Table 3. Stepwise multiple regression analysis between percent changes in lipid parameters and age, %dWC, and %dBMI

	Women					Men				
	β	95%CI		Standardized β	*p* value	β	95%CI		Standardized β	*p* value
Model 1										
Dependent variable, %dLDL										
%dBMI	0.72	0.44	0.99	0.15	<0.001	0.86	0.62	1.10	0.16	<0.001
age						−0.08	−0.15	−0.01	−0.05	0.019
Dependent variable, %dHDL										
%dBMI	−0.23	−0.43	−0.03	−0.07	0.026	−0.70	−0.88	−0.53	−0.17	<0.001
Dependent variable, %TG										
%dBMI	2.08	1.42	2.75	0.18	<0.001	4.47	3.78	5.16	0.28	<0.001
Model 2										
Dependent variable, %dLDL										
%dWC	0.16	0.05	0.26	0.08	0.005	0.25	0.09	0.41	0.07	0.002
age						−0.11	−0.18	−0.04	−0.07	0.003
Dependent variable, %dHDL										
%dWC						−0.24	−0.36	−0.12	−0.09	<0.001
Dependent variable, %TG										
%dWC	0.33	0.06	0.60	0.07	0.015	1.12	0.64	1.60	0.10	<0.001

Model 1. Independent variables include age, %dWC, and %dBMI. For model 2, independent variables included age and %dWC. Standardized β values are the estimates resulting from analysis performed on standardized variables.

heart disease or hypertension[12]. They found that changes in WHR were associated with changes in total cholesterol and triglycerides in men; however, statistical significance was lost after controlling for changes in BMI. On the other hand, after controlling for changes in WHR, changes in BMI remained to be associated with changes in total cholesterol and triglycerides in both genders. Of note, even before controlling for changes in BMI, WC change was not found to be associated with either total cholesterol or triglycerides in women. Wing *et al.* concluded that changes in WHR may not be independently related to changes in cardiovascular risk factors. Pascale *et al.* showed that in subjects participating in a year-long weight loss program, weight loss, but not reductions in WHR, was significantly related with improvements in fasting glucose, fasting insulin, and HbA1, although the magnitude of WHR reduction was strongly related to the amount of weight lost especially in men[13].

Similar to Wing *et al.*'s study, the current study indicated certain gender differences in the association between WC change and lipid parameter change, especially in the model not controlled for BMI. As HDL-C and TG are closely related to insulin sensitivity, and thus visceral fat mass, the closer relationship of %dBMI than %dWC with %dHDL and %dTG was rather unexpected. It is possible that WC measurements may be less reliable than weight and height measurements, which reduced the predictive power of %dWC for lipid changes. The correlation between %dWC and %dBMI was relatively weak, especially in women. This finding may indicate that a loss (gain) of BMI did not necessarily result in a loss (gain) in WC over a one-year period, and that men appear to lose (or gain) weight in their abdominal area more readily than women, which was consistent with previous observations[8, 12]. The finding that %dWC did not predict lipid changes independently of %dBMI may suggest that changes in BMI might be a more reliable goal to avoid adverse lipid changes than changes in WC.

It has recently been demonstrated that measuring both general and abdominal adiposity provides a better assessment of the risk of death[14]; therefore, we cannot lessen the importance of reducing WC and thus control visceral adiposity; in this sense, whether percent changes in abdominal fat demonstrated by computed tomography will have a greater impact on serum lipid data than %dWC should be examined in future studies[15].

The current study has several potential limitations. First, individuals who, for unknown reasons, did not visit our institute in the second year were not enrolled in the current study, which may cause some bias. Second, we do not have sufficient information 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.

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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 $(WC2 - WC1)/WC1 \times 100$, $(BMI2 - BMI1)/BMI1 \times 100$, and $(BPs2 - BPs1)/BPs1 \times 100$, 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: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ ($\times$ 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: $\text{HOMA-IR} = [\text{fasting immunoreactive insulin } (\mu U/ml) \times \text{fasting plasma glucose } (mg/dl)]/405$ [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.

