Age-Associated Increase in Abdominal Obesity and Insulin Resistance, and Usefulness of AHA/NHLBI Definition of Metabolic Syndrome for Predicting Cardiovascular Disease in Japanese Elderly with Type 2 Diabetes Mellitus

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Key Words

Diabetes • Obesity • Waist circumference • Insulin resistance • Metabolic disease clustering

Abstract

Background: Management of metabolic syndrome (MetS) seems to constitute an efficient strategy to attain successful ageing. Although the clinical entity of MetS in patients with diabetes mellitus has been discussed, there is very little information on MetS-type cardiometabolic risk factor clustering in diabetic elderly. **Objective:** To determine the relationship among age-associated changes in obesity, insulin resistance, and clustering of MetS-type risk factors, in association with vascular complications, in Japanese elderly with type 2 diabetes. **Methods:** A cross-sectional study was conducted of 812 diabetic elderly enrolled in the Japanese Elderly Diabetes Intervention Trial. Information on diabetes, blood examinations and complications was obtained. Abdominal obesity, insulin resistance and prevalence of MetS risk factor clustering, defined by three sets of criteria from the International Diabetes Federation (IDF), the Japanese Society of Internal Medicine (JSIM), and the American Heart

Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI), were analyzed. **Results:** Waist circumference and insulin resistance estimated by homeostasis model assessment insulin resistance (HOMA-IR) increased with age, followed by a partial decrease at age 80 and over. Prevalence of IDF-MetS and JSIM-MetS also increased with age at least until the age of 80, whereas the incidence of AHA/NHLBI-MetS did not show any apparent age changes. There was a significant crude linear association between waist circumference and HOMA-IR, which was highly elevated in IDF and AHA/NHLBI overlapping with MetS, and also elevated in AHA/NHLBI without abdominal obesity. Although IDF-MetS and JSIM-MetS, which specify abdominal obesity, did not always appear to be associated with cardiovascular diseases, AHA/NHLBI-MetS, comprising both abdominal obesity and non-abdominal obesity, independently correlated with coronary heart disease and stroke after adjustment for other risk factors of atherosclerotic diseases. **Conclusion:** There was an age-associated increase in the prevalence of abdominal obesity and insulin resistance in elderly diabetic Japanese subjects, with a clear relationship between waist circumference and insulin resistance. However, insulin resistance was elevated not only in cases with but also in those

without abdominal obesity if accompanied by clustering of metabolic disorders. The AHA/NHLBI definition of MetS proved to be the most useful to predict cardiovascular disease in the diabetic elderly.

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Introduction

Metabolic syndrome (MetS) consists of multiple, interrelated risk factors of metabolic origin that appear to directly promote the development of cardiovascular disease. Recently, MetS has been reported to be associated with impaired activities of daily living (ADLs) and cognitive decline of the elderly [1, 2]. Thus, management of risk factors and prevention of MetS seem to constitute an efficient strategy to attain successful ageing. Although insulin resistance and visceral adiposity could play a pivotal role in promoting atherosclerosis, the real cause may be a more complex interaction between genetic and environmental factors [3, 4].

The clinical usefulness of MetS for risk prediction for individuals with type 2 diabetes remains a matter of debate. It has been reported that insulin resistance and MetS are predictive of accelerated atherosclerosis in type 2 diabetic patients [5–14]. On the other hand, a recent reappraisal of MetS endorsed by the American Diabetes Association and the European Association for the Study of Diabetes argues that MetS is an entity of little or no prognostic use for diabetic patients [15]. They emphasized that it remains unclear whether identification of MetS confers a clinical advantage over identification and treatment of its individual components. Although the term MetS may not be applicable to diabetic subjects, even detractors agree that there are diabetic elderly who have increased insulin resistance associated with MetS-type cardiometabolic risk factor clustering [5–14].

Moreover, ageing is associated with increased insulin resistance in addition to type 2 diabetes [16]. Thus, the impact of abdominal obesity on insulin resistance and clustering of metabolic risk factors in diabetic elderly remains unknown. To date, for Asian elderly with type 2 diabetes, there is limited information on age-associated changes in abdominal obesity, insulin resistance and clustering of metabolic risk factors, and their association with vascular complications.

