Table 2
Prognostic variables for 1 year major adverse cardiac events after acute myocardial infarction

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age (year^{-1})	1.026	0.982–1.071	0.2511	1.009	0.912–1.098	0.9921
Women	4.292	1.484–12.500	0.0072	24.390	1.499–500.000	0.0248
Log-time to admission to hospital (h^{-1})	10.543	2.678–41.506	0.0008	4.301	0.345–53.560	0.2569
Hypertension	2.792	0.858–9.081	0.0880	4.368	0.634–30.118	0.1344
Diabetes mellitus	1.015	0.332–3.100	0.9794	0.771	0.125–4.760	0.7797
Total cholesterol (per mg/dL)	0.993	0.981–1.006	0.2751	0.983	0.962–1.005	0.1288
Log-triglyceride (per mg/dL)	0.395	0.037–4.234	0.4430	2.170	0.015–310.011	0.7596
HDL cholesterol (per mg/dL)	1.004	0.968–1.040	0.8458	1.010	0.950–1.075	0.7408
Smoking	0.976	0.344–2.772	0.9644	8.148	0.657–101.032	0.1024
Body mass index (per kg/m^2)	0.927	0.795–1.080	0.3296	1.093	0.856–1.396	0.4760
Killip class >1	2.899	1.495–5.623	0.0016	26.316	3.846–166.667	0.0008
Multi-vessel involvement	1.645	0.826–3.276	0.1564	4.132	0.6219–27.027	0.1420
Log-peak creatine kinase (per IU/L)	2.253	0.553–9.178	0.2571	1.463	0.193–11.070	0.7127

HDL, high-density lipoprotein.

occurred within the first year after AMI (10 women with 1-year MACE), while it was observed uniformly across the follow-up period in men (seven men with 1-year MACE). Therefore, we investigated the prevalent prognostic variables on 1-year MACE for all patients using multivariate analysis. The results showed that Killip class and female sex were independent and significant predictors (Table 2). However, during the entire follow-up period, MACE could be predicted only by Killip class (95% CI: 2.762–37.037, $p=0.0005$), but sex difference was not identified as an independent predictor of MACE in multivariate analysis (95% CI: 0.512–19.608, $p=0.2147$).

3.2. Serial changes in plasma adiponectin concentrations and clinical determinants of adiponectin on admission

We examined the serial changes in plasma adiponectin during hospitalization. Plasma adiponectin concentrations in women were significantly higher than men on admission (8.66 μg/mL [range: 6.6–14.08] versus 4.71 μg/mL [range: 3.47–7.27], $p<0.0001$), at 24 h (8.44 μg/mL [range: 5.38–10.96] versus 4.31 μg/mL [range: 3.15–6.67], $p<0.0001$), at 72 h (8.07 μg/mL [range: 5.33–10.62] versus 4.07 μg/mL [range: 3.02–6.54], $p<0.0001$), at 7 days (9.00 μg/mL [range: 6.28–11.96] versus 4.60 μg/mL [range: 2.98–7.82], $p<0.0001$), and at discharge (9.57 μg/mL [range: 6.05–11.99] versus 4.70 μg/mL [range: 3.23–7.81], $p<0.0001$) (Fig. 2).

To assess the determinants of plasma adiponectin concentrations on admission, multiple regression analysis was performed after a stepwise regression that included clinical variables such as age, sex, time to admission to hospital, hypertension, diabetes mellitus, total cholesterol, triglyceride, HDL cholesterol, smoking, BMI, Killip class, culprit coronary artery, and multivessel involvement. The results of this model ($R^2=0.428$, $p<0.0001$) revealed that plasma adiponectin concentrations were significantly associated with sex ($\beta=0.308$, $p<0.0001$), BMI ($\beta=-0.253$, $p=0.0006$), serum triglyceride ($\beta=-0.221$, $p=0.0015$) and age ($\beta=0.181$, $p=0.0171$).

3.3. Adiponectin as prognostic biomarker in men and women

The ROC area under the curves (mean ± S.E.M.) were 0.794 ± 0.068 (95% CI: 0.637–0.901) in men and 0.388 ± 0.107 (95% CI: 0.203–0.605) in women during the follow-up period. The sensitivity and specificity for prediction of MACE using the best cutoff level for plasma adiponectin on admission (3.8 μg/mL) were 73% and 70% in men, respectively. In case of women, the sensitivity and specificity were 58% and 60%, respectively, for the best cutoff level on admission of 8.5 μg/mL. The event-free survival curves using the above-mentioned cutoff levels in men and women are shown in Fig. 3. In men, patients with adiponectin ≤3.8 μg/mL on admission were more likely to develop MACE than those with adiponectin >3.8 μg/mL,

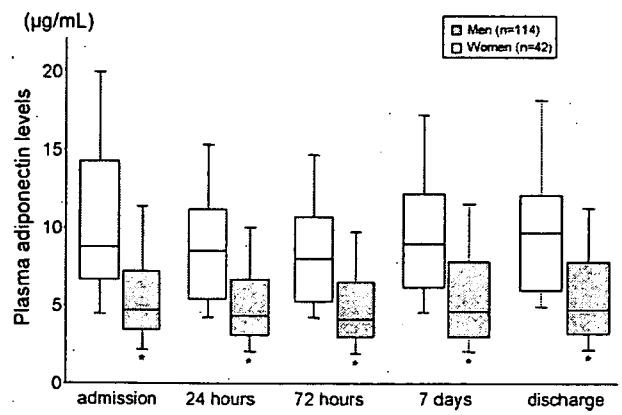

Fig. 2. Serial changes in plasma adiponectin concentrations in men and women. Values are expressed as the median value (25–75th percentile range). * $P<0.0001$ compared with women at the corresponding time point.

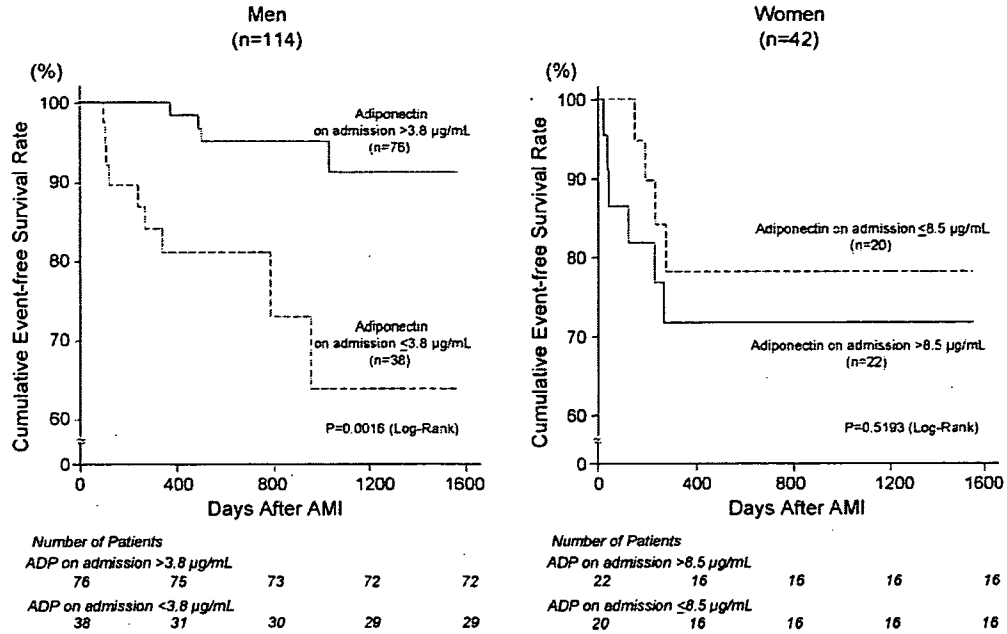

Fig. 3. Event-free survival after acute myocardial infarction (AMI) according to best cutoff value on admission in men (3.8 μg/mL) and women (8.5 μg/mL). ADP, adiponectin.

whereas no such correlation for the cutoff level of adiponectin was found in women.

