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Changes in Waist Circumference and Body Mass Index in Relation to Changes in Serum Uric Acid in Japanese Individuals

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ABSTRACT. ***Objective.*** Studies have shown that obesity is associated with an increase in serum uric acid; and few data are available on the relationship between changes in measures of obesity and changes in uric acid concentrations. We investigated the relationship among percentage changes in waist circumference (%dWC), body mass index (%dBMI), and serum uric acid (%dUA).

Methods. The data of 3153 individuals [1968 men, 1185 women (536 premenopausal, 649 postmenopausal)] who underwent general health screening over a 2-year period and were not taking antihyperuricemic medication were analyzed.

Results. Stepwise multiple regression analysis showed that %dBMI was associated positively with %dUA in postmenopausal women and men, and the association retained statistical significance after adjustment for changes in blood pressure and in renal function. Association between %dBMI and %dUA was not significant in premenopausal women. In men, %dWC was a predicting factor for %dUA, although it did not remain significant when %dBMI was used as a covariate in the statistical model. Multivariate logistic regression analysis showed that the odds ratio of the association between the lowest %dBMI quartile (%dBMI < −1.86) and the lowest %dUA quartile (%dUA < −7.41) was 2.04 (95% CI 1.35–3.07) in postmenopausal women and 1.46 (95% CI 1.14–1.86) in men.

Conclusion. Weight loss may represent an effective nonmedical strategy for reducing serum UA levels, especially in postmenopausal women and men. (J Rheumatol First Release Dec 23 2009; doi:10.3899/jrheum.090736)

Key Indexing Terms:
WAIST CIRCUMFERENCE BODY MASS INDEX URIC ACID
GLOMERULAR FILTRATION RATE BLOOD PRESSURE

Obesity and serum uric acid (UA) are both associated with enhanced insulin resistance and incidence of metabolic syndrome[1-3]. In addition, measures of obesity have been reported to be positively associated with serum levels of UA[4,5], an association that may be caused by impaired renal clearance of UA in the condition of obesity[6]. The finding that a reduction in weight, and thus in body mass index (BMI), may have a significant effect on serum UA[7] and renal urate excretion[6] suggests that changes in weight may play a role in the regulation of serum UA levels, although the reverse scenario might also be possible[8]. In our study, by analyzing individuals who underwent general health screening, we examined the influence of changes in waist circumference (WC) and BMI on changes in UA, and the dependency/independency on changes in either blood pressure or renal function, which is the possible critical factor affecting serum UA levels in healthy subjects[9].

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MATERIALS AND METHODS

Study population. The study was approved by The Ethical Committee of Mitsui Memorial Hospital. Between October 2005 and October 2006, 11,558 individuals underwent general health screening at our institute. Of these, 3326 individuals (2113 men, 1213 women) underwent general health screening during this period (first visit) and again the following year (second visit). Among these 3326 individuals, 3179 (1968 men, 1211 women) reported taking no antihyperuricemic drugs at either visit. Among the 1211 women, 1185 (98%) answered the questionnaire concerning whether they still had menstruation, and were enrolled for study. Therefore, we analyzed data of 3153 individuals (1968 men, 1185 women). The mean ± standard deviation (SD) interval between the 2 visits of the individuals enrolled was

356.2 ± 51.7 days. WC, BMI, UA, systolic blood pressure, and estimated glomerular filtration rate (eGFR) at the first visit were designated WC1, BMI1, UA1, BPs1, and eGFR1, respectively, and at the second visit WC2, BMI2, UA2, BPs2, and eGFR2.

The percentage differences between values of WC1 and WC2, BMI1 and BMI2, UA1 and UA2, BPs1 and BPs2, and eGFR1 and eGFR2 were designated %dWC, %dBMI, %dUA, %dBPs, and %deGFR. All participants were seen after an overnight fast. Height and weight were determined, and BMI was expressed as weight (kilograms) divided by the square of height (meters). With the subject standing, waist circumference was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians[10].

Laboratory analysis. Blood samples were taken after an overnight fast. Serum levels of low density lipoprotein (LDL), high density lipoprotein (HDL) cholesterol, and triglycerides were determined enzymatically. Serum UA was measured by the uricase-peroxidase method, and hemoglobin A_{1C} by latex agglutination immunoassay. Creatinine was measured by TBA-200FR (Toshiba Medical Systems, Tochigi, Japan) using a commercial kit. Accuras Auto CRE (Shino-test, Tokyo, Japan) eGFR was calculated by the equation: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ (× 0.739 if female)[11]. This equation was recently determined by a multicenter study, and differs from the equation[12] that we used in previous studies[13-15]. Blood pressure was measured after about 10 min of rest with an automated sphygmomanometer.

Statistical analysis. Data are expressed as the mean ± SD unless stated otherwise. Analyses of variance with trend analysis and stepwise multiple regression analysis were conducted as appropriate to assess the statistical significance of differences between groups using SPSS II (SPSS Inc., Chicago, IL, USA). A value of $p < 0.05$ was taken to be statistically significant.

RESULTS

Baseline characteristics. We enrolled 536 premenopausal women, 649 postmenopausal women, and 1968 men for study. At the first visit the mean age of premenopausal women was 43.1 ± 5.51 years, postmenopausal women 59.1 ± 6.8 years, and men 53.3 ± 10.2 years. The sex-nonspecific range of the first to the fourth %dUA quartiles (maximum/minimum) was –47.2/–7.5, –7.4/–1.2, 0.0/7.1, and 7.2/77.8 (Table 1). A plot of WC1 and BMI1 compared to UA1 is shown in Figure 1. In both men and women, there was a statistically significant correlation between WC1 or BMI1 and UA1. The correlation coefficient between WC1 and BMI1 was 0.626 ($p < 0.001$) in premenopausal women, 0.563 ($p < 0.001$) in postmenopausal women, and 0.838 ($p < 0.001$) in men.

Relationship between %dWC, %dBMI, and %dUA. The relationship between %dBMI and %dUA, although very weak, was significant in postmenopausal women and men, and the relationship between %dWC and %dUA was significant only in men (Figure 2). In premenopausal women, the relationships between %dWC and %dUA and between %dBMI and %dUA were not statistically significant. The correlation coefficient between %dWC and %dBMI was 0.267 ($p < 0.001$) in premenopausal women, 0.221 ($p < 0.001$) in postmenopausal women, and 0.484 ($p < 0.001$) in men.

We next performed stepwise multiple regression analysis (Table 2). In a model in which age, UA1, WC1, and %dWC were used as independent variables (model 1), %dWC was found to have independent predictive value for %dUA in men, but not in women. However, after adding BMI1 and %dBMI as independent variables, %dWC in men was no longer a predictor for %dUA (model 2). %dBMI was found to be a predictor for %dUA in postmenopausal women and men even after using either or both %dBPs and %deGFR as independent variables (models 3-5). On the other hand, in premenopausal women, %dBMI was not a significant predictor value for %dUA in any of these models. In addition, in a model in which age, UA1, BMI1, and %dBMI were used as independent variables, %dBMI again was not found to have significant predictive value for %dUA (data not shown). In model 5, variance inflation factor (VIF) scores of all the independent variables were less than 10 (data not shown).

Logistic regression analysis. When the highest %dUA quartile (%dUA ≥ 7.25) was used as a dependent variable, logistic regression analysis showed that the highest %dBMI quartile (%dBMI ≥ 1.47) had a significant positive association in postmenopausal women and in men after adjusting for UA1 and BMI1 (Table 3, model 1). In these groups, statistical significance was retained even after further adjustment for %dBPs and %deGFR (model 2). On the other hand, in premenopausal women, the highest %dBMI quartile was, unexpectedly, negatively associated with the highest %dUA quartile, although statistical significance was lost after further adjustment for %dBPs and %deGFR. In all 3 subgroups tested, %deGFR was negatively associated with the highest quartile of %dUA.

