have significantly more restenosis of the lumen than non-diabetic patients, as determined by quantitative coronary angiographic analysis, regardless of the treatment modality for diabetes[9] Serial intravascular ultrasound analysis has shown that accelerated intimal hyperplasia in the stented lesion is the main cause of the increased restenosis in diabetic patients[23] In contrast, most risk factors for CAD are not associated with an increased risk of restenosis[2,3] In the present study, we found no significant correlation of the various risk factors for CAD to ISR, except for diabetes. Thus, our result is quite consistent with previous reports in which diabetes is a potent risk factor for restenosis after coronary stenting[3,5,24]

The mechanisms involved in the development of ISR in diabetic patients have been extensively investigated in animal models. The metabolic alterations caused by diabetic hyperglycemia or hyperinsulinemia are considered to be involved in many of the pathophysiologic processes leading to restenosis. Long-term hyperglycemia leads to the formation of advanced glycation endproducts (AGEs); the accumulation of AGEs and their receptors in the vessel wall has been implicated in the neointimal formation after vascular injury in diabetic rats[25] Hyperinsulinemia rather than hyperglycemia may be of crucial importance in promoting the exaggerated neointimal hyperplasia after balloon injury. Hyperinsulinemia has been shown to induce cell proliferation through the activation of the Ras/MARK pathway in diabetic animals[26] Park et al evaluated 2 different models of DM: streptozotocin (STZ)-treated Sprague-Dawley rats (type 1 DM) and obese Zucker rats (type 2 DM). Neointimal hyperplasia was assessed by computerized morphometry after carotid balloon injury. Whereas there was no difference in the neointimal area in the STZ-treated rats compared with the controls, the neointimal area was markedly increased in the obese Zucker rats, which suggested the possibility that insulin resistance is associated with a propensity for neointimal proliferation[8] Although the data from animal studies have suggested several possible pathways that might underlie the exacerbation of ISR in diabetes, the precise mechanisms of ISR in clinical observations remain poorly defined.

Local and mechanical factors, such as implantation of multiple stents, longer stents, and small stent diameter, have been reported as independent predictors of ISR after coronary intervention[1–3,27] Kastrati et al reported that stent placement procedures yielding a final MLD of less than 3 mm increased the likelihood of restenosis by 50% and doubled the likelihood of target lesion revascularization! The lesion length was also reported to be a significant correlate of lumen loss at 6-month angiographic follow-up[28] However, factors related to the implanted stents did not seem to be the prime cause of ISR observed in the diabetic patients in the present study.

The present study showed for the first time that the markedly increased rate of post-stenting restenosis observed in diabetic patients is associated with an increased serum MDA-LDL concentration. This trend was not observed in the non-diabetic patients, suggesting the adverse effects of elevated serum MDA-LDL to ISR are peculiar to diabetic patients. MDA-modified LDL, one of the major oxidized LDL, has been known to play key roles in the progression of atherosclerosis[29,30] The serum level of MDA-LDL is increased in CAD patients, and is positively correlated with the thickness of the intima media in the carotid arteries[31] Circulating MDA-LDL is distributed in serum fractions containing small, dense LDL[18] and the elevated circulating MDA-LDL is considered to be a potent risk factor for atherosclerosis[32] On the other hand, the level of circulating MDA-LDL is reported to be elevated in patients with diabetes[33] and in STZ-induced diabetic rats[34] The mechanisms underlying the increase in MDA-LDL in diabetes have not been fully clarified, although enhancement of lipoperoxidation and decreased glutathione levels are reportedly involved in the elevated level of MDA-LDL[35] Interestingly, treatment with pravastatin, an HMG-CoA reductase inhibitor, can normalize elevated MDA-LDL levels without affecting the LDL-cholesterol level, suggesting that its effects might be attributable to decreased LDL oxidation[34] The precise pathway between elevated serum MDA-LDL and increased ISR was not defined in this study. Oxidized LDL has been reported to exert direct cytotoxicity on endothelial cell, to promote synthesis and secretion of adhesion molecules, and to increase monocyte chemotaxis and adhesion[11,12] Oxidized LDL increases vascular smooth muscle cell proliferation[13,14] and the mitogenic effect of oxidized LDL on vascular smooth muscle cells is mediated by the activation of the Ras/Raf/MEK/MAPK pathway[36] The inflammatory and proliferative effects of oxidized LDL may be accountable for the enhancement of neointimal cell proliferation that leads to ISR in diabetic patients.

The source of the elevated serum MDA-LDL in the diabetic patients who developed restenosis was uncertain in this study; however, the observed increase in MDA-LDL did not seem to be derived from local restenosis site (ie, neointima in the stent). First, pathology of the restenosis site consists of proliferated neointima and lacks a lipid core of oxidized LDL that might be the source of circulating MDA-LDL. Second, increased serum MDA-LDL levels were not observed in non-diabetic patients, including those who developed ISR (Fig 1). Finally, serum MDA-LDL levels were not altered after treatment of restenosis with balloon angioplasty to mechanically abrogate the neointima at the restenosis site (Fig 4). Interestingly, serum MDA-LDL was positively correlated with HbA_{1c} level in diabetic patients (Fig 2), although HbA_{1c} did not relate to ISR itself (Fig 3). These results support the notion that the elevation of serum MDA-LDL is attributable to the metabolic abnormalities of T2DM and acts as a promoter of ISR in diabetic patients.

The present study clearly showed that an elevated level of serum MDA-LDL in diabetic patients relates to ISR. However, because measurement of MDA-LDL was performed during the follow-up period in this study, it is uncertain whether the MDA-LDL level at the time of PCI predicts future ISR. In this respect, diabetic patients tend to have no apparent angina symptoms, even when significant restenosis has occurred. Thus, measurement of serum MDA-LDL during follow-up period, seems to be useful as an indicator of the potential development of ISR in these less symptomatic diabetic patients.

In conclusion, an elevated serum MDA-LDL concentration appears to be a major adverse factor for ISR in diabetic patients. Further studies are necessary to investigate the upstream and downstream pathways leading to ISR associated with elevated MDA-LDL and to determine the origin of the increased serum MDA-LDL in diabetic patients.

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Impact of Metabolic Syndrome on the Long-Term Survival of Patients With Acute Myocardial Infarction

— Potential Association With C-Reactive Protein —

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Background Population-based cohort studies demonstrate that metabolic syndrome (MeS) is associated with increased risk for cardiovascular diseases and related mortalities. The present study was designed to investigate the prognostic impact of MeS in patients with acute myocardial infarction (AMI).

Methods and Results The study group was 461 AMI patients without a history of previous myocardial infarction. On the basis of the National Cholesterol Education Program Adult Treatment Panel III criteria, MeS was defined having at least 3 of the following 5 conditions: dysglycemia (impaired fasting glucose, current use of insulin or oral hypoglycemic drugs), hypertriglyceridemia, low high-density lipoprotein-cholesterol level, hypertension and obesity. The prevalence of MeS was 37% (n=172). C-reactive protein (CRP) levels increased with the increase in the number of conditions of MeS. During follow-up at a median of 17.6 months, the incidence of major adverse cardiovascular events (MACE) was significantly different between patients with and without MeS. Furthermore, after adjustment of predictive factors (age, sex, Killip class, multivessel coronary artery disease, low ejection fraction and high CRP level), MeS was an independent risk factor for MACE.

Conclusions In patients with AMI, MeS is associated with systemic inflammation and is an important predictor for MACE, which suggests the need for early identification and medical intervention for secondary prevention of MeS. (*Circ J* 2008; **72:** 415–419)

Key Words: Glucose; Inflammation; Metabolic syndrome; Myocardial infarction

Several population-based studies have shown that metabolic syndrome (MeS) is an independent predictor of cardiovascular diseases, including acute myocardial infarction (AMI)[1–3] It has also become clear that MeS is strongly associated with systemic inflammation characterized by high levels of C-reactive protein (CRP)[4,5]

Although the number of deaths caused by AMI has declined over the past decade, the incidence of recurrent myocardial infarction (MI) is unchanged[6,7] which indicates the importance of understanding the underlying risk factors that lead to secondary cardiac events. Therefore, this study was designed to investigate the long-term prognostic impact of MeS in patients with AMI.

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Methods

Study Patients

From January 2000 to December 2002, 465 patients who had an AMI without a previous MI were admitted to the coronary care unit of the National Cardiovascular Center, Japan. Four patients complicated with severe inflammatory diseases such as sepsis, pneumonia and pyelonephritis were excluded, leaving a total of 461 patients who were retrospectively analyzed in the present study. The study protocol was approved by the institutional review board.

Definitions

AMI was defined as the presence of any 2 of the following 3 conditions: typical chest pain for at least 30 min, typical electrocardiogram changes (ST elevation, ST depression, T inversion and new pathological Q waves in at least 2 adjacent leads) and elevation of serum creatine kinase level to more than twice the upper normal limit.