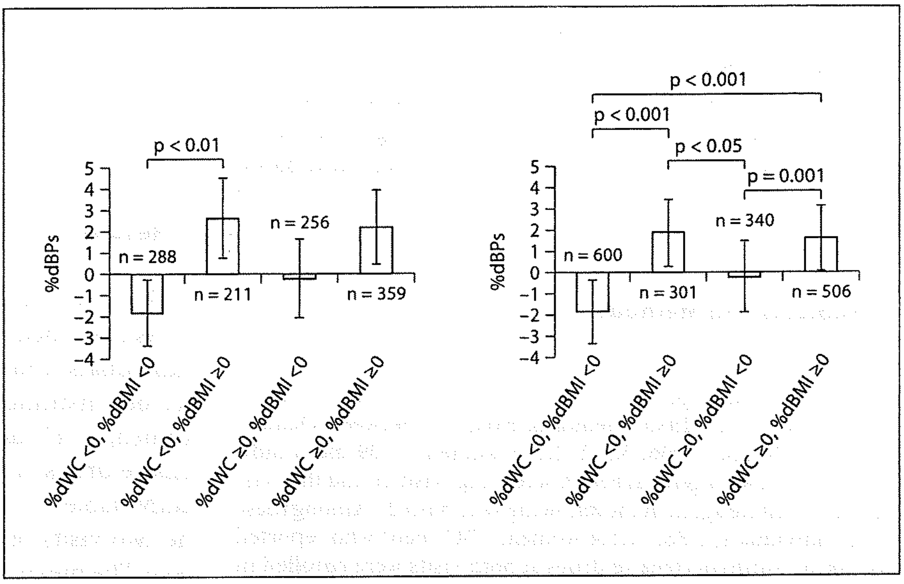

Fig. 1. Comparison of the age-adjusted %dBPs in four subgroups categorized according to the gain or loss of %dWC and %dBMI values. p values were from the result of the Tukey's post-hoc analysis following analyses of variance. Mean ± 95% confidence interval is shown in each group.

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.

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

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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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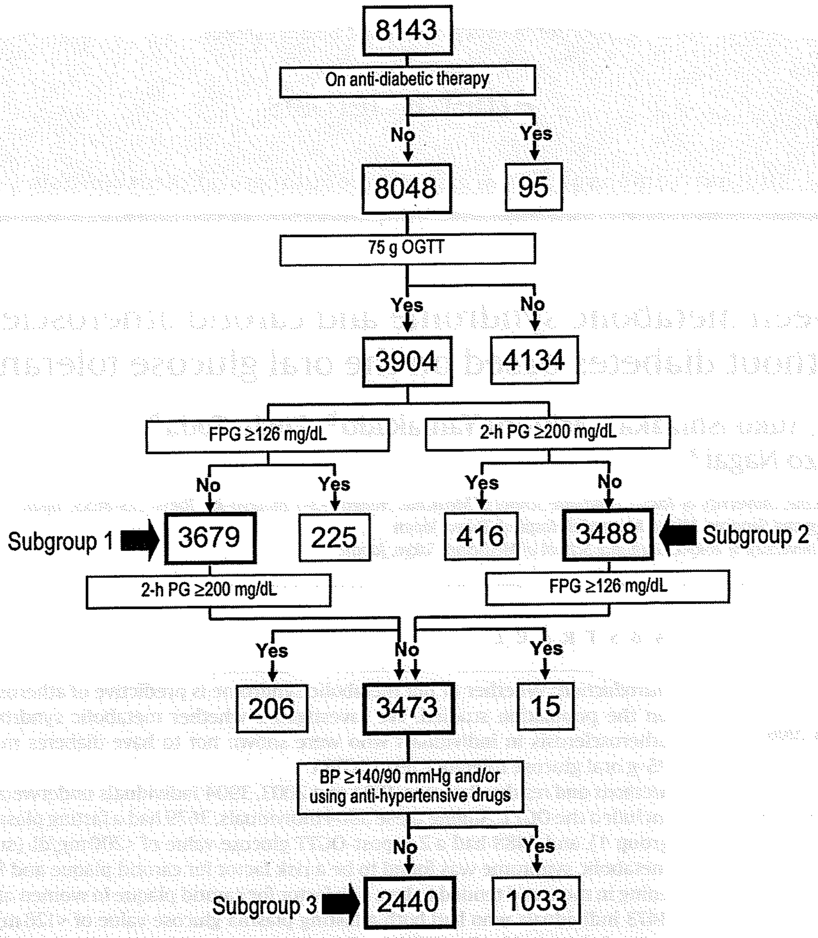

Fig. 1. Flow chart showing selection of the four subgroups.

