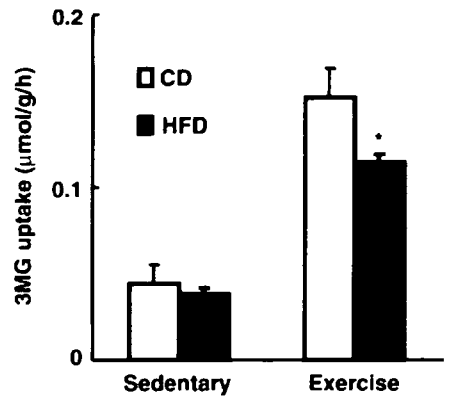

Fig. 2. High-fat diet attenuates activation of insulin-independent GT induced by one bout of moderate-intensity endurance exercise. Rats ran on a treadmill for 1 hour at 19 m/min at a 15% incline. Soleus muscles were isolated from exercised rats immediately after the cessation of running and from rats kept sedentary. Isolated muscles were incubated for 20 minutes in the absence of insulin, and 3MG uptake was determined. Data are means ± SE; n = 5 to 9 per group. *$P < .05$ vs CD-fed group.

phosphorylation of the Ser473 residue of Akt in muscles dissected 2 hours after exercise and stimulated with insulin in vitro (Fig. 5). Despite the significant increase in insulin-stimulated 3MG uptake in muscles from exercised rats (Fig. 3), Akt phosphorylation in muscle was not affected by exercise in CD- or in HFD-fed rats. The level of basal and insulin-stimulated Akt phosphorylation was not affected by the dietary manipulation.

3.7. HFD dose not change muscle GLUT4 protein level

To test the possibility that the decrease in insulin-independent and insulin-dependent GT activity caused by HFD is mediated by a reduction in the GLUT4 content of skeletal muscle, we measured soleus muscle GLUT4 protein content (Fig. 6). The GLUT4 protein content did not differ between soleus muscles from CD- and HFD-fed rats.

3.8. HFD does not change muscle glycogen concentration, but increases muscle triglyceride content

Basal and postexercise glycogen concentrations were similar in soleus muscle in CD- and HFD-fed rats (Table 2). In contrast, muscle triglyceride content was higher in muscle from HFD-fed rats than from CD-fed rats (Table 2) ($P < .05$).

3.9. Effect of one bout of endurance exercise on blood lactate concentration

To evaluate the intensity of exercise, we measured blood lactate concentration at rest and immediately after exercise. Compared with basal values, exercise increased blood lactate by 1.8 times in CD-fed rats (from 1.7 ± 0.2 to 3.1 ± 0.1 mmol/L, $P < .05$) and by 2.1 times in HFD-fed rats (from 1.6 ± 0.1 to 3.4 ± 0.2 mmol/L, $P < .05$). Blood lactate concentration did not differ between dietary groups.

4. Discussion

Endurance exercise has long been advocated as beneficial for patients with insulin resistance associated with type 2 diabetes mellitus and obesity. This is based partly on the observation that, even in people with insulin resistance, endurance exercise stimulates muscle glucose uptake in skeletal muscle by 2 distinct mechanisms: one insulin independent and one insulin dependent (reviewed in Hayashi et al [1]). Reversal of the short-term increase in GT after cessation of contractile activity is followed by a marked increase in the sensitivity of muscle to insulin. We found a significant increase in insulin-independent GT followed by insulin-dependent GT in rat soleus muscle after a 1-hour bout of treadmill running in both the CD-fed and HFD-fed rats. In both dietary groups, the mild increase in blood lactate concentration (<4 mmol/L) (Results) and significant reduction in muscle glycogen content (Table 2) after exercise suggest that rats performed moderate-intensity endurance exercise and that muscle glucose utilization was substantially activated by exercise. Similar lactate concentration and glycogen content also indicate that the exercise intensity did not differ between the dietary groups.

Although we found that exercise activated GT in skeletal muscle from both CD- and HFD-fed rats, the absolute rates of insulin-independent and insulin-dependent GT were lower in muscles from HFD-fed rats than in muscles from CD-fed rats; in contrast, muscle GLUT4 levels were similar between the groups (Figs. 2 and 3). Our results are consistent with previous studies demonstrating that exercise-stimulated insulin-independent GT is impaired in muscles from HFD-fed rats in the absence of a reduction in muscle GLUT4 content [5,6]. Liu et al [4] measured insulin-dependent GT in

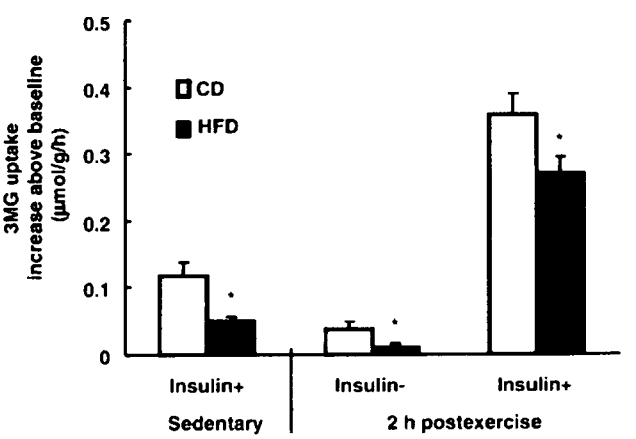

Fig. 3. One bout of endurance exercise activates insulin-dependent GT after exercise, but does not fully compensate for reduced insulin sensitivity in muscle from HFD-fed rats. Soleus muscles were isolated from exercised rats 2 hours after exercise and from sedentary rats. Isolated muscles were incubated for 30 minutes in the absence (insulin −) or presence of 0.9 nmol/L insulin (insulin+), and 3MG uptake was determined. Baseline (insulin-independent) activity was subtracted in each diet group. Data are means ± SE; n = 10 per group. *$P < .05$ vs CD-fed group.

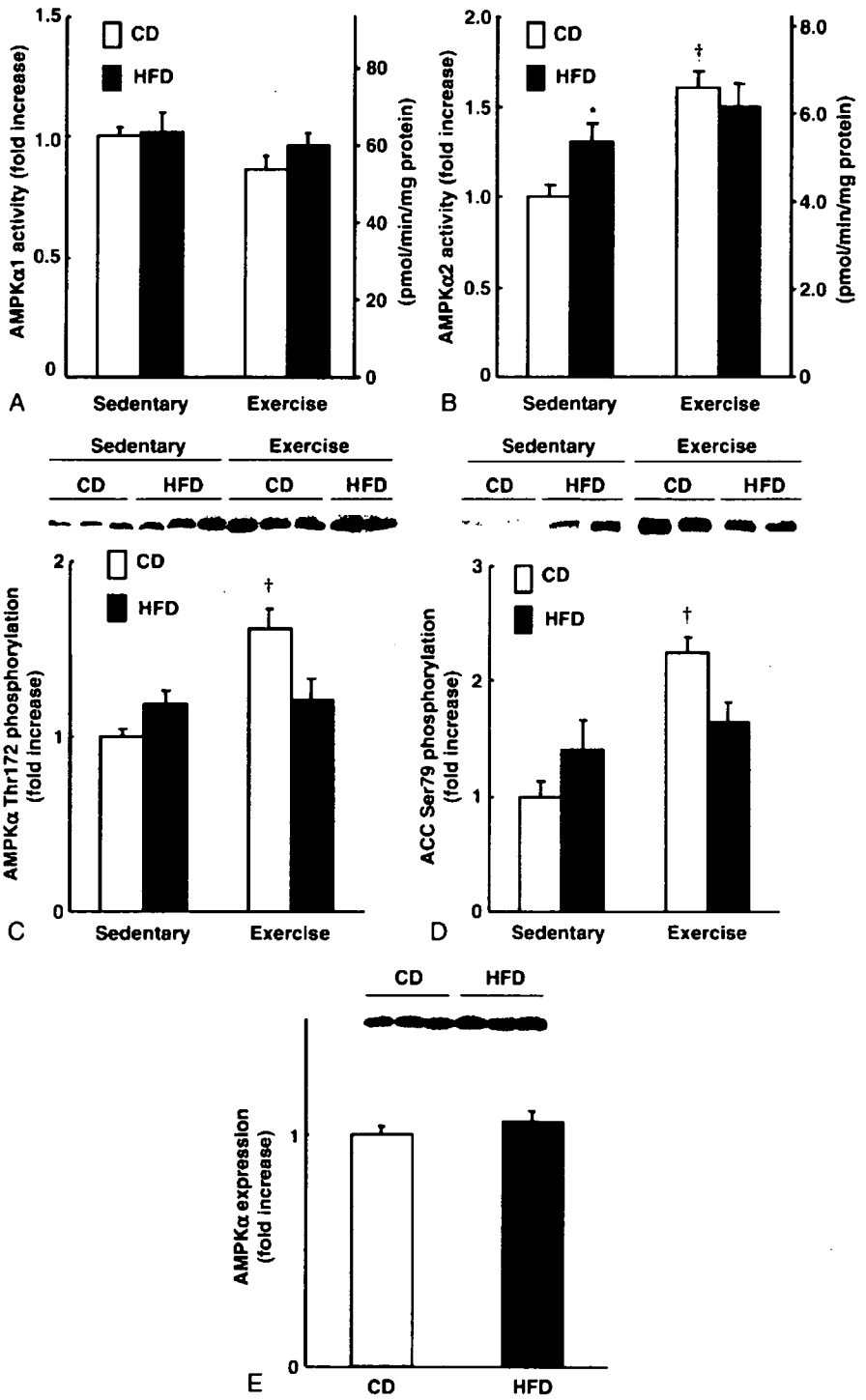

Fig. 4. High-fat diet attenuates muscle AMPKα2 activation induced by one bout of endurance exercise. Soleus muscles were isolated from exercised rats immediately after exercise and from sedentary rats. Isoform-specific AMPK activity was determined in anti-AMPKα1 (A) and α2 (B) immunoprecipitates. Muscles were also subjected to Western blot analysis using antiphosphorylated AMPK (C), antiphosphorylated ACC (D), and anti-AMPKα (E) antibodies. Fold increases are expressed relative to the activity of muscles from the sedentary CD-fed group. Data are means ± SE; n = 13 to 16 per group. *$P < .05$ vs CD-fed group, †$P < .05$ vs corresponding sedentary group.