Significant coronary artery stenosis was defined as stenosis in more than 75% of the vessels. Multivessel coronary disease was defined as a significant stenosis of 1 or more vessels other than the infarct-related artery. Left main coronary disease was considered to be double vessel involvement. Left ventricular ejection fraction (LVEF) was measured by the Simpson's method on left ventriculography or echocardiography, and left ventricular dysfunction was defined as a LVEF <40%. Congestive heart failure at admission was diagnosed on the basis of physical examination, such as presence of moist rales on chest auscultation and

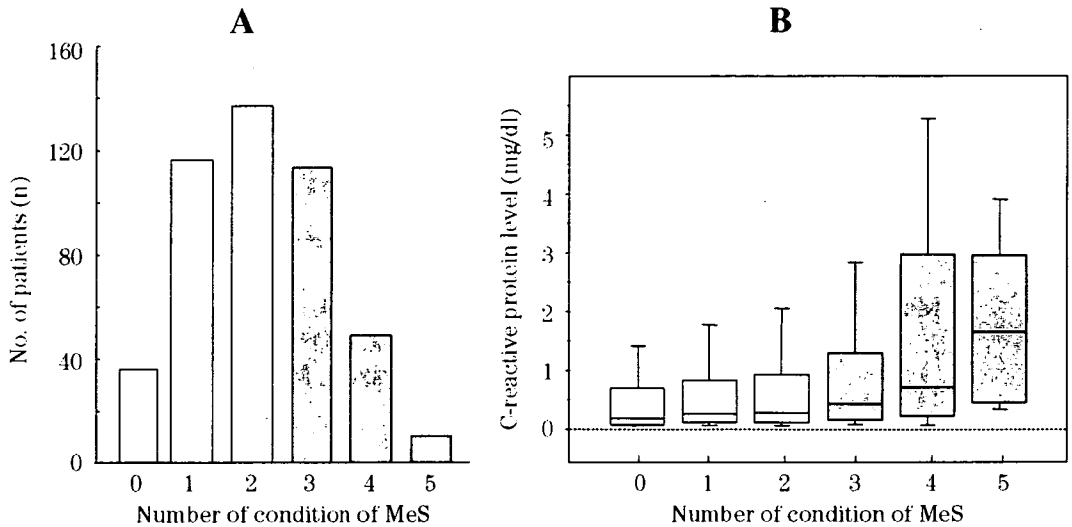

Fig 1. (A) Distribution of the number of conditions of metabolic syndrome (MeS) among 461 patients with acute myocardial infarction. (B) Distribution of C-reactive protein level according to the number of conditions of MeS. Box plots demonstrate median, and 25th, and 75th percentile values for C-reactive protein.

pulmonary congestion on the chest roentgenogram.

The presence of atherosclerotic disease was confirmed by a history of cerebral infarction, presence of arteriosclerosis obliterans or aortic aneurysm.

MeS was defined as having at least 3 of the following 5 conditions set by the recent National Cholesterol Education Program (NCEP) Adult Panel III (ATP-III) report[8] with modifications: dysglycemia, hypertension, hypertriglyceridemia, decreased level of high-density lipoprotein (HDL)-cholesterol, and obesity. Dysglycemia was defined as a fasting glucose >6.11 mmol/L; for the purpose of this analysis, the dysglycemia definition was also met by current use of insulin or oral hypoglycemic drugs. Hypertension was defined as a systolic blood pressure >130 mmHg and/or a diastolic blood pressure >85 mmHg; for the purpose of this analysis, hypertension was also met by current use of antihypertensive drugs. Hypertriglyceridemia was defined as a serum triglyceride level >1.69 mmol/L. Low HDL-cholesterol was defined as a serum level <1.03 mmol/L in men and <1.29 mmol/L in women. Obesity was defined as a body mass index >25 kg/m^2 according to the guidelines of the Japan Society for the Study of Obesity, because the body structure of Japanese is smaller than that of Caucasians and Africans and therefore the World Health Organization criteria appear to be inappropriate for Japanese[9,10]

In addition, the CRP level was defined as high if >0.3 mg/dl, on the basis of previous studies[4,11,12]

Laboratory Measurements

To assess the glycemic and lipid profiles, venous blood samples were drawn in the morning during fasting conditions in the stable phase of AMI (median: 9 days from the onset of AMI). Serum glucose concentration was measured using a glucose oxidase method (Glucose GA-1140; Arkray, Kyoto, Japan). Total cholesterol, triglyceride and HDL-cholesterol concentrations were determined by enzymatic methods using a Toshiba TBA 80M analyzer (Toshiba, Japan). Low-density lipoprotein was calculated using Friedewald's formula.

Serum CRP level was measured by the N Latex CRP II monoassay using a nephelometric technique with a nephelometric analyzer (BN II, Dade Behring, Germany). Additional measurements of CRP level were also performed in the acute phase (median: 2 days from the onset of AMI) and just before discharge (median: 15 days from the onset of AMI). The lower detection limit of this test was 0.06 mg/dl.

Blood samples were analyzed in the hospital central laboratory in a blinded fashion.

Follow-up Study

A follow-up study by reviewing medical records or by telephone interview was carried out for all patients. The endpoints were death from any cause and major adverse cardiovascular events (MACE), which included cardiac death, nonfatal MI, heart failure, and the need for percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG). The follow-up period for each patient was calculated from the onset of AMI.

Statistical Analysis

Means are expressed with SD for continuous variables, and medians are presented with 25–75th percentiles for skewed variables. Differences in categorical variables between 2 groups were evaluated with χ^2 test. Differences between means or medians for continuous variables were evaluated with t-test or Mann-Whitney U-test, as appropriate. Survival and event-free survival curves were analyzed by the Kaplan-Meier method and comparison between curves was carried out by log-rank test. Multivariate analysis of death and MACE was evaluated with Cox's proportional hazard model. Results were considered significant when the p-value was <0.05. Statistical analysis was performed with StatView 5.0 software (SAS Institute, Cary, NC, USA).

Results

Prevalence and Characteristics of Patients With MeS

Among the 461 AMI patients (326 men, 135 women), 172 had MeS (Fig 1A), a prevalence of 37%. Patients with MeS were more likely to be young and female and to have a history of systemic atherosclerotic disease than patients

Table 1 Comparison of the Patients' Clinical and Angiographic Characteristics

	MeS(+)	MeS(−)	p value
Age (years)	65.9±11.8	68.2±11.6	0.04
Female, % (n)	35% (61)	26% (74)	0.02
Dysglycemia	61% (105)	18% (52)	<0.01
Hypertriglyceridemia	49% (84)	10% (28)	<0.01
Low HDL-cholesterol	94% (161)	40% (117)	<0.01
Hypertension	86% (148)	54% (156)	<0.01
Obesity (BMI ≥25 kg/m²)	49% (84)	13% (39)	<0.01
Atherosclerotic disease, % (n)	28% (49)	20% (57)	0.04
Smoking, % (n)	73% (125)	70% (201)	0.53
LDL-cholesterol (mmol/L)	3.28 (2.73–3.90)	3.42 (2.75–3.79)	0.56
CRP (mg/dl)	0.54 (0.18–1.57)	0.26 (0.12–0.82)	<0.01
Killip class ≥2, % (n)	15% (26)	15% (43)	0.99
Multivessel disease, % (n)	52% (85)	46% (131)	0.33
Anterior MI, % (n)	43% (73)	48% (139)	0.25
PCI, % (n)	71% (122)	75% (216)	0.39
Stent use, % (n) to no. of PCI	79% (96)	78% (168)	0.42
CABG, % (n)	11% (19)	9% (25)	0.42
Peak CK (U/L)	1,953 (1,125–3,477)	1,841 (973–3,142)	0.43
LVEF <40%, % (n)	31% (53)	30% (85)	0.75
Medications during follow-up period			
Oral hypoglycemics, % (n)	28% (48)	7% (21)	<0.01
Insulin, % (n)	15% (25)	4% (12)	<0.01
β-blocker, % (n)	58% (100)	44% (127)	<0.01
Statin, % (n)	40% (68)	33% (96)	0.16
Aspirin, % (n)	97% (166)	94% (271)	0.28
ACEI, % (n)	65% (112)	57% (164)	0.08
ARB, % (n)	11% (18)	8% (24)	0.50

Data are mean±SD, percentage, or median value (interquartile range).
MeS, metabolic syndrome; HDL, high-density lipoprotein; BMI, body mass index; LDL, low-density lipoprotein; CRP, C-reactive protein; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; CK, creatine kinase; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker.

without MeS (Table 1). However, Killip class, incidence of multivessel coronary artery disease and the proportion of coronary revascularization by PCI or CABG, peak creatine kinase, left ventricular dysfunction and anterior wall MI were similar between the 2 groups.