Logistic regression analysis showed that the lowest %dBMI quartile (%dBMI < –1.86) had a significant positive association with the lowest %dUA quartile (%dUA < –7.41) in postmenopausal women and men, and this remained statistically significant even after further adjustment for %dBPs and %deGFR (model 2). But in premenopausal women, association between the lowest %dBMI quartile and lowest %UA was not statistically significant regardless of this further adjustment.

DISCUSSION

Analyzing data of individuals who underwent general heath screening and who were taking no antihyperuricemic medication, we found that correlation between percentage changes in BMI (%dBMI) and in UA (%dUA) was statistically significant in postmenopausal women and in men, but not in premenopausal women.

Stepwise multiple regression analysis showed that %dWC is a significant independent variable for %dUA in men, where UA1, WC1, and %dWC was used as possible independent variables (model 1); however, the relationship lost statistical significance after further adjustment for BMI1 and %dBMI (Table 3). %dWC was not found to be a

Table 1. Baseline characteristics at the first visit according to %dUA quartiles.

Variables	Total, n	% dUA Quartile First (range –47.2/–7.5)	Second (range –7.4/–1.2)	Third (range 0.0/7.1)	Fourth (range 7.2/77.8)	p for Trend
Women/men	1185/1968	290/496	252/483	327/514	316/475	
Baseline data at visit 1						
Age, yrs	52.8 ± 10.2	52.6 ± 10.6	53.3 ± 10.1	52.9 ± 10.0	52.3 ± 10.2	0.225
Waist circumference, cm	82.3 ± 9.2	82.8 ± 9.6	82.7 ± 9.1	82.2 ± 8.7	81.7 ± 9.3	0.074
Body mass index, kg/m^2	22.8 ± 3.1	23.0 ± 3.3	22.8 ± 3.0	22.8 ± 3.0	22.6 ± 3.1	0.056
Systolic blood pressure, mmHg	123 ± 19	124 ± 20	123 ± 19	122 ± 19	123 ± 19	0.636
LDL-cholesterol, mg/dl	129.1 ± 31.2	130.2 ± 31.3	129.4 ± 29.5	129.8 ± 31.3	126.9 ± 32.2	0.147
HDL-cholesterol, mg/dl	60.7 ± 15.3	60.7 ± 15.8	60.5 ± 15.5	60.8 ± 14.8	60.9 ± 15.1	0.980
Triglyceride, mg/dl	111 ± 72	112 ± 75	115 ± 81	109 ± 67	109 ± 65	0.249
Uric acid, mg/dl	5.5 ± 1.3	5.8 ± 1.5	5.7 ± 1.2	5.4 ± 1.3	5.1 ± 1.2	< 0.001
Fasting glucose, mg/dl	96 ± 21	97 ± 20	96 ± 19	95 ± 18	96 ± 25	0.486
Hemoglobin A1c, %	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.7	5.3 ± 0.9	0.941
Blood urea nitrogen, mg/dl	14.1 ± 3.5	14.6 ± 4.0	14.3 ± 3.2	14.1 ± 3.3	13.6 ± 3.5	< 0.001
Serum creatinine, mg/dl	0.77 ± 0.29	0.79 ± 0.42	0.78 ± 0.15	0.76 ± 0.15	0.75 ± 0.34	0.068
Estimated glomerular filtration rate, ml/min/1.73m^2	68.3 ± 11.8	67.3 ± 11.8	67.8 ± 11.5	68.1 ± 11.4	70.2 ± 12.4	< 0.001
Antihypertensive medication, n (%)	306 (9.7)	78 (9.9)	78 (10.6)	76 (9.0)	74 (9.4)	0.736
Antidiabetic medication, n (%)	74 (2.3)	19 (2.4)	14 (1.9)	24 (2.9)	17 (2.1)	0.632
Postmenopause (female), n (%)	649 (54.8)	152 (52.4)	141 (56.0)	194 (59.3)	162 (51.3)	0.165
Current smoker, n (%)	734 (23.3)	180 (22.9)	173 (23.5)	197 (23.4)	184 (23.3)	0.992
Percent change between 2 visits						
%dBMI	–0.28 ± 3.1	–0.70 ± 3.41	–0.46 ± 3.06	0.01 ± 2.88	–0.03 ± 2.98	< 0.001
%dWC	0.17 ± 6.12	–0.02 ± 6.33	–0.35 ± 6.14	0.64 ± 6.14	0.35 ± 5.83	0.008
%deGFR	1.8 ± 10.0	6.3 ± 10.0	2.6 ± 9.0	0.9 ± 9.1	–2.5 ± 10.0	< 0.001

predictive value for %dUA in premenopausal or postmenopausal women. By contrast, %dBMI was found to be a predictor for %dUA, even after adjustment for WC1, %dWC, %dBPs, and %deGFR in postmenopausal women and men, although it was not significant in premenopausal women. In premenopausal women, %dBMI was not a significant predictive value for %dUA in the model in which age, UA1, BMI1, and %dBMI were used as independent variables; therefore, failure of %dBMI as a predictor for %dUA in premenopausal women may not fully be explained by the multicollinearity between %dWC and %dBMI. These findings collectively indicate that mode of association between change in BMI and change in UA differs between premenopausal and postmenopausal women.

There are several previous studies in which changes in obesity measures have been analyzed in relation to the changes in UA over a certain period of time. For example, Heyden, *et al* showed that there was a stepwise progression from decreased UA levels associated with maximum weight loss to increased levels with maximum weight gain[16]. In addition, Rathmann, *et al*[7] analyzed the data of 1249 male and 1362 female subjects aged 17–35 years from the Coronary Artery Risk Development in Young Adults (CARDIA) Study who attended a 10-year followup. They reported that changes in BMI and WC were associated with changes in UA in a statistical model adjusted for age and baseline UA levels[7]. In contrast, we found that %dBMI was, but %dWC was not, significantly associated with %dUA in multiple linear regression (Table 2, models 2-5). This might be because statistical significance had been weakened after %dWC and %dBMI were simultaneously included into the statistical model; however, %dWC was not significantly associated with %dUA in women even before the adjustment for %dBMI (model 1). From our epidemiological study, we cannot determine what would have caused the different observations between the findings of Rathmann, *et al*[7] and our own. However, considering that circulating insulin levels may have potential to regulate serum UA levels[17], the difference might derive from the difference in insulin sensitivity[18,19] and/or difference in the effect of obesity on insulin resistance[20] among various ethnicities. This possibility should be investigated in future studies. Choe, *et al* found that mean changes in BMI, but not in WC, were statistically different between subjects who had decreased or had no change in UA and those with increased UA during a 1-year followup in men who underwent health promotion screening[9]. They also found that changes in serum creatinine levels, but not in systolic or diastolic blood pressure, were significantly different between subjects who had decreased or unchanged UA levels and those with increased UA[9] — a finding that is, in one sense, in agreement with our observations.