Furthermore, we examined the serial changes in plasma adiponectin in relation to the development of MACE in men and in women (Fig. 4). Plasma adiponectin concentrations on admission were significantly lower in men who developed future MACE than those free of MACE (2.60 μg/mL [range: 1.74–3.87] versus 4.98 μg/mL [range: 3.70–8.06], $p = 0.0008$) and the same results were obtained at other time points (24 h: 2.20 μg/mL [range: 1.85–4.31] versus 4.40 μg/mL [range: 3.27–7.06], $p = 0.0009$; 72 h: 2.63 μg/mL [range: 1.65–3.70] versus 4.52 μg/mL [range: 3.24–6.69], $p = 0.0003$; 7 days: 2.43 μg/mL [range: 2.03–4.34] versus 4.74 μg/mL [range: 3.37–8.29], $p = 0.0023$; discharge: 2.67 μg/mL [range: 2.06–4.68] versus 4.93 μg/mL [range: 3.45–8.33], $p = 0.0033$). On the other hand, plasma

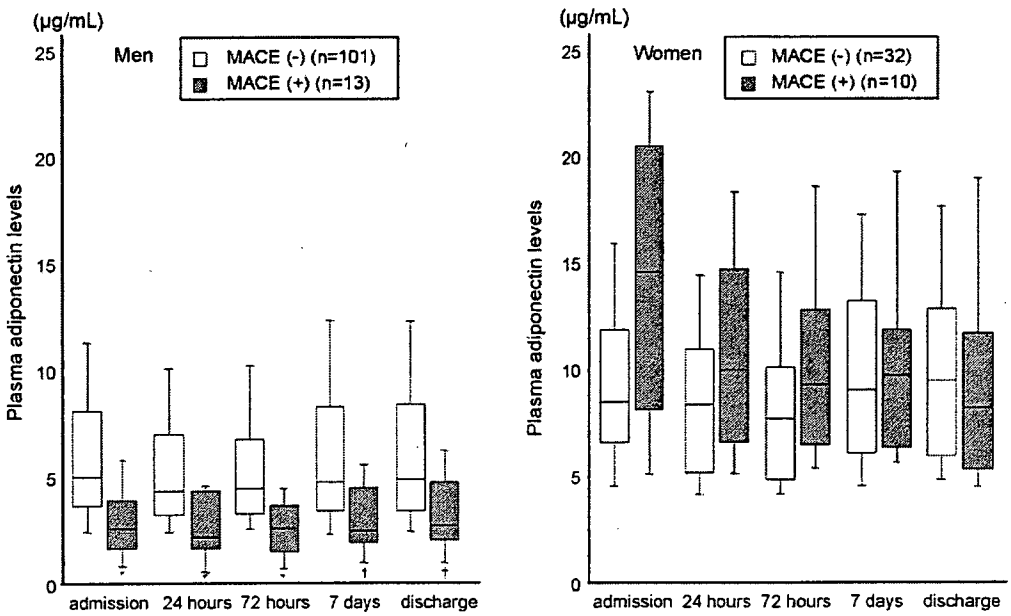

Fig. 4. Serial changes in plasma adiponectin concentrations in men and in women patients with acute myocardial infarction who subsequently developed major adverse cardiac events [MACE(+)] or did not develop major adverse cardiac events [MACE(−)] during follow-up. Values are expressed as the median value (25–75th percentile range). $^{*}p < 0.001$ and $^{\dagger}p < 0.005$, compared with MACE(−) patients at the corresponding time point.

Table 3
Predictors of post-AMI major adverse cardiac events in men

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age (year^{-1})	0.987	0.941–1.037	0.6080			
Log-time to admission to hospital (h^{-1})	2.425	0.614–9.588	0.2063			
Hypertension	0.841	0.282–2.506	0.7559			
Diabetes mellitus	2.155	0.724–4.639	0.1679			
Total cholesterol (per mg/dL)	0.995	0.983–1.007	0.3941			
Triglyceride (per mg/dL)	1.000	0.996–1.003	0.8208			
HDL cholesterol (per mg/dL)	0.959	0.912–1.009	0.1059			
Smoking	1.786	0.393–8.130	0.4528			
Body mass index (per kg/m^2)	1.072	0.918–1.252	0.3796			
Killip class >1	8.300	2.773–24.846	0.0002	5.944	1.859–19.009	0.0027
Multi-vessel involvement	1.302	0.435–3.902	0.6369			
Log-peak creatine kinase (per IU/L)	4.233	0.852–21.022	0.0776			
Log-adiponectin (per μg/mL)						
Admission	0.023	0.004–0.136	<0.0001	0.053	0.010–0.288	0.0007
24 h	0.023	0.004–0.118	<0.0001			
72 h	0.012	0.002–0.072	<0.0001			
7 days	0.026	0.004–0.182	0.0002			
Discharge	0.052	0.008–0.302	0.0010			
Log-Δadiponectin (per μg/mL)[a]						
24 h	0.331	0.003–41.585	0.6537			
72 h	0.108	0.001–7.988	0.3105			
7 days	2.493	0.091–68.082	0.5883			
Discharge	15.277	0.316–738.730	0.1683			

HDL, high-density lipoprotein.
[a] Log-difference between plasma adiponectin concentrations at each subsequent blood sampling point and on admission (μg/mL).

adiponectin concentrations on admission tended to be higher in women who developed future MACE than those who did not, albeit insignificantly at all time points (admission: 14.67 μg/mL [range: 8.18–20.93] versus 8.60 μg/mL [range: 6.60–12.62], $p = 0.1839$; 24 h: 10.02 μg/mL [range: 6.96–14.50] versus 8.44 μg/mL [range: 5.21–10.96], $p = 0.2877$; 72 h: 9.35 μg/mL [range: 6.74–12.69] versus 8.22 μg/mL [range: 5.04–10.39], $p = 0.2148$; 7 days: 9.72 μg/mL [range: 6.61–11.74] versus 9.05 μg/mL [range: 6.28–13.46], $p = 0.6053$; discharge: 8.47 μg/mL [range: 5.82–11.47] versus 9.75 μg/mL [range: 6.07–13.00], $p = 0.7010$).

The delta change in plasma adiponectin concentration during follow-up (i.e., difference between plasma adiponectin concentration at each subsequent blood sampling point and on admission) in women with future MACE was greater than that of women who did not develop MACE (24 h: −2.20 μg/mL [range: −5.04 to −0.58] versus −0.55 μg/mL [range: −1.87 to 0.03], $p = 0.0479$; 72 h: −3.57 μg/mL [range: −6.50 to −1.10] versus −1.48 μg/mL [range: −2.02 to −0.29], $p = 0.0628$; 7 days: −3.49 μg/mL [range: −7.51 to 0.02] versus −0.37 μg/mL [range: −1.56 to 2.12], $p = 0.0549$; discharge: −2.07 μg/mL [range: −7.98 to −0.71] versus 0.52 μg/mL [range: −1.56 to 2.00], $p = 0.0106$). These findings suggest that the development of MACE after AMI may be associated with plasma adiponectin levels in men, but with marked reduction of plasma adiponectin during follow-up after AMI in women.

In women, the ROC area under the curves (mean ± S.E.M.) for the delta change in plasma adiponectin concentration at 24, 72 h, 7 days and at discharge were 0.735 ± 0.098 (95% CI: 0.516–0.886), 0.725 ± 0.104 (95% CI: 0.500–0.886), 0.732 ± 0.102 (95% CI: 0.505–0.889), and 0.785 ± 0.090 (95% CI: 0.572–0.919), respectively. The ROC area under the curve for the delta change in plasma adiponectin concentration at discharge was the highest in women and was therefore applied for MACE as a prognostic variable in logistic regression analysis of this group. On the other hand, in the same analysis for men we used plasma adiponectin concentrations on admission because fluctuations in these concentrations were small. The results of logistic regression analysis showed that plasma adiponectin concentration on admission was an independent and significant predictor of MACE in men (Table 3). In women, the delta change in plasma adiponectin concentration at discharge was an independent and significant predictor of MACE (Table 4).

The sensitivity and specificity of ROC curve for prediction of MACE in women using the best cutoff value for the delta change in plasma adiponectin concentration at discharge (−1.7 μg/mL) were 75% and 70%, respectively. Therefore, we divided women subjects into two subgroups using the delta change in adiponectin concentration to assess the prognosis of women with AMI. Female patients with delta change in plasma adiponectin levels at discharge ≤ −1.7 μg/mL were significantly more likely to develop cardiac events than those

Table 4
Predictors of post-AMI major adverse cardiac events in women

	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age (year^{-1})	0.999	0.937–1.064	0.9705			
Log-time to admission to hospital (h^{-1})	5.022	1.256–30.083	0.0250	4.468	0.858–23.273	0.0754
Hypertension	5.747	0.729–45.455	0.0968			
Diabetes mellitus	0.864	0.223–3.345	0.8331			
Total cholesterol (per mg/dL)	0.987	0.969–1.005	0.1537			
Triglyceride (per mg/dL)	0.990	0.975–1.004	0.1592			
HDL cholesterol (per mg/dL)	1.004	0.962–1.074	0.8519			
Smoking	1.524	0.323–7.194	0.5946			
Body mass index (per kg/m^2)	0.905	0.745–1.099	0.3142			
Killip class >1	4.649	1.330–16.247	0.0161	1.860	0.451–7.674	0.3908
Multi-vessel involvement	1.676	0.473–5.940	0.4240			
Log-peak creatine kinase (per IU/L)	1.331	0.264–6.708	0.7291			
Log-adiponectin (per μg/mL)						
Admission	10.315	0.795–133.772	0.0743			
24 h	6.056	0.356–103.142	0.2130			
72 h	6.669	0.442–105.390	0.1778			
Discharge	0.671	0.037–12.036	0.7865			
Log-Δadiponectin (per μg/mL)[a]						
24 h	0.0000908	0.160×10^{-7} to 0.515	0.0348			
72 h	0.001	0.176×10^{-6} to 4.662	0.1080			
7 days	0.001	0.384×10^{-6} to 0.247	0.0141			
Discharge	0.000126	0.608×10^{-6} to 0.026	0.0010	0.00028	0.937×10^{-7} to 0.088	0.0053

HDL, high-density lipoprotein.
[a] Log-difference between plasma adiponectin concentrations at each subsequent blood sampling point and on admission (μg/mL).