The CRP data for the acute phase was available for 449 patients (median, 2 days after onset of MI). Because 20 patients died in hospital (including 11 patients who died within 3 days of admission because of cardiogenic shock) and 7 patients did not undergo data sampling just before discharge, the CRP data for the chronic phase was available in 422 patients. Although the serum CRP level in the acute phase was similar between the 2 groups (median CRP level of patients with MeS: 1.2 mg/dl vs that of patients without MeS: 1.5 mg/dl, p=0.70), those measured just before discharge (median, 15 days after the onset of infarction) were higher in the patients with MeS than in the patients without MeS (median, 0.54 vs 0.26 mg/dl, p<0.01). As shown in Fig 1B, there was a linear increase in the CRP level as the number of conditions of MeS increased; the median CRP levels for patients with 0, 1, 2, 3, 4, and 5 conditions were 0.19, 0.26, 0.29, 0.43, 0.73, and 1.66 mg/dl, respectively. In the multivariate analysis, CRP level was significantly associated with MeS, but not with infarct size or left ventricular dysfunction.

Medications during the follow-up period, such as insulin, oral hypoglycemic drugs and β-blockers were frequently used in the patients with MeS (Table 1). However, both patient groups similarly received other cardiovascular medications, including statins, aspirin, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers.

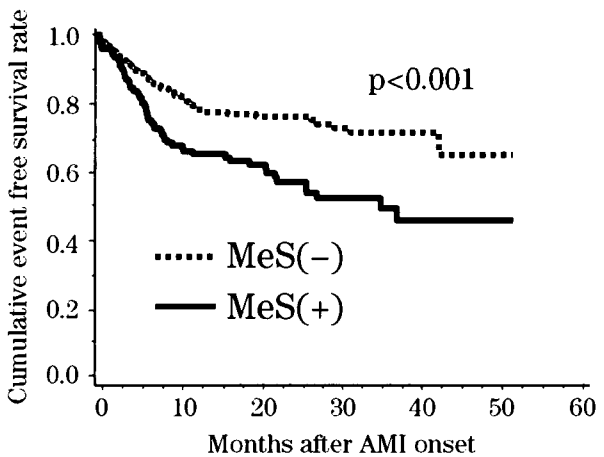

Fig 2. Cumulative event-free survival curves in acute myocardial infarction (AMI) patients with (solid line) and without (dotted line) metabolic syndrome (MeS).

Long-Term Mortality and MACE

During follow-up of a median of 17.6 months (interquartile range: 6.3–30.1), 33 patients died from various causes and 124 patients had at least 1 MACE: cardiac death in 20, heart failure in 24, nonfatal MI in 11 and revascularization in 69 patients. Regarding the occurrence of MI, there were 13 cases of fatal and non-fatal MI during the follow-up. Fig 2 shows that the cumulative-event-free survival rate of patients with MeS was significantly lower than that of the patients without MeS. In the unadjusted Cox's proportional hazard model analysis, the hazard ratio (HR) for MACE in

Table 2 Multivariate Analysis of Predictors of Clinical Outcome

	Death		MACE	
	HR (95%CI)	p value	HR (95%CI)	p value
Age >70 years	3.31 (1.13–9.66)	0.02	1.15 (0.77–1.73)	0.48
Female	3.06 (1.27–7.34)	0.01	1.21 (0.79–1.87)	0.36
Multivessel disease	1.29 (0.45–3.63)	0.62	1.35 (0.90–2.02)	0.14
Killip class ≥2	1.86 (0.76–4.71)	0.16	2.10 (1.29–3.43)	<0.01
LVEF <40%	7.06 (2.50–19.9)	<0.001	1.44 (0.96–2.18)	0.07
CRP ≥0.3 mg/dl	5.57 (1.62–19.2)	<0.01	1.41 (0.94–2.07)	0.09
MeS	1.27 (0.54–3.04)	0.58	1.83 (1.24–2.70)	<0.01

HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiac events. Other abbreviations see in Table 1.

Table 3 Prognostic Value of MeS for MACE

MACE	HR (95%CI)	p value
Cardiac death	0.96 (0.30–3.03)	0.95
Fatal and nonfatal MI	0.84 (0.23–2.70)	0.76
Nonfatal MI	1.02 (0.28–3.69)	0.97
CHF (Killip class ≥2)	2.60 (1.01–6.66)	0.04
Coronary revascularization	2.10 (1.27–3.47)	<0.01

Adjusted for age >70 years, female gender, multivessel disease, Killip class ≥2, LVEF <40, and CRP >0.3 mg/dl.
CHF, congestive heart failure. Other abbreviations see in Tables 1, 2.

patients with MeS was 2.05. When we performed multivariate Cox's proportional hazard model analysis for several potential confounders, including age >70 years, female gender, Killip class ≥2, multivessel coronary disease, left ventricular dysfunction (LVEF <40%) and CRP >0.3 mg/dl, MeS remained an independent risk factor for MACE (HR 1.83, 95% confidence interval (CI) 1.24–2.70; p<0.01) after adjustment (Table 2). Multivariate analysis also demonstrated that elevated CRP level even in the stable period, appeared to be a potential determinant of death (HR 5.57, 95% CI 1.61–19.2; p<0.01) and of MACE (HR 1.40, 95% CI 0.94–2.07; p=0.09). To further explore the synergic effect of MeS and CRP, we divided the study patients into 4 groups on the basis of the presence or absence of MeS and on the basis of CRP levels less than or greater than 0.3 mg/dl.[7] When setting patients without MeS and with a low CRP level (<0.3 mg/dl) as the reference, the relative risks of future cardiovascular events following AMI were 1.82 (95% CI 1.12–2.95) in patients without MeS and with a high CRP level (≥0.3 mg/dl), 2.24 (95% CI 1.21–4.16) in patients with MeS and a low CRP level, and 2.56 (95% CI 1.56–4.20) in patients with MeS and a high CRP level. These findings suggest there is a synergistic effect between MeS and CRP for experiencing cardiovascular events in patients following AMI.

We then assessed individual cardiac events among the MACE that were associated with MeS. In the multivariate analysis, MeS was significantly associated with repeated coronary revascularization and congestive heart failure (Table 3). Furthermore, we assessed the individual conditions of MeS for MACE and of the 5 components, only dysglycemia was found to be a significant risk factor for MACE after adjustment (Table 4).

Discussion

The major findings of the present study are that MeS is associated with MACE and that a high CRP level is independently associated with mortality after AMI during a 17.6-month follow-up. Moreover, of the 5 conditions of MeS, dysglycemia is the most important factor in mortality and MACE.

The Observatoire des Infarctus de Cote-d'Or Survey demonstrated that the prevalence of MeS in patients with AMI was 46% and that MeS was associated with in-hospital outcome (eg, development of heart failure several days after the onset of AMI).[13] In that survey population (n=633), only 20–25% of patients underwent reperfusion therapy, so the impact of MeS on long-term prognosis (after discharge) remains unknown, particularly in the recent reperfusion era.

In our study, the AMI patients with MeS had a higher incidence of atherosclerotic disease and a higher CRP level measured during the stable period (median, 15 days after onset) than AMI patients without MeS. In patients with AMI, the CRP level reaches its peak approximately 2–4 days after AMI onset,[14,15] in accordance with the extent of myocardial necrosis.[16] Independent of infarct size, the CRP level measured in the stable period (25 days after AMI onset) has been reported to be significantly associated with long-term mortality in patients with AMI.[17] Taken together with the present result by multivariate analysis that CRP level measured in the stable period of AMI was associated only with MeS, but not with infarct size and cardiac func-

Table 4 Incidence and Significance of Each Condition of the MeS for Clinical Outcomes

	Prevalence	Death		MACE	
		HR (95%CI)	p value	HR (95%CI)	p value
Dysglycemia	34.2%	2.39 (0.93–6.11)	0.07	1.61 (1.07–2.41)	0.02
Hypertriglyceridemia	24.3%	0.93 (0.23–3.67)	0.91	1.30 (0.84–2.02)	0.24
Low HDL-cholesterol	60.3%	1.64 (0.55–4.92)	0.37	1.38 (0.89–2.15)	0.15
Hypertension	65.9%	1.27 (0.41–4.00)	0.68	0.83 (0.54–1.24)	0.37
Obesity (BMI ≥25 kg/m²)	26.9%	0.35 (0.11–1.13)	0.08	1.26 (0.84–1.90)	0.09

Adjusted for age >70 years, female gender, multivessel disease, Killip class ≥2, LVEF <40, and CRP >0.3 mg/dl.
Abbreviations see in Tables 1, 2.

tion, it appears that systemic inflammation may be part of the pathophysiology of MeS![18] Therefore, an understanding of the interactions between metabolic and inflammatory pathways may be important with regard to secondary prevention of MACE after AMI.

We found that MeS is significantly associated with repeated coronary revascularization and congestive heart failure, a finding that may be related to the development of new coronary stenosis or restenosis during the follow-up period, leading to myocardial ischemia and left ventricular dysfunction. Previous studies also show that a persistent inflammatory response plays an important role in the post infarction remodeling process![16]

As shown in Table 2, dysglycemia, defined as impaired fasting glucose or previous diabetic medication, is the most important among the 5 conditions of MeS, which may be related to a previous observation that the onset of diabetes follows elevated levels of atherosclerotic risk factors![19] Therefore, it is therapeutically important to simultaneously improve glucose intolerance, abnormal lipid metabolism, blood pressure level and inflammation![20–22]

Controversy exists as to whether the MeS is more than the sum of its independent metabolic components. An important finding in the present study is that MeS is closely associated with elevation of CRP. Moreover, MeS seems to have a synergistic effect on CRP. Because inflammation participates centrally in the process of atherosclerosis![23] MeS may indicate a potential risk for future cardiovascular diseases. Further studies are needed to address this issue.

