**Figure 2a**). No significant stenotic lesions were detected in 153 (26.3%) patients. The percentages of patients with multivessel stenosis (2VD+3VD) were significantly greater in the CKD group (P<0.001). The CKD group had a significantly higher number of stenotic coronary arteries then the normal and the mild reduction groups (**Figure 2b**). Although blood pressure and LVEF did not differ significantly among the 3 groups, the CKD group had a significantly higher plasma level of BNP than the other 2 groups (**Table 1**).

At the end of the 3-year follow-up eGFR had decreased from 72.1±0.9 to 62.4±0.8 ml·min^{-1}·1.73 m^{-2} (median, 63.4; interquartile range, 50.1–73.9; P<0.001). The rate of decline was 3.2±0.2 ml·min^{-1}·1.73 m^{-2}·year^{-1} and showed a normal distribution; 79 (13.8%) patients were newly diagnosed with

CKD during the follow up. On the other hand, no CKD patient showed improvement of eGFR during the same period.

We examined the factors related to the deterioration of renal function. **Table 2** compares the clinical background of patients with unchanged renal function (ie, patients included in the upper half of the percent deterioration of eGFR) with that of patients with worsened renal dysfunction (the lower half). Age, systolic blood pressure, prevalence of diabetes mellitus, baseline eGFR, plasma BNP, number of coronary risk factors and number of CAG and PCI during follow-up per patient were found to be significantly higher in the lower half group (ie, the group showing a greater reduction of eGFR). There was no significant difference in the medications nor in the frequency of administration of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) between the 2 groups. The number of stenotic coronary arteries was significantly greater in patients with decreased renal dysfunction compared with patients with unchanged renal function. The percent eGFR deterioration during follow up was significantly higher in the patients whose diagnostic CAG revealed multivessel disease (**Figure 3**). Stepwise multiple regression analysis was performed to evaluate the independent determinants of the percent eGFR deterioration (**Table 3**) and it was found that the number of stenotic coronary arteries, systolic blood pressure, prevalence of diabetes mellitus, baseline eGFR and plasma BNP, but not the number of CAG and PCI, showed an independent and significant association with the percent eGFR deterioration during follow-up.

Discussion

The incidence of cardiovascular disease increases in patients with reduced renal function. Although the exact mechanisms by which impaired renal function relates to cardiovascular disease remain unclear, many possibilities have been suggested; for example, renal dysfunction activates the renin–angiotensin system and sympathetic nervous system, elevates blood pressure, causes anemia and vascular stiffness and calcification, and so on.[16,17] In the present study, the average number of stenotic coronary arteries was significantly bigger in the CKD group compared with the other 2 groups, which may explain at least in part the poor prognosis of CKD patients. CKD patients were older than patients in the other groups, as reported in previous studies,[1,2,16,17] and this may also have affected the severity of CAD because age has been reported to be a risk factor for CAD.[18] In addition, the CKD group had a significantly higher plasma level of BNP, even though blood pressure and LVEF did not differ among the 3 groups. This finding suggests that patients in the CKD group have a larger cardiac overload, although decreased renal clearance of BNP may explain its high plasma level.

On diagnostic CAG, 26.2% of the patients had CKD. In previous general population studies, 17.5% of subjects in the United States, and 10.3% of subjects in Japan were reported to have CKD.[1,19] Compared with those reports, the percentage of patients with CKD found in the present study was very high and may be because they already had a substantial number of coronary risk factors. Furthermore, patients in the CKD group were older than those in the other 2 groups.

During follow-up, the eGFR rate of decline was approximately $3\,ml \cdot min^{-1} \cdot 1.73\,m^{-2} \cdot year^{-1}$. Although eGFR is a function of age, 3 years is too short a period to explain this deterioration. eGFR decreases by only $0.1\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ from $60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$ if serum Cr in a patient aged 60 years is 1.0 mg/dl. It has been reported that the eGFR rate of decline is approximately $1\,ml \cdot min^{-1} \cdot 1.73\,m^{-2} \cdot year^{-1}$ in Western countries,[20] or $0.36\,ml \cdot min^{-1} \cdot 1.73\,m^{-2} \cdot year^{-1}$ in the Japanese general population.[21] Compared with previous data, the patient groups we analyzed had a very poor prognosis regarding renal function. There was no difference between the 2 groups in the usage of ACEI or ARB, which are known to have a renal protective effect. Multivariate analysis showed that the number of stenotic coronary arteries was significantly associated with the percent eGFR deterioration, whereas age, the total number of CAG and PCI during follow-up, and LVEF were not. This finding suggests that CAD can independently affect the prognosis of renal function.