epitrochlearis muscle in the presence of half-maximally effective concentration of insulin (0.8 nmol/L) after rats swam for 2 hours. They found no increase after exercise in insulin-dependent GT in muscles from HFD-fed rats because of the maintenance of a high level of insulin-independent GT in skeletal muscle even at 3.5 hours after exercise. In

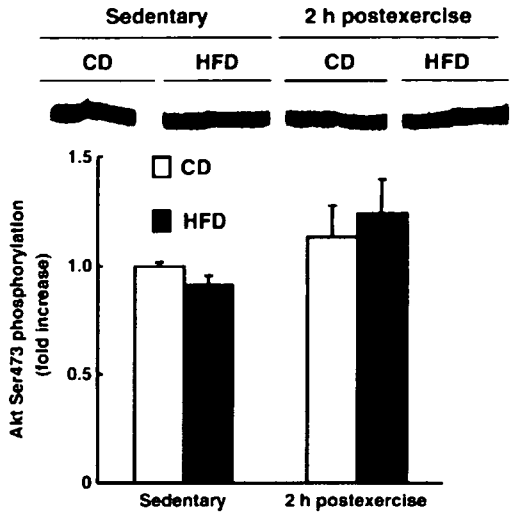

Fig. 5. One bout of endurance exercise does not affect insulin-stimulated phosphorylation of Akt in CD- and HFD-fed rats. Soleus muscles were isolated from exercised rats 2 hours after exercise and from sedentary rats, and then incubated for 30 minutes in the presence of insulin (0.9 nmol/L). Muscles were subjected to Western blot analysis using antiphosphorylated Akt antibody. Fold increases are expressed relative to the level in muscles from the sedentary CD-fed group. Data are means ± SE; n = 9 per group.

contrast, insulin-independent GT was substantially lower 2 hours after exercise in our study; and insulin-dependent GT was lower in muscles from HFD-fed animals (Fig. 3). Thus, it seems reasonable to speculate that prolonged HFD feeding evokes "exercise resistance" as well as insulin resistance; that is, HFD does not allow physiological exercise to activate GT or insulin sensitivity to the level achieved by similar exercise in skeletal muscle of CD-fed animals.

The blunted AMPK activation during exercise may be part of the mechanism leading to impaired exercise-

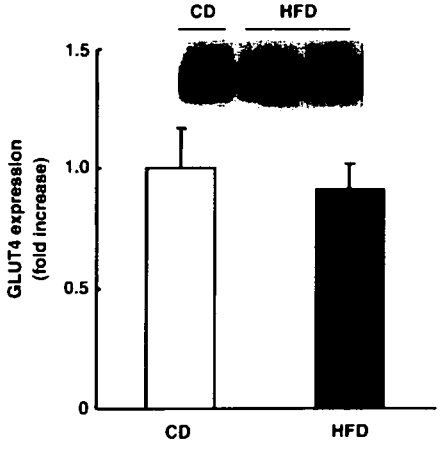

Fig. 6. High-fat diet feeding does not change muscle GLUT4 protein level. The GLUT4 protein level was determined in soleus muscle using Western blot analysis. Fold increases are expressed relative to the level in the CD-fed group. Data are means ± SE; n = 6 to 7 per group.

Table 2
Muscle glycogen and triglyceride concentrations in rats under HFD and CD feeding

	Sedentary	Immediate postexercise	2 h postexercise
Muscle glycogen (μmol·g wet weight)			
CD	23.6 ± 0.8	7.6 ± 0.6†	18.1 ± 1.0‡
HFD	22.4 ± 0.6	8.9 ± 0.4†	15.9 ± 0.5‡
Muscle triglycerides (μmol/g wet weight)			
CD	6.1 ± 0.5	4.9 ± 0.1†	5.0 ± 0.3†
HFD	7.8 ± 0.2*	7.1 ± 0.5*	6.5 ± 0.5†*

Soleus muscles were isolated from sedentary and exercised rats immediately and 2 hours after exercise, and glycogen and triglycerides concentrations were determined. Data are means ± SE; n = 6 to 14 per group.

* $P < .05$ vs CD-fed group.

† $P < .05$ vs sedentary group.

‡ $P < .05$ vs immediate postexercise group.

stimulated glucose metabolism in skeletal muscle. In the present study, short-term exercise increased the activity of the α2 isoform of muscle AMPK from baseline in CD-fed rats, but not in HFD-fed rats. Correspondingly, exercise stimulated the phosphorylation of AMPKα Thr172 and ACC Ser79 only in muscles from CD-fed animals. AMPK is a heterotrimeric serine-threonine protein kinase comprising a catalytic α subunit and regulatory β and γ subunits. Two distinct α isoforms, α1 and α2, are expressed in skeletal muscle; and both isoforms can be activated in response to muscle contraction by AMP-independent or AMP-dependent mechanisms [13]. AMPK has been implicated in a number of exercise-stimulated metabolic events in skeletal muscle, including insulin-independent GT and GLUT4 translocation [12,19-21], insulin sensitivity [22-24], fatty acid oxidation by the inactivation of ACC [12,25,26], GLUT4 expression [12,27-31], and glycogen utilization [14,32-34]. The mechanism underlying the significantly higher basal α2 activity in muscle from HFD-fed rats than in CD-fed rats (Fig. 4B) is unknown; but increased serum leptin concentration might play a role because, in vivo, both short- [35] and long-term [36] administrations of leptin activate AMPKα2 activity.

Although the predominant activation of AMPKα2 by exercise is consistent with most previous studies [12,37,38], we have recently reported that AMPKα1 activity is more sensitive to physical or physiological stress than AMPKα2 is and that AMPKα1 activity increases markedly during dissection, whereas AMPKα2 activity does not change [13]. Thus, it may be difficult to measure the α1 activity because it is disturbed by additional activation during dissection: only after high-intensity exercise, when the activation by muscle contraction exceeds that of the isolating stimuli, would AMPKα1 activity be detectable. In our 2006 study [13], we stabilized isolated muscle in KRBP for 60 minutes, which decreased α1 activity to a constant level and allowed us to observe the activation of AMPKα1 by electrical stimulation. This α1 activation was associated with corresponding increases in AMPKα phosphorylation, insulin-independent GT, and ACC phosphorylation.

Moreover, α1 was activated even by low-intensity contraction, which was characterized by the absence of an increase in AMP concentration or in the ratio of AMP to adenosine triphosphate. These observations suggest that the α1 isoform is the predominant form activated by low-intensity contractions and lead us to believe that activities of both α2 and α1 isoforms increase in response to moderate-intensity treadmill exercise used in our current study.

The mechanisms underlying the postexercise increase in insulin sensitivity, which probably relates to GLUT4 translocation in exercised muscle [39], are presumed to be mediated by multiple factors, including AMPK [22-24], muscle glycogen concentration, humoral factors, and autocrine-paracrine mechanisms (reviewed in Hayashi et al [1]). In the present study, Akt phosphorylation in response to insulin stimulus in muscle of HFD-fed rats did not decrease at rest or after exercise despite the blunted insulin-dependent GT. This result is consistent with a previous study showing that muscle insulin resistance induced by an HFD is not accompanied by impairment of Akt activation [40] and with studies demonstrating that the postexercise increase in insulin sensitivity does not accompany an enhancement of the insulin signal [22,39,41,42]. We conclude that some functional changes in the GLUT4 translocation system or signal transduction mechanism distal to Akt phosphorylation play a role in HFD-induced insulin resistance and impaired postexercise increase in insulin sensitivity.

People with type 2 diabetes mellitus exhibit remarkable muscle insulin resistance and abnormal lipid metabolism, which are also common among HFD-fed individuals. In contrast, previous studies have shown that the insulin-independent GT system activated by exercise is intact in diabetic people, unlike in the case of HFD-fed experimental animals. Kennedy et al [43] showed that muscles from people with type 2 diabetes mellitus retain the capacity to translocate GLUT4 to the sarcolemma in response to short-term exercise. Correspondingly, Musi et al [38] demonstrated that exercise normally activates muscle AMPK in people with type 2 diabetes mellitus. We note that individuals with type 2 diabetes mellitus generally have normal muscle GLUT4 protein levels [44,45]. Similarly, the genetically insulin-resistant obese Zucker rat has severe defects in insulin-stimulated glucose uptake [46] and GLUT4 translocation [47] despite normal levels of total muscle GLUT4 protein [46]. In contrast, these animals have normal increases in contraction-stimulated glucose uptake [48] and GLUT4 translocation [49,50]. To our knowledge, no study has addressed whether insulin sensitivity increases normally after a single bout of endurance exercise in people with type 2 diabetes mellitus or obese Zucker rats. Our finding that the HFD attenuated contraction-induced GT in muscle raises the possibility that the pathophysiological condition induced by the HFD differs from the condition exhibited by humans with type 2 diabetes mellitus and genetically insulin-resistant animals.