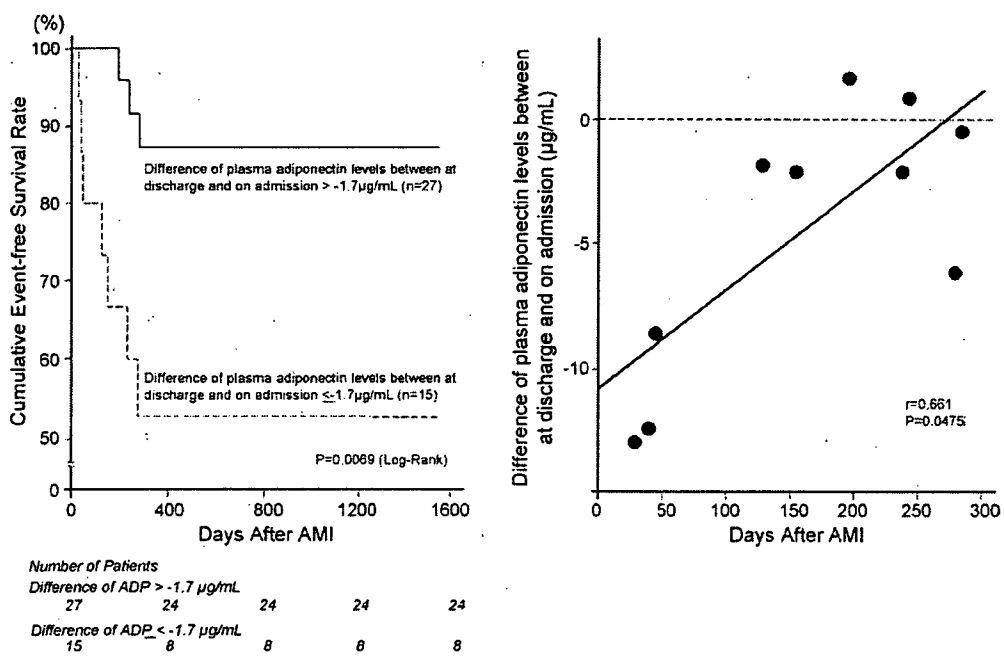

Fig. 5. *Left*: event-free survival after acute myocardial infarction (AMI) according to best cutoff value of the difference of plasma adiponectin concentrations between at discharge and on admission in women (−1.7 μg/mL). *Right*: correlation between the difference of plasma adiponectin levels between at discharge and on admission and the number of days after AMI in women. ADP, adiponectin.

with a delta change >−1.7 μg/mL (Fig. 5, left). Furthermore, the delta change in plasma adiponectin concentrations at discharge correlated with the number of days from the onset of AMI to the occurrence of MACE (Fig. 5, right).

4. Discussion

In the present study, we found that plasma adiponectin concentrations during the post-AMI course were lower in men than those in women. Furthermore, plasma adiponectin concentrations on admission were significantly influenced by sex. Low plasma adiponectin concentrations were associated with poor prognosis in men, while a reduction in adiponectin concentration during hospitalization correlated with future cardiac events in women with AMI. Especially in women, a decrease in plasma adiponectin concentration correlated with the number of days from AMI onset to the occurrence of MACE.

Previous studies reported sex differences in adiponectin concentrations in healthy subjects [11]. Our results showed lower plasma adiponectin concentrations in men than in women even after the onset of AMI. While sex hormones are considered to affect adiponectin levels, all women in the present study were postmenopausal. Recent reports indicated that testosterone reduced plasma adiponectin concentrations by inhibiting its secretion from adipocytes [11,12] and that testosterone replacement therapy caused a decrease of adiponectin level in hypogonadal patients [12]. However, other studies showed that plasma adiponectin concentrations were comparable between pre- and postmenopausal women and they were not affected by hormone replacement therapy in postmenopausal women [11,19]. A remarkable decline in adiponectin levels occurs during the progression of puberty in boys, however, such change is not observed in girls [20]. The testosterone levels in boys correlate negatively with adiponectin levels, whereas estradiol concentrations in girls are not associated with adiponectin [20]. The sex difference in adiponectin may be observed under the influence of testosterone-regulated adiponectin. In fact, in men, testosterone levels decrease gradually with age, however; the levels are relatively maintained at a range that cannot be ignored [21]. Therefore, sex differences should be taken into account in studies of adiponectin.

Our results showed that low adiponectin concentrations during the post-AMI follow-up were associated with poor prognosis in men. Our results are in agreement with those reported by Pischon et al. [10] who showed that high plasma adiponectin concentrations were associated with future lower risk of AMI in men. Based on the results of several experimental studies, adiponectin is considered to be involved in the initiation and progression of atherosclerosis through its anti-atherosclerotic effects [22]. Furthermore, adiponectin was reported to increase the expression of tissue inhibitor of metalloproteinases in human monocyte-derived macrophages, which is known to control the rupture of atherogenic plaque lesions [23]. Therefore, in men, persistently low adiponectin levels may indirectly promote the progression of coronary artery disease, by canceling its protective anti-atherosclerotic actions, leading to future cardiac events.

This study demonstrated that MACE in women after AMI was greater than that in men. The increase in 1-year MACE can be explained by Killip class and sex, whereas the difference in overall mortality is explained only by Killip class. As for this reason, 1-year MACE seems to increase in women, but is later followed by an increase in MACE in men. This excess 1-year MACE in women cannot be explained by the frequency of prevalent risk factors. There is conflicting information on whether short-term mortality after AMI is higher in women than in men after adjustment for prognostic factors (1–4). The data reported by Vaccarino et al. [24,25] indicated that younger women who survive hospitalization for myocardial infarction had a higher mortality rate than men. However, they did not identify the factors that could explain the sex differences. Therefore, a novel marker to unravel a mystery of sex-related differences is required and we paid much attention to plasma adiponectin levels and those changing pattern in AMI. In our study, we examined post-AMI MACE, rather than mortality, as the primary endpoint and all women who developed MACE did so within the first year after AMI. Furthermore, our results indicated that marked reduction of plasma adiponectin levels was closely associated with the occurrence of MACE in women. Plasma adiponectin concentrations in women who developed future MACE were comparable to those without MACE at discharge, however, adiponectin concentrations at the time of development of MACE could be further decreased relative to their levels at discharge. Therefore, especially in women, marked reduction from relatively high plasma adiponectin concentrations may trigger the progression of coronary atherosclerosis, which may be aggravated by low plasma concentrations of adiponectin. There is some possibility of occurrence of MACE provided that plasma adiponectin levels at discharge are still lower than those on admission in women.

The precise mechanism of the reduction of plasma adiponectin concentrations immediately after the onset of AMI remains unclear. Adiponectin accumulates in the vascular subendothelial space when the endothelial barrier is damaged [8]. We reported previously that adiponectin might target the ruptured plaques resulting in their consumption in the circulating plasma [7]. In addition, adiponectin may play a role in the scaffold of formed collagen in myocardial remodeling after ischemic injury by its uptake into the interstitium and around the infarcted lesion, which may decrease plasma adiponectin levels [26]. Therefore, this protein is considered to have vessel repair and tissue healing properties and reduced concentrations during the post-AMI period may be accounted for by the consequence of coronary plaque rupture followed by infarcted myocardium. Plasma adiponectin has been recently recognized to exist in three isoforms: (1) trimer, basic unit of the multimeric adiponectin, referred to

as low molecular weight (LMW) adiponectin, (2) hexamer, linked two subunits of trimer, known as middle molecular weight (MMW) adiponectin, and (3) a high molecular weight (HMW) adiponectin comprising 12–18 subunits [27,28]. The HMW adiponectin levels in women are higher than those in age- and BMI-matched men because testosterone regulates the secretion of HMW adiponectin from adipocytes, whereas the MMW and LMW adiponectin levels are comparable between the two sexes [12]. Therefore, there may be sex-related differences in total adiponectin levels. It has been proposed recently that patients with coronary heart disease have a selective reduction in HMW adiponectin, suggesting that the oligomeric complex distribution of adiponectin is critical for anti-atherogenic activity [29]. It is also possible that the absolutely small amount of circulating total adiponectin, including the HMW component, in men and the decrease of total adiponectin caused by selective consumption of the HMV component in women, contributes to the development of coronary artery disease in men and women, respectively. Recent studies reported the involvement of total adiponectin levels in future coronary events in men but not in women [10,30]. HMW adiponectin levels or the ratio of HMW to total adiponectin may be of prognostic significance especially in women. In short, persistently low adiponectin concentrations in men and marked reductions of adiponectin in women after AMI may be suggestive of future cardiac events. Adiponectin may not only act as a marker of cardiovascular risk but also a causal risk factor.