It has been suggested that atherosclerosis causes renal dysfunction. Our study confirms that common mechanisms promote CAD and CKD. O'Hare et al showed that the frequency of increased Cr was significantly higher in those with a reduced ankle–brachial blood pressure index among subjects who participated in the Atherosclerosis Risk in Communities (ARIC) Study.[9] Elsayed et al[10] monitored renal function for 9.3 years on average in subjects from the ARIC Study and the Cardiovascular Health Study. In patients with cardiovascular disease, the odds ratio for worsening of renal failure was significantly high. Furthermore, in the Framingham Heart Study the new onset of renal disease was closely related to the coexistence of coronary risk factors.[11] These findings imply that the presence of atherosclerosis is a risk factor for worsening of renal dysfunction.

Prevalence of diabetes mellitus and a high systolic blood pressure also showed a significant association with reduced eGFR. It has been demonstrated that renal dysfunction worsens more rapidly in diabetic patients[22] and hypertensive patients.[23] Moreover, multivariate analysis revealed a significant relation between baseline eGFR and the rate of reduction in eGFR, which means that the reduction in eGFR in 3 years was greater in patients with a greater baseline eGFR. The reason for this cannot be clarified from the data obtained in the present study. However, it is possible that the decrease in eGFR in diabetic patients in the state of glomerular hyperfiltration may be even greater.

Another possible explanation for the worsening of renal dysfunction in patients with severe CAD is that they may be more exposed to contrast medium. Contrast medium-induced acute kidney injury (AKI) is a serious iatrogenic complication after CAG or PCI. In previous studies, contrast medium-induced AKI was reported as an increased risk of death or late cardiovascular events.[24,25] CKD, diabetes mellitus, and larger volumes of contrast medium administered in a single procedure were demonstrated to be independent risk factors for contrast medium-induced AKI.[26] There have been no reports regarding whether procedural times of CAG and PCI affect the long-term prognosis of renal dysfunction. However, in the present study contrast medium did not seem to cause the eGFR deterioration observed in the patients with multivessel CAD because the procedural times of CAG and PCI were not independent determinants. We examined the effect of the cumulative amount of contrast media administered in 3 years and did not find a significant relationship between eGFR deterioration and the amount of contrast media ($r=0.06$, NS, $n=318$). We could not collect information regarding whether any patient developed AKI after the first CAG or not. AKI itself may have an effect on the long-term prognosis of renal function.

Study Limitations

In the original definition by the K/DOQI,[27] CKD is defined

as GFR <60 ml·min^{-1}·1.73 m^{-2} or having markers of kidney damage even without GFR decrease. Proteinuria has been sometimes referred as a marker of kidney damage, and in the previous studies, proteinuria has been reported to be a possible marker predicting prognosis of renal function.[21] In the present study, we did not include proteinuria in the definition of CKD in order to concentrate on the change in GFR of the patients with CAD over the 3-year period, but this may give some weakness to our data.

There is a common tendency to refrain from catheter examinations of patients with decreased GFR because of the possibility of inducing an acute deterioration by the use of contrast media. This might have brought some bias to the present study because patients with a more severe clinical presentation tended to undergo CAG even if they had decreased GFR. However, the eGFR was normally distributed in the present study, as reported for the Japanese general population,[28] so the bias, if present, may be small.

Conclusion

Patients with CKD have more severe CAD, which may be why there is a high rate of cardiovascular events in CKD patients, that is, the so-called cardiorenal association. Moreover, patients with more severe CAD had a poor prognosis for renal function itself. CAD seemed to be an independent risk factor for worsening of renal dysfunction.

Acknowledgment

This study was supported in part by research grants from the Japan Science Technology Agency (Core Research for Evolutionary Science and Technology) to Y.H.

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