In conclusion, MeS is associated with a high CRP level and is an important predictor for MACE following AMI. This finding suggests the need for early identification and medical intervention of this underlying disease for preventing future adverse cardiac events.

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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 impédance 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.

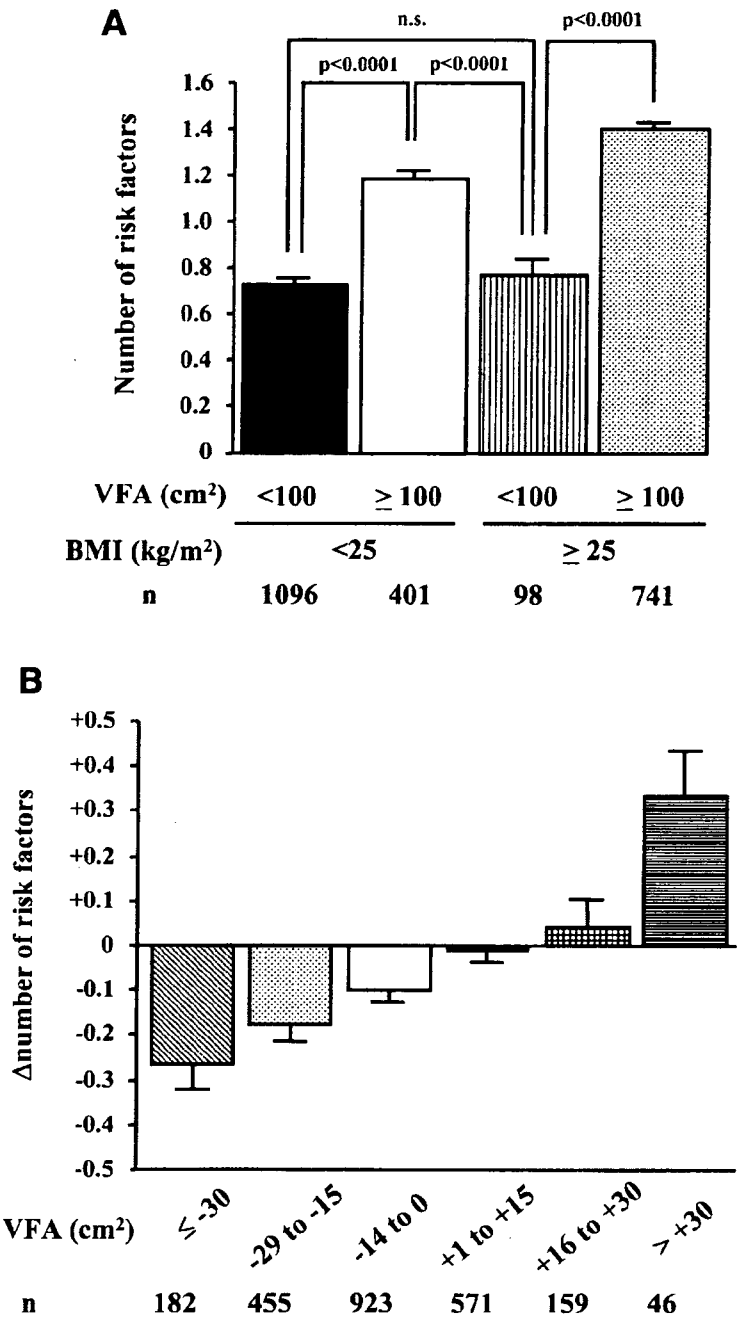

Figure 1—A: *Relationship between number of metabolic risk factors and body fat distribution. Subjects were divided according to their BMI (cutoff value 25 kg/m²) and VFA (cutoff value 100 cm²), measured in 2004. Data are means ± SE.* B: *Correlation between changes in VFA and changes in the number of 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 Δ*n*. 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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Hypoadiponectinemia in type 2 diabetes mellitus in men is associated with sympathetic overactivity as evaluated by cardiac ^{123}I-metaiodobenzylguanidine scintigraphy

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Abstract

Hypoadiponectinemia is associated with insulin resistance. However, there is very limited information about the relationship between plasma adiponectin and cardiac autonomic nervous function. We tested the hypothesis that hypoadiponectinemia is associated with cardiac sympathetic overactivity in patients with type 2 diabetes mellitus. Thirty-three male type 2 diabetic patients not on insulin treatment were classified into a hypoadiponectinemia group (plasma adiponectin concentration, <4.0 μg/mL; age, 58.6 ± 8.6 years [mean ± SD]; n = 14) and an age-matched normoadiponectinemia group (serum adiponectin concentration, ≥4.0 μg/mL; age, 58.2 ± 8.1 years; n = 19). In each patient, baroreflex sensitivity, heart rate variability, plasma norepinephrine concentration, and cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphic findings were assessed. Compared with the normoadiponectinemia group, the hypoadiponectinemia group had a higher body mass index ($P < .01$), higher plasma concentrations of glucose and insulin ($P < .05$ and $P < .01$, respectively), higher homeostasis model assessment of insulin resistance (HOMA-IR) values ($P < .005$), higher plasma triglyceride levels ($P < .05$), and lower plasma high-density lipoprotein cholesterol levels ($P < .05$). In the hypoadiponectinemia group, the autonomic function measurements included a lower baroreflex sensitivity ($P < .05$) and a lower delayed myocardial uptake of ^{123}I-MIBG ($P < .01$) with a higher washout rate ($P < .05$). Multiple regression analysis revealed that the plasma adiponectin level was independently associated with HOMA-IR ($F = 9.916$) and the percent washout rate of ^{123}I-MIBG ($F = 5.985$). Our results suggest that in middle-aged men with type 2 diabetes mellitus, hypoadiponectinemia is associated with cardiac sympathetic overactivity as determined by ^{123}I-MIBG scintigraphy.

1. Introduction

Adiponectin is a hormone that is produced by adipocytes [1]. In patients with type 2 diabetes mellitus, low plasma adiponectin levels are associated with insulin resistance [2,3]. Low plasma adiponectin levels have also been shown to be an independent predictor of type 2 diabetes mellitus [4]. Most importantly, plasma adiponectin and insulin resistance are strongly associated with the development of coronary artery disease [5,6]. Cardiac autonomic nerve dysfunction is strongly related to cardiovascular mortality in type 2 diabetic patients [7]. Although insulin resistance depresses cardiac autonomic nervous function in these patients [8-10], there is limited information on the relationship between plasma adiponectin and cardiac autonomic nervous function [11]. In subjects with insulin resistance, sympathetic overactivity may play a central role in pathogenesis [12,13]. In this regard, cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy is a sensitive diagnostic tool that allows the direct assessment of sympathetic nervous function [14]. Plasma adiponectin levels have been found to be lower in men than in women, probably because of the effects of androgen [15]. In the present study, we investigated the association between plasma adiponectin levels and cardiac autonomic function in relation to insulin resistance in middle-aged male patients with type 2 diabetes mellitus.

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2. Methods and design

2.1. Subjects

Sixty-five consecutive Japanese male patients with type 2 diabetes mellitus who were admitted to our department in 2003 were screened. Type 2 diabetes mellitus was defined as a fasting plasma glucose concentration of 126 mg/dL or greater or a 2-hour plasma glucose concentration of 200 mg/dL or greater after a 75-g oral glucose load, or the self-reported use of antidiabetic medication [16]. Of the 65 patients, the 33 patients who did not have organic heart disease were enrolled. Patients with macroalbuminuria (>300 mg/d) or abnormal plasma creatinine concentrations (≥ 1.2 mg/dL) were excluded. Patients treated with insulin were also excluded. Plasma adiponectin concentrations were measured in venous blood obtained between 6:00 and 7:00 AM after an overnight fast by using a commercially available enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals, Tokyo, Japan) [6]. Hypoadiponectinemia was defined as a plasma adiponectin concentration of less than 4.0 μg/mL [6]. Based on these results, 33 patients were classified as belonging to either the hypoadiponectinemia group (age, 58.6 ± 8.6 years [mean ± SD]; n = 14) or the normoadiponectinemia group (age, 58.2 ± 8.1 years; n = 19). The clinical characteristics of the studied patients are summarized in Table 1. After secondary hypertension was excluded, essential hypertension was defined as a diastolic blood pressure of 90 mm Hg or higher, a systolic blood pressure of 140 mm Hg or higher, or self-reported use of antihypertensive medication [17]. Dyslipidemia was defined as fasting triglyceride level of 200 mg/dL or higher or high-density lipoprotein (HDL) cholesterol level less than 35 mg/dL [17]. Insulin resistance was evaluated by using the homeostasis model assessment of insulin resistance (HOMA-IR) according to the following formula: HOMA-IR = {(fasting plasma insulin [μU/mL] × fasting plasma glucose [mmol/L])/22.5} [18]. Prior written informed consent was obtained from all patients, and the study protocol was approved by the institutional review board of Oita University.