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)

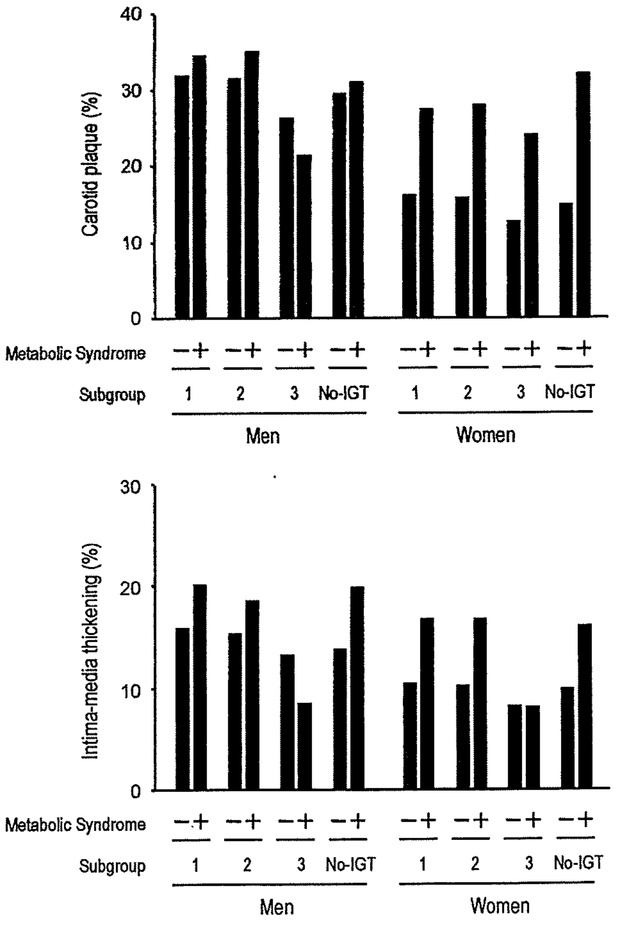

Fig. 2. Prevalence of carotid plaque and carotid intima-media thickening according to the presence or absence of metabolic syndrome in subgroups.

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 $\geq$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.

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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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Association between Changes in Obesity Parameters and Incidence of Chronic Kidney Disease in Japanese Individuals

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Key Words

Chronic kidney disease · Body mass index · Waist circumference · Health screening

Abstract

Obesity increases the risk for chronic kidney disease (CKD). By analyzing data on individuals who underwent general health screening in two consecutive years, we investigated whether changes in body mass index (BMI) or waist circumference (WC) were associated with the appearance or disappearance of the CKD components; micro-/macroalbuminuria ($\geq$30 mg urinary albumin per gram creatinine) and a low estimated glomerular filtration rate (eGFR; <60 ml/min/1.73 m^2). Logistic regression analysis showed that in men with micro-/macroalbuminuria at the first visit, a BMI reduction of $\geq$0.42 or a WC reduction of $\geq$3.0 cm over the 1-year period resulted in a significantly reduced incident of micro-/macroalbuminuria at the second visit. On the other hand, a BMI gain of $\geq$0.33 over 1 year in men without micro-/macroalbuminuria and a low eGFR at the fist visit significantly increased the incident of micro-/macroalbuminuria and a low eGFR, respectively, at the second visit. These findings indicate that lowering the obesity indexes in men with micro-/macroalbuminuria reduced the incidence of this condition at the 1-year follow-up and that, on the contrary, an increase in BMI in men without micro-/macroalbuminuria and a low eGFR at the first examination increased the risk of these conditions during the 1-year follow-up period.

Introduction

Chronic kidney disease (CKD), now recognized as a potential risk factor for cardiovascular disease as well as for end-stage renal disease [1], is a worldwide public health problem [2]. Several cross-sectional and longitudinal epidemiological studies showed that obesity may increase the prevalence and incidence of CKD [3–8] and end-stage renal disease [9], although there might be differences according to gender and ethnicity [9–11]. However, fewer studies have investigated whether changes in obesity indexes, such as body weight, body mass index (BMI), and waist circumference (WC), are associated with changes in CKD status [12–14]. In the current study, we retrospectively analyzed data on individuals who underwent general health screening at our institute for 2 consecutive years and investigated whether changes in obesity indexes were associated with changes in CKD status in these Japanese individuals.

