these rats show chronic hypertension, structural alterations of small cerebral arteries, reduction in cerebral blood flow and white matter lesions (Yamori and Horie, 1977; Lin et al., 2001; Fujita et al., 2008). We recently also investigated autoregulatory responses of the perforating arteries in SHR-SP (Morishita et al., 2006). Our microangiographic studies revealed that perforating arteries of SHR-SP are already dilated under normal blood pressure and therefore lose their distensibility in response to induced hypotension. Pathological alterations of perforating arteries observed in SHR-SP may result in a reduced compensatory response to an increase in blood flow during hypotension. This implies that impaired vascular responses of perforating arteries deserve to be recognized as partly responsible for the pathogenesis of cerebral small-vessel disease.

Following limitations are considered. 1) Although changes of vascular caliber were consistently measured in this study, changes in local CBF during stepwise hypotension were not determined. Combined observation of CBF by means of laser-Doppler flowmetry (Barzo et al., 1993) would help to reveal the microcirculation of deep brain regions more precisely. 2) Angiographic analysis of the present study was performed under the anesthesia with pentobarbital sodium. Effects of barbiturates on the cerebral vessels have not been evaluated. However, any differential effects of pentobarbital on perforating and cortical arterioles have not been demonstrated (Hendrich et al., 2001).

On the other hand, angiographic imaging of the perforating arteries in comparison with cortical arterioles has several impacts for the medical community. This study facilitates the investigation of not only the microcirculation in the deep brain region, but also the pathogenesis of the cerebral small-vessel disease in atherosclerotic conditions, such as ageing, hypertension and diabetes. Further steps of research can be conducted to find the molecular basis of impaired cerebrovascular reactivity using the rodent models for neurological disorders (Kidoguchi et al., 2006).

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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) of 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

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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.

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 ≥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 cm^2 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 mmol/l for men or <50 mmol/l 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).