2.2. Echocardiography

M-mode 2-dimensional echocardiography and cardiac Doppler recordings were obtained by using a phase-array echo-Doppler system. The left ventricular mass was calculated according to Devereux et al [19]: left ventricular mass = {1.04([LVIDd + IVSTd + PWTd]^3 − LVIDd^3) − 14 g}, where LVIDd is the left ventricular internal dimension at end diastole; IVSTd the interventricular septal thickness at end diastole, and PWTd the posterior wall thickness at end diastole. To calculate the left ventricular mass index (LVMI), the left ventricular mass was divided by the body surface area. Based on pulsed Doppler recordings, the peak velocity of early (E) and late ventricular filling (A) was determined, and the ratio (E/A) and deceleration time were measured to assess cardiac diastolic function.

2.3. Plasma norepinephrine concentration, heart rate variability, and baroreflex sensitivity

All subjects were studied while in the supine position in a quiet room between 9:00 and 11:00 AM [6-8]. A catheter was inserted into the right cubital vein, and the arterial blood pressure was recorded noninvasively by tonometry (Jentow-7700; Nihon Colin, Komaki, Japan) [20]. Arterial blood pressure and a 12-lead electrocardiogram (ECG) were monitored simultaneously; data were stored in a PCM data recorder (RD-200T; TEAC, Tokyo, Japan). Holter ECG recordings (model 459, Del Mar Avionics, Irvine, CA) were also obtained. After an interval of 30 minutes to allow the patient to stabilize, the patient was asked to breathe at a rate of 15 breaths per minute measured with a metronome. Subsequently, blood samples were obtained from the venous catheter to measure plasma norepinephrine concentration. The baroreflex sensitivity (BRS) was assessed with the phenylephrine method [8-10]. Phenylephrine (2-3 μg/kg) was injected over 15 seconds to increase the systolic blood pressure by 15 to 40 mm Hg. The BRS was calculated as the slope of the linear regression line relating the systolic blood pressure changes to the RR interval changes. Regression lines with more than 20 data points and a correlation coefficient (r) greater than 0.8 were accepted for analysis. The mean of the 2 slope values was taken as the BRS value.

Table 1
Clinical characteristics of the studied patients

	Hypo-AD (n = 14)	Normo-AD (n = 19)	P
Age (y)	58.6 ± 8.6	58.2 ± 8.1	NS
Duration of diabetes (y)	7.9 ± 5.4	7.2 ± 5.8	NS
Essential hypertension (%)	65	74	NS
Dyslipidemia (%)	48	53	NS
Drug use (%)			
Sulfonylurea	48	53	NS
α Glucosidase inhibitors	42	41	NS
Statin	39	41	NS
Calcium-channel antagonists	47	41	NS
Angiotensin-converting enzyme inhibitors	29	24	NS
Angiotensin receptor blockers	52	59	NS
Body mass index (kg/m^2)	27.0 ± 1.4	24.3 ± 3.4	< .01
Systolic blood pressure (mm Hg)	132 ± 18	130 ± 14	NS
Diastolic blood pressure (mm Hg)	77 ± 11	75 ± 9	NS
Heart rate (beats/min)	68 ± 6	67 ± 9	NS
Fasting plasma glucose (mg/dL)	156 ± 28	140 ± 25	< .05
Fasting immunoreactive insulin (μU/mL)	8.3 ± 2.6	6.1 ± 1.7	< .01
HOMA-IR	3.2 ± 1.0	2.1 ± 0.7	< .005
Hemoglobin A_{1c} (%)	7.7 ± 1.2	7.5 ± 1.0	NS
Total cholesterol (mg/dL)	211 ± 23	196 ± 27	NS
Triglyceride (mg/dL)	165 ± 55	132 ± 32	< .05
HDL cholesterol (mg/dL)	37 ± 8	45 ± 13	< .05
Uric acid (mg/dL)	6.4 ± 1.6	5.9 ± 1.3	NS
Creatinine (mg/dL)	0.8 ± 0.2	0.7 ± 0.2	NS
Creatinine clearance (mL/min)	83 ± 36	104 ± 32	NS

Data are mean ± SD unless otherwise indicated. Hypo-AD indicates hypoadiponectinemia group; Normo-AD, normoadiponectinemia group.

Heart rate variability (HRV) was analyzed by using a 300-second interval on the Holter ECG recordings obtained immediately before phenylephrine injection. The power spectrum of the RR interval was computed by a fast Fourier transform and expressed as the area under the power spectrum [8-10]. We calculated the power of 2 spectral bands, the low-frequency component (LF) at 0.04 to 0.15 Hz and the high-frequency component (HF) at 0.15 to 0.40 Hz. Based on their skewed distribution, the measured values of HRV were transformed to natural logarithmic values. The ratio of LF to HF (LF/HF) was also computed. Whereas HF represents cardiac vagal activity, LF is a mixture of vagal and sympathetic activities [21]. The LF/HF was used to estimate cardiac sympathetic activity [21].

2.4. Cardiac ^{123}I-MIBG scintigraphy

Metaiodobenzylguanidine is a guanethidine analogue that is accumulated in the norepinephrine storage granules in postganglionary sympathetic neurons. Radioactive labeling of MIBG allows visualization of the sympathetic neuronal tissue in richly innervated organs such as the heart [14]. Planar and single-photon emission computed tomography studies were performed at 15 minutes and 4 hours after the injection of 111 MBq of ^{123}I-MIBG with a rotating gamma camera (ZLC 7500, Siemens, Munich, Germany). The data were analyzed using analysis software (SCINTIPAC, Shimadzu, Kyoto, Japan). The anterior planar images from the early and delayed ^{123}I-MIBG studies were analyzed visually. To do the semiquantitative analysis, regions of interest were drawn over the whole heart, and a 10 × 10-mm area over the upper mediastinum on the early and delayed planar images was used to calculate the mean heart-mediastinum (H/M) ratio. After correcting for the physical decay of iodine 128, the percent washout rate (WR) of the tracer from the myocardium was determined over a 4-hour period.

2.5. Statistical analysis

Data are presented as mean ± SD. Differences between the 2 groups were analyzed by the unpaired Student t test, χ^2 test, or Fisher exact probability test as appropriate. A value of $P < .05$ was considered statistically significant. Simple (Spearman rank) correlation coefficients between the plasma adiponectin concentration and the various variables were calculated, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with plasma adiponectin concentration. On the multivariate analysis, F values of 4 or greater were considered statistically significant.

3. Results

As shown in Table 1, the 2 groups had a similar mean age and there were no significant differences with respect to duration of diabetes, number of patients with essential hypertension or dyslipidemia, and medications administered. The hypoadiponectinemia group had significantly higher body mass index ($P < .01$), fasting plasma glucose concentrations ($P < .05$), and insulin concentrations ($P < .01$), resulting in a higher HOMA-IR ($P < .005$). There was no significant difference in hemoglobin A_{1c} between the 2 groups. The plasma triglyceride was higher ($P < .05$) and the HDL cholesterol was lower ($P < .05$) in the hypoadiponectinemia group. The plasma creatinine and creatinine clearance were not significantly different. The hemodynamic data listed in Table 1 were obtained immediately before BRS assessment. The resting heart rate, as well as the systolic and diastolic blood pressures, was not significantly different. With respect to the echocardiographic findings, there were no significant differences in LVIDd and LVIDs at end systole (48 ± 4 vs 50 ± 4 mm and 31 ± 4 vs 33 ± 3 mm, respectively), IVSTD (9.0 ± 1.3 vs 9.5 ± 1.5 mm), PWTd (9.5 ± 1.2 vs 10.1 ± 1.2 mm), ejection

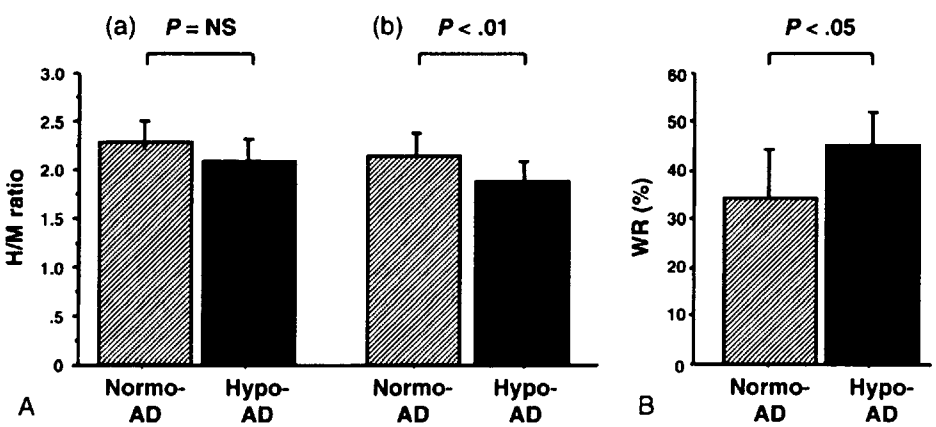

Fig. 1. Comparison of cardiac ^{123}I-MIBG scintigraphic findings in the type 2 diabetic patients with normoadiponectinemia (Normo-AD) and hypoadiponectinemia (Hypo-AD). A, Myocardial uptake of ^{123}I-MIBG in the early (a) and delayed (b) phases. Myocardial uptake of ^{123}I-MIBG is expressed as the mean H/M ratio. B, Percent WR of ^{123}I-MIBG. Data are mean ± SD.

fraction (70% ± 5% vs 69% ± 4%), and LVMI (113 ± 29 vs 121 ± 19 g/m^2). However, the E/A ratio was greater (0.95 ± 0.27 vs 0.77 ± 0.18, $P < .05$) and the deceleration time was longer (253 ± 27 vs 230 ± 31 msec, $P < .05$) in the hypoadiponectinemia group.