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Subjects and Methods

Study Population

The study was approved by The Ethical Committee of Mitsui Memorial Hospital. At our institution, 3,312 (1,203 women, 2,109 men) individuals underwent general health screening including that on urinary albumin excretion between October 2005 and October 2006 (first visit) and also in the subsequent year (second visit). Among the 3,312 individuals, data on 2,861 (1,114 women, 1,747 men) who reported not taking anti-hypertensive drugs at both visits were used for the present study. The mean ± SD of the interval between the two visits of the enrolled individuals by the study subjects was 355 ± 52 days. Individuals who were taking antihypertensive medications were excluded from the analysis because certain depressor drugs may affect renal function and the extent of proteinuria [15, 16] and because the database did not include information on the class of drugs used. At the time of the health examination, recommendations may have given to overweight or obese subjects to reduce body weight. However, in analyzing data for this study, there was no intention to examine which strategies for weight control, if any, would have an impact on the status of CKD during the follow-up.

In Japan, regular health check-ups for employees are legally mandated; thus, the majority of these subjects did not have serious health problems. In addition, all or most of the costs of the screening are usually paid by the company to which they belong or by each subject. In addition, there are several courses in the heath screening program; however, which to choose is up to each individual, but not to physicians or company one belongs to. Therefore, the study population is not considered to be enriched for certain diseased condition.

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, and creatinine was determined by the enzymatic method. Plasma glucose was measured by the hexokinase method and serum insulin was measured by enzyme immunoassay.

Creatinine and urine albumin were measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) and by Accute (Toshiba Medical Systems), respectively, using commercially available kits, Accuras Auto CRE (Shino-test, Tokyo, Japan) and IATRO U-ALB by turbidimetric immunoassay (Mitsubishi Kagaku Iatron, Tokyo, Japan), respectively. Serum creatinine was calibrated using the following formula: serum creatinine (Jaffe method) = 0.2 + serum creatinine (enzyme method). Glomerular filtration rate (GFR) was estimated by equations of the simplified version of Modification of Diet in Renal Disease (MDRD) [17], where 0.881 is a coefficient for eGFR specific to the Japanese population [18]: estimated GFR (eGFR) for Japanese = $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.881 \times 0.742$ (for females). eGFR values <60 ml/min/1.73 m^2 were classified as low [19]. For the diagnosis of micro-/macroalbuminuria, spot urine samples were collected and analyzed; micro-/macroalbuminuria was defined to be present when the urinary albumin excretion ratio (UAER), expressed as milligrams per gram creatinine, was ≥30 mg/g. Normoalbuminuria, microalbuminuria, and macroalbuminuria were defined as a UAER of <30, 30–299, and ≥300 mg/g, respectively. Micro-/macroalbuminuria and a low eGFR were considered to be the components of CKD [19]. The difference in BMI and WC between the two visits was designated as ΔBMI and ΔWC, respectively.

Statistical Analysis

Skewed variables (TG, UAER) are presented as median values (interquartile range). Other data are expressed as the mean ± SD unless stated otherwise. Analyses of variance, the Mann-Whitney U test, χ^2 tests, and logistic regression analysis were conducted as appropriate to assess the statistical significance of differences between groups using computer software, Dr. SPSS II (Chicago, Ill., USA). A value of $p < 0.05$ was taken to be statistically significant.

Results

Baseline Characteristics

The mean ± SD age of the individuals enrolled was 52.0 ± 10.1 years at the first visit (table 1). Of the 88 females and 149 males with micro-/macroalbuminuria, 83 and 134, respectively, had microalbuminuria and 5 and 15, respectively, had macroalbuminuria.

Changes in BMI and WC Values between the Two Visits

The mean BMI at the second visit was slightly lower than that at the first visit ($p < 0.001$, by paired t test) in men, but did not differ significantly in women. The mean WC at the second visit was slightly larger than that at the first visit ($p < 0.001$, by paired t test) in women and smaller ($p < 0.001$, by paired t test) in men. In this study, we calculated quartiles of WC or BMI by taking into the entire population. Ranges for each quartile for ΔBMI and ΔWC are shown in table 2. About half of the subjects had a decreased WC value at the second visit. The correlation coefficient between the first-visit BMI and ΔBMI was –0.09 ($p = 0.010$) in women and –0.09 ($p = 0.002$) in men, and that between the first-visit WC and ΔWC was –0.31 in women ($p < 0.001$) and –0.28 ($p < 0.001$) in men.