What would be the possible underlying mechanisms that explain the difference in the mode of association between

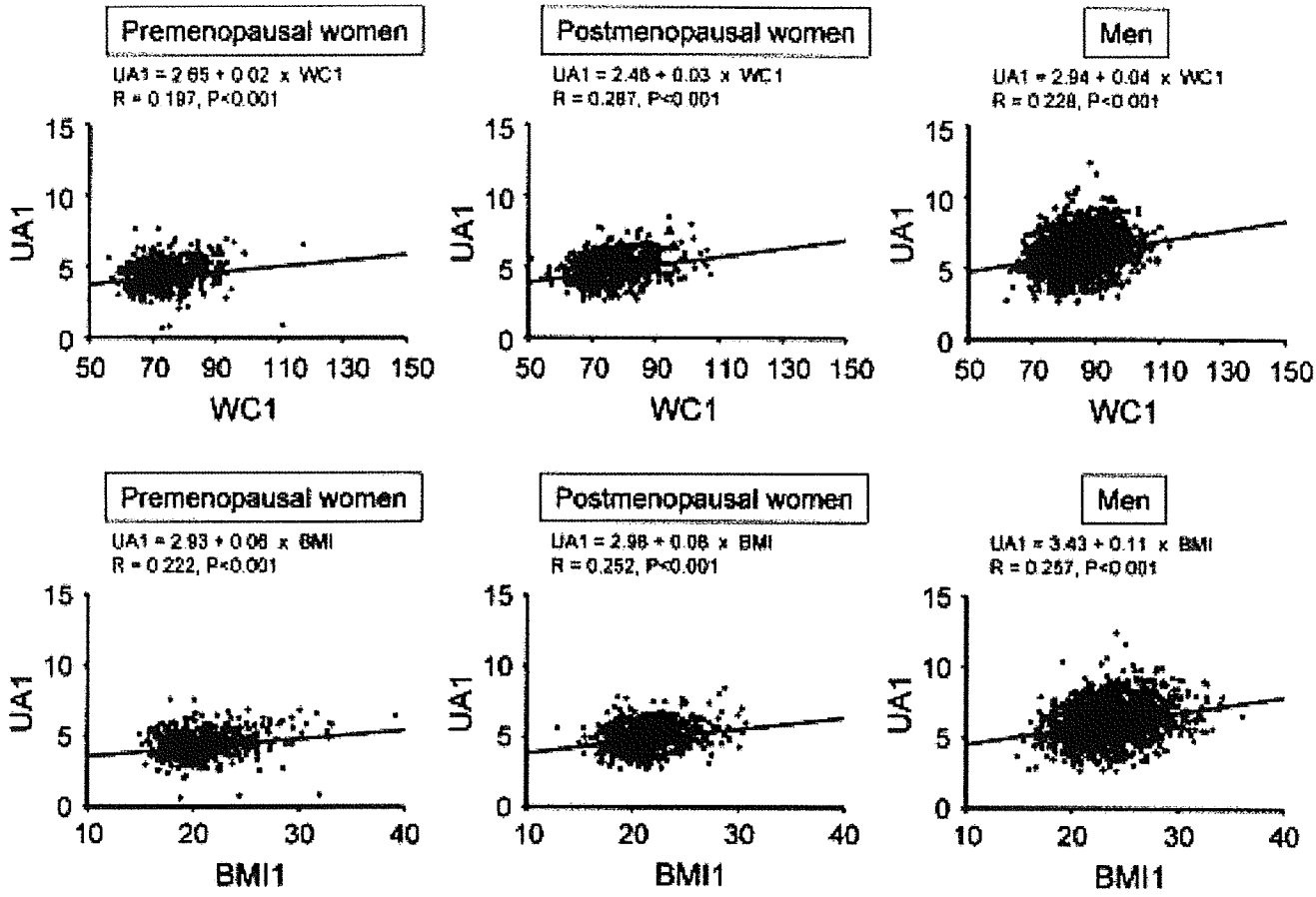

Figure 1. Scatterplot and linear regression between waist circumference at the first visit (WC1) and uric acid at the first visit (UA1) and those between body mass index at the first visit (BMI1) and UA1 in premenopausal and postmenopausal women and in men. Serum uric acid values were not adjusted for age or other possible confounders.

%dBMI and %dUA between premenopausal and postmenopausal women? It has been reported that certain alterations in UA metabolism may occur after the menopause; menopause leads to an increase in serum UA levels[21,22], and this may be in part attributed to decreased estrogen production and subsequent reduction of the fractional excretion of UA[23]. In addition, a recent study suggested that association between insulin resistance and serum UA levels may be greater in postmenopausal women than premenopausal women[24]. Whether these phenomena are related to the difference in the mode of association between %dBMI and %dUA of premenopausal and postmenopausal women remains to be investigated.

We previously showed that obesity or overweight was significantly associated with chronic kidney disease[14], and that changes in obesity measures may be associated with changes in eGFR and urinary excretion of albumin[25]. The strength of the current study was that we demonstrate that change in BMI was positively associated with change in UA in postmenopausal women and men independent of change in eGFR. In addition, we show that mode of association between %dBMI and %dUA was different between premenopausal and postmenopausal women, which may have relation with the fact that menopause causes the elevation of serum UA[21,22,26]. However, controlling BMI is neither unnecessary nor ineffective in keeping the metabolic measures in optimal ranges in "premenopausal" women, because weight gain may result in the reduced insulin sensitivity and aggravation of cardiovascular risk also in premenopausal women[27].

Data for visceral fat volume measured by computed tomography were not available in our study. Recent reports showed that subcutaneous fat accumulation is related to impaired urinary UA excretion[6], whereas visceral fat accumulation is linked closely to the overproduction of uric acid[28], and that serum UA levels are increased both in individuals with subcutaneous fat obesity and in those with visceral fat obesity[28]. It remains to be determined whether changes of WC will lead to an increase in urinary UA excretion in our population, and whether there is a relationship between %dUA and change in visceral fat volume.

Our study has several potential limitations. First, we had no information on the extent to which modifications of lifestyle and dietary habits affected observed changes in