In summary, our study provides new evidence to suggest that moderate-intensity endurance exercise activates both insulin-independent and insulin-dependent components of muscle GT even when combined with HFD-induced insulin resistance. However, these metabolic effects are significantly reduced by an HFD: and consequently, exercise cannot compensate totally for muscle insulin resistance in HFD-fed rats. Although the precise mechanism is not clear, an HFD may evoke these metabolic impairments by reducing AMPK activation in contracting skeletal muscle. Appropriate fat intake might be important for efficient activation of glucose metabolism by exercise.

Acknowledgments

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Associations of Obesity Measures With Metabolic Risk Factors in a Community-Based Population in Japan

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Background The association of obesity measures (ie, body mass index (BMI), waist circumference (WC) and waist-to hip ratio (WHR)) with metabolic risk factors in community-based populations has not been well studied.
Methods and Results In the present study 759 men and 1,255 women aged between 30 and 79 years, without histories of stroke or coronary heart diseases, were dichotomized at the medians of BMI-WHR, WC-WHR and BMI-WC. The accumulation of 4 metabolic risk factors (risk_sum) were examined: high blood pressure (≥130/85 mmHg or on antihypertensive therapy); high triglycerides (≥170 mg/dl); low high-density lipoprotein-cholesterol (<40 mg/dl); and impaired glucose tolerance (hemoglobin A1c ≥5.6% or on antidiabetic therapy). BMI and WC correlated well in both men (r=0.871) and women (r=0.874). All 3 obesity measures related with the metabolic risk factors. The area under the receiver-operating characteristic curve for BMI, WC and WHR to predict the risk_sum ≥2 for men was 0.683, 0.709, and 0.700, respectively, and 0.715, 0.739, and 0.746, respectively, for women.
Conclusions BMI may be used instead of WC if the latter is not available. When WC is measured, hip circumference also should be measured because the WHR may be the most valuable measure of obesity. (*Circ J* 2007; **71:** 776–781)

Key Words: Body mass index; Metabolic risk factors; Waist circumference; Waist-to hip ratio

Obesity is a major risk factor for cardiovascular disease and as measures of obesity, the body mass index (BMI), waist circumference (WC) and waist-to hip ratio (WHR) are the most frequently used![1-17] In the new criteria for 'obesity disease' in Japan recently developed by the Japan Society for the Study of Obesity, visceral fat area (VFA) of 100 cm^2 was proposed as a cut-off point for defining obesity, or alternatively a WC of 85 cm in men and 90 cm in women could be considered because these values approximated the VFA![1] More recently, in their study involving 27,000 participants from 52 countries, Yusuf et al have shown that WHR showed a graded and highly significant association with myocardial infarction risk worldwide, and stated that a definition of obesity based on WHR increased the estimate of myocardial infarction attributable to obesity in most ethnic groups![2]

Accordingly, we examined the relationship between each obesity measure and metabolic risk factors in a community-based population in Japan.

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Methods

Participants

Of 2,892 local residents who underwent a mass medical examination in 1999 at Shigaraki town (the town name at the time of the study; population of approximately 15,000), a mountain farming community in central Japan, a total of 2,395 participants who gave informed consent after a full explanation of this study were enrolled![8,19] Of these participants, 381 were excluded for the following reasons: 146 had a history of transient ischemic attack, stroke, angina pectoris, or myocardial infarction; and 235 were outside the age range of 30 to 79. We thus had 2,014 participants (759 men, 1,255 women). The study was approved by the Institutional Review Board of Shiga University of Medical Science (No. 11-15, 1999).

Anthropometric and Blood Pressure (BP) Measurements

The waist and hip circumferences were measured with a standard tape measure while the subject was standing. WC was measured over the unclothed abdomen at the level of the umbilicus, and hip circumference was measured over a light undergarment at the level of the widest diameter around the buttocks. Both measurements were taken by the same person, each measurement was performed in triplicate and the average value was used to calculate the waist and hip circumferences. Systolic BP (SBP) and diastolic BP (DBP) were measured twice by a well-trained nurse using a standard sphygmomanometer on the right arm while the subject was seated after having rested for at least 5 min. Korotokov's 1st and 5th points were regarded as the SBP

Table 1 Characteristics of the Men and Women, in 1999, at Shigaraki Town, Shiga, Japan

	Men (n=759)	*Women (n=1,255)*
Age (years)	*59.0±12.8*	*56.7±13.4*
Height (cm)	*165.8±6.6*	*152.8±6.7*
Weight (kg)	*62.7±9.5*	*53.0±8.2*
BMI (kg/m²)	*22.8±2.9*	*22.7±3.2*
WC (cm)	*81.9±8.6*	*72.9±8.2*
Hip (cm)	*92.9±5.3*	*92.1±5.8*
WHR	*0.88±0.07*	*0.79±0.06*
SBP (mmHg)	*133±18*	*128±19*
DBP (mmHg)	*79±11*	*76±11*
Smoking (%)	*50*	*6.2*
Drinking (%)	*58*	*7.8*
Alcohol (g/d)	*23±22*	*3.2±7.1*
HTN Rx (%)	*18.7*	*20.7*
DM Rx (%)	*6.6*	*3.2*
HDL-C (mg/dl)	*53±14*	*60±14*
TG (mg/dl)	*154±105*	*121±71*
HbA1c (%)	*5.2±0.9*	*5.1±0.7*

BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN Rx, percentage of participants on antihypertensive medication; DM Rx, percentage of participants on antidiabetic medication; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; Hb, hemoglobin.

and DBP, respectively. The mean of the 2 measurements from each subject was used for the data analysis. BMI was calculated as weight (kg) divided by the square of the height (m).

Assessment of Lifestyle Factors

Daily alcohol intake and number of cigarettes smoked per day was assessed by face-to-face interview. Current smoking was defined as smoking cigarettes during the past month. Alcohol drinkers were defined as those drinking alcohol on 2 days per week or more. Ethanol consumption per day was estimated assuming that concentrations of alcohol were 5% for beer, 12% for wine, 40% for liquor, 16% for sake (Japanese rice wine) and 25% for shochu (Japanese spirits made from barley, sweet potato, or rice or any combination of these)[20]

Biochemistry

Non-fasting blood was drawn and hemoglobin A1c (HbA1c), and serum total cholesterol, high-density lipoprotein-cholesterol (HDL-C), triglycerides (TG) and glucose concentrations were determined at a single laboratory (Medic, Shiga). The measurement precision and accuracy of the serum lipids were certificated through a lipid standardization program by Osaka Medical Center for Cancer and Cardiovascular Diseases, which is a member of the Cholesterol Reference Method Laboratory Network (CRMLN) controlled by the Centers for Disease Control and Prevention (Atlanta)[21] HbA1c was measured by the latex particle agglutination method.

Metabolic Risk Factors

Besides obesity, we defined 4 metabolic risk factors in the present study as follows: high BP was defined as SBP ≥130 mmHg, or DBP ≥85 mmHg, or the use of antihypertensive agents. Impaired glucose tolerance was defined as HbA1c ≥5.6% or on medication for diabetes[22] High TG was defined as non-fasting serum concentration ≥170 mg/dl[23] Low HDL-C was defined as serum concentration <40 mg/dl

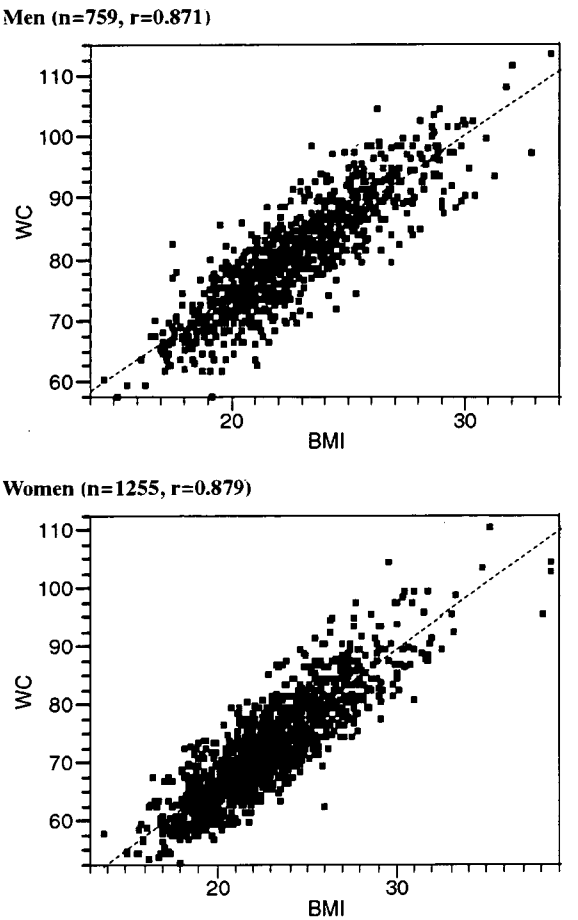

Fig 1. The correlation between body mass index (BMI) and waist circumference (WC) was good in both men (n=759, r=0.871) and women (correlation coefficient 0.871 and 0.874, respectively).

for men and women. The risk_sum was defined as the sum of these 4 metabolic risk factors for each participant (0–4).