With respect to the results of the cardiovascular autonomic function tests, the BRS was lower in the hypoadiponectinemia group (6.0 ± 3.3 vs 9.4 ± 4.8 ms/mm Hg, $P < .05$), whereas plasma norepinephrine concentrations were similar (239 ± 99 vs 217 ± 112 pg/mL, P = not significant [NS]). The HRV analysis showed that the HF power and the LF/HF ratio were not significantly different (4.1 ± 1.7 vs 3.8 ± 1.4 ln ms^2, P = NS; 1.6 ± 0.9 vs 1.3 ± 0.9, P = NS, respectively). On cardiac ^{123}I-MIBG scintigraphy, although the H/M ratio in the early phase was not significantly different (2.12 ± 0.22 vs 2.27 ± 0.25, P = NS; Fig 1A[a]), in the delayed phase, the H/M ratio was lower in the hypoadiponectinemia group (1.94 ± 0.35) than in the normoadiponectinemia group (2.33 ± 0.31, $P < .01$; Fig. 1A[b]). The percent WR of ^{123}I-MIBG was higher in the hypoadiponectinemia group (42.5% ± 9.0% vs 34.5% ± 11.8%, $P < .05$; Fig. 1B). Table 2 shows the correlations between plasma adiponectin concentration and clinical variables for all of the patients in both groups. Plasma adiponectin concentration correlated negatively with body mass index, fasting plasma insulin, HOMA-IR, triglyceride, and percent WR of ^{123}I-MIBG, and positively with plasma HDL cholesterol, BRS, and H/M ratios in the early and delayed phases. Stepwise multiple regression analysis was done using these 9 variables. Plasma adiponectin concentration was found to be independently associated with HOMA-IR (F = 9.196) and the percent WR of ^{123}I-MIBG (F = 5.985) (Table 3).

Table 2
Correlations of plasma adiponectin with other variables

Parameters	Univariate	
	r	P
Age	−0.212	NS
Duration of diabetes mellitus	−0.190	NS
Body mass index	−0.372	.0332
Systolic blood pressure	−0.242	NS
Diastolic blood pressure	−0.120	NS
Heart rate	−0.335	NS
Total cholesterol	−0.089	NS
Triglyceride	−0.369	.0346
HDL cholesterol	−0.422	.0114
Uric acid	−0.228	NS
Fasting plasma glucose	−0.334	NS
Fasting immunoreactive insulin	−0.427	.0132
HOMA-IR index	−0.496	.0033
Hemoglobin A_{1c}	−0.206	NS
Creatinine	−0.202	NS
Creatinine clearance	0.333	NS
EF	0.155	NS
LVIDd	−0.317	NS
LVIDs	−0.236	NS
IVSTd	−0.153	NS
PWTd	−0.316	NS
LVMI	−0.297	NS
E/A ratio	0.151	NS
Deceleration time	−0.189	NS
Baroreflex sensitivity	0.407	NS
Plasma norepinephrine	−0.111	NS
HF power	0.091	NS
LF/HF	−0.252	NS
H/M ratio at early phase	0.401	.0206
H/M ratio at delayed phase	0.482	.0046
Percent WR of ^{123}I-MIBG	−0.423	.0142

Table 3
Stepwise regression analyses between plasma adiponectin and various parameters

Independent variable	Regression coefficient	SE	Standard regression coefficient	F
To adiponectin intercept	19.312			
HOMA-IR	−2.523	0.832	−0.444	9.196
Percent WR of ^{123}I-MIBG	−0.174	0.071	−0.358	5.985

F values equal to or greater than 4 were considered statistically significant.

4. Discussion

In the present study, middle-aged male type 2 diabetic patients with hypoadiponectinemia had a higher body mass index, higher fasting plasma concentrations of glucose and insulin, higher HOMA-IR, higher plasma triglyceride levels, and a lower plasma HDL cholesterol level than patients who had normoadiponectinemia. The body mass index, fasting plasma insulin concentration, HOMA-IR, plasma triglyceride concentration, and plasma HDL cholesterol concentration had a significant correlation with the plasma adiponectin concentration, which suggests a strong association between hypoadiponectinemia and insulin resistance [2,3]. Because there is a substantial association between these variables, it is possible that hypoadiponectinemia is associated with the overall abnormalities seen in glucose and lipid metabolism. Thus, although the present study was designed to assess the impact of hypoadiponectinemia, the obtained results might have been predominantly influenced by insulin resistance rather than hypoadiponectinemia.

In the present study, ^{123}I-MIBG scintigraphy showed that the H/M ratio in the delayed phase was decreased and the percent WR of ^{123}I-MIBG was increased in the hypoadiponectinemia group, and the percent WR of ^{123}I-MIBG was independently associated with plasma adiponectin concentration, which suggests that there is substantial sympathetic overactivity in patients with low plasma adiponectin concentration. These findings are novel. There is a growing body of evidence that sympathetic overactivity may play a central role in the pathogenesis of insulin resistance [22,23]. Recent experimental studies have also suggested that sympathetic overactivity has a role in the regulation of adiponectin expression [24,25]. Fasshauer et al [24] reported that adiponectin messenger RNA expression was inhibited by β-adrenergic stimulation via protein kinase A in 3T3-L1

adipocytes. More recently, Delporte et al [25] demonstrated that β-adrenergic stimulation down-regulated adiponectin messenger RNA in cultured mouse explants from the visceral and subcutaneous regions. Based on these experimental observations, it can be postulated that in patients with insulin resistance substantial sympathetic overactivity might reduce the adiponectin gene expression. However, it is still unclear whether low plasma adiponectin concentration, as observed in the clinical setting, is the cause or the result of sympathetic overactivity. With respect to vagal function, the BRS value was lower in patients with hypoadiponectinemia than in patients with normoadiponectinemia and was positively correlated with plasma adiponectin. Because there is a strong interaction between sympathetic and vagal activity [11], it is uncertain whether the low BRS value observed in the hypoadiponectinemia patients reflects relatively depressed vagal activity in response to sympathetic overactivity.

Until now, very limited information was available on the relationship between plasma adiponectin and cardiac autonomic nervous function. Wakabayashi and Aso [11] studied the relationship between plasma adiponectin concentration and the power spectral analysis of HRV in 105 patients with type 2 diabetes mellitus (51 women and 54 men); they reported that plasma adiponectin concentration showed an independent negative association with the 24-hour LF/HF ratio. Based on this observation, they concluded that a sympathovagal balance favoring relative sympathetic activation was associated with hypoadiponectinemia in patients with type 2 diabetes mellitus [11]. Although our HRV analysis did not show an association with plasma adiponectin concentration, our ^{123}I-MIBG scintigraphic findings appear to support their conclusion.

It is noteworthy that diastolic function, as determined by E/A ratio and deceleration time, is depressed in patients with hypoadiponectinemia. The exact mechanisms that explain the association between hypoadiponectinemia and diastolic dysfunction have not been elucidated. In a recent study demonstrating the association between insulin resistance and diastolic function in patients with type 2 diabetes mellitus and subjects with impaired glucose tolerance [26], the authors speculated that the insulin resistance may be involved in the onset of cardiac fibrosis, as shown in an experimental rat model of the prestage of type 2 diabetes mellitus [27].

Some methodological issues have to be addressed. First, 64% of hypoadiponectinemia patients and 74% of normoadiponectinemia patients had been diagnosed as having essential hypertension. In addition, 48% of hypoadiponectinemia patients and 53% of normoadiponectinemia patients had been diagnosed as having dyslipidemia. All these patients were being treated with one or more antihypertensive drugs and/or a statin, as shown in Table 1. These medications might have affected our results. Second, the present study included a relatively small number of patients because of our strict inclusion criteria. Third, there is currently no "gold standard" for the assessment of human sympathetic nervous activity to use as a comparison with other techniques. In fact, the reason why the patients with hypoadiponectinemia did not show an altered HRV or altered plasma norepinephrine levels, as expected, cannot be explained rationally. Regarding the HRV analysis, we analyzed ECG recording data using a 300-millisecond interval at rest obtained immediately before phenylephrine injection. The analysis using 24-hour data could have detected the sympathetic overactivity such as increased LF/HF. With respect to the levels of plasma norepinephrine, Grassi and Esler [28] mentioned that plasma norepinephrine measurements provide global indices of sympathetic nervous function but provide no information on regional sympathetic nervous system function. The authors, therefore, suggested that the sensitivity of the plasma norepinephrine approach in detecting increased sympathetic activity is not optimal [28]. Based on our observations, it is likely that ^{123}I-MIBG scintigraphy may be fairly sensitive in detecting cardiac sympathetic overactivity, at least in the population of patients that we studied. Finally, we divided the patients into 2 groups based on the criteria used for Japanese patients with coronary artery disease [6]. It remains to be determined whether this cutoff index (<4.0 μg/mL) is valid for use in type 2 diabetic patients.