To address the need for elucidation concerning metabolic risk factor clustering in diabetic elderly, we conducted a large-scale prospective study of the Japanese Elderly Diabetes Intervention Trial (J-EDIT) [17, 18]. The

questions we addressed were: (1) prevalence of abdominal obesity, insulin resistance, and MetS-type risk factor clustering as defined by different sets of criteria; (2) possible connections between abdominal obesity and insulin resistance, and (3) the predictive power of MetS-type clustering of metabolic risk factors for cardiovascular diseases in diabetic elderly. To answer these questions, we analyzed the baseline measures of the J-EDIT.

Methods

Participants

J-EDIT started in 2001 with an enrolment of 1,173 diabetic subjects aged 65 years or over and with serum HbA1c levels of $\geq 7.0\%$ from 42 institutes in Japan. The J-EDIT protocol, which is in accordance with the provisions of the Declaration of Helsinki, received ethical approval from the institutional review boards of all of the participating institutes. Written informed consent was obtained from all patients. All examinations relevant for this study were completed by 812 subjects, 371 of whom were men. The remaining 361 subjects were excluded because some of their data were missing.

Diagnostic Criteria for MetS

In this study, we applied the three different sets of criteria proposed for the diagnosis of MetS by the International Diabetes Federation (IDF), the Japanese Society of Internal Medicine (JSIM) and the American Heart Association and the National Heart, Lung, and Blood Institute (AHA/NHLBI) [19–21]. According to IDF and JSIM criteria, there is a strong correlation between abdominal obesity and insulin resistance, which makes the presence of abdominal obesity a condition for diagnosis of MetS [19, 20]. A Japanese study concluded that a visceral fat area in excess of 100 cm² measured by means of CT scanning corresponds to a waist circumference of 85 cm for men and ≥ 90 cm for women [22]. In 2005, moreover, the IDF recognized specific cutoffs by sex and ethnicity [23]. However, new data support the use of alternative waist circumference cutoffs for the prediction of cardiovascular complications [24–26]. In 2007, the IDF recommended new waist circumference cutoffs for Japanese, 90 cm for men and 80 cm for women [19]. However, these cutoffs for waist circumference in the definition of MetS for Japanese have remained a matter of debate. For our study, we therefore adopted two criteria, one from the IDF (2007) and one from the JSIM. On the other hand, AHA/NHLBI has introduced alternative criteria, which have the advantage of avoiding emphasis on a single cause [21]. The resulting three definitions for MetS are as follows.

(1) The IDF definition of MetS (IDF-MetS) specifies abdominal obesity with waist circumference cutoffs of ≥ 90 cm for men or ≥ 80 cm for women plus any one of the following factors [19]: (a) elevated triglyceride (≥ 150 mg/dl) or specific treatment for this lipid abnormality; (b) reduced HDL-cholesterol of < 40 mg/dl for men or < 50 mg/dl for women, and (c) elevated systolic blood pressure (≥ 130 mm Hg) or diastolic blood pressure (≥ 85 mm Hg) or treatment for previously diagnosed hypertension.