Statistical Analysis

SAS version 9.1 for Windows (SAS Institute, Cary, NC, USA) was used for all analyses. The Pearson correlation coefficient was used to test the correlation between BMI and WC in men and women, separately. The participants were divided into 4 groups according to BMI-WHR at the median of each variable for men or women. Male and female data were combined for the analyses. The participants were also divided into 4 groups according to WC-WHR and BMI-WC at the median of each variable for men and women. The t-test was used to compare the means of continuous variables in 2 groups and the chi-square test was used to compare dichotomous variables. To compare the means of risk_sum among the 4 groups, one-way analysis of variance adjusted for age and sex followed by the Tukey's multiple comparison test was used. Partial correlation coefficients were calculated for BMI, WC or WHR and the 4 metabolic risk factors, as well as the risk_sum after adjustment for age and sex. The relative ability of the 3 measures of obesity to predict the risk_sum ≥2 was evaluated in men and women separately by calculating the area under the receiver-operating characteristic (ROC) curves using SAS logistic procedure. Area under the ROC curve

Table 2 Characteristics and Risk Factors According to BMI-WHR Categories

	WHR < Median	WHR ≥ Median	p value
BMI < Median			
n	764	242	
Men (%)	39.5	31.8	0.031
Age (years)	53.9±14.2	64.1±10.5	<0.0001
BMI (kg/m²)	20.1±1.5	21.0±1.1	<0.0001
WC (cm)	68.9±6.1	75.1±5.7	<0.0001
WHR	0.77±0.05	0.85±0.05	<0.0001
High blood pressure (%)	37.3	59.1	<0.0001
High TG (%)	11.7	17.8	0.014
Low HDL-C (%)	4.8	9.1	0.014
IGT (%)	6.8	16.5	<0.0001
Risk_sum	0.61±0.74	1.02±0.83	<0.0001*
BMI ≥ Median			
n	272	736	
Men (%)	37.5	37.8	0.937
Age (years)	52.6±12.7	61.0±11.1	<0.0001
BMI (kg/m²)	24.0±1.3	25.6±2.4	<0.0001
WC (cm)	75.9±6.1	84.5±7.6	<0.0001
WHR	0.80±0.05	0.88±0.06	<0.0001
High blood pressure (%)	48.2	73.6	<0.0001
High TG (%)	23.6	35.7	0.0002
Low HDL-C (%)	9.6	15.1	0.0231
IGT (%)	27.2	40.2	<0.0001
Risk_sum	0.90±0.92	1.44±0.95	<0.0001*

*Tukey test.
IGT, impaired glucose tolerance; risk_sum, sum of risk factors. Other abbreviations see in Table 1.
*The mean risk_sum of BMI < Median & WHR < Median group vs BMI ≥ Median & WHR < Median group, p<0.0001; the mean risk_sum of BMI < Median & WHR ≥ Median group vs BMI ≥ Median & WHR ≥ Median group, all p<0.0001.

Table 3 Characteristics and Risk Factors According to WC-WHR Categories

	WHR < Median	WHR ≥ Median	p value
WC < Median			
n	841	150	
Men (%)	37.7	39.3	0.721
Age (years)	53.4±14.1	62.3±11.1	<0.0001
BMI (kg/m²)	20.5±1.9	20.9±1.5	0.0054
WC (cm)	69.0±5.8	73.1±5.1	<0.0001
WHR	0.77±0.05	0.84±0.05	<0.0001
High blood pressure (%)	36.5	60.7	<0.0001
High TG (%)	12.5	17.3	0.103
Low HDL-C (%)	5.1	10.0	0.018
IGT (%)	6.3	14.0	0.0009
Risk_sum	0.60±0.75	1.02±0.86	<0.0001*
WC ≥ Median			
n	172	851	
Men (%)	37.2	37.5	0.946
Age (years)	53.4±12.7	61.7±11.0	<0.0001
BMI (kg/m²)	23.9±1.9	25.0±2.7	<0.0001
WC (cm)	78.1±5.6	83.7±7.5	<0.0001
WHR	0.80±0.05	0.88±0.06	<0.0001
High blood pressure (%)	52.9	71.9	<0.0001
High TG (%)	21.5	34.1	0.0013
Low HDL-C (%)	9.3	14.3	0.078
IGT (%)	11.6	19.3	0.017
Risk_sum	0.95±0.88	1.40±0.94	<0.0001*

*Tukey test.
Abbreviations see in Tables 1,2.
*The mean risk_sum of WC < Median & WHR < Median group vs WC ≥ Median & WHR < Median group, p<0.0001; the mean risk_sum of WC < Median & WHR ≥ Median group vs WC ≥ Median & WHR ≥ Median group, all p<0.0001.

of 0.5 represents chance performance: 1.0 indicates perfect predictive ability.

Sensitivity analyses were performed for the above Tukey's multiple comparison test, ROC analysis and partial correlation coefficients analysis by changing the cut-off value for the definition of high TG from 170 to 150, and to 200 mg/dl, and by changing the cut-off value of HbA1c for the definition of impaired glucose tolerance from 5.6% to 6.0%.

All p values were 2-tailed, and $p<0.05$ was considered significant.

Table 4 Characteristics and Risk Factors According to BMI-WC Categories

	WC < Median	WC ≥ Median	p value
BMI < Median			
n	792	118	
Men (%)	39.7	36.4	0.51
Age (years)	55.0±14.3	63.7±10.7	<0.0001
BMI (kg/m²)	19.9±1.4	21.2±0.9	<0.0001
WC (cm)	68.9±6.0	77.7±4.9	<0.0001
WHR	0.78±0.06	0.85±0.05	<0.0001
High blood pressure (%)	39.0	58.5	<0.0001
High TG (%)	11.6	15.3	0.26
Low HDL-C (%)	5.4	8.5	0.19
IGT (%)	7.8	14.4	0.018
Risk_sum	0.64±0.75	0.97±0.72	<0.0001*
BMI ≥ Median			
n	199	905	
Men (%)	31.2	37.6	0.09
Age (years)	53.8±13.2	59.8±11.8	<0.0001
BMI (kg/m²)	23.1±0.8	25.3±2.4	<0.0001
WC (cm)	72.3±4.8	83.4±7.6	<0.0001
WHR	0.78±0.05	0.87±0.07	<0.0001
High blood pressure (%)	44.7	70.1	<0.0001
High TG (%)	19.6	34.1	<0.0001
Low HDL-C (%)	7.5	14.1	0.012
IGT (%)	6.0	18.5	<0.0001
Risk_sum	0.78±0.89	1.37±0.96	<0.0001*

*Tukey test.
Abbreviations see in Tables 1,2.
*The mean risk_sum of BMI < Median & WC < Median group vs BMI ≥ Median & WC < Median group, p<0.0001; the mean risk_sum of BMI < Median & WC ≥ Median group vs BMI ≥ Median & WC < Median group, all p<0.0001.

Table 5 Partial Correlation Coefficients for BMI, WC or WHR and the 4 Metabolic Risk Factors as Well as the Sum of Risk Factors After Adjustment for Age and Sex, in 759 Men and 1,255 Women in 1999, at Shigaraki Town, Shiga, Japan

	BMI		WC		WHR	
	r	p value	r	p value	r	p value
High blood pressure (%)	0.26	<0.0001	0.26	<0.0001	0.23	<0.0001
High TG (%)	0.24	<0.0001	0.26	<0.0001	0.25	<0.0001
Low HDL-C (%)	0.11	<0.0001	0.15	<0.0001	0.18	<0.0001
IGT (%)	0.13	<0.0001	0.15	<0.0001	0.14	<0.0001
Risk_sum	0.34	<0.0001	0.37	<0.0001	0.36	<0.0001

Abbreviations see in Tables 1,2.

Results

Table 1 shows the characteristics of the male and female participants. Among the 3 obesity measures, the mean BMI was similar in both sexes; however, the mean WC and WHR were larger in men than in women. The medians of BMI, WC and WHR were 22.56 kg/m², 82.0 cm, and 0.882, respectively, for men and 22.33 kg/m², 72.0 cm, and 0.787, respectively, for women. Half of the male participants were current smokers compared with 6.2% of the female participants. More than half of the male participants had drank alcohol compared with 7.8% of the female participants. Approximately 20% of the participants were taking antihypertensive medications.

Fig 1 shows the correlation between BMI and WC in the men and women, which was good in both sexes.

Table 2 shows the combined characteristics of the men and women and the risk factors according to BMI and WHR categories divided into 4 groups at the median of each variable. Regardless of whether a participant's BMI was above or less than the median, the mean age and the frequencies of risk components were higher in those with a WHR larger than or equal to the median than in those with a WHR less than the median. One-way analysis of variance adjusted for age and sex followed by the Tukey's multiple comparison test showed statistically significant (p<0.0001) differences between the mean risk_sum of the BMI < median & WHR < median group and that of the BMI < median & WHR ≥ median group, between the mean risk_sum of the BMI < Median & WHR < median group and the BMI ≥ median & WHR < median group, and between the mean risk_sum of the BMI < median & WHR ≥ median group and the BMI ≥ median & WHR ≥ median group.