Changes in the Prevalence of Micro-/ Macroalbuminuria and a Low eGFR between the Two Visits

Figure 1 shows the number of subjects with micro-/macroalbuminuria and a low eGFR at the first and second visits. Of those with micro-/macroalbuminuria at the first visit, 34% did not have micro-/macroalbuminuria at the second visit, but 4% of subjects who did not have micro-/macroalbuminuria at the first visit had de-

Table 1. Clinical characteristics and laboratory data

Variables	Women (n = 1,114)		Men (n = 1,747)	
	Visit 1	Visit 2	Visit 1	Visit 2
Age, years	51.3 ± 9.9	52.3 ± 9.9	52.5 ± 10.1	53.4 ± 10.1
Height, cm	157.1 ± 5.7	157.1 ± 7.8	169.7 ± 5.9	169.7 ± 5.9
Weight, kg	52.3 ± 7.7	52.3 ± 7.8	67.8 ± 9.2	67.6 ± 9.3
BMI	21.2 ± 2.9	21.2 ± 2.9	23.5 ± 2.7	23.5 ± 2.8
ΔBMI	–	0.0 ± 0.7	–	-0.1 ± 0.7
WC, cm	76.2 ± 8.6	76.9 ± 8.9	85.3 ± 7.5	85.0 ± 7.4
ΔWC, cm	–	0.7 ± 6.0	–	-0.3 ± 3.8
Systolic BP, mm Hg	116 ± 18	115 ± 18	124 ± 17	124 ± 18
Diastolic BP, mm Hg	72 ± 11	72 ± 11	79 ± 11	79 ± 11
Total cholesterol, mg/dl	217 ± 36	215 ± 34	210 ± 32	207 ± 31
LDL-cholesterol, mg/dl	130 ± 30	127 ± 30	128 ± 32	126 ± 31
HDL-cholesterol, mg/dl	69 ± 14	68 ± 14	56 ± 14	56 ± 13
TG, mg/dl	84 ± 46	84 ± 42	127 ± 80	126 ± 101
TG, median (interquartile range)	74 (55–99)	74 (54–101)	107 (77–152)	102 (74–144)
Uric acid, mg/dl	4.5 ± 0.9	4.5 ± 0.9	6.1 ± 1.2	6.0 ± 1.2
Fasting glucose, mg/dl	90 ± 17	91 ± 14	98 ± 21	99 ± 20
Hemoglobin A_{1C}, %	5.2 ± 0.6	5.2 ± 0.5	5.4 ± 0.8	5.5 ± 0.7
Antidiabetic medication, n (%)	5 (0.4)	9 (0.8)	46 (2.6)	58 (3.3)
Blood urea nitrogen, mg/dl	13.4 ± 3.2	13.6 ± 3.3	14.4 ± 3.5	14.5 ± 3.5
Serum creatinine, mg/dl	0.63 ± 0.09	0.62 ± 0.09	0.86 ± 0.28	0.84 ± 0.30
UAER, median (interquartile range)	7.5 (5.1–12.2)	7.9 (5.4–13.1)	5.2 (3.7–10.0)	5.6 (3.9–10.7)
UAER ≥30 mg/g Cr, n (%)	88 (7.9)	91 (8.2)	149 (8.5)	165 (9.4)
eGFR, ml/min/1.73 m^2	69.5 ± 9.3	70.1 ± 9.2	70.9 ± 10.0	71.8 ± 10.2
Low eGFR, n (%)	155 (13.9)	138 (12.4)	212 (13.1)	201 (11.5)
Current smoker	99 (8.9)	93 (8.3)	581 (33.3)	542 (31.0)

Data are means ± SD, median (interquartile range), n, or percentage. BMI = Body mass index; WC = waist circumference; BP = blood pressure; TG = triglycerides; UAER = urinary albumin excretion rate; eGFR = estimated glomerular filtration rate.