Table 1. Demographic and clinical parameters of the patients

	Male	Female	All subjects
n	371	441	812
Age, years	71.4 ± 4.5	72.0 ± 4.6	71.8 ± 4.6
Duration of diabetes, years	16.7 ± 10.2	15.7 ± 8.8	16.2 ± 9.5
Systolic blood pressure, mm Hg	137.1 ± 15.8	138.6 ± 17.3	137.9 ± 16.7
Diastolic blood pressure, mm Hg	76.2 ± 9.6	75.5 ± 10.0	75.8 ± 9.9
HbA1c, %	8.0 ± 0.9	8.0 ± 0.9	8.0 ± 0.9
Fasting plasma glucose, mg/dl	169.7 ± 50.5	165.1 ± 50.7	167.2 ± 50.6
Fasting plasma insulin, µU/ml	9.3 ± 10.0	10.2 ± 8.5	9.8 ± 9.3
Urine Alb, mg/g Cr	226.4 ± 597.9	184.5 ± 499.7	203.7 ± 546.8
Serum cholesterol, mg/dl	192.7 ± 31.2	209.5 ± 34.5	201.8 ± 34.1
Serum HDL-C, mg/dl	52.9 ± 15.5	60.3 ± 19.4	56.9 ± 18.1
Serum LDL-C, mg/dl	114.9 ± 28.0	123.7 ± 32.0	119.7 ± 30.5
Serum triglyceride, mg/dl	129.2 ± 84.1	129.4 ± 66.4	129.3 ± 74.9
Current smokers, %	28.4	5.8	16.2
OHA use, %	62.5	61.7	62.1
Insulin use, %	25.3	31.1	28.5
Medication for hypertension, %	47.3	61.9	55.1
Medication with fibrates, %	3.2	4.3	3.8
Medication with statin, %	18.9	43.1	32.0
History of CHD, %	15.5	15.6	15.6
History of stroke, %	14.7	11.3	12.9

Data are presented as means ± SD or as percentages. OHA = Oral antihyperglycemic agents; CHD = coronary heart disease.

(2) The JSIM definition of MetS (JSIM-MetS) specifies abdominal obesity with waist circumference cutoffs of ≥85 cm for men or ≥90 cm for women, plus any one of the following factors [20]: (a) elevated triglyceride (≥150 mg/dl) or reduced HDL-cholesterol (<40 mg/dl) or specific treatment for these lipid abnormalities, and (b) elevated systolic blood pressure (≥130 mm Hg) or diastolic blood pressure (≥85 mm Hg) or treatment for previously diagnosed hypertension.

(3) The AHA/NHLBI definition of MetS (AHA/NHLBI-MetS) specifies two or more of the following conditions [21]: (a) waist circumference of ≥90 cm for men or ≥80 cm for women; (b) elevated triglyceride (≥150 mg/dl) or specific treatment for lipid abnormality; (c) reduced HDL-cholesterol of <40 mmol/l for men or 50 mmol/l for women, and (d) elevated systolic blood pressure (≥130 mm Hg) or diastolic blood pressure (≥85 mm Hg) or treatment for previously diagnosed hypertension.

Assessment of Diabetes Mellitus and Complications

Information about diabetes mellitus, blood examinations and complications were obtained from clinical charts. Waist circumference was measured at the umbilicus level. Information regarding cigarette smoking was collected using a standardized questionnaire.

After overnight fasting, blood samples were taken by vein puncture to assess serum levels of glucose, HbA1c, total cholesterol, triglyceride, and HDL-cholesterol. Insulin resistance was assessed from levels of fasting glucose and insulin concentration by means of the homeostasis model assessment (HOMA) formula: fasting insulin (µU/ml) × fasting glucose (mg/dl)/405 [27].

This method was not applicable to subjects treated with insulin. Serum LDL-cholesterol levels were calculated using Friedewald's equation, except for triglyceride levels of >400 mg/dl, in which case the LDL cholesterol data were recorded as 'missing'.

Information about a previous history of coronary heart disease (CHD) and stroke and findings from a 12-lead electrocardiogram (ECG) were obtained for all patients to assess cardiovascular disease at baseline. CHD was considered to be present when diabetic patients had at least one of the following: a history of myocardial infarction and angina characterized by a typical clinical picture (chest pain, chest oppression, dyspnea, typical ECG alteration). Stroke events were defined as a constellation of neurological deficits of sudden or rapid onset for which there was no apparent cause other than a vascular accident. Cases with asymptomatic lesions detected by brain imaging were not included.

Statistical Analysis

Data are presented as means ± SD or as percentages unless otherwise specified. Association of waist circumference with HOMA insulin resistance (HOMA-IR) was tested using simple and multiple logistic regression. Variables among the MetS subgroups were compared using ANOVA and statistical differences were tested with Dunnett's statistical test. Backward logistic regression analysis was used to calculate the adjusted odds ratio (OR) and 95% confidence interval (CI) for risk factors with cardiovascular diseases. The SAS software package (Version 8.0; SAS, Cary, N.C., USA) was used for all analyses. $p < 0.05$ was considered significant.