Table 3 shows the combined characteristics of the men and women and the risk factors according to WC and WHR categories divided into 4 groups at the median of each variable for the men or women. Regardless of whether a participant's WC was above or less than the median, the mean age and the frequencies of risk components were higher in those with a WHR larger than or equal to the median than in those with less than the median WHR. One-way analysis of variance adjusted for age and sex followed by the Tukey's multiple comparison test showed statistically significant (p<0.0001) differences between the mean risk_sum of the WC < median & WHR < median group and that of the WC < median & WHR ≥ median group, between the mean

risk_sum of the WC<Median & WHR<median group and the WC≥median & WHR<median group, and between the mean risk_sum of the WC<median & WHR≥median group and the WC≥median & WHR≥median group.

Table 4 shows the combined characteristics of the men and women and the risk factors according to BMI and WC categories divided into 4 groups at the median of each variable for the men or women. The results were essentially similar to those in Tables 2 and 3. Table 5 shows the results of the partial correlation coefficients analyses. All 3 measures of obesity correlated significantly and very well with the 4 metabolic risk factors and the risk_sum.

The area under the ROC curve for BMI, WC and WHR to predict the risk_sum for men was 0.683, 0.709, and 0.700, respectively; and 0.715, 0.739, and 0.746, respectively, for women.

Sensitivity analyses by changing the cut-off value of TG for the definition of high TG from 170 to 150 and to 200 mg/dl, and by changing the cut-off value of HbA1c for the definition of impaired glucose tolerance from 5.6% to 6.0%, on the Tukey's multiple comparison test, ROC analysis and the partial correlation analyses yielded results generally similar to those for the main analyses.

Discussion

The present study has shown that BMI and WC correlated well in men and women, and all 3 obesity measures (ie, BMI, WC and WHR) related to metabolic risk factors fairly well by multiple comparison test. However, according to the ROC analyses WHR may predict the risk_sum ≥2 better than the other 2 measures, especially in women.

The merits of using BMI as an obesity measure are that it can be obtained easily from weight and height data, even from data taken many years ago when WC was not routinely obtained. Measurement errors in BMI appear to be smaller than for WC. However, WC has become the preferred measure for abdominal obesity, because it is the best surrogate measure for VFA or mass, as estimated from computer tomography[11,24] Several cross-sectional studies have related WC to the prevalence of diabetes[25] and cardiovascular risk factors[11,12,26] However, prospective studies regarding the association between each obesity measure and cardiovascular hard endpoints are needed to know which is the best measure of obesity. Several previous studies have examined the association of BMI, WHR, or WC, with cardiovascular disease[1-17] but their results have been conflicting. Some suggest that BMI is better than or at least as good as abdominal obesity[8,14,15] As to those who have a low BMI, some studies report they had excess cardiovascular mortality, especially if elderly or male[2,15] whereas others deny this association regardless of age[4,8]

Recently, in their case-control study involving 27,000 participants from 52 countries, Yusuf et al showed that among the obesity measures, WHR had a graded and strongest association with myocardial infarction risk in men and women, across all age and ethnic groups, in those with and without other cardiovascular risk factors[4] The importance of WHR was observed in the present study, too. The reasons for WHR being better than WC as a measure of risk may be as follows. First, the adjustment effect of measures of WC for pelvic girth. Second, and more importantly, the fact that WC and hip circumference have independent and opposite effects on cardiovascular risk. Namely, it has been noted in previous studies that hip circumference has an inverse association with cardiovascular risk factors or risk of myocardial infarction[4,13] Therefore, the division of WC by hip circumference should result in a stronger indicator for risk. Several factors have been postulated to account for the opposing effects of abdominal and lower-body fat on cardiovascular risk: humoral factors[27,28] different biochemical characteristics of fat in the 2 regions[29,30] and larger hips possibly reflecting increased gluteal muscle or an increased overall skeletal muscle mass.

The main strength of the present study is its population-based samples. The study is limited by (1) its cross-sectional design, which meant we could not evaluate prognostic significance of the obesity measures, and (2) not having fasting blood samples. However, the cut-off values for non-fasting HbA1c and TG used in the present study are evidence-based. In their study on the utility of HbA1c in predicting diabetes risk, Edelman et al found that the annual incidence of diabetes significantly increased in patients with baseline HbA1c ≥5.6%[22] Iso et al found an association between non-fasting TG and the risk of coronary heart disease at TG concentrations >171 mg/dl[23] Furthermore, in the present study sensitivity analyses by changing the cut-off value of TG and HbA1c for the definition of high triglycerides and impaired glucose tolerance yielded results generally similar to those for the main analyses.

In conclusion, because BMI and WC correlated very well in men and women, BMI may be used instead of WC when the latter is not available, such as in a cohort study. When WC is measured, hip circumference also should be measured because based on the ROC analyses in the present study WHR may be the most valuable measure of obesity.

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Effect of Combined Cardiovascular Risk Factors on Individual and Population Medical Expenditures

— A 10-Year Cohort Study of National Health Insurance in a Japanese Population —

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Background Although obesity is required for some criteria defining metabolic syndrome, clustering of other risk factors also indicates an increased risk of cardiovascular disease. Whether the relationship between cardiovascular risk factor clustering and medical expenditures differs with body mass index (BMI) requires investigation, especially in a population with a low prevalence of obesity such as that in Japan.

Methods and Results A 10-year cohort study of 4,478 Japanese National Health Insurance beneficiaries aged 40–69 years in a community between 1990 and 2001 was carried out in the present study. The clustering of cardiovascular risk factors showed a positive and graded relationship to personal medical expenditures in participants who are overweight (BMI ≥25.0) and normal weight (BMI <25.0). The individual medical expenditures per month were 1.7-fold higher for participants with 2 or 3 risk factors and overweight than for those without these factors (26,782 vs 15,377 Japanese yen). Differences in the geometric means were similarly significant after adjustment for other confounding factors. However, the excess medical expenditures by risk clustering of normal weight categories within the total medical expenditures were higher than those of overweight categories because more participants were of normal weight.

Conclusions Cardiovascular risk factor clustering and being overweight can be a useful predictor of medical expenditures in a Japanese population. (*Circ J* 2007; **71:** 807–813)

Key Words: Medical expenditures; Metabolic components; Overweight; Risk factors

Hypertension, dyslipidemia, diabetes and obesity are cardiovascular risk factors that are difficult to control, but which are widespread in many developed countries[1] These factors are often clustered[2–6] which has resulted in a high incidence of cardiovascular disease accounted for by metabolic syndrome, recognized as visceral fat accumulation[2,7] The individual components of metabolic syndrome impose a major economic burden on the health-care system[8–12] However, few studies have examined the combined effects of multiple cardiovascular risk factors on medical expenditures[13,14]

Furthermore, the National Cholesterol Education Program considers each risk factor to have a similar effect on atherosclerosis[15] On the contrary, the International Diabetes Federation defines waist circumference as a requirement for a diagnosis of metabolic syndrome[16] However, other studies have shown that high-risk individuals with metabolic risk factors often go undetected if obesity is a required criterion[17,18] Thus, whether the relationship between cardiovascular risk factor clustering and medical expenditures differs with body mass index (BMI) should be determined, especially in a population with a low prevalence of obesity such as the Japanese.

The present study examines the influence of cardiovascular risk factor clustering on medical expenditures in individuals who are overweight and of normal weight defined by BMI. Our a priori hypothesis is that clustering of cardiovascular risk factors has a positive, graded association with medical expenditures. Furthermore, we investigated whether overweight participants with risk factor clustering actually have high medical expenditures and if so, the proportion of the excess medical expenditures in the total medical expenditures consumed by these participants.

Methods

Medical Expenditures in Japan

Medical expenditures in Japan are based on a public medical insurance institution[19,20] that comprises 2 systems. Everyone living in Japan is required to enrol in either of the 2 insurance systems, and this is called 'health-insurance for

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all'. One is for employees and their dependants and the other is for self-employed individuals, such as farmers and fishermen, retirees and their dependants. The 2 systems respectively cover 65.3% and 34.7% of the overall population. All prices are strictly controlled by a fee schedule that is set by the National Government, and calculated on the basis of 'fee-for-service'. The fee schedule is constant, regardless of insurance system. Furthermore, the same fee schedule applies to all clinics and hospitals that are approved to provide medical services under the public medical insurance system.

Study Population

Our study cohort comprised 4,535 Japanese beneficiaries of the National Health Insurance (NHI). Details of the cohort study have been reported elsewhere[9,21,22] Briefly, the 40–69-year-old participants lived in 7 rural towns and a village in Shiga Prefecture, West Japan, and had undergone a baseline survey between 1989 and 1991. In 1990, the study area had 82,155 residents, including 31,564 individuals aged 40–69 years, of whom 11,900 were NHI beneficiaries. Therefore, the participants in the present study represented approximately 38% of all NHI beneficiaries in this age group within this community. Monthly NHI claim files for over 10 years within the Shiga NHI Organizations were linked with the baseline survey data. Deleting the names of the participants from the linked data protected their privacy. We excluded 57 participants as a result of information missing from the baseline survey. Accordingly, 4,478 participants (1,921 men and 2,557 women) were included in the analysis. The Institutional Review Board of Shiga University of Medical Science for ethical issues approved the present study (No.16-15).