Table 2. Range for each quartile of ΔBMI and ΔWC

	Q1	Q2	Q3	Q4
ΔBMI	–5.33/–0.42 (–0.75)	–0.41/–0.04 (–0.21)	–0.04/0.32 (0.13)	0.33/3.67 (0.62)
ΔWC, cm	–21.0/–3.0 (–5.0)	–2.9/–0.1 (–1.5)	0.0/2.7 (1.0)	2.8/23.0 (5.0)

BMI = Body mass index; WC = waist circumference. Medians are given in parentheses.

veloped micro-/macroalbuminuria at the second visit (fig. 1a, b). Of individuals who had a low eGFR at the first visit, 28% did not have a low eGFR at the second visit, but alternatively, 3% of individuals who did not have a low eGFR at the first visit had a low eGFR at the second visit.

Association between Changes in BMI or WC and Albuminuric Status

Next, we investigated whether decreases in BMI and WC values were associated with changes in CKD status (fig. 2a, b). Logistic regression analysis adjusted for age, systolic blood pressure, HDL- and LDL-cholesterol, fast-

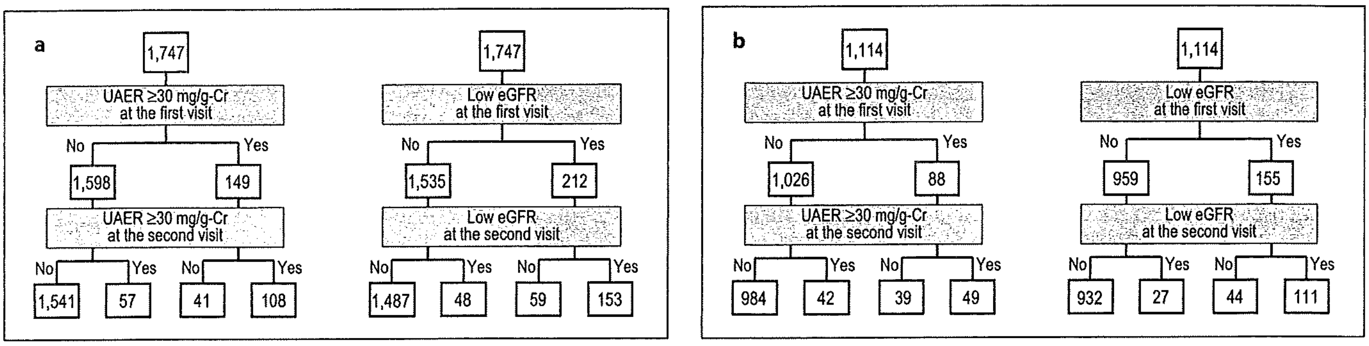

Fig. 1. Flow chart showing the number of men without micro-/macroalbuminuria or a low eGFR at the times of visit 1 and visit 2. **a** Men. **b** Women.