Table 2. Age-associated changes in BMI, waist circumference, HOMA-IR, and prevalence of MetS risk factors

	Men, age group				Women, age group			
	65–69	70–74	75–79	80–85	65–69	70–74	75–79	80–85
BMI	23.8 ± 3.2	23.9 ± 3.1	23.9 ± 3.1	23.6 ± 2.7	23.6 ± 3.5	24.1 ± 3.8	24.5 ± 3.7	22.8 ± 3.3
Waist circumference, cm	85.8 ± 8.9	85.0 ± 8.1	87.6 ± 8.1	88.3 ± 10.0	80.6 ± 10.4	82.7 ± 10.7	84.5 ± 11.2	79.6 ± 10.2
HOMA-IR	3.81 ± 4.0	3.37 ± 3.1	4.37 ± 5.8	2.83 ± 2.0	3.17 ± 2.7	3.49 ± 3.0	4.80 ± 3.6	3.54 ± 4.1
IDF-MetS, %	28.6	30.4	33.3	42.1	47.9	59.6	59.6	46.9
JSIM-MetS, %	51.7	47.4	59.7	68.4	19.4	23.0	31.7	25.0
AHA/NHLBI-MetS, %	56.5	52.6	59.7	57.9	72.2	83.2	80.8	65.6
Hypertension, %	79.6	74.6	84.5	84.2	77.8	87.6	91.3	96.9
IDF and AHA/NHLBI								
Low HDL-C, %	38.1	30.6	35.2	31.6	60.4	65.8	65.4	46.9
High triglyceride, %	26.5	30.6	25.4	36.8	29.2	36.6	30.8	25.0
JSIM dyslipidemia, %	36.1	37.3	33.8	47.4	30.6	39.1	32.7	28.1

Data are presented as means ± SD or as percentages. BMI = Body mass index; HOMA-IR = homeostasis model assessment, insulin resistance; MetS = metabolic syndrome; IDF = International Diabetes Federation; JSIM = Japanese Society of Internal Medicine; AHA/NHLBI = American Heart Association and the National Heart, Lung, and Blood Institute.

Results

Age-Associated Increase in Abdominal Obesity, Insulin Resistance and MetS-Type Risk Factor Clustering

Demographic and clinical parameters of the 812 study participants are listed in table 1. Age-associated changes in BMI, waist circumference, and HOMA-IR are listed in table 2. BMI did not show any apparent changes for men, although waist circumference increased with age. Waist circumference also increased for women, followed by a decrease at the age of 80 or over. HOMA-IR similarly increased with age, but decreased from the age of 80 for both men and women. The increase in insulin resistance seemed to correlate with the age-associated increase in abdominal obesity of diabetic elderly.

The overall prevalence of MetS-type risk factor clustering based on IDF, JSIM and AHA/NHLBI criteria was 44.0, 37.1 and 67.7%, respectively. The incidence of IDF-MetS and JSIM-MetS, which specify abdominal obesity, increased with age, but decreased at age 80 or over for women (table 2). In contrast, the prevalence of AHA/NHLBI-MetS did not show any apparent change with ageing.

As for the individual components of MetS, the prevalence of hypertension was highest and increased with age. Among diabetic elderly aged 80–85 years, hypertension was found in 84.2% of men and 96.9% of women. The prevalence of low HDL-cholesterol also increased with age, but started to decrease at the age of 80 and over.

We also investigated whether diabetic patients with a longer history of diabetes and/or more serious hyperglycemia might show an increased prevalence of MetS-type risk factor clustering, but no such trend could be found in any type of criteria-defined MetS (data not shown).