Baseline Survey and Follow-up

The baseline survey was performed by standardized methods in accordance with the Manual for Health Check-ups under the Medical Service Law for the Aged, issued by the Japan Public Health Association in 1987[23] Public health nurses measured blood pressure with a standard mercury sphygmomanometer in individuals who had rested for at least 5 min. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or taking anti-hypertensive medication. Diabetes was defined as a history of diabetes or glucosuria detected by a spot urine test with a dipstick containing a color pad. Serum high-density lipoprotein (HDL)-cholesterol and triglycerides as a marker of dyslipidemia were not measured at the baseline examination. Accordingly, dyslipidemia was defined as hypercholesterolemia with a total cholesterol level ≥5.69 mmol/L (220 mg/dl).

All participants were classified into the following categories on the basis of clustering of cardiovascular risk factors (hypertension, diabetes and hypercholesterolemia): none, 1, and 2–3. Because visceral fat accumulation was not measured at the baseline survey and the prevalence of obesity (BMI >30 kg/m^2) was very low (1.3%), we used a BMI of 25 kg/m^2 or greater as an indicator of being overweight in the present study[24] Smoking and alcohol consumption habits were determined from interviews administered by the public health nurses.

Information on medical expenditures for each participant was obtained from the monthly NHI claim files, starting from April in the year following their initial health check-up until March 2001. Medical expenditures are expressed in Japanese yen and US dollars (ie, 100 Japanese yen= SUS 0.848, at the exchange rates published on November 7th, 2006). Data regarding medical expenditures for each individual differed depending on the period of subscription to the NHI. The medical expenditures for each participant were therefore divided by the period of subscription, and are expressed as expenditures per month of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.

Data Analysis

We evaluated medical expenditures per person per month in each of 3 categories according to the number of cardiovascular risk factors. Because the distribution of real medical expenditures was positively skewed, the data were logarithmically transformed to normalize the distribution and the results are expressed as geometric means. For participants with expenditures of 0 yen per month, logarithmic transformations were achieved by replacing 0 yen with 1 yen. Fifteen participants had total medical expenditures of 0 yen and 16 had outpatient medical expenditures of 0 yen. To compare total and outpatient medical expenditures per person in each category we performed an analysis of covariance after adjusting for age, sex, BMI, smoking (non-smoker or current smoker) and alcohol consumption (none, occasional or daily consumption) with the Bonferroni correction for multiple post-hoc comparisons. A similar analysis was also performed after stratifying by BMI at 25 kg/m^2. The significance of multiplicative interaction between risk factor clustering and being overweight for medical expenditures was examined by cross-product terms in the model. Because 2,604 participants had inpatient medical expenditures of 0 yen, logarithmic transformations were not performed, and we applied the Kruskal–Wallis test to compare inpatient medical expenditures among the 3 categories.

Furthermore, we compared the medical expenditures per person between overweight and normal weight participants with individual cardiovascular risk factors.

Finally, we calculated excess medical expenditures attributable to the number of metabolic risk factors. The excess medical expenditures were estimated as follows: Σ [(the arithmetic mean of total medical expenditures in each of the 5 groups except for normal weight and no risk factor group, ie, (1) normal weight with 1 risk factor, (2) normal weight with 2 or 3 risk factors, (3) overweight alone, (4) overweight with 1 other risk factor, and (5) overweight with 2 or 3 other risk factors−the arithmetic mean of total medical expenditures in normal weight and no risk factor group)×(the number of individuals in each of the 5 categories.)]. We also examined the ratio of excess medical expenditure to the entire total medical expenditures of the population.

The statistical package SPSS 14.0J for Windows performed these analyses. All probability values were 2-tailed and the significance level was established at $p<0.05$.

Results

The prevalence of being overweight was 21.0% (men, 18.1%; women, 23.3%) of the entire study population. Table 1 summarizes the baseline risk characteristics of the 4,478 participants grouped according to risk factor clustering. Among them, 12.9% (men, 10.7%; women, 14.5%) had 2 or 3 risk factors, and 39.5% (men, 40.8%; women,

Table 1 Baseline Risk Characteristics in 1989–1991 of 4,478 National Health Insurance Beneficiaries in Shiga, Japan, Grouped by Sex and Risk Status

Risk characteristics	Risk status category			p value
	None	1 risk factor	2 or 3 risk factors	
Men				
No. of participants (%)	931 (48.5)	782 (40.7)	208 (10.8)	
Age (years)*	52.4±8.3	55.2±8.0	55.6±8.0	<0.01
Body mass index (kg/m²)*	22.1±2.5	22.9±2.7	24.0±2.9	<0.01
Smoking habit†				
Current smoker (%)	61.0	58.7	59.1	0.61
Drinking habit†				
Non-drinker (%)	21.3	19.4	22.1	
Occasional drinker (%)	22.4	19.3	24.0	0.18
Daily drinker (%)	56.3	61.3	53.8	
Hypertension (%)	0.0	67.4	94.7	<0.01
Hypercholesterolemia (%)	0.0	23.0	76.9	<0.01
Diabetes (%)	0.0	9.6	35.1	<0.01
Women				
No. of participants (%)	1,204 (46.1)	984 (38.5)	369 (14.4)	
Age (years)*	52.0±8.1	56.0±7.5	58.2±6.5	<0.01
Body mass index (kg/m²)*	22.3±2.7	23.4±3.1	24.4±2.9	<0.01
Smoking habit†				
Current smoker (%)	3.6	3.3	2.7	0.71
Drinking habit†				
Non-drinker (%)	79.9	79.6	80.8	
Occasional drinker (%)	16.5	16.2	15.4	0.92
Daily drinker (%)	3.6	4.3	3.8	
Hypertension (%)	0.0	54.2	97.6	<0.01
Hypercholesterolemia (%)	0.0	43.6	93.8	<0.01
Diabetes (%)	0.0	2.2	12.5	<0.01

*One way analysis of variance.
†Chi-square test.
Values located after the mark, ±, indicate standard deviation.

Table 2 Medical Expenditures (Total, Outpatient and Inpatient) per Person Grouped by Number of Cardiovascular Risk Factors, After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Medical costs per person per month				
		Total		Outpatient		Inpatient
		Arithmetic mean	Adjusted geometric mean	Arithmetic mean	Adjusted geometric mean	Arithmetic mean
None	2,135	16,400 yen (139 dollars)	7,361 yen (62 dollars)	8,545 yen (72 dollars)	5,420 yen (46 dollars)	7,872 yen (67 dollars)
1 risk factor	1,766	23,002 yen (195 dollars)	9,382 yen† (80 dollars)	12,470 yen (106 dollars)	7,034 yen† (60 dollars)	10,538 yen (89 dollars)
2 or 3 risk factors	577	25,090 yen (213 dollars)	10,562 yen† (90 dollars) p<0.01*	15,494 yen (131 dollars)	7,929 yen† (67 dollars) p<0.01*	9,597 yen (81 dollars) p<0.01‡

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
*Analysis of covariance adjusted for age, sex, body mass index, smoking habit and drinking habit.
†Significance, vs none, for multiple post-hoc comparisons with Bonferroni correction, p<0.05.
‡Kruskal Wallis test.

38.6%) had 1 risk factor. In both groups with 1 or more risk factors, the prevalence of hypertension was highest followed by hypercholesterolemia. Smoking and alcohol consumption did not significantly differ between the 3 groups in both men and women. The mean BMI values were higher in participants with more risk factors.

Total person-years were 40,815 and the mean follow-up was 9.0 years. Sex-specific analyses of the medical expenditures among the 3 categories showed similar results for men and women. Therefore, we reported our findings for men and women combined. Table 2 shows that during follow-up, the total medical expenditures per person per month with 2–3 risk factors (25,090 yen or SUS 213) and with 1 risk factor (23,002 yen or SUS 195) were higher than those in the group with no risk factors (16,400 yen or SUS 139). The geometric means of total medical expenditures after adjusting for other confounding factors showed significant differences in personal medical expenditures between the 3 categories.

Table 3 shows the medical expenditures per person in normal weight and overweight groups stratified by a BMI of 25.0 kg/m². The total medical expenditures were highest in overweight individuals with 2–3 risk factors (26,782 yen or SUS 227). On the contrary, the total medical expenditures were lowest in the normal weight group with no risk factors (15,377 yen or SUS 130). The relationship between

Table 3 Total Medical Expenditures per Person Grouped by Number of Cardiovascular Risk Factors, Stratified by Having Overweight (BMI ≥25.0) or Not After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Total medical costs per person per month	
		Arithmetic mean	Adjusted geometric mean
None			
BMI<25.0	1,849	15,377 yen (130 dollars)	6,985 yen (59 dollars)
BMI≥25.0	286	23,011 yen (195 dollars)	9,168 yen† (78 dollars)
1 risk factor			
BMI<25.0	1,336	24,245 yen (206 dollars)	9,091 yen† (77 dollars)
BMI≥25.0	430	19,143 yen (162 dollars)	10,703 yen† (91 dollars)
2 or 3 risk factors			
BMI<25.0	351	24,002 yen (203 dollars)	10,263 yen† (90 dollars)
BMI≥25.0	226	26,782 yen (227 dollars)	12,048 yen† (102 dollars) p<0.01*

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
**Analysis of covariance adjusted for age, sex, smoking habit and drinking habit.*
†Significance, vs none without overweight, for multiple post-hoc comparisons with Bonferroni correction, p<0.05.
BMI, body mass index.