The patient population was relatively small in the present study and the study was limited to the Japanese population. However, we merely tested a plasma marker for predicting later onset of cardiac events. The present study demonstrated that plasma adiponectin concentrations could be potentially used as a marker for prediction of post-AMI MACE. We measured consecutive plasma adiponectin concentrations up to discharge after the onset of AMI but we did not measure them at the occurrence of MACE. However, the pattern of changes in plasma adiponectin concentrations was quite different between men and women, which might provide a clue to solve the problem of whether women have more unfavorable short-term post-AMI outcome than men. Further studies of larger and other ethnic populations are needed to confirm our findings.

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Brief report

A novel index of insulin resistance determined from the homeostasis model assessment index and adiponectin levels in Japanese subjects

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Abstract

Insulin resistance is the principal cause of glucose intolerance and type 2 diabetes and induces progression of severe atherosclerosis in these patients. Adiponectin, the adipose-specific proteins, is known to correlate negatively with insulin resistance in patients with obesity and type 2 diabetes. The purpose of this study was to evaluate the potential of using serum adiponectin levels as a marker of insulin resistance in various states of insulin resistance. Furthermore, we attempted to establish a modified index of the homeostasis model assessment index (HOMA-IR), calculated from the product of serum insulin and plasma glucose levels divided by serum adiponectin levels (HOMA-AD).

We recruited 117 Japanese subjects with various degrees of glucose tolerance and determined serum adiponectin levels and insulin sensitivity (*M*-value) by using the euglycemic hyperinsulinemic clamp technique. *M*-value, the gold standard index of insulin resistance, correlates significantly and independently with fasting insulin ($r = -0.313$, $P < 0.001$), glucose ($r = -0.319$, $P < 0.001$), and adiponectin ($r = 0.241$, $P < 0.002$) levels. *M*-values were more significantly correlated with HOMA-AD ($r = -0.643$, $P < 0.001$) than HOMA-IR values ($r = -0.591$, $P < 0.001$). In subjects with moderate hyperglycemia (fasting glucose levels > 8.0 mmol/L, $n = 30$), HOMA-AD showed a more significant correlation with the *M*-value than HOMA-IR ($r = -0.535$, $P = 0.005$ versus $r = -0.461$, $P = 0.010$).

We would therefore like to propose a novel index, HOMA-AD, as a simple and adequate index for determining insulin resistance even in diabetic patients with overt hyperglycemia.

Keywords: Insulin resistance; HOMA-IR; Adiponectin

Abbreviations: HOMA-IR, homeostasis model assessment of insulin resistance; BMI, body mass index; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose levels

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1. Introduction

Insulin resistance, as well as impaired pancreatic β-cell function, is the principal cause of glucose intolerance and type 2 diabetes. Insulin resistance is also well-correlated with central obesity, lipid abnormality, and hypertension, and accumulation of these metabolic abnormalities, so called metabolic syndrome, results in severe atherosclerosis. Treatment of insulin resistance with thiazolidine diones or metformin improves mortality and decreases cardiovascular events. It is therefore important to evaluate the extent of insulin resistance in obese and type 2 diabetic patients, and to treat them with improvement of life styles and/or medication.

Several techniques are used to evaluate insulin resistance in humans, and among them, the *M*-value determined by the euglycemic hyperinsulinemic clamp technique is considered the gold standard [1]. Since this method is complicated and expensive to be utilized in epidemiological studies, the homeostasis model assessment index (HOMA-IR) [2], calculated from fasting glucose and insulin levels, has been mainly applied in clinical studies. However, several studies demonstrated that HOMA-IR failed to detect insulin resistance in individuals with normal and impaired glucose tolerance [3,4]. In addition, this index may be inadequate in diabetic subjects with moderate hyperglycemia, where insulin secretory ability fails to compensate for the impaired homeostasis of glucose [5]. Therefore, a more accurate index is necessary for determining insulin resistance especially in diabetic patients.

Adiponectin, the most abundant of adipose-specific proteins, is known to modulate the action of insulin via activation of AMP-activated protein kinase in the muscle and the liver [6]. Serum adiponectin levels were found to correlate directly with whole-body insulin sensitivity in patients with obesity and type 2 diabetes [7]. Therefore, in this study, we examined the correlation between adiponectin levels and HOMA-IR and *M*-values, and established a novel index of insulin resistance, which can be used even for individuals with hyperglycemia by modifying HOMA-IR by taking into account adiponectin levels.

2. Materials and methods

A total of 117 Japanese subjects with various degrees of glucose tolerance, including individuals with type 2 diabetes (T2DM; $n = 89$, 54.7 ± 10.8 years, BMI 26.2 ± 18.5), impaired glucose tolerance (IGT; $n = 5$, 43.2 ± 19.8 years, BMI 25.3 ± 3.2), and normal glucose tolerance (NGT; $n = 23$, 49.7 ± 10.2 years, BMI 25.5 ± 4.3) were enrolled in this study carried out in Osaka University Hospital, Osaka City University Hospital, and Ryukyu University Hospital. The study was approved by the Ethical Committee for Human Studies at each hospital. After giving a detailed explanation of the study using a document, written informed consent was obtained from each subject.

During the euglycemic hyperinsulinemic clamp study, the target levels of plasma glucose and insulin were 5.5 mmol/L and 600 pmol/L, respectively. When the rate of exogenous glucose infusion reached a steady-state level, we evaluated insulin sensitivity as the average rate of exogenous glucose infusion for 30 min (*M*-value). We also determined plasma glucose, insulin, and adiponectin concentrations at the beginning of the glucose clamp test to simultaneously assess insulin sensitivity. Adiponectin levels were determined using a validated latex kit (LTX) employing an adiponectin-specific antibody (Otsuka Pharmaceutical and Mitsubishi Kagaku Iatron, Tokyo, Japan) [8]. We calculated the HOMA-IR values, and divided it by adiponectin levels to establish a more accurate index (HOMA-AD) for determining insulin resistance using the following formula:

$$\text{HOMA-AD} = \frac{\text{fasting insulin (mU/L)} \times \text{fasting glucose (mg/dL)}}{\text{adiponectin (}\mu\text{g/mL)}}$$

Data are represented as means ± S.D. Laboratory data were compared using unpaired *t*-test. Pearson's correlation co-efficient and stepwise multivariate regression analysis was performed to evaluate the relationship between the *M*-value and other parameters. The indexes of insulin resistance were log-transformed to yield a normal distribution before analysis.

3. Results

Fasting glucose levels were significantly higher in T2DM (7.4 ± 1.7) than NGT and IGT (5.1 ± 0.6 and 5.9 ± 1.2 mmol/L, $P < 0.001$). Fasting insulin and adiponectin levels were similar among three groups (NGT, 48.0 ± 20.4, 5.8 ± 2.2; IGT, 46.8 ± 18.0, 6.8 ± 3.3; T2DM, 56.7 ± 51.6 pmol/L, 6.1 ± 2.8 μg/mL). HOMA-IR was significantly higher in T2DM (3.1 ± 2.6) than NGT and IGT (1.8 ± 0.8, 2.1 ± 0.9, $P < 0.05$). The *M*-values were significantly higher in NGT (6.0 ± 2.5 mg/kg/min) than T2DM and IGT (4.6 ± 2.3, 4.9 ± 1.9 mg/kg/min, $P < 0.05$).

The *M*-value significantly correlated with glucose ($r = -0.345$, $P < 0.001$), insulin ($r = -0.518$, $P < 0.001$), adiponectin ($r = 0.369$, $P < 0.001$), and HOMA-IR ($r = -0.591$, $P < 0.001$). Multivariate regression analysis revealed that the *M*-value correlates significantly and independently with fasting insulin ($r = -0.313$, $P < 0.001$), glucose ($r = -0.319$, $P <$

0.001), adiponectin ($r = 0.241$, $P < 0.002$) levels and BMI ($r = -0.185$, $P = 0.032$).

HOMA-AD was significantly higher in T2DM (257 ± 250, $P < 0.05$) than NGT and IGT (166 ± 115, 100 ± 35.5). HOMA-AD values showed the highest correlation with M-values ($r = -0.643$, $P < 0.001$, Fig. 1) among the evaluated parameters, including HOMA-IR ($r = -0.591$, $P < 0.001$). Multivariate regression analysis also revealed that the M-value correlates most significantly and independently with HOMA-AD ($r = -0.284$, $P < 0.001$). We also validated the relation of HOMA-IR and HOMA-AD with M-value in patients with type 2 diabetes ($n = 87$). We found the similar results that HOMA-AD showed higher correlation with M-value ($r = -0.667$) than HOMA-IR ($r = -0.617$). Moreover, HOMA-IR is known to become inaccurate under hyperglycemic condition, where the homeostasis between glucose and insulin is disrupted. In subjects with moderate hyperglycemia (fasting glucose levels > 7.8 mmol/L, $n = 30$), HOMA-AD showed a more significant correlation with the M-value than HOMA-IR ($r = -0.538$, $P = 0.002$ versus $r = -0.461$, $P = 0.010$).