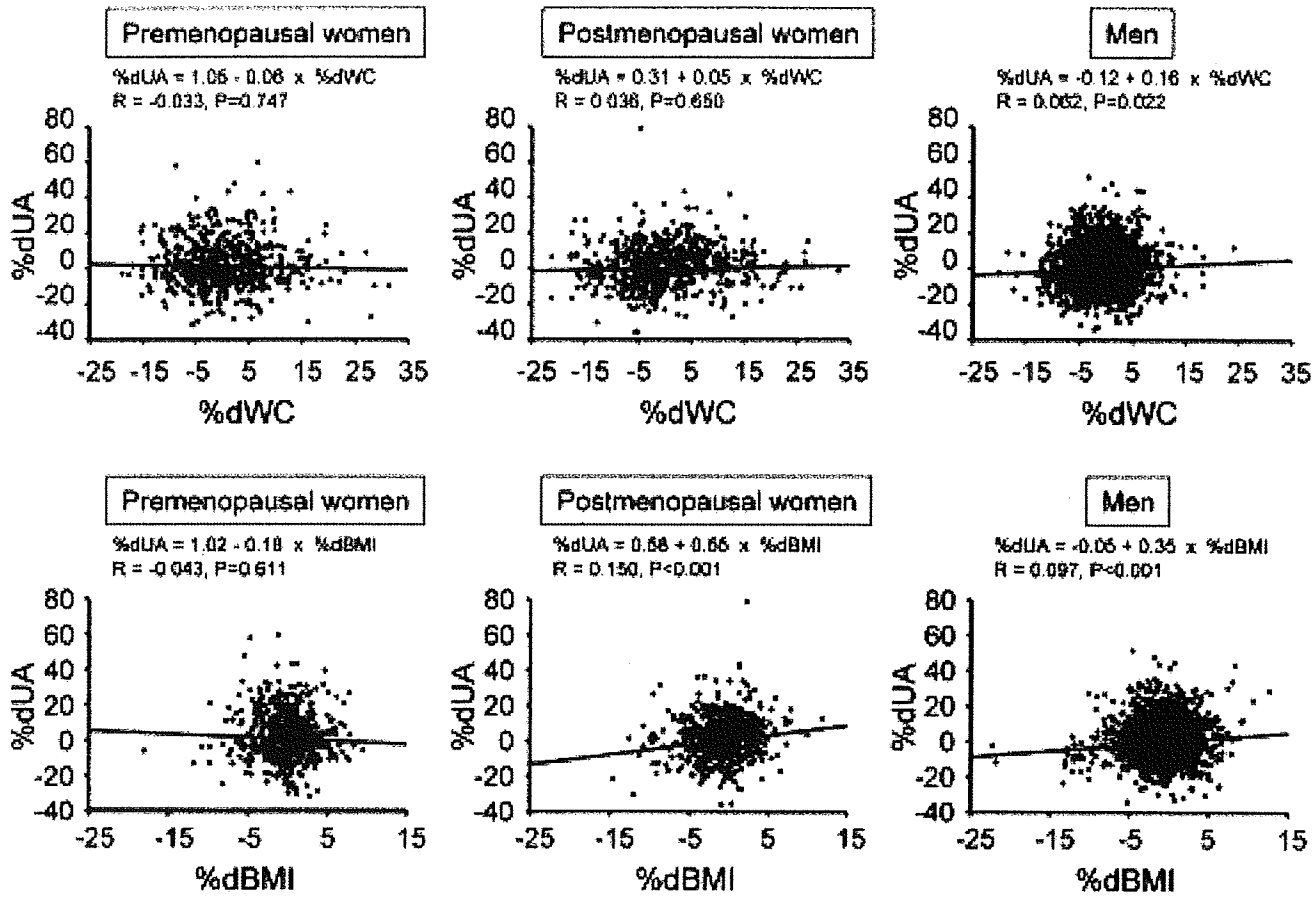

Figure 2. Scatterplot and linear regression between percentage change in waist circumference (%dWC) and percentage change in uric acid (%dUA), and those between percentage change in BMI (%dBMI) and %dUA in premenopausal and postmenopausal women and in men. Serum uric acid values were not adjusted for age or other possible confounders.

general/abdominal obesity, as no program to reduce weight was conducted by our institute. Second, we did not take into account participants' level of alcohol consumption or number of cigarettes smoked; both may affect serum UA levels[29,30]. Third, blood samples were taken from individuals in fasting condition, which may have affected their serum creatinine levels, and thus eGFR.

In summary, during a 1-year period, percentage changes in BMI (%dBMI) were associated positively with percentage changes in serum UA levels (%dUA) in postmenopausal women and men, but not in premenopausal women. This relationship was, at least in part, independent of changes in blood pressure and renal function. Weight loss may represent an effective strategy to decrease serum UA levels without use of antihyperuricemic medications, especially in postmenopausal women and men.

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Table 2. Stepwise multiple regression analysis using %dUA as the dependent variable.

	ß	(95% CI)	Standardized ß	p
Premenopausal women				
Model 1				
UA1	–4.21	(–5.42, –3.00)	–0.28	< 0.001
Model 2				
UA1	–4.21	(–5.42, –3.00)	–0.28	< 0.001
Model 3				
UA1	–4.21	(–5.42, –3.00)	–0.28	< 0.001
Model 4				
% deGFR	–0.43	(–0.53, –0.33)	–0.34	< 0.001
UA1	–3.70	(–4.84, –2.56)	–0.25	< 0.001
Model 5				
%deGFR	–0.43	(–0.53, –0.33)	–0.34	< 0.001
UA1	–3.70	(–4.84, –2.56)	–0.25	< 0.001
Postmenopausal women				
Model 1				
UA1	–3.09	(–4.05, –2.13)	–0.24	< 0.001
Model 2				
UA1	–3.04	(–4.00, –2.09)	–0.24	< 0.001
%dBMI	0.53	(0.26, 0.81)	0.14	< 0.001
Model 3				
UA1	–3.04	(–4.00, –2.09)	–0.24	< 0.001
%dBMI	0.53	(0.26, 0.81)	0.14	< 0.001
Model 4				
%deGFR	–0.33	(–0.41, –0.25)	–0.30	< 0.001
UA1	–2.83	(–3.73, –1.92)	–0.22	< 0.001
%dBMI	0.55	(0.29, 0.81)	0.15	< 0.001
Model 5				
%deGFR	–0.33	(–0.41, –0.25)	–0.30	< 0.001
UA1	–2.83	(–3.73, –1.92)	–0.22	< 0.001
%dBMI	0.55	(0.29, 0.81)	0.15	< 0.001
Men				
Model 1				
UA1	–2.51	(–2.90, –2.12)	–0.27	< 0.001
%dWC	0.14	(0.04, 0.25)	0.06	0.008
Model 2				
UA1	–2.49	(–2.88, –2.10)	–0.27	< 0.001
%dBMI	0.32	(0.17, 0.48)	0.09	< 0.001
Model 3				
UA1	–2.51	(–2.89, –2.12)	–0.27	< 0.001
%dBMI	0.38	(0.22, 0.54)	0.10	< 0.001
%dBPs	–0.06	(–0.10, –0.02)	–0.06	0.006
Model 4				
%deGFR	–0.36	(–0.40, –0.31)	–0.32	< 0.001
UA1	–2.29	(–2.66, –1.92)	–0.25	< 0.001
%dBMI	0.35	(0.21, 0.50)	0.10	< 0.001
Model 5				
%deGFR	–0.36	(–0.40, –0.31)	–0.32	< 0.001
UA1	–2.29	(–2.66, –1.92)	–0.25	< 0.001
%dBMI	0.35	(0.21, 0.50)	0.10	< 0.001

Model 1. Independent variables include age, UA1, WC1, and %dWC. Model 2. Independent variables include Model 1 + BMI1 and %dBMI. Model 3. Independent variables include Model 2 + %dBPs. Model 4. Independent variables include Model 2 + %deGFR. Model 5. Independent variables include Model 2 + %dBPs and %deGFR. UA: uric acid; BMI: body mass index; BPs: systolic blood pressure; eGFR: estimated glomerular filtration rate.

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Table 3. Logistic regression analysis using the highest or lowest %dUA quartile as the dependent variable.

	Independent Variable			
	%dUA ≥ 7.2%		%dUA < −7.5%	
	OR (95% CI)	p	OR (95% CI)	p
Premenopausal women				
Model 1				
%dBMI quartile				
First			1.19 (0.73, 1.94)	0.474
2 and 3	1 Reference			
4	0.65 (0.42, 0.99)	0.046	1.00 Reference	
Model 2				
%dBMI quartile				
First			1.41 (0.85, 2.34)	0.181
2 and 3	1.00 Reference			
4	0.71 (0.45, 1.10)	0.126	1.00 Reference	
%deGFR	0.93 (0.91, 0.95)	< 0.001	1.06 (1.04, 1.08)	< 0.001
%dBPs	0.99 (0.97, 1.01)	0.225	1.00 (0.98, 1.02)	0.804
Postmenopausal women				
Model 1				
%dBMI quartile				
First			2.04 (1.37, 3.03)	< 0.001
2 and 3	1.00 Reference			
4	1.60 (1.06, 2.41)	0.025	1.00 Reference	
Model 2				
%dBMI				
First			2.04 (1.35, 3.07)	0.001
2 and 3	1.00 Reference			
4	1.72 (1.12, 2.63)	0.013	1.00 Reference	
%deGFR	0.95 (0.93, 0.97)	< 0.001	1.05 (1.03, 1.07)	< 0.001
%dBPs	0.98 (0.97, 1.00)	0.039	1.00 (0.98, 1.01)	0.684
Men				
Model 1				
%dBMI quartile				
First			1.35 (1.07, 1.69)	0.011
2 and 3	1.00 Reference			
4	1.38 (1.08, 1.76)	0.010	1.00 Reference	
Model 2				
%dBMI quartile				
First			1.46 (1.14, 1.86)	0.002
2 and 3	1.00 Reference			
4	1.49 (1.15, 1.92)	0.002	1.00 Reference	
%deGFR	0.94 (0.92, 0.95)	< 0.001	1.07 (1.06, 1.08)	< 0.001
%dBPs	1.00 (0.99, 1.01)	0.300	1.00 (0.99, 1.01)	0.715

Model 1. Independent variables include age, UA1, BMI1, and %dBMI quartiles. Model 2. Independent variables include Model 1 + %dBPs and %deGFR. UA: uric acid; BMI: body mass index; BPs: systolic blood pressure; eGFR: estimated glomerular filtration rate.