Table 4 Total Medical Expenditures per Person Grouped by Type of Cardiovascular Risk Factors, Stratified by Having Overweight (BMI ≥25.0) or Not After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Total medical costs per person per month	
		Adjusted geometric mean (Model 1)*	Adjusted geometric mean (Model 2)**
Hypertension			
BMI<25.0	1,098	9,045 yen (77 dollars)	11,407 yen (97 dollars)
BMI≥25.0	519	11,026 yen† (94 dollars)	12,991 yen (110 dollars)
Hypercholesterolemia			
BMI<25.0	803	9,252 yen (78 dollars)	9,210 yen (78 dollars)
BMI≥25.0	312	10,420 yen† (88 dollars)	10,551 yen (89 dollars)
Diabetes			
BMI<25.0	153	15,308 yen (130 dollars)	15,139 yen (128 dollars)
BMI≥25.0	63	18,974 yen (161 dollars)	19,497 yen (165 dollars)

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
**Model 1, analysis of covariance adjusted for age, sex, smoking habit and drinking habit.*
***Model 2, analysis of covariance adjusted for age, sex, smoking habit, drinking habit and other risk factors except for categorized risk factor; for example, in hypertension, hypercholesterolemia and diabetes were adjusted.*
†Significance, between normal weight and overweight, p<0.05.
Abbreviation see in Table 3.

the number of risk factors and adjusted geometric means of medical expenditures in both the normal weight and overweight groups was positively graded. The increase in the rate of medical expenditures according to the number of risk factors was not parallel; however, the interaction term between the number of cardiovascular risk factors and overweight criteria did not reach statistical significance (p=0.351). Individual medical expenditures per month were higher in overweight individuals, than in the normal weight group when the number of other cardiovascular risk factors was consistent.

Table4 shows the medical expenditures between overweight and normal weight participants with hypertension, hypercholesterolemia and diabetes. The medical expenditures per person in all 3 groups were higher in the overweight group than in the normal weight group. The difference in medical expenditures between overweight and normal weight were largest in diabetics.

The calculated excess medical expenditures attributable to normal weight individuals with 1 risk factor, those who were of normal weight with 2–3 risk factors, only overweight, overweight with 1 other risk factor and overweight with 2–3 other risk factors were 11,847,648 yen, 3,027,375 yen, 2,183,324 yen, 1,619,380 yen and 2,577,530 yen, respectively. Fig 1 shows the share of each excessive medical cost of the total medical expenditures of the entire population. The excess medical expenditures of the 2 normal weight categories combined (16.5%) were higher than

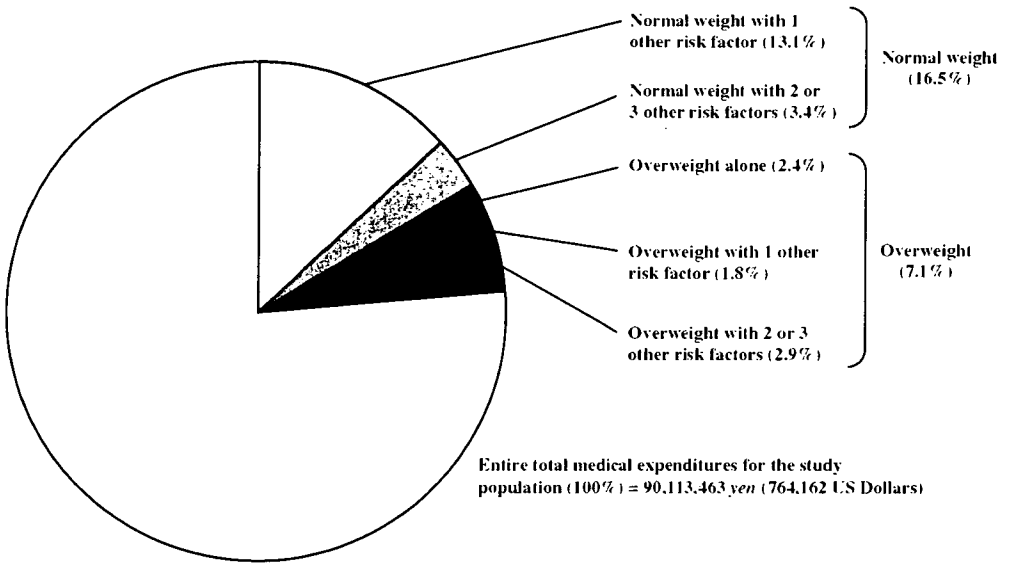

Fig 1. Ratio (%) of excess medical expenditures related to number of cardiovascular risk factors stratified by body mass index (25 kg/m^2) in whole population after 10-year follow-up, from 1990 to 2001, in National Health Insurance in Shiga, Japan (men and women combined). White area represents predicted medical expenditures if all participants were of normal weight without risk factors.

those of 3 overweight categories combined (7.1%).

Discussion

We performed a follow-up study of a Japanese community between 1990 and 2001 and found a positive graded relationship between clustering of cardiovascular risk factors and personal medical expenditures irrespective of being overweight. The mean personal medical cost was higher in overweight, than in normal weight individuals when the number of other risk factors was consistent. Furthermore, the total medical expenditures were the highest in overweight individuals with 2–3 risk factors. Nevertheless, the excess medical expenditures in these participants in entire population were only a few percent and the excess expenditures observed in normal weight categories were rather higher than those in overweight categories.

Findings from the Framingham study have already shown that the risk of atherosclerotic disease increases with combinations of risk factors, such as hypertension, glucose intolerance and hypercholesterolemia.[25] Japanese epidemiological studies have also found similar results in community[6] and occupational[26] settings. However, few studies to our knowledge have investigated the association between cardiovascular risk clustering or metabolic syndrome and medical expenditures.[13,14] Most other studies have focused on the effect of hypertension combined with diabetes on medical economics.[22,27,28]

The continuous increase in medical expenditures is an important concern in most developed countries.[29] Furthermore, the effect of cardiovascular diseases on medical economics is a major concern. For example, the medical expenditures for cardiovascular disease including hypertension was 20.4% of the total national medical expenditures in the Japanese population aged 45–69 years, which was larger than any other disease groups during 2001.[30] The effective way to control medical expenditures incurred by cardiovascular diseases is to detect those at high risk and provide intensive health and lifestyle guidance or opportunities for early clinical visits for primary care. The present findings showed that overweight people with cardiovascular risk clustering should be detected as priority targets for a high-risk strategy[31] and that overweight people with cardiovascular risk factors such as hypertension, hypercholesterolemia and diabetes can also be potential targets for high-risk strategies that could significantly affect individual medical expenditures. If an individual has accumulated visceral fat or impaired glucose tolerance, which is now classified as a metabolic syndrome, then their medical expenditures should be reduced by implementing appropriate dietary measures and by increasing physical activity.

By contrast, irrespective of high individual medical expenditures, the proportion of excess medical expenditures in the normal weight categories with 1 or more other risk factors was higher than those of all overweight categories combined. The low proportion of excess medical expenditures incurred by overweight individuals is a result of relatively small number of overweight participants identified in the present study. The 1989 to 1991 baseline survey defined only 21% of participants as being overweight (25 kg/m^2 or more). Accordingly, from the viewpoint of an entire population and a population strategy[31] regardless of being overweight, the presence of other cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia significantly effects medical expenditures. Normal weight people with other risk factors, especially in non-Western populations with a low prevalence of obesity, should be carefully considered.

The present study has several limitations. First, the public medical insurance system in Japan differs from that in other countries. Therefore, absolute values of medical expenditures for the participants in the present study might not be directly relevant to other populations. Second, we clustered risk factors from a single measurement at the baseline survey, which generated a regression dilution bias. Third, we did not have values for fasting blood glucose,

triglycerides or HDL-cholesterol, which are important components of metabolic syndrome![5] We used BMI as an indicator of being overweight. One report indicates that waist circumference predicts visceral fat accumulation (which plays a major role on atherosclerosis) better than BMI![32] Accordingly, we might have underestimated or misclassified obesity or being overweight by the BMI method. Finally, details of medical diagnoses, medical treatment status (eg, prescriptions), clinical condition and cause of mortality were not available. Thus, further studies are required to clarify the effects of these variables.

In conclusion, cardiovascular risk clustering and being overweight can be a useful predictor of medical expenditures. On the contrary, the sum of excess medical expenditures because of risk factor clustering in normal weight individuals is larger than that in overweight individuals because of the relatively small ratio of overweight individuals in Japan. However, the obesity epidemic is not restricted to Western countries. Furthermore, mean BMI is rapidly increasing in Asian countries such as Japan. Accordingly, being overweight might increase population medical expenditures in the future.

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Appendix 1

The Health Promotion Research Committee of the Shiga NHI Organizations

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Reduction of Visceral Fat Is Associated With Decrease in the Number of Metabolic Risk Factors in Japanese Men

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Visceral fat accumulation is associated with the development of metabolic disorders such as glucose intolerance, dyslipidemia, hypertension, and atherosclerotic cardiovascular diseases (1–8). However, the relationship between reduction of visceral fat and decrease in the number of metabolic risk factors has not been defined in the general population. Recently, we developed a new technique, the abdominal bioelectrical impedance analysis (BIA), to evaluate visceral fat area (VFA) (9). The aim of this study was to investigate whether reduction of visceral fat, estimated by the BIA, is associated with a decrease in the number of metabolic risk factors.