In conclusion, the present study suggests that, in middle-aged male patients with type 2 diabetes mellitus, hypoadiponectinemia is associated with sympathetic overactivity as evaluated by cardiac ^{123}I-MIBG scintigraphy.

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Effects of Aerobic Exercise on Metabolic Syndrome Improvement in Response to Weight Reduction

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Abstract

OKURA, TOMOHIRO, YOSHIO NAKATA, KAZUNORI OHKAWARA, SHIGEHARU NUMAO, YASUTOMI KATAYAMA, TOMOAKI MATSUO, AND KIYOJI TANAKA. Effects of aerobic exercise on metabolic syndrome improvement in response to weight reduction. *Obesity*. 2007;15:2478–2484.

Objective: The objective was to test effects of aerobic exercise training on metabolic syndrome (MetSyn) improvement in response to weight reduction.

Research Methods and Procedures: A total of 459 overweight and obese women (age, 49 ± 9 years; BMI, 28 ± 3 kg/m^2) were recruited for a baseline examination to test the relationship between cardiorespiratory fitness and metabolic syndrome prevalence; among these, 67 subjects with MetSyn were treated with 14-week weight-loss programs, which included low-calorie diet and aerobic exercise. The MetSyn was defined according to the Examination Committee of Criteria for "Metabolic Syndrome" in Japan. Maximal oxygen uptake ($\dot{V}O_{2max}$) during a maximal cycling test was measured as an index of cardiorespiratory fitness at baseline and after the intervention.

Results: In the baseline examination, age- and BMI-adjusted odds ratios for MetSyn prevalence in the low, middle, and upper thirds of $\dot{V}O_{2max}$ were 1.0 (referent), 0.50 (95% confidence interval, 0.26 to 0.95), and 0.39 (95% confidence interval, 0.14 to 0.96), respectively (linear trend, p = 0.02). The adjusted odds ratios for MetSyn improvement in the two interventions with diet alone and diet plus exercise were 1.0 and 3.68 (95% confidence interval, 1.02 to 17.6; p = 0.04), respectively.

Discussion: These results suggest that adding aerobic exercise training to a dietary weight-reduction program further improves MetSyn (adjusted odds ratio, 3.68) in obese women, compared with diet alone. Further studies on an association between $\dot{V}O_{2max}$ change and MetSyn improvement are needed.

Key words: exercise intervention, diet, aerobic exercise, metabolic syndrome

Introduction

Metabolic syndrome is a cluster of interrelated risk factors (visceral obesity, dyslipidemia, hyperglycemia, and hypertension) (1) that increase susceptibility to cardiovascular disease (2,3) and type 2 diabetes (4,5). The National Cholesterol Education Program's Adult Treatment Panel III report (6) stated that the increasing prevalence of obesity has been accompanied by a parallel increase in the prevalence of metabolic syndrome, which together constitutes the "obesity epidemic."

Cross-sectional data indicate that high levels of cardiorespiratory fitness are associated with low prevalence of metabolic syndrome (7–9). Several prospective studies have found that cardiorespiratory fitness is a significant predictor for metabolic syndrome incidence (10,11). Another study found that 20 weeks of aerobic exercise training reduced metabolic syndrome prevalence (12). Clinical intervention studies in obese people have also revealed that regular aerobic exercise training clearly improves risk factors for metabolic syndrome (13,14).

Detecting metabolic syndrome in asymptomatic obese individuals is useful in identifying high-risk individuals for intensive primary preventive therapy (15), and lifestyle

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therapy is recognized as an important approach in the various clinical and educational settings of obesity treatment. However, little is known of the effects of diet and/or aerobic exercise training on metabolic syndrome improvement in obese individuals.

We have investigated these issues in overweight and obese Japanese women. On the basis of the studies cited above, we hypothesized that change in cardiorespiratory fitness, defined as maximal oxygen uptake ($\dot{V}O_{2max}$)[1], would be a predictor for improvement in metabolic syndrome in obese subjects during weight reduction. We first determined whether cardiorespiratory fitness was associated with metabolic syndrome prevalence at baseline. Next, we assigned subjects with metabolic syndrome to two treatment groups, which received diet therapy alone or with aerobic exercise training, and we investigated the effects of cardiorespiratory fitness change and these two treatments on metabolic syndrome improvement during weight reduction.

Research Methods and Procedures

Subjects

Participants were sedentary overweight and obese Japanese women who were recruited through advertisements in local newspapers in Ibaraki prefecture, Japan, and participated in a 14-week weight-reduction program between 2000 and 2004. Before the program, we excluded subjects who smoked, had concomitant renal, hepatic, or cardiac disease, or were being treated with hormone replacement or drugs, which could affect the variables of the study. Consequently, 459 women, 34 to 66 years of age, were chosen as subjects (Table 1) after they met the following criteria: 1) sedentariness, defined as exercise-induced energy expenditure of <60 minutes/wk, and 2) overweight or obesity, defined as a BMI of, respectively, >25 kg/m^2 and >30 kg/m^2 (16). Of these women, 185 were postmenopausal and 274 were premenopausal. Menopause was defined as the absence of menses for at least 12 months, as reported by questionnaire. This study conformed to the principles outlined in the Helsinki Declaration and was approved by the Review Board of the University of Tsukuba. The aim and design of the study were explained to each subject before she gave her written, informed consent.

Research Procedures

First, we cross-sectionally examined the relationship between cardiorespiratory fitness and metabolic syndrome prevalence in all subjects. Next, 67 subjects were diagnosed as having the metabolic syndrome according to the criteria for the Japanese population, which are described below (17). To increase subjects' adherence to the weight loss programs, the subjects' personal lifestyles (occupations, daily schedules, etc.) and preferences were taken into account, and the 67 subjects were assigned to two 14-week weight-reduction programs consisting of a low-calorie diet (n = 24; target energy intake, 1200 kcal/d) or the diet-plus-aerobic exercise (n = 43). Three subjects in the diet alone group and 5 in the diet plus exercise group were unable to complete the study successfully for personal reasons. As a consequence, 21 subjects in the diet alone group and 38 subjects in the diet plus exercise group completed the study requirements. Assays and measurements were carried out before and after the 14-week intervention period. We prospectively examined the relationship between cardiorespiratory fitness change and metabolic syndrome improvement in response to weight reduction.

Table 1. Baseline characteristics of subjects (n = 459)

Characteristic	Value
Age (yrs)	49 ± 9
BMI (kg/m^2)	27.5 ± 3.4
Waist (cm)	99.4 ± 9.5
Visceral fat area (cm^2)	96 ± 47
Systolic BP (mm Hg)	132 ± 18
Diastolic BP (mm Hg)	83 ± 11
Triglycerides (mM)	1.21 ± 0.86
HDL-C (mM)	1.64 ± 0.39
Glucose (mM)	5.49 ± 1.16
$\dot{V}O_{2max}$ (mL/kg per min)	25.2 ± 4.0
$\dot{V}O_{2max}$ (mL/min)	1714 ± 280
Visceral fat obesity (%)	42
High BP (%)	54
High triglycerides (%)	16
Low HDL-C (%)	2
High glucose (%)	13
No. of subjects with metabolic syndrome (%)	67 (15)

BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; $\dot{V}O_{2max}$, maximal oxygen uptake. Values are mean ± SD unless specified otherwise.

Anthropometric Variables

Body mass was measured to the nearest 0.1 kg using a digital scale, height was measured to the nearest 0.1 cm using a wall-mounted stadiometer, and BMI was calculated as mass (kg) divided by height squared (m^2). Waist girth was measured to the nearest 0.1 cm at the level of the umbilicus with subjects in the standing position.

[1] Nonstandard abbreviations: $\dot{V}O_{2max}$, maximal oxygen uptake; CT, computed tomography; CI, confidence interval.

Visceral Fat Area by CT Scans

Visceral fat area (cm^2) was measured at the level of the umbilicus (L4–L5) using computed tomography (CT) scans (SCT-6800TX, Shimadzu, Tokyo, Japan) performed on subjects in the supine position and was calculated using a computer software program (FatScan, N2system, Osaka, Japan) (18). The intra-class correlation for repeated determinations of visceral fat area in our laboratory was 0.99.