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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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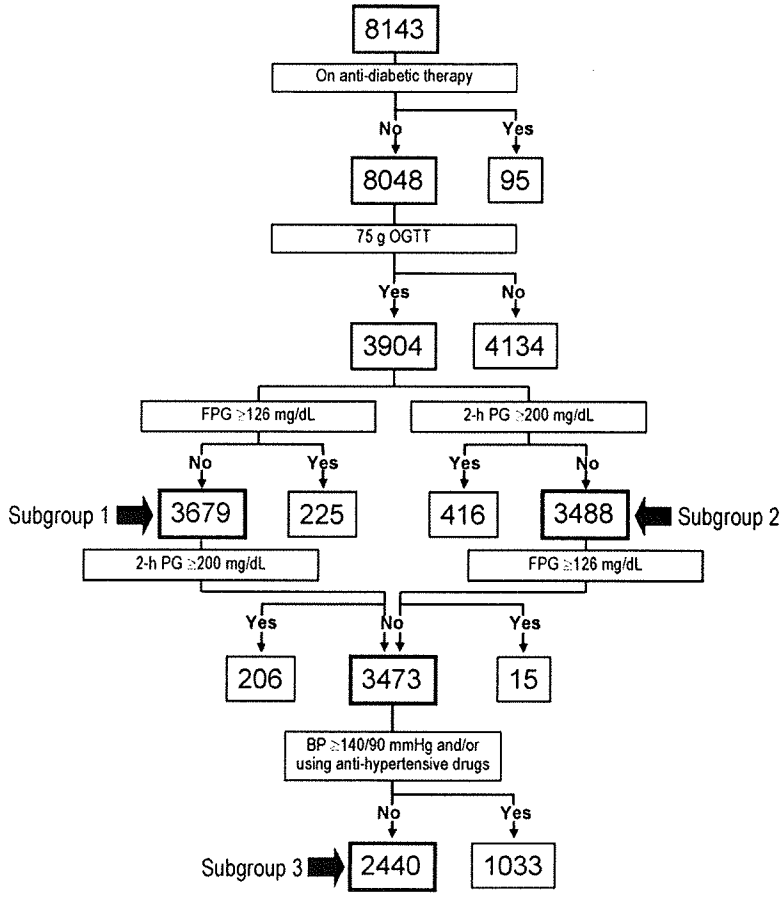

Fig. 1. Flow chart showing selection of the four subgroups.

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)

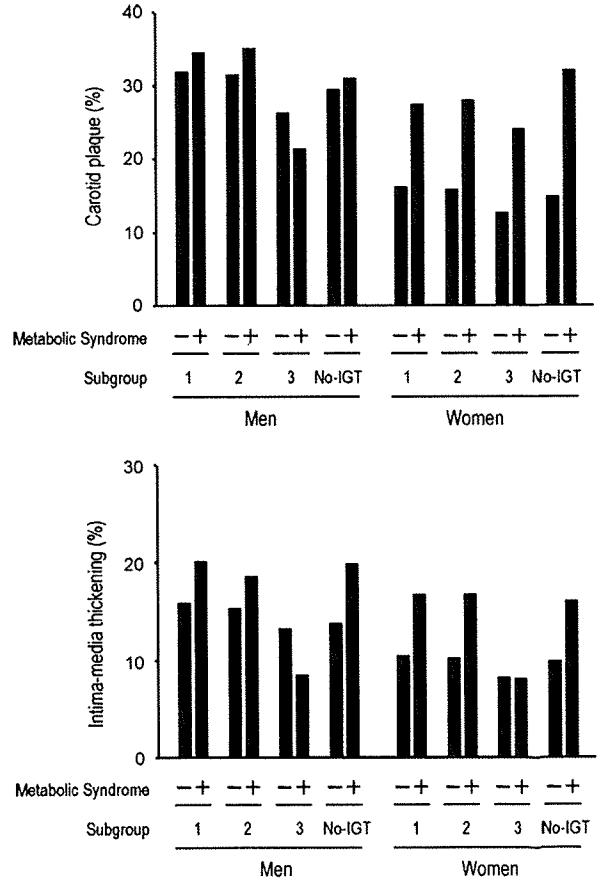

Fig. 2. Prevalence of carotid plaque and carotid intima-media thickening according to the presence or absence of metabolic syndrome in subgroups.

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 ≥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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Original Article

Impact of Changes in Waist Circumference and BMI over One-Year Period on Serum Lipid Data in Japanese Individuals

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Aim: Loss or gain in obesity indexes, such as body mass index (BMI) and waist circumference (WC), may affect serum lipid parameters. We therefore analyzed the impact of changes in WC and BMI over a one-year period on serum levels of LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), and triglycerides (TG).
Methods: We analyzed the data of 3,111 individuals who were not on lipid- lowering medication and who underwent general health screening two years running.
Results: The correlation between percent changes of WC (%dWC) and BMI (%dBMI) were both statistically significantly correlated with percent changes in LDL-C (%dLDL), HDL-C (%dHDL), and TG (%dTG) except that between %dWC and %dHDL in women. In multiple regression analysis, %dBMI, but not %dWC, was found to be an independent predictor of %dLDL, %dHDL, and %dTG. When %dBMI was excluded from the variables, %dWC was identified as an independent factor predicting %dLDL and %dTG; however, in individuals with %dBMI of ≥ 0, %dWC was not found to be a predictor of percent changes in any lipid parameters tested in this model.
Conclusion: Percent changes in BMI were found to be an independent predictor of adverse changes in lipid parameters in both genders. Although percent changes in WC (%dWC) also tended to confer adverse changes in lipid parameters, this relationship did not remain statistically significant after controlling for %dBMI. It is suggested that changes in obesity parameters are an important goal to avoid adverse lipid changes, although there might be some gender differences.

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Key words; Waist circumference, Body mass index, LDL-C, Health screening

Introduction

It is well known that obesity parameters, such as body weight, body mass index (BMI), and waist circumference (WC), may be related with values of serum lipid parameters, including low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) as well as other established cardiovascular risk factors[1, 2]. Although there are in general substantial correlations among various obesity parameters, some parameters may provide better prediction of insulin resistance than others[3, 4]. On the other hand, fewer studies have analyzed the effect of changes in obesity parameters on changes in these lipid parameters in the general population[5]. To this end, the aim of the current study was to investigate the relationship between changes in obesity parameters over a one-year period and changes in lipid parameters over the same period in Japanese individuals.