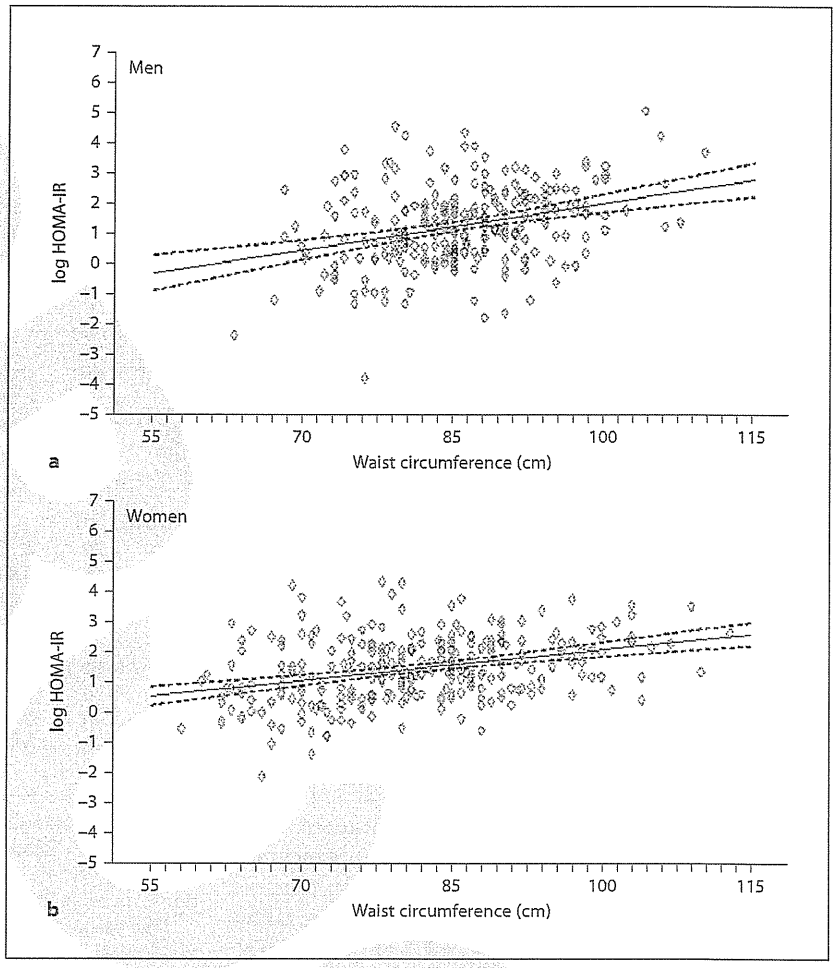

Fig. 1. Relationship between waist circumference and insulin resistance. Association of HOMA-IR with waist circumference of men (**a**) and women (**b**) in the J-EDIT. Log-transformed HOMA-IR (log HOMA-IR) was associated with waist circumference in a crude linear manner (coefficient = 0.051, $p < 0.0001$, $R^2 = 0.105$ 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
IDF					
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
JSIM					
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
AHA/NHLBI					
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			
Factors other than MetS					
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 (JDCS), 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 JDCS 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 disease. 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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LETTER TO THE EDITOR

Hasegawa Dementia Scale – Revised, for screening of early Alzheimer's disease in the elderly with type 2 diabetes

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Dear Editor,

Cognitive dysfunction of elderly subjects with type 2 diabetes has received considerable attention in connection with dementia because diabetes increases the risk of Alzheimer's disease (AD).[1–3] AD often remains unrecognized or misdiagnosed at the earliest stages.[4] While the general clinicians' contribution is essential for an early diagnosis of AD, detection of mild cognitive decline associated with AD in diabetic patients may be difficult because diabetes is usually accompanied by mild cognitive decline such as memory disturbance and delayed mental processing speed.[5] A succinct cognitive measurement is thus needed to identify the transitional state between aging and early AD in the diabetic elderly. For this purpose, a dementia index using some weighted subscales of the Mini-Mental State Examination (MMSE) has been proposed, but its sensitivity was not satisfactory.[6]

The Hasegawa Dementia Scale – Revised (HDS-R), comprising a series of items to measure orientation, memory, attention/calculation and verbal fluency, is a brief and reliable measurement for the evaluation of global cognitive function.[7,8] The HDS-R stresses the weight of memory and verbal fluency more than the MMSE does, which is likely to be useful for diagnosing early AD.[4,8–10] It has also been suggested that the HDS-R is superior to the MMSE for cognitive screening of early AD.[11]

Although memory and metal processing speed are often compromised in diabetes, characteristics of the HDS-R subscales still remained unidentified in diabetic elderly.[5] In the study presented here, we conducted a preliminary cross-sectional analysis to investigate the profiles of the HDS-R and identify psychometric predictors for early AD in the diabetic elderly. We compared the changes of the HDS-R in diabetic and non-diabetic elderly, with and without early AD, which would help to clarify the specific impairment of cognitive domains in diabetic patients with early AD.

We recruited 186 elderly subjects aged 65 years or over, being treated at Kobe University Hospital and consisting of four groups: 42 non-diabetic, non-demented subjects (control), 57 subjects with type 2 diabetes (DM), 24 diabetic AD patients (DM-AD) and 63 non-diabetic AD subjects (AD). The four groups of subjects were similar in age and length of education (75.5 ± 5.9 and 11.5 ± 3.4 for control, 73.3 ± 5.7 and 10.1 ± 2.9 for DM, 73.8 ± 6.2 and 10.9 ± 2.1 for DM-AD, and 74.3 ± 6.6 and 10.5 ± 2.1 years for AD, respectively). Subjects suffering from alcohol abuse and with neurological deficits due to a previous stroke were excluded. Diagnosis of diabetes was based on clinical chart data.[12] Hemoglobin A1c was $7.9 \pm 1.2\%$ for the DM group and $7.8 \pm 1.6\%$ for the DM-AD group ($P = 0.076$).