Possible Connections between Abdominal Obesity and Insulin Resistance

Overall, HOMA-IR was 4.2 ± 5.0 for diabetic elderly. The relationship between waist circumference and insulin resistance is shown in figure 1. Simple regression analysis showed that log-transformed HOMA-IR was associated with waist circumference in a crude linear manner (coefficient = 0.051, $p < 0.0001$, $R^2 = 0.105$ for men; coefficient = 0.034, $p < 0.0001$, $R^2 = 0.116$ for women). This was demonstrated by an increase in HOMA-IR of 1.1 for men and 0.6 for women for every 10-cm increment in waist circumference. After adjustment for sex, age, systolic blood pressure, HbA1c, triglyceride, and HDL-C, the association remained statistically significant (coefficient = 0.034, $p < 0.0001$).

For any of the three definitions, HOMA-IR was higher for subjects with MetS than for those without MetS (4.34 ± 3.65 for IDF-MetS and 3.21 ± 3.50 for non-IDF-MetS, $p = 0.0003$; 4.33 ± 3.95 for JSIM-MetS and 3.30 ± 3.33 for non-JSIM-MetS, $p = 0.0022$; 4.03 ± 3.58 for AHA/NHLBI-MetS and 3.04 ± 3.57 for non-AHA/NHLBI-MetS, $p = 0.0022$).

Fig. 1. Relationship between waist circumference and insulin resistance. Association of HOMA-IR with waist circumference of men (a) and women (b) in the J-EDIT. Log-transformed HOMA-IR (log HOMA-IR) was associated with waist circumference in a crude linear manner (coefficient = 0.051, $p < 0.0001$, $R^2 = 0.105$ for men; coefficient = 0.034, $p < 0.0001$, $R^2 = 0.116$ for women).

It has been proposed that HOMA-IR is useful for estimating insulin resistance of type 2 diabetic patients [28], but the degree of association between HOMA-IR and clamp insulin resistance for diabetic patients treated with oral antihyperglycemic agents of the class insulin secretagogues has remained unclear. In this connection, Emoto et al. [29] have reported that HOMA-IR strongly correlates with clamp insulin resistance in type 2 diabetic patients treated with sulfonylureas (SUs) as well as in those treated with diet alone. Furthermore, Spearman's correlation coefficients for HOMA-IR and waist circumference were similar for subjects taking SU drugs and those who had used neither SU drugs nor glinides (data not shown). Such evidence indicates that it seems likely that waist circumference is associated with insulin resistance in diabetic elderly, regardless of treatment with oral

antihyperglycemic agents of the class insulin secretagogues.

Insulin Resistance of Metabolic Factor Clustering with and without Abdominal Obesity

We compared the clinical characteristics of IDF-MetS and AHA/NHLBI-MetS by dividing the study population into 3 subgroups, non-MetS, AHA/NHLBI-only, and IDF&AHA/NHLBI (table 3). There was no difference in age among the subgroups. HOMA-IR was especially elevated in the IDF&AHA/NHLBI group, as was waist circumference. Interestingly, in the AHA/NHLBI-only group, HOMA-IR was moderately elevated without an accompanying increase in waist circumference. Furthermore, the mean duration of diabetes for MetS with overlapping patterns was significantly shorter than that for

Table 3. Clinical characteristics of subgroups of IDF-MetS and AHA/NHLBI-MetS risk factor clustering

	Non-MetS	AHA/ NHLBI only	IDF&AHA/ NHLBI
Number	263	192	357
Age, years	71.9 ± 4.7	71.0 ± 4.5	72.1 ± 4.5
Waist circumference, cm	78.2 ± 7.9	77.7 ± 6.8	91.4 ± 7.3*
HOMA-IR	3.04 ± 3.6	3.46 ± 3.4	4.34 ± 3.7*
Duration of diabetes, years	16.1 ± 10.3	14.0 ± 8.2	13.6 ± 8.7*

For abbreviations see table 2. Data are means ± SD or actual numbers.

* $p < 0.001$, † $p = 0.004$, ‡ $p = 0.012$, in comparison with non-MetS.

non-MetS. These results suggest that there are two distinct ways for insulin resistance to increase in diabetic elderly, one is in association with abdominal obesity and the other is not relevant to abdominal obesity.