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Table 1a. Baseline Characteristics at the First Visit According to %dWC

Variables	%dWC quartiles				*p* for trend
	First (range: −21.2–−3.4)	Second (range: −3.4–−0.1)	Third (range: 0.0–3.2)	Fourth (range: 3.2–33.3)	
Women					
n	324	193	216	407	
Age, years	52.2±10.2	51.4±10.2	51.4±9.8	50.4±9.3	0.110
Height, cm	156±5	159±6	157±6	158±6	0.021
Weight, kg	51.3±7.5	53.2±8.6	53.7±8.5	52.2±6.9	0.002
WC, cm	78.9±8.5	77.9±9.4	76.8±8.5	73.5±7.9	<0.001
BMI, kg/m^2	21.0±2.9	21.6±3.3	21.7±3.2	21.0±2.7	0.003
Systolic blood pressure, mmHg	117±18	120±20	117±17	116±19	0.242
Diastolic blood pressure, mmHg	73±10	74±12	73±11	72±12	0.225
Pulse rate, bpm	64±8	64±8	64±9	63±9	0.614
LDL-cholesterol, mg/dL	129±32	130±33	129±33	123±32	0.036
HDL-cholesterol, mg/dL	70±14	68±15	68±14	69±15	0.582
riglyceride (interquartile range), mg/dL	75 (55.5–98.5)	75 (55–108)	77 (54–103)	69 (54–90)	0.040
Uric acid, mg/dL	4.6±1.0	4.5±1.0	4.6±0.9	4.4±0.9	0.156
Fasting glucose, mg/dL	89±15	92±18	92±22	90±17	0.188
Haemoglobin A1C, %	5.1±0.5	5.2±0.5	5.2±0.8	5.1±0.6	0.602
Anti-hypertensive medication, n (%)	17 (5.3)	11 (5.7)	6 (2.8)	14 (3.4)	0.306
Anti-diabetic medication, n (%)	1 (0.3)	0	1 (0.5)	4 (1.0)	0.400
Blood urea nitrogen, mg/dL	13.3±3.7	13.5±3.4	13.3±3.1	13.4±3.2	0.928
Serum creatinine, mg/dL	0.66±0.48	0.63±0.09	0.62±0.09	0.63±0.09	0.368
Current smoker, n (%)	35 (10.8)	14 (7.3)	11 (5.1)	44 (10.8)	0.056
Men					
n	453	571	574	373	
Age, years	54.3±10.2	53.2±10.0	53.5±10.5	51.8±10.1	0.008
Height, cm	170±6	169±6	169±6	169±5	0.919
Weight, kg	68.7±10.0	68.3±9.2	68.2±9.1	67.4±8.8	0.246
WC, cm	88.0±7.8	86.7±7.1	85.3±7.2	82.9±7.5	<0.001
BMI, kg/m^2	23.8±3.0	23.8±2.7	23.8±2.8	23.5±2.8	0.278
Systolic blood pressure, mmHg	129±20	128±20	126±18	122±16	<0.001
Diastolic blood pressure, mmHg	82±12	81±12	80±11	78±10	<0.001
Pulse rate, bpm	64±10	63±9	63±9	62±10	0.185
LDL-cholesterol, mg/dL	131±30	130±30	130±30	127±30	0.291
HDL-cholesterol, mg/dL	57±14	55±14	55±13	57±13	0.280
riglyceride (interquartile range), mg/dL	109 (76–154)	109 (79–157)	110 (77–160)	98 (73–143)	0.287
Uric acid, mg/dL	6.1±1.3	6.1±1.2	6.1±1.2	6.1±1.2	0.628
Fasting glucose, mg/dL	102±24	99±20	98±18	99±24	0.013
Haemoglobin A1C, %	5.5±0.8	5.4±0.8	5.3±0.7	5.4±0.9	0.022
Anti-hypertensive medication, n (%)	51 (11.3)	70 (12.6)	74 (12.9)	39 (10.5)	0.676
Anti-diabetic medication, n (%)	17 (3.8)	10 (1.8)	15 (2.6)	15 (4.0)	0.128
Blood urea nitrogen, mg/dL	14.7±4.2	14.6±3.5	14.3±3.2	14.3±3.0	0.144
Serum creatinine, mg/dL	0.87±0.52	0.85±0.13	0.86±0.13	0.84±0.11	0.429
Current smoker, n (%)	140 (30.9)	193 (33.8)	172 (30.0)	127 (34.0)	0.407

Methods

Study Population

The study was approved by the Ethics Committee of Mitsui Memorial Hospital. Between October 2005 and October 2006, 11,558 individuals underwent general health screening at our institute. Of these, 3,312 individuals (1,203 women, 2,109 men)

Table 1b. Baseline Characteristics at the First Visit According to %dBMI

Variables	%dBMI quartiles				*p* for trend
	First (range: −21.8–−1.8)	Second (range: −1.8–−0.2)	Third (range: −0.2–1.4)	Fourth (range: 1.4–15.6)	
Women					
n	267	263	290	320	
Age, years	51.9±10.1	52.7±9.9	51.2±9.2	49.6±9.9	0.001
Height, cm	156±5	156±6	158±6	158±6	0.005
Weight, kg	53.0±7.7	52.7±8.1	51.9±7.4	52.2±7.7	0.290
WC, cm	77.1±8.6	77.1±9.1	75.6±9.0	75.9±8.2	0.076
BMI, kg/m^2	21.6±3.0	21.5±3.1	20.8±2.8	21.1±3.0	0.002
Systolic blood pressure, mmHg	120±20	118±18	116±18	116±18	0.054
Diastolic blood pressure, mmHg	75±12	74±11	73±11	72±11	0.041
Pulse rate, bpm	64±9	64±8	63±9	64±9	0.171
LDL-cholesterol, mg/dL	132±37	132±30	125±29	121±31	<0.001
HDL-cholesterol, mg/dL	68±14	69±15	70±15	69±14	0.293
riglyceride (interquartile range), mg/dL	78 (58–104)	75 (56–105)	72 (53–100)	67 (51.5–91)	<0.001
Uric acid, mg/dL	4.5±1.0	4.5±0.9	4.6±0.9	4.5±1.0	0.470
Fasting glucose, mg/dL	90±17	93±27	89±13	89±12	0.038
Haemoglobin A1C, %	5.1±0.5	5.2±0.8	5.2±0.5	5.1±0.5	0.012
Anti-hypertensive medication, n (%)	11 (4.1)	13 (4.9)	12 (4.1)	12 (3.8)	0.913
Anti-diabetic medication, n (%)	0	3 (1.1)	1 (0.3)	2 (0.7)	0.315
Blood urea nitrogen, mg/dL	13.5±3.0	13.3±3.3	13.7±3.9	13.1±3.1	0.181
Serum creatinine, mg/dL	0.62±0.09	0.62±0.10	0.68±0.51	0.62±0.09	0.022
Current smoker, n (%)	19 (7.1)	22 (8.4)	23 (7.9)	40 (12.5)	0.095
Men					
n	510	515	488	458	
Age, years	54.0±10.2	54.5±10.0	53.4±10.2	51.1±10.3	<0.001
Height, cm	169±6	169±6	170±6	170±6	0.190
Weight, kg	68.7±9.7	67.5±9.0	68.8±9.5	67.7±8.8	0.050
WC, cm	87.0±7.6	85.5±7.3	86.4±7.7	84.9±7.5	0.002
BMI, kg/m^2	23.9±2.8	23.6±2.9	23.9±2.8	23.5±2.7	0.020
Systolic blood pressure, mmHg	128±19	126±19	127±18	124±18	0.004
Diastolic blood pressure, mmHg	81±12	80±12	81±11	79±11	0.010
Pulse rate, bpm	63±9	63±9	64±9	62±9	0.231
LDL-cholesterol, mg/dL	132±31	130±29	129±29	127±31	0.026
HDL-cholesterol, mg/dL	55±13	56±14	56±13	56±14	0.774
riglyceride (interquartile range), mg/dL	111 (79–158)	107 (75–158)	110 (76–153)	102 (75–148)	0.253
Uric acid, mg/dL	6.2±1.3	6.0±1.2	6.0±1.1	6.1±1.2	0.312
Fasting glucose, mg/dL	100±21	101±23	99±18	98±23	0.088
Haemoglobin A1C, %	5.5±0.8	5.4±0.8	5.3±0.7	5.4±0.8	0.049
Anti-hypertensive medication, n (%)	67 (13.1)	70 (13.6)	42 (8.6)	55 (12.0)	0.065
Anti-diabetic medication, n (%)	16 (3.1)	14 (2.7)	11 (2.3)	16 (3.5)	0.692
Blood urea nitrogen, mg/dL	14.6±4.1	14.5±3.2	14.2±3.2	14.5±3.4	0.307
Serum creatinine, mg/dL	0.88±0.50	0.86±0.13	0.84±0.12	0.85±0.13	0.245
Current smoker, n (%)	162 (31.8)	163 (31.7)	151 (30.9)	156 (34.1)	0.758

underwent general health screening during this period (first visit) and again the following year (second visit). Among these 3,312 individuals, 3,111 (1,140 women, 1,971 men) who reported not taking anti-hyperlipidemic drugs at both visits were enrolled in the present study. The mean±standard deviation (SD) of the interval between the two visits of the individuals enrolled was 355±52 days. The percent difference in