The control group members were not diabetic and assessed as normal after follow up with neurological evaluation. All participants were evaluated with a standardized, reliable assessment of dementia.[13] AD was clinically diagnosed as probable AD according to the clinical criteria of NINCDS-ADRDA.[14] The optimal cut-off HDS-R score for dementia is 20/21 for Japanese populations.[11] Early AD for the present study was therefore defined as an HDS-R score of 21 or over for patients diagnosed as probable AD, and the diagnosis of every patient was re-assessed with a 1-year follow up. The data were analyzed with SPSS ver. 15.0J (SPSS, Chicago, IL, USA). ANOVA was used for all between-group comparisons and significance was set at $P = 0.05$.

The standard HDS-R score was significantly lower for AD and DM-AD than for control and DM (Table 1). DM showed a similar HDS-R profile to that of control. Temporal orientation and recall of three words by

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Table 1 Comparison of HDS-R standard scores and individual item scores

HDS-R	Control	DM	DM-AD	AD
Total score	26.6 (2.4)	26.7 (1.7)	23.3 (2.1)[a,f]	23.4 (2.0)[a,f]
Age	1.0 (0)	1.0 (0)	1.0 (0.2)	1.0 (0.2)
Temporal orientation	3.8 (0.5)	3.9 (0.4)	2.9 (1.1)[a,f]	2.8 (1.2)[a,f]
Spatial orientation	2.0 (0)	2.0 (0)	2.0 (0.2)	2.0 (0.1)
Registration (words)	3.0 (0.2)	3.0 (0.1)	3.0 (0)	3.0 (0.2)
Attention/calculation	1.8 (0.4)	1.8 (0.4)	2.0 (0.2)	1.8 (0.5)
Digit span backward	1.7 (0.5)	1.5 (0.6)	1.4 (0.6)[e]	1.5 (0.7)
Recall (words)	4.4 (1.7)	4.0 (1.3)	3.3 (1.5)[b,h]	2.8 (1.7)[a,f]
Registration (objects)	4.6 (0.7)	4.8 (0.4)	4.3 (0.6)[g]	4.2 (0.8)[c,f]
Word fluency	4.4 (1.3)	4.8 (0.7)	3.6 (1.9)[i,d,f]	4.5 (1.0)
AD index	70.5 (2.9)	70.8 (2.3)	66.0 (2.9)[a,f]	66.9 (3.2)[a,f]

AD, non-diabetic subjects with Alzheimer's disease; DM, non-demented subjects with type 2 diabetes; DM-AD, diabetic patients with Alzheimer's disease; HDS-R, Hasegawa Dementia Scale – Revised. The AD index was calculated with the formula: (temporal orientation + registration + immediate recall of five objects + word fluency)/(total HDS-R) × 100 (%). Data are shown as mean (standard deviation). Significance: [a]P vs control ($P < 0.001$), [b]P vs control ($P = 0.004$), [c]P vs control ($P = 0.005$), [d]P vs control ($P = 0.009$), [e]P vs control ($P = 0.046$), [f]P vs DM ($P < 0.001$), [g]P vs DM ($P = 0.001$), [h]P vs DM ($P = 0.041$), [i]P vs AD ($P = 0.002$).

DM-AD and AD were significantly impaired compared with those by control and DM. Digit span backward was significantly impaired in DM-AD compared with control and tended to be lower in AD ($P = 0.061$). Registration of five objects by AD was significantly lower than that by control and DM, and was more impaired in DM-AD than in DM. Word fluency was comparable for control, DM and AD, but markedly impaired in DM-AD compared with the other groups. There were no differences in inter-group comparison of the results for age, spatial orientation, registration of words and attention/calculation (serial 7's).