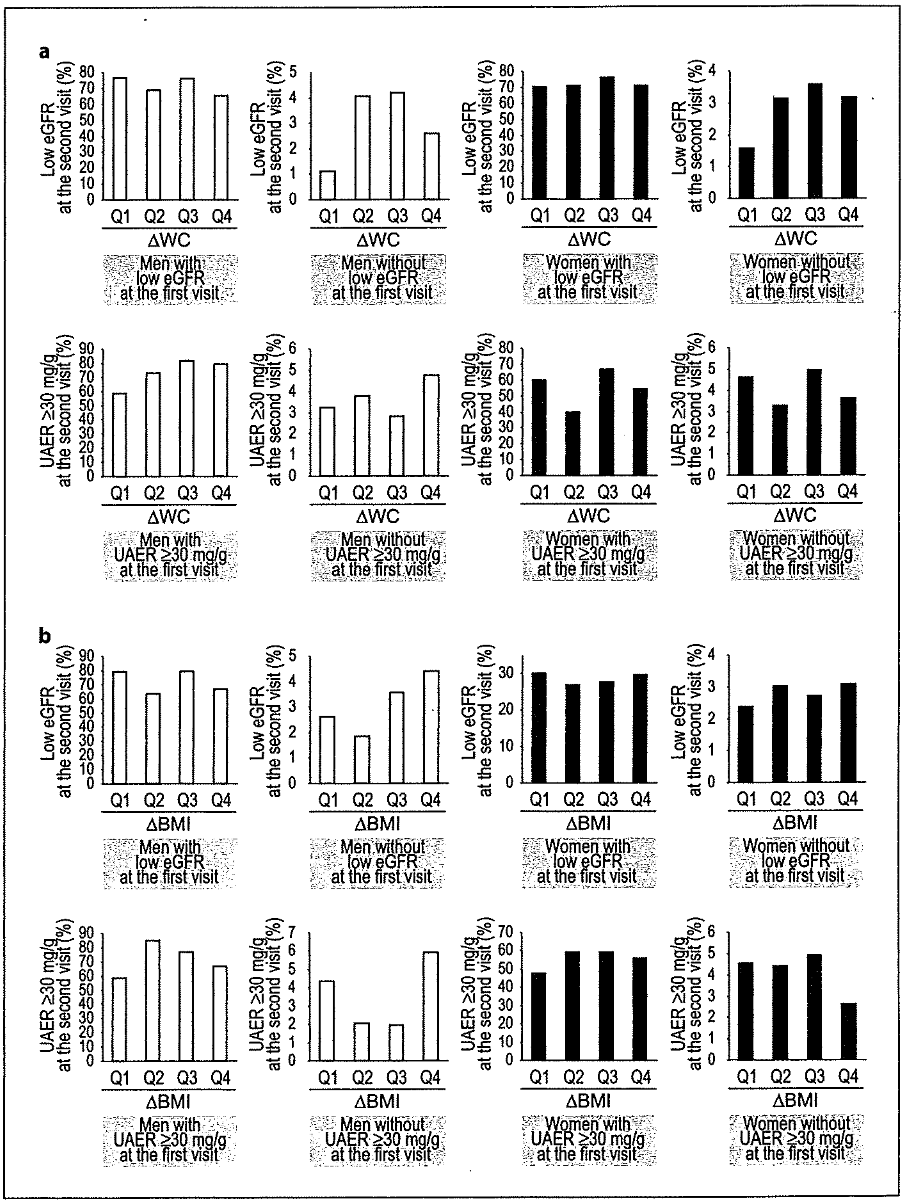

Fig. 2. Prevalence of a low eGFR and elevated levels of albuminuria at visit 2 in subjects with and without a low eGFR or micro-/macroalbuminuria at visit 1 according to quartiles of the difference in waist circumference between visit 1 and visit 2 (ΔWC) (**a**) and the difference in body mass index between the visit 1 and visit 2 (ΔBMI) (**b**).

Table 3. Logistic regression analysis with the lowest Δwaist circumference or Δbody mass index quartile as an independent variable and micro-/macroalbuminuria at the second visit as a dependent variable in individuals with micro-/macroalbuminuria at the first visit

Variables	Age adjusted		Multivariate adjusted*	
	OR (95% CI)	p value	OR (95% CI)	p value
Male (n = 149)				
ΔWC-Q2, Q3, Q4	1.00	–	1.00	–
ΔWC-Q1	0.36 (0.16–0.80)	0.012	0.31 (0.13–0.73)	0.007
Female (n = 88)				
ΔWC-Q2, Q3, Q4	1.00	–	1.00	–
ΔWC-Q1	1.20 (0.41–3.53)	0.735	1.01 (0.33–3.14)	0.987
Male (n = 149)				
ΔBMI-Q2, Q3, Q4	1.00	–	1.00	–
ΔBMI-Q1	0.37 (0.16–0.84)	0.018	0.36 (0.15–0.84)	0.018
Female (n = 88)				
ΔBMI-Q2, Q3, Q4	1.00	–	1.00	–
ΔBMI-Q1	0.51 (0.17–1.54)	0.232	0.52 (0.16–1.74)	0.289

BMI = Body mass index; WC = waist circumference.
* Multivariate adjusted: Adjusted for age, systolic blood pressure, HDL-cholesterol, LDL-cholesterol, fasting plasma glucose, and smoking status.

ing plasma glucose, and smoking status showed that, compared with the higher three ΔBMI quartiles, the lowest ΔBMI quartile (≥0.42 reduction) was associated with a significantly lower risk for micro-/macroalbuminuria at the second visit in men who had micro-/macroalbuminuria at the first visit (table 3). Similarly, compared with the higher three ΔWC quartiles, the lowest ΔWC quartile (≥3.0 cm reduction) was associated with significantly lower risk for micro-/macroalbuminuria at the second visit in men who had micro-/macroalbuminuria at the first visit. In contrast, in women, who had micro-/macroalbuminuria at the first visit, neither a ≥0.42 reduction in BMI nor a ≥3.0-cm reduction in WC significantly reduced the prevalence of micro-/macroalbuminuria at the second visit. Compared with the lower three ΔBMI quartiles, the highest ΔBMI quartile (≥0.33 gain) was associated with a significantly higher risk for micro-/macroalbuminuria at the second visit in men who did not have micro-/macroalbuminuria at the first visit (table 4).