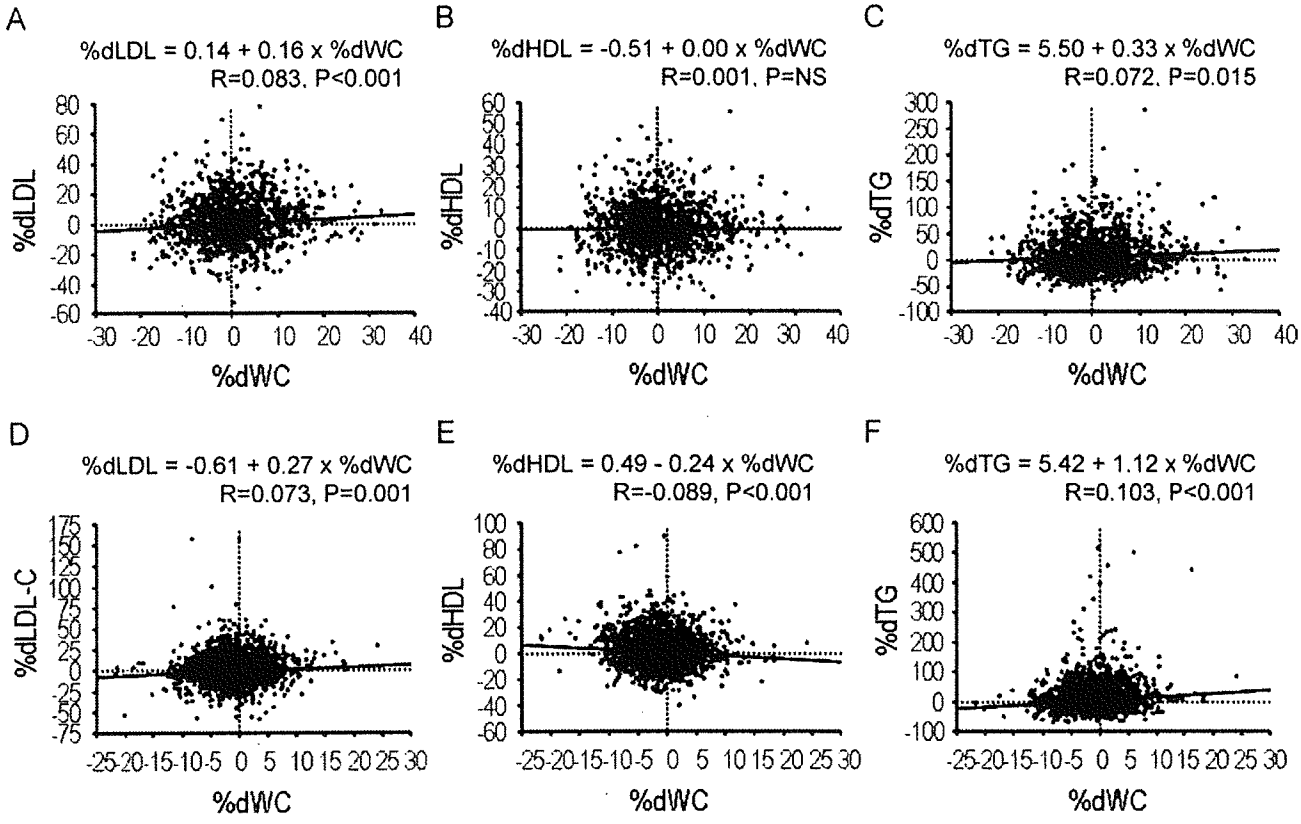

Fig. 1. Linear correlation between %dWC and %dLDL (A), %dHDL (B), and %dTG (C) in women and that between %dWC and %dLDL (D), %dHDL (E), and %dTG (F) in men.

the value of WC, BMI, serum levels of LDL-C, HDL-C, and TG between first and second visits was designated as %dWC, %dBMI, %dLDL, %dHDL, and %dTG respectively. All subjects were seen after an overnight fast. Height and weight were determined, and BMI was expressed as weight (in kilograms) divided by the square of the height (in meters). Waist circumference was measured at the umbilical level to the nearest 1 cm by trained physicians and technicians with the subject standing[6].

Laboratory Analysis

Blood samples were taken from the subjects after an overnight fast. Serum levels of TC, HDL-C, and TG were determined enzymatically. Serum uric acid was measured by the uricase-peroxidase method and hemoglobin A1C was determined using the latex agglutination immunoassay. Blood pressure was measured after about 10 min of rest using an automated sphygmomanometer.

Statistical Analysis

Data are expressed as the mean ± SD unless otherwise stated. Analyses of variance with trend analysis, linear regression analysis and stepwise multiple regression analysis were conducted as appropriate to assess the statistical significance of differences between groups using computer software, StatView ver. 5.0 (SAS Institute, NC) and Dr. SPSS II (SPSS Inc., Chicago, IL). A value of $p < 0.05$ was taken to be significant.

Results

Baseline Characteristics

The mean ± SD age of the individuals enrolled was 51.3 ± 9.8 years in women and 53.3 ± 10.2 years in men at the first visit. The sex-nonspecific ranges (min/max) was −21.2/−3.4, −3.4/−0.1, 0.0/3.2, and 3.2/33.3 for each %dWC quartile, and −21.8/−1.8, −1.8/−0.2, −0.2/1.4, and 1.4/15.6 for each %dBMI quartile. Baseline characteristics of the subjects according to %dWC quartile and %dBMI quartile are described in **Table 1a, 1b**. There was no statistically