For psychometric screening of early AD, we adapted the AD index of HDS-R so as to represent the ratios of sum of temporal orientation, recall of words, digit span backward, registration of five objects and word fluency to the total HDS-R score. As expected, this index was strongly reduced in DM-AD and AD, and showed a significant difference between DM and DM-AD (Fig. 1). Adoption of a cut-off value of 70 for the AD index resulted in screening for DM-AD with a sensitivity of 92% and a specificity of 74% for all diabetic patients. This index was also reasonable for screening non-diabetic subjects for AD (sensitivity, 81%; specificity, 67%).

These results imply that there are characteristic differences in the HDS-R profiles of diabetic elderly with and without early AD. For a comparison of mental status between normal and early AD, the AD index of HDS-R is especially relevant for diabetic subjects. Our previous studies using a similar MMSE subset analysis demonstrated that serial 7's performance is markedly impaired in diabetes, while temporal orientation and recall are substantially affected by AD.[6] Consequently, diabetic patients with early AD show overlapping MMSE profiles resulting from both diabetes and AD. HDS-R, on the other hand, showed scores for two impaired cognitive domains in AD-DM not shown by MMSE, that is, impaired digit span backward and word fluency, as well as reduced temporal orientation and recall which are also observed in MMSE. Word fluency and digit span backward are thought to represent the function of semantic memory and working memory, respectively.[15] DM-AD in our study showed more diffuse and severe cognitive impairment than did DM and AD. Interestingly, inclusion of word fluency and digit span backward in the AD index of the HDS-R resulted in pronounced improvement in the sensitivity and specificity of the identification of cognitively impaired individuals.

The HDS-R has been established as a reliable tool for screening of dementia.[8] Although all subjects diagnosed as having AD in this study had HDS-R scores of 21 or over, the AD index of the HDS-R seemed to be useful to screen early AD among diabetic elderly. This new AD index may greatly help to discriminate early AD in the daily clinical practice of diabetic elderly.

In conclusion, the AD index of the HDS-R appears to be satisfactory for detecting early AD in the diabetic elderly. However, the clinical usefulness of this index needs to be validated by large-scale prospective studies.

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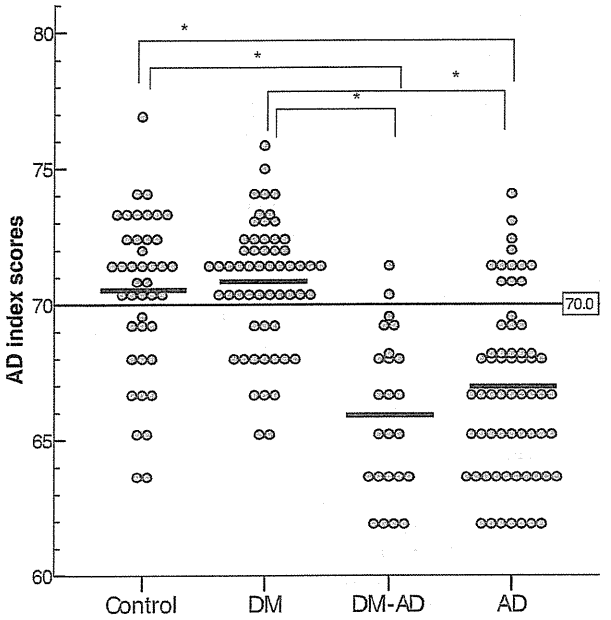

Figure 1 Illustration of the Alzheimer's disease (AD) index of Hasegawa Dementia Scale – Revised (HDS-R) in four clinical groups of the current study. Distribution of the AD index in control, DM, DM-AD and AD groups was shown. The AD index of HDS-R represented the ratios of sum of temporal orientation, recall of words, digit span backward, registration of five objects and word fluency to the total HDS-R score. Asterisks denote significant differences ($P < 0.0001$) between the groups. A dashed line indicates the average of AD index in each group. AD, non-diabetic subjects with Alzheimer's disease; DM, non-demented subjects with type 2 diabetes; DM-AD, diabetic patients with Alzheimer's disease; HDS-R, Hasegawa Dementia Scale – Revised.