RESEARCH DESIGN AND METHODS

— The study group comprised 2,336 Japanese men (aged mean ± SD 48.0 ± 10.5 years, BMI 24.2 ± 2.9 kg/m^2), who were employees of Amagasaki City Office, an urban area, and had undergone annual health check-ups in both 2004 and 2005. After the health check-up, the medical staff provided risk factor–oriented, rather than obesity-oriented, health promotion programs to select individuals with visceral fat accumulation and multiple risk factors, with the aim of encouraging a scientific understanding of the spectrum of metabolic syndrome from visceral fat accumulation to atherosclerotic cardiovascular diseases. In this study, we used VFA estimated by the BIA, which was shown to correlate significantly with VFA determined by computed tomography (9). The measurement of VFA by BIA complied with the Guidelines of the Ethical Committees of Osaka University. Informed consent was obtained from all subjects.

Overall obesity was defined as BMI of >25 kg/m^2 (10). We investigated the presence of three metabolic risk factors: elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg), dyslipidemia, and dysglycemia/impaired glucose tolerance. Dyslipidemia represented hypertriglyceridemia (fasting or postprandial triglyceride of ≥1.69 or 2.27 mmol/l [11,12], respectively, and/or low HDL cholesterol [HDL cholesterol <1.04 mmol/l]). Dysglycemia/impaired glucose tolerance represented hyperglycemia (fasting or postprandial serum glucose concentration of >6.1 or >7.77 mmol/l [13], respectively). Subjects who received specific treatment(s) for each of the metabolic risk factors were considered positive for that factor.

Statistical analysis

Fischer's protected least significant difference test and Kruskal-Wallis were used to analyze the relationship between the number of metabolic risk factors and body fat distribution and between change in the number of metabolic risk factors and change in VFA, respectively. Significance level was set at $P < 0.05$.

RESULTS — BMI and VFA varied considerably among individuals. We divided subjects into two groups according to BMI and into two groups according to VFA (Fig. 1*A*). Visceral fat accumulation was defined as VFA of ≥100 cm^2 (10,14). Among 1,497 nonobese subjects (BMI <25 kg/m^2), 401 (26.8%) had visceral fat accumulation. The mean number of metabolic risk factors in subjects with VFA ≥100 cm^2 was significantly higher than in those with VFA <100 cm^2, irrespective of BMI. Importantly, the mean number of metabolic risks was significantly higher in subjects with VFA ≥100 cm^2 plus BMI <25 kg/m^2 than in those with VFA <100 cm^2 plus BMI ≥25 kg/m^2 ($P < 0.0001$) (Fig. 1*A*). These results suggest that assessment of visceral fat accumulation is important in identifying subjects with multiple risk factors.

Next, we investigated the correlation between a 1-year change in VFA (ΔVFA) and change in the number of metabolic risk factors (Δn) within the same period in the 2,336 subjects. VFA decreased within 1 year in 53.1% (1,241 of 2,336) of participants, increased in 33.2% (776 of 2,336), and did not change in 13.7% (319 of 2,336).

We divided these subjects into six bins of ΔVFA (every 15 cm^2). ΔVFA correlated significantly with Δn ($P < 0.0001$) (Fig. 1*B*). When the subjects who received new treatment after 2004 were excluded from the analysis, reduction of visceral fat was also associated with a significant decrease in the number of metabolic risk factors ($P < 0.0001$) (data not shown).

CONCLUSIONS — We demonstrated that *1*) irrespective of BMI (< or ≥25 kg/m^2), subjects with visceral fat accumulation estimated by BIA had a cluster of metabolic risk factors and *2*) falls in VFA within 1 year were associated with a significant decrease in the number of metabolic risk factors.

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Abbreviations: BIA, bioelectrical impedance analysis; VFA, visceral fat area.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

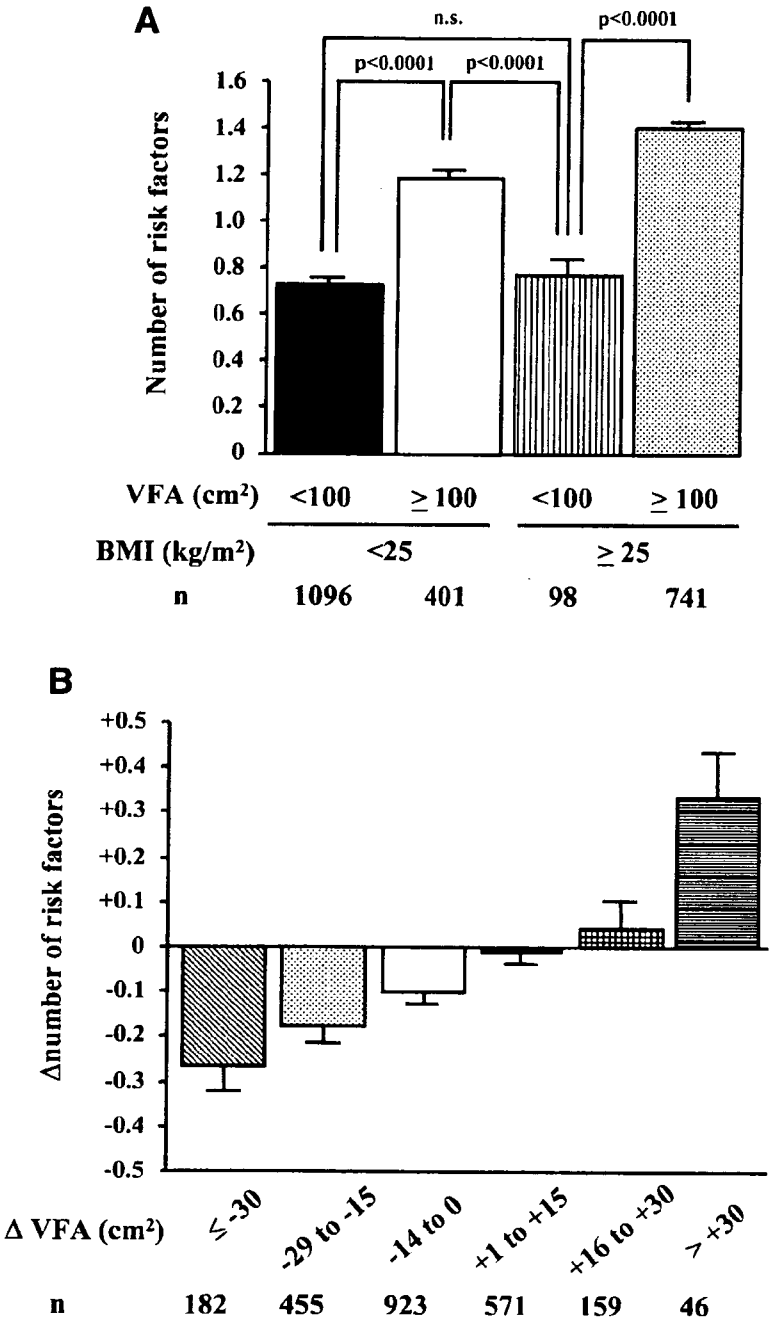

Figure 1—A: *Relationship between number of metabolic risk factors and body fat distribution. Subjects were divided according to their BMI (cutoff value 25 kg/m²) and VFA (cutoff value 100 cm²), measured in 2004. Data are means ± SE.* B: *Correlation between changes in VFA and changes in the number of metabolic risk factors. Δnumber of metabolic risk factors represents changes in the number of metabolic risk factors from 2004 to 2005. ΔVFA indicates change in VFA from 2004 to 2005. Subjects were divided into six 15-cm² bins of ΔVFA. Data are means ± SE.*

Importantly, our results also demonstrated that subjects with visceral fat accumulation but without overall obesity (VFA ≥100 cm² plus BMI <25 kg/m²) exhibited significantly more metabolic risk factors than overall obese subjects without visceral fat accumulation (VFA <100 cm² plus BMI ≥25 kg/m²). There is ample evidence for the role of visceral fat accumulation in the development of metabolic disorders (4–8,15). Collectively, the above results indicate that assessment of visceral fat accumulation using VFA estimated by BIA is useful for identifying high-risk groups for atherosclerotic cardiovascular diseases.

Our results also demonstrated in a large population sample that changes in VFA within 1 year correlated significantly with Δn. Several reports demonstrated in obese subjects that reduction of visceral fat correlated with improvement in glucose and lipid metabolism (16–19). However, there is little information on the effect of reduction of visceral fat on the number of metabolic risk factors in a large general population sample. Here, we showed in 2,336 subjects that changes in VFA within 1 year correlated significantly with changes in the number of metabolic risk factors. These results suggest that intervention strategies directed toward reduction of visceral fat could result in the reduction or disappearance of risks for atherosclerotic cardiovascular diseases. Since BIA is quite simple and noninvasive for evaluation of visceral fat amount, it could be used in routine clinical practice and large-scale studies for assessment of visceral fat accumulation.

In conclusion, we demonstrated that reduction of visceral fat was closely associated with a decrease in the number of metabolic risk factors in Japanese men.

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