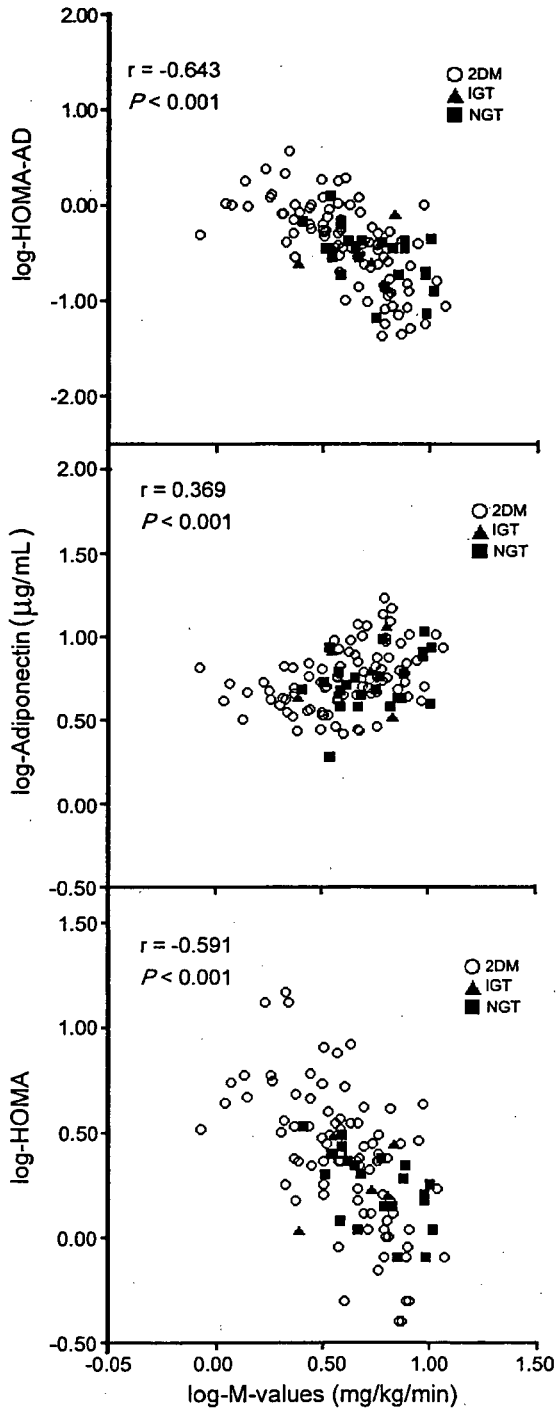

Fig. 1. Correlation between adiponectin levels, HOMA-IR, and HOMA-AD, and M-values determined by the euglycemic hyperinsulinemic clamp test in patients with various states of glucose tolerance.

4. Discussion

In the present study, the M-value significantly correlated with fasting plasma glucose and fasting serum insulin and adiponectin levels in Japanese subjects. Therefore, we generated a modified index of HOMA-IR (HOMA-AD) by taking account into adiponectin levels; found that this index is a more accurate indicator for assessing insulin resistance than HOMA-IR. This index is simply based on glucose, insulin, and adiponectin levels in fasting blood sample.

Although HOMA-IR is easy to calculate, there are several limitations in its use, especially in subjects with fasting hyperglycemia. In this study, HOMA-IR showed lower correlation with M-value in type 2 diabetic patients with moderate hyperglycemia (FPG ≧8 mmol/L). Since hyperglycemia is induced by the inadequate secretion of insulin, the homeostasis between fasting glucose and insulin levels may be disrupted in these subjects. Moreover, circulating glucose is excreted into the urine under moderate hyperglycemic condition. Therefore, we speculate that the accuracy of these surrogate insulin resistance indexes could be lowered by elevation of plasma glucose in type 2 diabetic patients.

Modification of HOMA-IR with adiponectin levels resulted in an index exhibiting a good correlation with M-values even in subjects with moderate hyperglycemia. Therefore, we would like to propose HOMA-AD as a novel and beneficial index for determining insulin resistance in individuals with various levels of insulin resistance.

HOMA-IR is known to correlate with insulin resistance in various races, but the distribution and average of HOMA-IR were different among these races [9,10]. The adiponectin level is also known to correlate with the level of insulin resistance, as well as HOMA-IR, in the various races [5,7]. Therefore, the findings in this study could be limited for Japanese subjects. The further study is needed to evaluate the usefulness of HOMA-AD in the various races.

In summary, the present study demonstrated that HOMA-AD is a more adequate predictor of insulin resistance in non-diabetic and diabetic individuals compared with the established surrogate index, HOMA-IR. HOMA-AD is therefore the most suitable index for use in epidemiological studies, even for diabetic patients with moderate hyperglycemia.

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Corrigendum

Corrigendum to "A novel index of insulin resistance determined from the homeostasis model assessment index and adiponectin levels in Japanese subjects" [Diabetes Res. Clin. Pract. 77 (2007) 151–154]

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The author regrets that when the above article was published Dr. Shinichiro Ueda was omitted from the author list. The full and correct version appears above.

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Metabolic Syndrome and C-Reactive Protein in the General Population

— JMS Cohort Study —

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Background In recent years some studies have shown that metabolic syndrome (MS) is associated with inflammation, indicated by high-sensitivity C-reactive protein (hsCRP), but there have been few population-based studies, especially in Japan.

Methods and Results The study subjects were 2,191 men and women examined between 1992 and 1995 with the necessary data to ascertain MS as part of the Jichi Medical School Cohort Study. CRP was measured by nephelometry. There were 109 subjects defined as having MS (5.0%), and the proportion of MS cases was higher in men (9.4%) than in women (1.8%). Geometric mean and median CRP in the MS group was higher than that in the non-MS (geometric mean; $p<0.001$, median: 0.312 mg/L in MS and 0.122 mg/L). Proportion of MS increased with CRP, after the subjects were divided by tertile of CRP (odds ratio, 95% confidence interval 1st tertile as a reference; 2nd tertile: 2.9, 1.5–5.9, 3rd tertile: 5.7, 3.1–11.1).

Conclusion Inflammation, measured by the concentration of hsCRP, was elevated in cases of MS in the general Japanese population. Longitudinal data should be examined in the future. (*Circ J* 2007; **71:** 26–31)

Key Words: C-reactive protein; Cardiovascular diseases; General population; Japanese; Metabolic syndrome

Metabolic syndrome (MS) comprises obesity, dyslipidemia, diabetes mellitus (DM) or impaired glucose tolerance, and hypertension, and is closely associated with cardiovascular morbidity and mortality in the general population[1–5]

In 1999, MS was defined by the World Health Organization (WHO)[6] and in 2001 another definition was proposed by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation, and the Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, ATP III)[7] Further definitions have been proposed recently by various organizations or associations; for example, in Japan, the definition of MS was determined in collaboration with 8 scientific associations in 2005[8]

Several studies have reported that C-reactive protein (CRP), a representative acute phase reactant, is a marker of cardiovascular diseases (CVD)[9–13] as well as a precursor of diabetes and other metabolic disorders[14] The relationship between CRP and MS has been examined[15–20] Ridker et al reported CRP levels were higher among women with MS and that CRP added prognostic information on the risk for CVD in healthy American women[15] In Japan, there has been 1 study of healthy men[16] and another small-scale study of men and women[20] In the present study, we examined the relationship between MS and CRP in a large-scale general population of both sexes in Japan.

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Methods

Subjects

We conducted the present study as part of the Jichi Medical School (JMS) Cohort Study, which was a prospective population-based cohort study based on a total of 12,490 study subjects, started in 1992 to clarify risk factors of cardiovascular and cerebrovascular diseases in Japanese. Details on the JMS Cohort Study design and some descriptive data have been published previously[21]

Mass screening for CVD has been conducted in Japan since 1983 in accordance with the health and medical service law for the aged, and we used this system to collect the data for this study. In each community, a local government office sent personal invitations to all subjects by mail.

Data were obtained in Takasu, Wara and Sakuma between April 1992 and July 1994, and a total of 2,191 subjects were eligible. The participation rate for people invited to the mass screening examination was 56%.