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Research article

Association of higher carbohydrate intake with depressive mood in elderly diabetic women

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Background: The rates of co-morbid depression with elderly diabetes are reportedly high. Although the intake of several nutrients has been suggested to be associated with depressive symptoms, the chronic effects of carbohydrate intake on mood remain unclear. In the current study, the association of the carbohydrate energy/total energy (C/E ratio) and other factors with depressive mood in the diabetic elderly were investigated.
Patients and methods: The data from elderly diabetics (299 males and 354 females) were analyzed. Single and multiple logistic regression analyses to search for associations with depressive mood, defined by GDS-15 scores of 6 and higher, were performed.
Results: In women, a higher CE ratio, history of cerebrovascular disease, and lower activities of daily living were statistically significantly associated with depressive mood. In men, the CE ratio was not significantly associated with depressive mood.
Conclusions: A higher CE ratio was significantly associated with depressive mood in elderly diabetic women, but not in men.

Keywords: depression, elderly, carbohydrate, diabetic neuropathy , cerebrovascular disease, calorie

Introduction

The rates of co-morbid depression with elderly diabetes are high,[1] and the course of depression in diabetic patients is chronic and severe.[2] Therefore, it is important to prevent depression from developing in diabetic patients. Investigating the factors associated with depressive symptoms in diabetics may be a first step to this end.

The mechanism of increased co-morbidity of depression in diabetics is unclear, but several hypotheses have been proposed.[3] First, diabetes may induce various psychosocial hardships such as dietary restrictions and daily treatment demands. Some patients may also have physical disadvantages caused

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by diabetic complications. Several studies reported that diabetic microvascular complications, especially diabetic neuropathy, were risk factors for the development of depression in diabetics.[4–6] Another hypothesis is that depression is the result of associated cerebrovascular disease.[7] A smoking habit was also reported as a risk factor for depression in diabetics.[8]

The intake of certain nutrients has been suggested to be associated with depressive symptoms.[9,10] A large Finnish study found that a low frequency of fish consumption was significantly associated with depression only in women.[11] The acute effects of carbohydrate intake on mood have also been studied, and mixed results were reported.[12] Acute carbohydrate intake may induce a small increase in energy,[13] followed by a fall in energy.[14] The chronic effects of carbohydrate intake on mood, however, remain unclear. Wurtman and Wurtman[15,16] hypothesized that carbohydrate intake increases the synthesis of serotonin in the brain through the increased transport of tryptophan into the brain. However, there has been little evidence, thus far, that carbohydrate intake enhances mood by stimulating serotonin synthesis.[11]

In the current study, we investigated the effects of carbohydrate intake on the depressive mood of elderly Japanese diabetics. To this end, we explored the relationship between carbohydrate intake and scores on the Geriatric Depression Scale (GDS)-15 in the baseline data from the Japanese Elderly Diabetes Intervention Trial (J-EDIT). To adjust for the difference of total calorie intake, the percentage of carbohydrate-derived calories in the total daily calorie intake was calculated as the main variable (calories from carbohydrate/total calorie intake, CE ratio). Interestingly, the existence of a gender difference in the association of food intakes and mood has been reported.[17] Therefore, the statistical analysis was performed separately in this study for men and women.

Patients and methods

Study subjects

We analyzed the baseline data of the J-EDIT that had been collected at registration. The J-EDIT study was initiated in 2001 as a prospective intervention study of elderly Japanese people with diabetes mellitus for the purpose of determining how to prevent several diabetic complications.[18] A total of 1173 diabetic subjects were enrolled in 39 institutes and hospitals in Japan. They were all aged 65 years or over, and had serum HbA1c levels of at least 7.5%, or at least 7.0% with one of the following co-morbidity factors: hypertension (130/85 mmHg and over); obesity (a body mass index [BMI] of at least 25 kg/m^2); or dyslipidemia (total cholesterol of at least 200 mg/dl, low-density lipoprotein [LDL] of at least 120 mg/dl, high-density lipoprotein [HDL] of 40 mg/dl or less, and/or triglycerides of at least 150 mg/dl). Diabetic nephropathy was determined as a mean urinary albumin-to-creatinine ratio of 30 μg/mg or greater. The study protocol was approved by the ethical committee in all of the enrolled institutes, and written informed consent was obtained from each patient.