Association between Changes in BMI or WC and a Low eGFR Status

Compared with the lower three quartiles, the highest ΔBMI quartile (≥0.33 gain) was associated with a significantly higher risk for a low eGFR at the second visit in men who did not have a low eGFR at the first visit (tables 5–6). The lowest quartile of either ΔBMI or ΔWC was not associated with reduced risk for a low eGFR at the second visit in those who had a low eGFR at the first visit in either gender.

Discussion

In the current study, we demonstrated that a WC reduction of ≥2.8 cm or a BMI reduction of ≥0.42 over a period of one year in men with micro-/macroalbuminuria at the first visit significantly reduced the risk for micro-/macroalbuminuria at the second visit (OR 0.31, 95% CI 0.13–0.73 and OR 0.36, 95% CI 0.15–0.84, respectively), after multivariate adjustment. On the other hand, a BMI gain of ≥0.33 over one year in men without micro-/macroalbuminuria or a low eGFR at the first visit significantly increased the risk at these conditions at the second visit (OR 2.50, 95% CI 1.44–4.37 and OR 1.94, 95% CI 1.04–3.61, respectively). Neither of these associations reached statistical significance in women. These data collectively suggest that the albuminuric status may be altered when men with micro-/macroalbuminuria have a substantial decrease in WC or BMI, and, in reverse, the

Table 4. Logistic regression analysis with the highest Δwaist circumference or Δbody mass index quartile as an independent variable and micro-/macroalbuminuria at the second visit as a dependent variable in individuals without micro-/macroalbuminuria at the first visit

Variables	Age adjusted		Multivariate adjusted*	
	OR (95% CI)	p value	OR (95% CI)	p value
Male (n = 1,598)				
ΔWC-Q1, Q2, Q3	1.00	–	1.00	–
ΔWC-Q4	1.52 (0.83–2.78)	0.177	1.62 (0.88–2.99)	0.120
Female (n = 1,026)				
ΔWC-Q1, Q2, Q3	1.00	–	1.00	–
ΔWC-Q4	0.87 (0.44–1.69)	0.674	0.87 (0.44–1.70)	0.677
Male (n = 1,598)				
ΔBMI-Q1, Q2, Q3	1.00	–	1.00	–
ΔBMI-Q4	2.41 (1.39–4.19)	0.002	2.50 (1.44–4.37)	0.001
Female (n = 1,026)				
ΔBMI-Q1, Q2, Q3	1.00	–	1.00	–
ΔBMI-Q4	0.57 (0.25–1.31)	0.185	0.60 (0.26–1.37)	0.221

BMI = Body mass index; WC = waist circumference.

* Multivariate adjusted: Adjusted for age, systolic blood pressure, HDL-cholesterol, LDL-cholesterol, fasting plasma glucose, and smoking status.

Table 5. Logistic regression analysis with the lowest Δwaist circumference or Δbody mass index quartile as an independent variable and a low eGFR at the second visit as a dependent variable in individuals with a low eGFR at the first visit

Variables	Age adjusted		Multivariate adjusted*	
	OR (95% CI)	p value	OR (95% CI)	p value
Male (n = 212)				
ΔWC-Q2, Q3, Q4	1.00	–	1.00	–
ΔWC-Q1	1.39 (0.68–2.88)	0.369	1.33 (0.63–2.80)	0.454
Female (n = 155)				
ΔWC-Q2, Q3, Q4	1.00	–	1.00	–
ΔWC-Q1	0.84 (0.38–1.85)	0.664	0.90 (0.39–2.08)	0.808
Male (n = 212)				
ΔBMI-Q2, Q3, Q4	1.00	–	1.00	–
ΔBMI-Q1	1.60 (0.80–3.23)	0.185	1.49 (0.73–3.04)	0.276
Female (n = 155)				
ΔBMI-Q2, Q3, Q4	1.00	–	1.00	–
ΔBMI-Q1	0.73 (0.30–1.81)	0.500	0.91 (0.34–2.38)	0.833

BMI = Body mass index; WC = waist circumference.

* Multivariate adjusted: Adjusted for age, systolic blood pressure, HDL-cholesterol, LDL-cholesterol, fasting plasma glucose, and smoking status.