Variables

Waist circumference was considered an optimal measurement. It was measured at the level of the high point of the iliac crest. Body height was measured in stockinged feet. Body weight was recorded with the subjects clothed, and 0.5 kg in summer and 1.0 kg in other seasons was subtracted from the recorded weight. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

Systolic and diastolic blood pressures (BP) were measured

Table 1 General Characteristics of the Total Study Subjects by Sex

	Men	n=920	Women	n=1,271	p value
Age (years)	*57.1*	*12.2*	*56.3*	*12.0*	*NS*
BMI (kg/m²)	*22.7*	*2.8*	*22.9*	*3.1*	*NS*
SBP (mmHg)	*128.9*	*21.4*	*131.1*	*22.5*	*0.02*
DBP (mmHg)	*77.6*	*12.4*	*77.1*	*13.1*	*NS*
Fasting glucose (mg/dl)	*95.7*	*17.3*	*92.8*	*16.2*	*<0.001*
TC (mg/dl)	*186.1*	*33.0*	*196.4*	*33.5*	*<0.001*
Triglyceride (mg/dl)§	*100.6*	*(58.7–172.3)*	*87.4*	*(55.5–137.6)*	*<0.001*
HDL-C (mg/dl)	*48.3*	*13.6*	*51.3*	*11.9*	*<0.001*
CRP (mg/L)§	*0.152*	*(0.028–0.830)*	*0.113*	*(0.022–0.577)*	*<0.001*
Physical activity index	*35.9*	*10.1*	*30.8*	*4.7*	*<0.001*
Current smoking (%)	*48.9*		*4.5*		*<0.001*
DM (%)†	*4.9*		*3.7*		*NS*
Hypertension (%)‡	*35.2*		*37.6*		*NS*
Past history¶					
Stroke (%)	*1.2*		*0.6*		*NS*
Myocardial infarction (%)	*1.4*		*0.3*		*<0.01*
Malignacy (%)	*0.7*		*1.8*		*0.03*
Hyperlipidemia (%)	*2.1*		*1.3*		*NS*

Data are mean and SD for variables, and percentage for proportions.
§Triglycerides and CRP: geometric mean (±SD).
p values were calculated with unpaired t-test for variables and with chi-square test for proportions.
†Diabetes mellitus was currently medicated and/or fasting glcose ≥126 mg/dl.
‡Hypertension was currently medicated and/or SBP ≥140 mmHg and/or DBP ≥90 mmHg.
¶Data were obtained by questionnaire.
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; CRP, C-reactive protein; DM, diabetes mellitus.

with a fully automated sphygmomanometer, BP203RV-II (Nippon Colin, Komaki, Japan), placed on the right arm of the subject who had rested while seated for 5 mins before measurement.

Physical activity index (PAI), which was developed in the Framingham Study,[22] was calculated for 24 h by totaling the weighted sum of hours spent at 5 activity levels: 1.0 for sedation including sleeping; 1.1 for quiet working, such as while seated; 1.5 for a light level of working such as while standing; 2.5 for a moderate level of working, and 5.0 for heavy work, during a normal working day.

CRP levels were measured using highly sensitive nephelometry, a latex particle-enhanced immunoassay (NA Latex CRP Kit, Dade Behring, Tokyo, Japan). The value in the calibrator was assigned using certified reference Material 470 (IRMM, Geel, Belgium), and international plasma protein reference material to achieve international standardization for the assay of CRP. The functionality of the assay was found to be satisfactory.[23] The interassay and intraassay coefficients of variation (CV) were 1.18% and 1.36%, respectively. The assay is sufficiently sensitive to detect 0.030 mg/L of CRP. Undetectable CRP values were recorded as 0.015 mg/L.

Total cholesterol and triglyceride levels were measured by enzymatic methods (Wako, Osaka, Japan; inter assay CV: 1.5% for total cholesterol and 1.7% for triglyceride). High-density lipoprotein-cholesterol (HDL-C) was measured using the phosphotungstate precipitation method (Wako, Osaka, Japan; interassay CV: 1.9%). Blood glucose was measured via an enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV: 1.9%.

MS

According to the 2005 definition and diagnostic criteria of MS in Japanese, subjects had to satisfy the following criteria: waist circumference ≥85 cm for men or ≥90 cm for women as an essential component combined with 2 or more of the following components: triglycerides ≥150 mg/dl and/or HDL-C <40 mg/dl; systolic BP (SBP) ≥130 mmHg and/or diastolic BP (DBP) ≥85 mmHg; fasting blood glucose ≥110 mg/dl.[8,24]

Statistical Analysis

Data of variables are expressed as mean±SD, except CRP. Distribution of CRP was skewed, and CRP was expressed as the geometric means±SD. P values were calculated with unpaired t-test for variables and with chi-square test for proportions, and $p<0.05$ was considered significant.

We divided the CRP values into tertiles, and the proportion of MS in each tertile was calculated and shown as a percentage in Table 3. Odds ratios (OR) and 95% confidence intervals (CI) were used to evaluate the association between CRP and MS.

Statistical analysis was performed using Statistical Analysis System 8.2 edition (SAS Institute, Inc, Cary, NC, USA).

Results

Table 1 shows the general characteristics of the subjects by sex. Mean age was 57.1±12.2 years in men and 56.3± 12.0 years in women. There were no significant differences in age, BMI or DBP between men and women. Fasting glucose, triglycerides, CRP, and PAI were higher in men than in women, and SBP, total cholesterol and HDL-C were higher in women than in men. The subjects were from the general population, and only a few had major past histories: stroke, 1.2% in men and 0.6% in women; myocardial infarction, 1.4% in men and 0.3% in women; malignancy, 0.7% in men and 1.8% in women. Regarding hyperlipidemia, we did not have specific data about statin use, but few subjects were medicated (2.1% in men, 1.3% in women).

The distributions of all subjects and subjects with MS

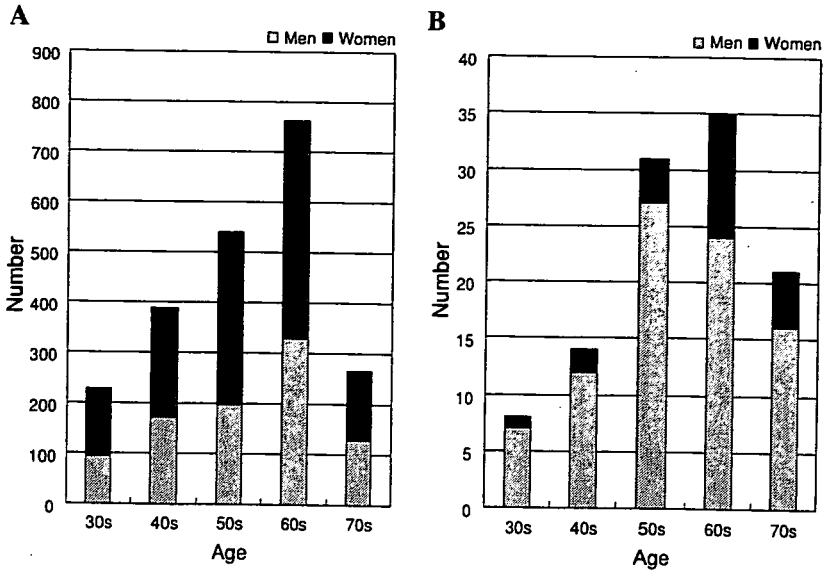

Fig 1. Distribution of all participants (A) and participants with metabolic syndrome (B) classified into 10-year age groups.

Table 2 General Characteristics of Subjects With or Without MS

	MS		*Non-MS*		*p value*
	n	*%*	*n*	*%*	
Men	*86*	*9.4*	*834*	*90.6*	
Age (years)	*58.5*	*12.2*	*56.9*	*12.2*	*NS*
BMI (kg/m²)	*26.1*	*1.8*	*22.4*	*2.6*	*<0.001*
SBP (mmHg)	*143.4*	*18.1*	*127.5*	*21.1*	*<0.001*
DBP (mmHg)	*85.9*	*11.4*	*76.8*	*12.2*	*<0.001*
Fasting glucose (mg/dl)	*107.8*	*26.3*	*94.5*	*15.5*	*<0.001*
TC (mg/dl)	*194.1*	*30.0*	*185.2*	*33.2*	*NS*
Physical activity index	*34.1*	*9.7*	*36.1*	*10.2*	*NS*
CRP (mg/L)§	*0.308*	*(0.068–1.398)*	*0.141*	*(0.026–0.773)*	*<0.001*
Women	*23*	*1.8*	*1,248*	*98.2*	
Age (years)	*62.7*	*11.0*	*56.2*	*12.0*	*0.01*
BMI (kg/m²)	*28.8*	*4.4*	*22.8*	*3.0*	*<0.001*
SBP (mmHg)	*149.7*	*20.1*	*130.8*	*22.4*	*<0.001*
DBP (mmHg)	*85.4*	*10.4*	*77*	*13.1*	*<0.001*
Fasting glucose (mg/dl)	*115.8*	*35.6*	*92.3*	*15.4*	*<0.001*
TC (mg/dl)	*211.1*	*32.4*	*196.2*	*33.4*	*0.04*
Physical activity index	*30.1*	*2.7*	*30.9*	*4.7*	*NS*
CRP (mg/L)§	*0.327*	*(0.107–1.002)*	*0.111*	*(0.022–0.567)*	*<0.001*
Total	*109*	*5.0*	*2,082*	*95.0*	
Age (years)	*59.4*	*12.1*	*56.5*	*12.1*	*NS*
BMI (kg/m²)	*26.7*	*2.8*	*22.6*	*2.8*	*<0.001*
SBP (mmHg)	*144.7*	*18.6*	*129.4*	*22.0*	*<0.001*
DBP (mmHg)	*85.8*	*11.2*	*76.9*	*12.8*	*<0.001*
Fasting glucose (mg/dl)	*109.4*	*28.6*	*93.2*	*15.5*	*<0.001*
TC (mg/dl)	*197.7*	*31.1*	*191.8*	*33.8*	*NS*
Physical activity index	*33.3*	*8.9*	*32.9*	*7.8*	*NS*
CRP (mg/L)§	*0.312*	*(0.074–1.309)*	*0.122*	*(0.023–0.644)*	*<0.001*