Of the 1173 enrolled cases (541 males and 632 females), the complete data of 299 males and 354 females were collected.

Diabetic complications and activities of daily living

Diabetic retinopathy was assessed by fundoscopic examination performed through dilated pupils by experienced ophthalmologists. Diabetic neuropathy was defined as either the loss of the Achilles tendon reflex without neuropathic symptoms, including paresthesia, or the presence of neuropathic symptoms. Although there were no exclusion criteria to register for the JEDIT, severely demented subjects were not selected because it was mandatory for the subjects to fill out several questionnaires.

The basic activities of daily living (ADL) were assessed using the Barthel index.[19]

Depressive mood

In the J-EDIT, the Geriatric Depression Scale-15 (GDS-15) was administered to most patients (781 of 1173) upon registration.[20] The GDS-15 is a global test of depression with a score of 0 to 15. A depressive mood is defined by GDS-15 scores of 6 and higher.[21]

Energy intakes

The total energy and carbohydrate intake in each subject was evaluated by a food-frequency questionnaire.[22] To adjust for the difference of total food intake among individuals, we calculated the percentage of calorie intake from carbohydrates in the total calorie intakes (CE ratio). The CE ratio was distributed normally both in men and women.

Statistical analysis

Logistic regression analysis to search for the association of carbohydrate energy/total energy (C/E ratio) and other factors with depressive mood defined by GDS-15 scores of 6 and higher[21] was performed. The explanatory variables applied were age, waist circumference, body mass index, fasting blood glucose, glycohemoglobin (HbA1c), total cholesterol, HDL cholesterol,

Table 1 Subjects' backgrounds

	Men	Women
Number	299	354
Age (years)	71.7 ± 4.5	72.3 ± 4.8
CE ratio (%)	59.4 ± 6.3	58.7 ± 5.9
Body mass index (kg/m²)	23.7 ± 3.0	24.1 ± 3.6
Waist circumference (cm)	86.3 ± 9.0	81.8 ± 10.5
HbA1c (%)	8.0 ± 0.9	8.0 ± 0.9
Fasting blood glucose (mg/dl)	168.2 ± 49.7	165.5 ± 52.0
Total cholesterol (mg/dl)	192.9 ± 31.9	210.3 ± 36.1
HDL cholesterol (mg/dl)	51.8 ± 16.2	59.6 ± 19.0
Triglyceride (mg/dl)	134.7 ± 111.0	132.9 ± 76.5
Serum albumin (g/dl)	4.2 ± 0.3	4.2 ± 0.4
Systolic blood pressure (mmHg)	135.3 ± 15.6	137.3 ± 16.0
Diastolic blood pressure (mmHg)	75.1 ± 9.6	74.5 ± 9.8
Existence of cerebrovascular disease (%)	14.4	12.2
Existence of retinopathy (%)	46.2	46.8
Existence of neuropathy (%)	57.1	56.9
Existence of nephropathy (%)	56.4	53.9
Existence of current smoking habit (%)	27.2	4.7
Barthel index (full score) (%)	19.0	20.0

Mean values ± SD.