Definition of Metabolic Syndrome

For the Japanese population, the Examination Committee of Criteria for "Metabolic Syndrome" in Japan (17) defined metabolic syndrome as the presence of visceral fat obesity (visceral fat area $\geq$100 cm^2) and two or more of the following criteria: 1) triglycerides $\geq$1.70 mM (150 mg/dL) and/or high-density lipoprotein cholesterol $<$1.04 mM (40 mg/dL), 2) systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure $\geq$90 mm Hg, and 3) fasting plasma glucose $\geq$6.1 mM (110 mg/dL). Systolic and diastolic blood pressures were taken from the left arm using a sphygmomanometer after the subjects rested at least 20 minutes in a sitting position. Cuff sizes were selected based on upper arm girth and length. A blood sample of ~10 mL was drawn from each subject after an overnight fast. Triglycerides were determined enzymatically, and fasting plasma glucose was assayed by a glucose oxidase method. Serum high-density lipoprotein-cholesterol was measured by the heparin-manganese precipitation method.

Maximal Oxygen Uptake

Maximal oxygen uptake ($\dot{V}O_{2max}$, mL/kg per min and mL/min) was determined during a graded exercise test using a cycle ergometer (818E, Monark, Stockholm, Sweden). After a 2-minute warm-up, the subject started with a workload of 15 W, which was increased by 15 W each minute until volitional exhaustion occurred. Pulmonary ventilation and gas exchange were measured breath-by-breath with an online data acquisition system (Oxycon α System, Mijnhardt, Breda, Netherlands).

Diet and Exercise Regimens

Dietary Protocol. Subjects were instructed to take a well-balanced supplemental food product (MicroDiet, Sunny-Health, Nagano, Japan) every day. It was developed for very low-energy diets (170 kcal per pack) and is comprised of protein, carbohydrates, fat, various amino acids, vitamins, and minerals. Two other meals per day were allowed, consisting, on average, of 240 kcal of protein, 480 kcal of carbohydrate, and 240 kcal of fat. Subjects also kept daily food diaries during the 14-week intervention period and learned about proper daily nutrition through weekly lectures and counseling by skilled dieticians.

Exercise Protocol. In addition to restricting energy intake, the subjects from the diet plus exercise training group performed a bench-stepping exercise 3 days/wk for 45 minutes per session, supervised in the hospital by two or three physical trainers. The bench-stepping exercise is a combination exercise of low impact aerobic dance and stepping with a step bench (10 to 20 cm high) (19). The exercise started with basic steps for the first 4 weeks and then progressed to combination of basic steps and lunge steps for the next 6 weeks, and finally progressed to more advanced lunge steps for the last 4 weeks. Subjects were instructed to perform the aerobic dance at a level that raised their heart rate to 70% to 85% of the corresponding heart rate at their $\dot{V}O_{2max}$. The target Borg's scale (ratings of perceived exertion) (20) ranged from 13 (fairly hard) to 17 (very hard).

Statistical Analysis

Values are mean $\pm$ standard deviation. Paired t tests were used to assess differences between variables before and after the weight-reduction intervention period. Unpaired t tests were used to test difference in variables between the two treatment groups. Qualitative data were analyzed by a χ^2 test. We used logistic regression to estimate odds ratios and 95% confidence intervals (CIs) as an index of the strength of associations between cardiorespiratory fitness and metabolic syndrome prevalence or improvement, and between treatment (diet alone vs. diet plus exercise) and metabolic syndrome improvement. Multivariate analyses were adjusted for age (years), menopause (yes/no), BMI (kg/m^2), and body weight change (kg). General linear model analyses [repeated-measure two-by-two way (baseline vs. after treatment) ANOVA with post hoc tests] were used to test for difference in measurement variables between groups with diet alone and diet plus exercise, and between baseline and after treatment. In each statistical analysis, probability values below 0.05 were regarded as significant. The data were analyzed with the Statistical Analysis System, version 9.01 for Microsoft Windows (SAS Institute, Inc., Cary, NC).

Results

At baseline, we observed an inverse gradient (linear trend, $p < 0.05$) of age- and BMI-adjusted odds ratios for metabolic syndrome prevalence in the low (average $\dot{V}O_{2max}$, 20.8 mL/kg per min), middle (average $\dot{V}O_{2max}$, 25.2 mL/kg per min), and upper (average $\dot{V}O_{2max}$, 29.5 mL/kg per min) thirds of $\dot{V}O_{2max}$. They were 1.0 (referent), 0.50 (95% CI, 0.26 to 0.95), and 0.39 (95% CI, 0.14 to 0.96), respectively (linear trend, $p = 0.02$) (Table 2). The significant trend (linear trend, $p = 0.03$) remained after adjustment for age, BMI, and menopausal status. The adjusted risks of metabolic syndrome were 48% (−6% to 75%) and 63% (−4% to 87%) lower in the middle and upper thirds of fitness, respectively, compared with the lower third. On average, each 1 mL/kg per min increment in $\dot{V}O_{2max}$ was associated with 7% lower risk of metabolic syndrome.

Table 2. Odds ratios and 95% CIs for metabolic syndrome according to $\dot{V}O_{2max}$ (mL/kg per min)

Covariates	$\dot{V}O_{2max}$ tertile			Linear trend
	Low	Middle	High	(p)
All (n = 459)				
No adjustment	1.0 (referent)	0.38 (0.21 to 0.68)	0.13 (0.05 to 0.28)	<0.001
Age, baseline BMI	1.0 (referent)	0.50 (0.26 to 0.95)	0.39 (0.14 to 0.96)	0.02
Age, menopause, baseline BMI	1.0 (referent)	0.52 (0.25 to 1.06)	0.37 (0.13 to 1.04)	0.03
Postmenopausal (n = 143)				
No adjustment	1.0 (referent)	0.39 (0.15 to 0.96)	0.24 (0.08 to 0.66)	<0.01
Age, baseline BMI	1.0 (referent)	0.45 (0.16 to 1.21)	0.45 (0.13 to 1.47)	0.14
Premenopausal (n = 212)				
No adjustment	1.0 (referent)	0.35 (0.09 to 1.12)	0.18 (0.03 to 0.70)	0.02
Age, baseline BMI	1.0 (referent)	0.53 (0.13 to 1.83)	0.34 (0.06 to 2.14)	0.26

CI, confidence interval; $\dot{V}O_{2max}$, maximal oxygen uptake.

Sixty-seven women (15% of all subjects) were diagnosed as having metabolic syndrome. The subjects were assigned to two groups, treated with a low-calorie diet (n = 24) or the diet-plus-aerobic exercise training (n = 43) (Table 3). Three subjects in the diet alone group and five in the diet plus exercise group were unable to complete the weight-reduction program successfully, for personal reasons. Consequently, 21 subjects in the diet alone group and 38 subjects in the diet plus exercise group were included in the final analysis. The average weight reductions in the diet group and diet plus exercise group were 6.0 kg and 8.8 kg, respectively. The prevalence of metabolic syndrome and metabolic syndrome risk factors was significantly decreased and improved in both groups. For the group treated with diet alone, of the 21 subjects with the metabolic syndrome at baseline, 15 (71%) were no longer diagnosed with the metabolic syndrome after the weight-loss treatment. For the group treated with diet plus exercise, of the 38 subjects with the metabolic syndrome at baseline, 36 (95%) were no longer diagnosed as having the metabolic syndrome after the weight-loss treatment.

We next examined whether treatment (diet alone vs. diet plus exercise) affected metabolic syndrome improvement in response to weight reduction (Table 4). The adjusted odds ratios in the groups with diet alone and diet plus exercise for metabolic syndrome improvement were 1.0 (referent) and 3.68 (95% CI, 1.02 to 17.6; linear trend, p = 0.04).

Discussion

Several organizations have recommended clinical criteria for the diagnosis of the metabolic syndrome (1,21). There are some slight differences in the criteria for diagnosis of the metabolic syndrome used by these organizations. According to the definition of the World Health Organization (22), insulin resistance is a required component and two other risk factors are sufficient for a diagnosis of metabolic syndrome. The National Cholesterol Education Program's Adult Treatment Panel III has stated that when three of five listed characteristics are present, a diagnosis of metabolic syndrome can be made (6). The criteria of the International Diabetes Federation include "central obesity" as an essential component and ethnic-specific values for waist girth (23). In the present study, we used Japanese-specific criteria recommended by the Examination Committee of Criteria for Metabolic Syndrome in Japan (17). This is in accordance with the International Diabetes Federation definition, whereas a slight difference was found in the criteria of low high-density lipoprotein cholesterol and high fasting plasma glucose between the two organizations. It is well known that Japanese individuals are likely to develop obesity-related disorders with even mild obesity (24). Inter-relations among anthropometric variables, body composition, fat distribution, and lipid/glucose metabolism, which may be affected by genetic factors, are quite different in the Japanese, U.S., and European populations. Therefore, we decided to use the Japanese-specific definition of metabolic syndrome.

A few prospective studies have revealed that physical activity and cardiorespiratory fitness are predictors of metabolic syndrome incidence (10,11). One study reported that a 20-week supervised aerobic exercise training reduced metabolic syndrome prevalence by 31% (12). The subjects in the above studies, however, were not all obese. Clinical intervention studies have shown that regular aerobic exercise training clearly improved risk factors for metabolic syndrome in obese people (13,14), but no study, to our