Data are mean and SD.
§CRP, geometric mean (±SD).
p value was calculated with unpaired t-test.
NS, not significant: p>0.05. MS, metabolic syndrome. Other abbreviations see in Table 1.

classified into 10-year age groups are shown in Fig 1. Those aged in their 60s comprised the greatest numbers for all subjects of each sex across the age groups. Although the 50s age group had the most men, the 60s age group had the most women.

Table 2 shows the data for subjects with or without MS. The MS group consisted of 109 men and women (5.0%), and had a higher proportion of men (9.4%) than women (1.8%). Geometric mean levels of CRP were similar in both men (0.308 mg/L) and women (0.327 mg/L). There was a similar tendency among other variables between the with and without MS group. Overall, mean age was 59.4±12.1 years in the MS group and 56.5±12.1 years in the non-MS group and there was no significant difference between the 2 groups. Mean value of total cholesterol was 197.7±31.1 mg/dl in the MS group and 191.8±33.8 mg/dl in the non-MS group, and mean PAI was 33.3±8.9 in the MS group and 32.9±7.8 in the non-MS group; there were no significant differences

Table 3 Effect of Diabetes on CRP With or Without MS

	MS		*Non-MS*	
	DM (+)	*DM (−)*	*DM (+)*	*DM (−)*
Men	*0.315*	*0.277*	*0.141*	*0.119*
Women	*0.418*	*0.224*	*0.111*	*0.102*

Data of CRP were shown in geometric mean.
Abbreviations see in Tables 1,2.

Table 4 Proportion of MS Divided by Tertile of CRP

	Tertile			
	1st	*2nd*	*3rd*	*Total*
MS	*12*	*34*	*63*	*109*
Non-MS	*717*	*700*	*665*	*2,082*
MS (%)	*1.7*	*4.6*	*8.7*	*5.0*

All subjects were divided by tertiles; cutoff points were 0.057 mg/L and 0.265 mg/L.
1st: first tertile, the lowest group; 2nd: second tertile, the next group; 3rd: third tertile, the highest group.
Abbreviations see in Tables 1,2.

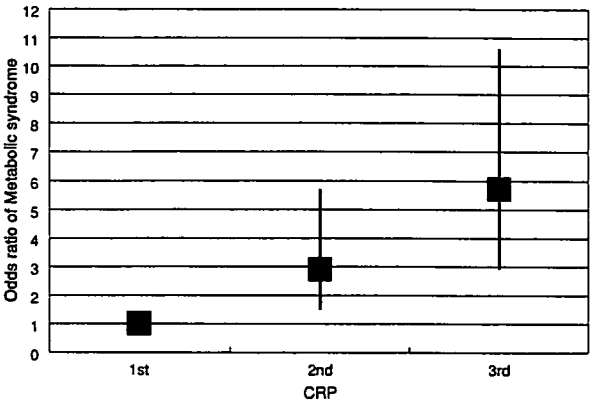

Fig 2. Odds ratios of metabolic syndrome for the 2nd and 3rd tertiles of C-reactive protein (CRP) were analyzed using the 1st tertile of CRP as a reference. 1st: first tertile (the lowest group); 2nd: second tertile (the next group); 3rd: third tertile (the highest group). Odds ratios (95% confidence interval) of 2nd and 3rd tertiles: 2.9 (1.5–5.9) and 5.7 (3.1–11.1).

in total cholesterol or PAI between the 2 groups. Mean values of BMI, SBP, DBP, fasting blood glucose in the MS group were significantly higher than those in the non-MS group (BMI: 26.7±2.8 kg/m^2 in MS and 22.6±2.8 kg/m^2 in non-MS, p<0.0001; SBP: 144.7±18.6 mmHg in MS and 129.4±22.0 mmHg in non-MS, p<0.0001; DBP: 85.8±11.2 mmHg in MS and 76.9±12.8 mmHg in non-MS, p<0.0001; fasting glucose: 109.4±28.6 mg/dl in MS and 93.2±15.5 mg/dl in non-MS, p<0.0001). Geometric means (± SD) of CRP were 0.312 mg/L (0.074–1.309 mg/L) in MS and 0.122 mg/L (0.023–0.644 mg/L) and CRP in the MS group was significantly higher than that in the non-MS (p<0.0001). As for the effect of DM on CRP values in those with or without MS, the difference between CRP values among subjects with and without MS was larger than the difference between CRP values among those with and without DM (Table 3).

The total subjects were divided into tertiles according to the CRP values, and the cutoff points were 0.057 mg/L and 0.265 mg/L. The proportion of MS cases divided by tertile of CRP was 1.7% in the 1st tertile, 4.6% in the 2nd tertile and 8.7% in the 3rd tertile, and in total, MS was 5.0% (Table 4). Using the 1st tertile of CRP as a reference, the OR of MS were significantly higher in the 2nd tertile (OR, 95% CI: 2.9, 1.5–5.9) and 3rd tertile (5.7, 3.1–11.1), and a dose–response relationship was seen between CRP and the prevalence of MS (Fig 2). These results were almost identical after exclusion of subjects with major past histories or with hyperlipidemia.

Discussion

We examined the relationship between MS and CRP in the 1990s in the general population of Japan as part of the analysis of baseline data in the JMS Cohort Study. The participation rate of eligible subjects among people invited to the mass screening examination was 56%. The Japanese criteria for MS were defined in 2005, and 2,191 subjects in 3 of the 12 areas of the JMS Cohort Study were analyzed to determine who had MS. The MS group had a higher proportion of men (9.4%) than women (1.8%). There were less subjects with MS because the study subjects were residents in rural areas, general population-based, and there were very few subjects with major past histories, such as stroke, myocardial infarction or malignancy. We did not have detailed data on status or medication for hyperlipidemia, but only a few subjects were being medicated for hyperlipidemia, so the influence of the statin use was thought to be negligible. In fact, after exclusion of the subjects with major past histories or with medication for hyperlipidemia, the results remained almost identical.

In this analysis, CRP was closely related to MS, and the mean concentration of CRP values was higher in the MS group than in the non-MS group.

The inflammatory process is known to play an important role in the pathogenesis of atherosclerosis, and CRP is a not only a strong marker of CVD[9–13] and ischemic stroke[25,26] but also may be involved in initiating atherosclerosis[27] Our colleagues have reported lower levels of CRP in Japanese compared with studies conducted in other Western countries[28] as well as intra-individual stability of CRP levels over an interval of 5 years[29]

In Western countries, MS is associated with mortality in older women[3] and with CVD in middle-aged[1,4] and elderly people[2,5] In diabetic patients, the new definition of MS in Japan was not predictive for CVD in either male or female patients in a prospective study, but a positive relationship according to WHO or NCEP-ATP III criteria was documented[30] In a case–control study, there was a positive association between MS and ischemic stroke in Japanese patients according to NCEP-ATP III criteria[31] Furthermore, Ridker et al reviewed CRP in relation to MS and CVD in a prospective study[32]

Several studies have reported a relationship between components of MS and CRP. A population-based study in the UK showed that CRP correlated with BMI and smoking, but not with other risk factors[11] In cohort studies using random sampling of the general population in the MONICA Augsburg Cohort Study, CRP predicted future myocardial infarction, and also correlated positively with BMI, BP and DM, but negatively with HDL-C[10] In the Cardiovascular Health Study, CRP correlated positively with BMI, waist circumference and triglyceride, and negatively with HDL-C[33] CRP was related to obesity in mono-

zygotic twins independent of genetic influence;[34] and in cross-sectional studies, MS was related to CRP. Laaksonen et al showed that CRP was a predictor of future MS in a population-based cohort study.[35]