Table 2 Results of univariate logistic regression analysis

	Odds ratio	95% CI	*P*-value
Age (years)	1.009	0.966–1.053	0.701
Waist circumference (cm)	1.012	0.993–1.032	0.221
Body mass index (kg/m²)	1.023	0.961–1.090	0.4771
Fasting blood glucose (mg/dl)	0.999	0.995–1.004	0.725
HbA1c (%)	0.862	0.676–1.098	0.230
Total cholesterol (mg/dl)	0.998	0.993–1.004	0.557
HDL cholesterol (mg/dl)	0.994	0.982–1.005	0.265
Triglyceride (mg/dl)	1.000	0.997–1.003	0.832
Serum albumin (g/dl)	0.533*	0.291–0.976	0.042
Systolic blood pressure (mmHg)	0.996	0.984–1.009	0.568
Diastolic blood pressure (mmHg)	1.014	0.993–1.035	0.205
Cerebrovascular disease	1.895*	1.049–3.424	0.034
Nephropathy	1.410	0.917–2.169	0.117
Neuropathy	1.107	0.727–1.687	0.635
Retinopathy	1.266	0.836–1.915	0.265
Current smoking habit	0.864	0.327–2.280	0.768
Barthel index (full score or not)	1.706*	1.006–2.894	0.048

*$P < 0.05$

triglyceride, serum albumin, systolic and diastolic blood pressure, history of cerebrovascular disease, history of diabetic retinopathy, history of diabetic neuropathy, history of diabetic nephropathy, current smoking habit, and Barthel index scores (full score or not).

Results

The backgrounds of the subjects involved are shown in Table 1. In the current study, 46% of the female participants (125 of 273) and 36% (89 of 253) of the male participants scored more than 6 on the GDS-15. The mean values of the CE ratios were 58.7 ± 5.9% and 59.4 ± 6.3% in the female and male participants, respectively.

Univariate logistic regression analysis demonstrated that a higher CE ratio was statistically significantly associated with depressive mood in women (odds ratio [OR] 1.037; 95% confident interval [CI] 1.001–1.074), but not in men (OR 0.998; 95% CI 0.962–1.036). Therefore, further analysis was performed only in women. The significantly associated variables with depressive mood defined by scores of 6 and more in the GDS-15 were serum albumin, the existence of a cerebrovascular history, and the Barthel index (Table 2). Multiple regression analysis with the CE ratio, these significant variables, and depression-associated variables (smoking and existence of diabetic neuropathy) was performed (model 1), and further analysis adding a diabetes-associated variable (HbA1c) was also performed (model 2). In the model 1 higher CE ratio, the existence of a

Table 3 Comparison of data for models 1 and 2

		Odds ratio	95% CI	*P*-value
Model 1				
	CE ratio	1.049*	1.010–1.089	0.014
	Serum albumin	0.541	0.292–1.004	0.051
	Existence of cerebrovascular disease	1.851*	1.002–3.420	0.049
	Existence of neuropathy	1.054	0.680–1.634	0.814
	Existence of current smoking habit	0.998	0.992–1.003	0.417
	Barthel index	1.897*	1.092–3.296	0.023
Model 2				
	CE ratio	1.051*	1.012–1.092	0.010
	Serum albumin	0.514*	0.274–0.962	0.038
	Existence of cerebrovascular disease	2.017*	1.080–3.764	0.028
	Existence of neuropathy	1.050	0.676–1.630	0.828
	Existence of current smoking habit	0.997	0.991–1.003	0.373
	Barthel index	1.862*	1.070–3.241	0.028
	HbA1c	0.804	0.624–1.036	0.092

*$P < 0.05$

cerebrovascular history and a lower Barthel index were significant variables (Table 3). The addition of HbA1c (model 2) gave very similar results (Table 3).

Discussion

Many studies have shown that the prevalence of depressive mood is higher in diabetic women than men,[23] and our findings were in agreement with these reports. The associations of co-morbidity of diabetic neuropathy,[6,24] cerebrovascular disease,[25] or lower physical function[26] with depressive mood in diabetics were also in agreement with previous reports. The current study, however, found that higher carbohydrate intake was associated with depressive mood in women, which to our knowledge is a new finding. In the current study, it was found that women who take more calories from carbohydrates tend to be more depressive. A 1% increase in the CE ratio leads to a 5% increase in the probability of a depressive mood in women.