Association of MetS-Type Risk Factor Clustering with Cardiovascular Disease

We examined the independent association of MetS-type risk factor clustering with cardiovascular diseases (table 4). Because sex is reportedly an independent factor associated with MetS [30–32], MetS and sex were included in the independent variables, while the other risk factors for atherosclerotic disease, such as age, HbA1c, duration of diabetes, smoking, total cholesterol, LDL-cholesterol, triglyceride, systolic blood pressure and diastolic blood pressure, were analyzed with backward stepwise regression. Age was found to be consistently associated with CHD, while JSIM-MetS and AHA/NHLBI-MetS, but not IDF-MetS, were also associated with CHD. When MetS was eliminated from the independent variables, age and diastolic blood pressure proved to be significantly associated with CHD, suggesting these factors independently correlate with CHD in diabetic elderly. For stroke, AHA/NHLBI-MetS was identified as a predictive factor. When MetS was eliminated from the independent variables, sex (men) and triglyceride showed a significant correlation with stroke. On the other hand, IDF-MetS and JSIM-MetS, which both specify the presence of abdominal obesity for MetS, were not associated with stroke. These results indicate that MetS of AHA/NHLBI definition is the most consistent predictor for CHD and stroke for diabetic elderly, even after adjustment for the risk factors of age, sex, blood pressure, dyslipidemia, and indices of diabetes.

Table 4. Association of MetS and other risk factors with cardiovascular disease

Previous history of CHD			Previous history of stroke		
	OR	95% CI		OR	95% CI
<i>IDF</i>					
MetS	1.44	0.91–2.28	MetS	1.16	0.70–1.92
Sex	1.39	0.88–2.19	Sex	1.69	1.03–2.75
Age	1.06	1.01–1.12	Age	1.05	0.99–1.10
DBP	0.98	0.95–0.99	TG	1.01	1.00–1.01
			DM duration	1.25	0.89–1.75
<i>JSIM</i>					
MetS	1.80	1.14–2.85	MetS	1.32	0.79–2.19
Sex	1.10	0.70–1.73	Sex	1.51	0.92–2.47
Age	1.06	1.01–1.11	Age	1.05	0.99–1.10
DBP	0.97	0.95–0.99	TG	1.01	1.00–1.01
			DM duration	1.27	0.90–1.78
<i>AHA/NHLBI</i>					
MetS	1.90	1.13–3.19	MetS	1.86	1.07–3.24
Sex	1.48	0.94–2.33	Sex	1.84	1.13–3.00
Age	1.06	1.01–1.12	Age	1.05	0.99–1.11
DBP	0.97	0.95–0.99			
<i>Factors other than MetS</i>					
Sex	1.26	0.82–1.95	Sex	1.63	1.01–2.61
Age	1.01	1.01–1.12	Age	1.05	0.99–1.11
DBP	0.98	0.96–0.99	TG	1.01	1.00–1.01
			DM duration	1.25	0.89–1.75

MetS = Metabolic syndrome; CHD = coronary heart disease; SBP = systolic blood pressure; DBP = diastolic blood pressure; TG = triglyceride; DM = diabetes mellitus. For other abbreviations, see table 2.

The association of IDF-MetS, JSIM-MetS and AHA/NHLBI-MetS with cardiovascular disease was examined. MetS and sex were included in the independent variables, and age, HbA1c, duration of diabetes, smoking, total cholesterol, LDL-cholesterol, TG, SBP and DBP were analyzed with backward stepwise regression.

Discussion

This J-EDIT study first provided evidence of MetS-type risk factor clustering in Asian (Japanese) elderly with type 2 diabetes. Several new findings are reported: (1) abdominal obesity, insulin resistance and prevalence of MetS-type risk factor clustering evidently increased with age, but somewhat decreased at the age of 80 and over; (2) overall insulin resistance was substantially elevated in diabetic elderly [28, 30], and there was a significant crude linear association between waist circumference and insulin resistance; (3) insulin resistance was elevated not only in cases with but also without abdominal

obesity if accompanied by clustering of metabolic disorders, and (4) AHA/NHLBI-MetS, comprising both abdominal obese and non-abdominal obese metabolic factor clustering cases, was the most useful for prediction of cardiovascular disease in diabetic elderly.