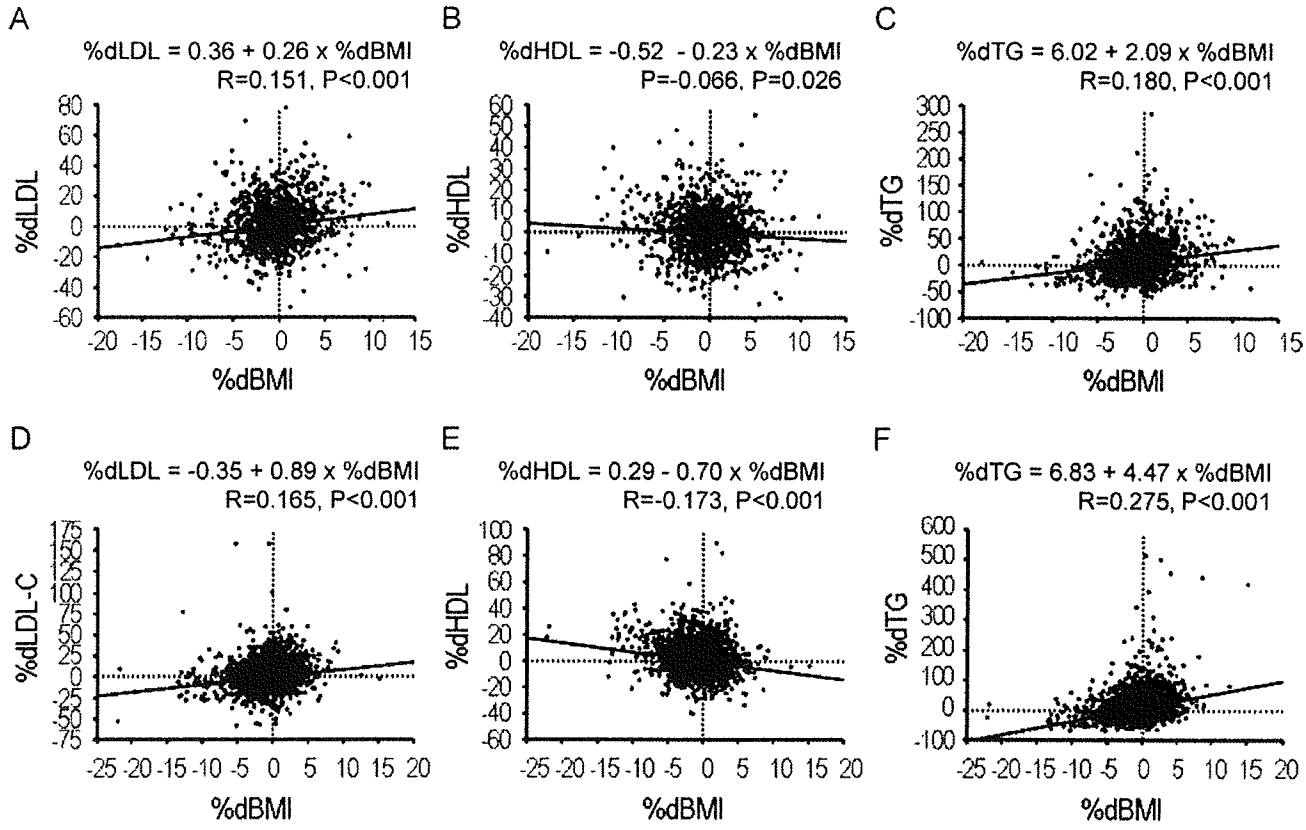

Fig. 2. Linear correlation between %dBMI and %dLDL (A), %dHDL (B), and %dTG (C) in women and that between %dBMI and %dLDL (D), %dHDL (E), and %dTG (F) in men.

significant trend in the rate of anti-hypertensive and anti-diabetic medications across four %dWC or %dBMI quartiles.

Association between Percent Changes in Obesity Parameters and Percent Changes in Lipid Parameters

Scatter plots of %dWC and percent changes in lipid parameters (**Fig. 1**) and %dBMI and percent changes in lipid parameters (**Fig. 2**) are shown. Except between %dWC and %dHDL in women, the correlation was found to be statistically significant between percent changes in obesity parameters and percent changes in lipid parameters; however, the coefficients of correlation were relatively small.

Table 2 describes the percent changes in lipid parameters by %dWC and %dBMI quartiles. In women, %dTG increased with increasing %dWC and with %dBMI. In men, %dLDL and %dTG increased and %dHDL decreased with increasing %dWC (**Table 2a**) and with %dBMI (**Table 2b**). Kappa coefficient between %dWC quartiles and %dBMI quartiles were found to be slight (women, 0.079, $p<0.001$; men, 0.171, $p<0.001$).

Stepwise Multiple Regression Analysis

The correlation coefficient between %dWC and %dBMI was 0.24 in women and 0.47 in men. The regression equation in each gender is as follows: $\%dBMI = -0.181 + 0.096 \times \%dWC$ (women), $\%dBMI = -0.287 + 0.319 \times \%dWC$ (men). We put both %dBMI and %dWC together with age into the statistical model of stepwise multiple regression analysis (**Table 3**, model 1) and it was found that %dBMI, but not %dWC, significantly predicts percent changes in all lipid parameters tested. When %dBMI was excluded from the independent variables, %dWC was identified as an independent factor predicting percent changes in lipid parameters, except for %dHDL in women (**Table 3**, model 2). In women or men with %dBMI of ≥ 0 (580 women, 890 men), %dWC was not found to be a predictor of percent changes in any lipid parameters tested (data not shown).

Table 2a. Percent changes in lipid parameters according to %dWC quartiles

Variables	%dWC quartiles				*p* for trend
	First (range: −21.2–−3.4)	Second (range: −3.4–−0.1)	Third (range: 0.0–3.2)	Fourth (range: 3.2–33.3)	
Women					
%dLDL	−1.24±14.32	0.44±14.68	0.39±15.80	1.43±15.31	0.127
%dHDL	−0.41±10.97	−0.35±11.93	−0.53±11.02	−0.64±10.90	0.989
%dTG	2.92±35.05	1.49±33.53	9.02±40.49	8.60±37.33	0.034
Men					
%dLDL	−0.26±17.05	−0.36±15.56	−0.31±17.25	0.38±14.93	0.040
%dHDL	2.15±13.23	0.36±11.83	0.08±12.17	−0.21±11.35	0.016
%dTG	−1.25±39.56	5.17±47.12	6.67±53.51	9.66±53.00	0.009

Table 2b. Percent changes in lipid parameters according to %dBMI quartiles

Variables	%dBMI quartiles				*p* for trend
	First (range: −21.8–−1.8)	Second (range: −1.8–−0.2)	Third (range: −0.2–1.4)	Fourth (range: 1.4–15.6)	
Women					
%dLDL	−1.48±16.44	−1.26±12.79	−0.06±14.24	3.42±15.81	<0.001
%dHDL	0.78±12.40	−1.38±10.75	−0.62±9.46	−0.76±11.59	0.147
%dTG	−2.31±33.46	3.58±33.84	6.59±41.32	13.90±35.91	<0.001
Men					
%dLDL	−4.34±16.61	−0.96±15.58	0.01±15.69	2.80±16.68	<0.001
%dHDL	2.94±13.12	0.75±11.37	−0.40±10.50	−1.18±13.29	<0.001
%dTG	−10.21±33.76	1.90±40.05	7.07±48.69	23.13±63.63	<0.001

Discussion

In the current study, both %dWC and %dBMI were positively associated with %dLDL and %dTG in both genders. In addition, %dWC and %dBMI were inversely associated with %dHDL in men, but not in women; however, the association between percent changes in these obesity parameters and percent changes in lipid parameters, when present, was weak. Similar results were obtained when either %dWC or %dBMI was used as a potent predictor of percent changes in lipid data; however the correlation between %dWC and %dBMI was found to be relatively weak, especially in women; the correlation coefficient was 0.47 in men and 0.24 in women. Stepwise multiple regression analysis showed that %dBMI, but not %dWC, was identified as an independent factor predicting % changes in lipid data tested. Notably, even when %dBMI was excluded from the variables, %dWC was not identified as a predictor of %dHDL in women.

Several previous studies showed an association between changes in obesity indexes and lipid parameter changes. For example, in a community-based sample of 3,325 young adults, a 10-year weight gain tended to confer adverse changes in levels of LDL-C, HDL-C, and TG[7]. Bonithon-Kopp *et al.* reported that changes in BMI and the waist to hip ratio (WHR) were positively associated with changes in TG[8]. Williams *et al.* reported that changes in BMI as well as WC had a greater probability of inducing hypercholesterolemia during 7 years of follow-up[9]. In middle-aged subjects free from known cardiovascular diseases and diabetes[10], a gain or loss of WC over 9 years significantly affected serum lipid data and the incidence of metabolic syndrome[11].

On the other hand, only a few studies have investigated whether WC change was associated with changes in lipid parameters independent of BMI. Wing *et al.* analyzed whether changes in WHR led to improvements in serum lipid concentrations independent of weight change in subjects with no history of