In Asia, Lee et al reported that CRP correlated with BMI, waist circumference, triglyceride, SBP, DBP and serum glucose, but negatively with HDL-C, and the mean concentration of CRP was approximately 2-fold that of those without MS, according to the criteria defined by NCEP-ATP III. In our study, the mean concentration of CRP was much lower than in other countries, even Korea; however, the mean concentration of CRP in the MS group was approximately 2-fold higher than that in the non-MS group.[17]

Nakanishi et al reported that CRP levels increased continuously with the level of fasting glucose in both sexes in the Japanese population.[36] In a cohort study, the risk of developing cardiac disease was 2.2-fold greater in the MS group than in the non-MS group, according to NCEP-ATP III criteria.[37] There are only 2 studies that have examined the relationship between MS and CRP in Japanese. Tamakoshi et al reported that the components of MS were associated with elevated CRP in healthy working men;[16] and Oda et al tried to develop a cut-off level for CRP to indicate MS in outpatient men and women.[20]

We did not have detailed drug information among subjects medicated for DM, hypertension or hyperlipidemia, which might have affected some data and is a study limitation. However, the strengths of the present study are: (1) that we examined the relationship between MS and CRP just after the Japanese criteria for MS were defined in 2005; (2) that the study samples came from a large general population in a multicenter study; and (3) that the data were obtained in the first half of the 1990s when there were very few studies of hsCRP, especially in Japan. In the new Japanese definition of MS, waist circumferences were ≥85 cm for men and ≥90 cm for women, but there were no thresholds associated with risk for CVD in Japanese diabetic patients.[30] Miyatake et al reported briefly that the prevalence of MS using the new Japanese definition was 30.7% in Japanese men and only 3.6% in Japanese women.[38] We also thought that waist circumference as a necessary component of MS was too strict, and we intend to investigate the risk for CVD in a future cohort study.

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Original Article

Blood Pressure Categories and Cardiovascular Risk Factors in Japan: The Jichi Medical School (JMS) Cohort Study

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Few studies have reported on risk factors by blood pressure categories based on antihypertensive treatment in the general population. We examined the associations between blood pressure categories and other risk factors in Japan. Cross-sectional study, multicenter population-based study was designed. A total of 11,302 men and women were eligible. Data were obtained from April 1992 to July 1995 in 12 rural districts in Japan. Subjects were divided into three categories: normotensives (with blood pressure <140/90 mmHg), treated hypertensives (antihypertensive treatment regardless of current blood pressure), and nontreated hypertensives (blood pressure ≥140/90 mmHg without hypertensive treatment). The proportions of normotensives, treated hypertensives, and nontreated hypertensives were 63%, 10%, and 27% among men, and 67%, 13%, and 20% among women, respectively. Total cholesterol, triglyceride, blood glucose, and body mass index were higher in treated or nontreated hypertensives than in normotensives. Fibrinogen, factor VIIc, and physical activity index were higher in treated hypertensives than in normotensives. High-density lipoprotein (HDL) cholesterol was higher in normotensives than in treated or nontreated hypertensives in women; but no tendency was shown in men. The proportions of dyslipidemia, impaired glucose tolerance, and metabolic syndrome were significantly higher in treated and nontreated hypertensives than in normotensive men and women. In conclusion, cardiovascular risk factors were higher in hypertensives with or without treatment than in normotensives in a general population in Japan. (*Hypertens Res* 2007; 30: 643–649)

***Key Words*: hypertension, risk factors, Japanese, population, blood pressure category**

Introduction

Hypertension is an important condition affecting overall health, and the prevalence of hypertension is highest in Japan as well as other countries (*1–4*). Chronic high blood pressure (BP) increases the incidence of cardiovascular diseases (CVD) such as stroke, myocardial infarction (*5–10*), and mortality (*11*). Many studies, including randomized controlled trials, have shown that antihypertensive treatment reduces the risk of CVD. However, BP control among hypertensive patients is often insufficient, and a considerable proportion of treated hypertensive patients have not achieved target BP (*4, 12–16*).

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Table 1. General Characteristics of the JMS Cohort Study

	Men			Women		
	n	Mean	SD	*n*	Mean	SD
Age (years)	4,415	55.2	12.0	6,887	55.3	11.3
Systolic blood pressure (mmHg)	4,115	131.4	20.6	6,887	128.1	21.2
Diastolic blood pressure (mmHg)	4,115	79.2	12.3	6,887	76.3	12.2
Total cholesterol (mg/dL)	4,383	184.9	34.2	6,847	196.9	34.7
HDL-cholesterol (mg/dL)	4,384	48.9	13.4	6,847	52.7	12.5
Triglycerides (mg/dL)[§]	4,383	108.2	(62.7–186.8)	6,846	95.1	(57.5–157.2)
Lipoprotein(a) (mg/dL)[§]	3,801	12.4	(4.5–33.8)	6,118	14.6	(5.7–37.3)
Fibrinogen (mg/dL)	2,508	243.0	57.3	4,098	249.8	55.6
Factor VIIc (mg/dL)	2,243	108.8	19.8	3,337	114.8	21.3
Blood glucose (mg/dL)	4,384	105.5	30.9	6,836	100.6	22.5
Body mass index (kg/m^2)	4,370	23.0	2.9	6,816	23.2	3.2
Physical activity index	4,372	35.6	9.5	6,811	31.6	5.4

[§]Geometric mean (±SD). HDL, high-density lipoprotein.

Nevertheless, few studies have examined risk factors based on BP categories with or without hypertensive treatment. Here we examined the association between BP categories and cardiovascular risk factors in a population-based study in Japan.

Methods

Subjects

There were 11,302 subjects in the present study (4,415 men and 6,887 women) for whom information on BP. Data were obtained between April 1992 and July 1995 in 12 districts in rural areas of Japan as part of the Jichi Medical School (JMS) Cohort Study. Details of that project, which was a population-based prospective cohort study aiming to clarify the risk factors of CVD, were reported elsewhere (*17*, *18*).

The normotensives were defined as subjects with systolic blood pressure (SBP) <140 mmHg and diastolic blood pressure (DBP) <90 mmHg, treated hypertensives were defined as subjects with antihypertensive treatment regardless of current BP, and nontreated hypertensives were defined as subjects with SBP ≥140 mmHg and/or DBP ≥90 mmHg without antihypertensive treatment. Dyslipidemia was defined as total cholesterol ≥220 mg/dL and/or triglyceride ≥150 mg/dL, and impaired glucose tolerance (IGT) was defined as fasting blood glucose (with no caloric intake for at least 3 h) of ≥110 mg/dL, or as casual blood glucose (for less than 3 h or without regard to time since last meal) of 140 mg/dL.

The diagnostic criteria of metabolic syndrome (MS) were decided in Japan in 2005. Although we used these criteria, waist circumference was not measured in most of the subjects, so instead we regard body mass index (BMI) ≥25 kg/m^2 as obesity according to the Japanese criteria of obesity. MS was defined by the following criteria: obesity (BMI ≥25 kg/m^2) as an essential component combined with two or more of the following components: triglycerides ≥150 mg/dL and/or high-densiy lipoprotein (HDL) cholesterol <40 mg/dL; SBP ≥130 mmHg and/or DBP ≥85 mmHg; fasting blood glucose ≥110 mg/dL or casual blood glucose ≥140 mg/dL.

The SBP and DBP were measured with a fully automated sphygmomanometer, BP203RV-II (Nippon Colin, Komaki, Japan) placed on the right arm of a seated subject who had rested in the sitting position for 5 min before the measurement. BMI was calculated as weight (kg)/height (m)^2.

Information about medical history and lifestyle was obtained by a questionnaire. Using the Framingham Study questionnaire, physical activity index (PAI) for a normal working day was estimated by calculating the weighted sum of hours spent at five levels: 1.0 for sedation including sleeping, 1.1 for quiet working such as that in a sitting position, 1.5 for a light level of working such as that in a standing position, 2.5 for a moderate level of working, and 5.0 for heavy work (*19*).

Total cholesterol and triglyceride were measured by an enzymatic method (Wako, Osaka, Japan; interassay coefficient of variation [CV]: 1.5% for total cholesterol and 1.7% for triglyceride). HDL cholesterol was measured using the phosphotungstate precipitation method (Wako; interassay CV: 1.9%). Blood glucose was measured *via* an enzymatic method (Kanto Chemistry, Tokyo, Japan; interassay CV: 1.9%).

Lipoprotein(a) (Lp(a)) levels were measured using an enzyme-linked immunosorbent assay (ELIZA) kit (Biopool, Uppsala, Sweden; interassay CV: 3.51%). The minimum detectable Lp(a) level was 1 mg/dL, and undetectable Lp(a) values were recorded as 0.5 mg/dL. Fibrinogen levels were determined with a one-stage clotting assay kit (Data-Fi, Dade Behring, Miami, USA; interassay CV: 2.5%). Factor VII activity was measured with a chromogenic assay using a human placenta–derived calcified thromboplastine reagent (Chromoquick, Behringwerke, Marburg, Germany), human factor VII–deficient plasma (Behringwerke), and a chro-