The incidence of MetS in the general population reportedly differs widely among ethnic groups and according to the definition of MetS [13, 33–38]. It has also been reported that the prevalence of MetS increases with age [39, 40]. However, the prevalence of MetS-type risk factor clustering among patients with known diabetes is consistently high regardless of ethnicity or definition [6–13, 30, 33, 41–48]. In the Japan Diabetes Complications Studies (JDACS), which was concerned with relatively younger diabetic patients aged 40–70 years, the prevalence of IDF-MetS risk factor clustering was 32% for men and 9.2% for women [47]. Although the inclusion criteria of JDACS and JEDIT were not the same, it seems likely that prevalence of MetS-type risk factor clustering in Japanese patients with type 2 diabetes increases with age, at least until the age of 80. To our knowledge, there are no epidemiological data of MetS-type risk factor clustering of diabetic elderly in the other ethnic groups.

Although we did not measure insulin resistance directly in this study, HOMA-IR has been shown to correlate well with direct methods in subjects with various degrees of glucose tolerance, including patients who have already developed diabetes [27]. The averages of HOMA-IR of younger diabetic subjects have been reported as 2.9–3.3 [28, 30]. In our diabetic elderly, insulin resistance was evidently high (4.2 ± 5.0), which may be due to the diabetic state itself and/or age-associated changes in body composition such as increases in fat mass and decreases in fat-free mass [16]. We therefore expected that the correlation of insulin resistance with abdominal obesity might become weaker in diabetic elderly, but there was in fact a significant linear association of insulin resistance with waist circumference, and the former was found to be higher in JSIM-MetS and IDF-MetS. In this respect, it should be pointed out that insulin resistance also increased moderately in MetS-type risk factor clustering without abdominal obesity, so that the mechanism for the increase in insulin resistance associated with non-obese type metabolic factor clustering remains to be clarified [40].

Evidence is accumulating that MetS is clinically relevant for the prediction of cardiovascular disease in non-diabetic elderly [49–51]. Our study is the first to demonstrate that AHA/NHLBI-MetS correlates independently with cardiovascular disease in diabetic elderly after adjustment for the other risk factors for atherosclerotic dis-

ease. It seems plausible that non-obese metabolic factor clustering together with increased insulin resistance has a major impact on the risk of cardiovascular diseases of diabetic elderly, because MetS with abdominal obesity does not always appear to be associated with cardiovascular diseases [10, 52–54]. Definitions of MetS-type risk factor clustering that specify abdominal obesity have not yet been developed for Asian (Japanese) diabetic elderly. Other studies have also identified the usefulness of the National Cholesterol Education Program (NCEP)-MetS and AHA/NHLBI-MetS for the prediction of cardiovascular disease in younger subjects with type 2 diabetes [9–10, 13]. On the other hand, Sone et al. [30] have demonstrated that NCEP-MetS has limited clinical usefulness as a predictor for Asian diabetic patients. Further prospective analyses are thus needed to investigate the clinical significance of MetS-type risk factor clustering without abdominal obesity for diabetic elderly.

There are certain limitations to our study. First, we performed a cross-sectional evaluation and our results are therefore subject to survival bias. Second, our study subjects were hospital-based patients with diabetes of relatively long duration, so that any inferences are of necessity limited to similar patient groups. On the other hand, this population sample represents the real-world scenario of type 2 diabetes in Japan.

In conclusion, abdominal obesity and insulin resistance were found to increase with age, at least until the age of 80, in Asian diabetic elderly, and a relationship between waist circumference and HOMA-IR was demonstrated. An important finding was that MetS-type metabolic factor clustering without abdominal obesity also showed elevated insulin resistance. AHA/NHLBI-MetS, comprising both obese and non-obese metabolic disease clustering, was found to be the most effective for the prediction of cardiovascular disease, whilst the significance of MetS with abdominal obesity in this respect remains unclear. An on-going prospective study of J-EDIT may help to clarify the pathophysiology of metabolic disease clustering and its association with cardiovascular disease and geriatric syndromes of diabetic elderly.

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