The underlining mechanism of the association of a higher CE ratio and depressive mood in older diabetic women is unclear. Carbohydrate intake itself and/or fluctuations of the blood glucose levels may induce some toxic effects on the central nervous system.[12] In addition, some evidence has shown that insulin resistance is associated with depressive symptoms through the alterations of insulin actions in the central nervous system[27] and, interestingly, animal experiments have indicated that insulin differentially acts on the neurons in males and females.[28] Another possibility is that a higher protein and/or fat intake ratio may protect against depression.[29]

On the other hand, a depressive mood may, in itself, induce carbohydrate craving, especially in women.[30] Serum glucocorticoids, which elevate in a depressive state,[31] increase the intake of 'comfort foods' like sucrose in animal experiments.[32] A report also suggested that depressed women had higher hypothalamic–pituitary–adrenal axis activity than men.[33] Wurtman and Wurtman[15] hypothesized that carbohydrate intake relieved depressive mood by increased serotonin synthesis in the brain and proposed that the intake of carbohydrates was an attempt to relieve depression.[16] The causal relationship between high carbohydrates and depressive mood should be studied further.

The current study was performed only in the diabetic elderly. The association between a high carbohydrate intake and depressive mood should be investigated in younger or non-diabetic persons to reveal whether this association is true in the general population.

Conclusions

A higher CE ratio, a history of cerebrovascular diseases, and lower ADLs were factors significantly associated with depressive mood in elderly diabetic women, but not in men. Further research is needed to disentangle the causal relationships between depressive mood and higher carbohydrate intake and/or other factors.

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特集：転倒危険者の早期発見から予防まで
―最新のエビデンスから―

各論

1．病因，病態と転倒
1）糖尿病と転倒

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Geriat. Med. 47(6)：693～696, 2009

特集 転倒危険者の早期発見から予防まで —最新のエビデンスから— 各論

KEY WORD ●高齢者糖尿病 ●転倒 ●インスリン治療 ●歩行 ●バランス

1．病因，病態と転倒
1）糖尿病と転倒

櫻井　孝

SUMMARY

近年，糖尿病が転倒の独立した危険因子であることを示す報告が集積している．高齢者では糖尿病により，転倒リスクが約1.6～2.5倍高まると報告される．その機序として，視野障害，末梢神経症，腎機能障害，起立時の血圧変動，インスリン使用などの関与が指摘されている．特にHbA_{1c} ≦6～7%であると，転倒のリスクが高いとする報告が注目される．また糖尿病では，筋強剛や歩行障害が進行する．高齢者糖尿病では，転倒のリスクを正しく評価し，積極的な転倒防止プログラムを履行すべきである．

はじめに

糖尿病は加齢とともに増加する．わが国では，高齢者の少なくとも1/6が糖尿病に罹患している[1]．高齢者，特に後期高齢者では，多くの老年症候群を合併することが多い．糖尿病性血管症，併存疾患のために生活機能が障害され，家族や社会の支援が十分に得られないとき，自立した療養が困難となる．このため高齢者糖尿病では，包括的な老年病学の評価を踏まえた治療計画が必要となる[2,3]．井藤らは，高齢者糖尿病で評価すべき項目として，糖尿病の病型・病態(内因性のインスリン分泌能，インスリン抵抗性)，血糖管理，糖尿病性血管症の評価に加えて，ADL，尿失禁の有無，認知機能，抑うつ，社会的サポート，経済状態などを総合的に評価することを提唱している[2,3]．

ところで転倒は高齢者の25～40%にみられ，約10回の転倒で1回の割合で重大な外傷を残す[4]．転倒・骨折により寝たきりとなると，生活機能やQOLが低下するのみならず，生命予後をも左右される．また身体外傷を来さなかった転倒でも，転倒に対する不安が高齢者の活動性やQOLを制限し，生活障害の原因となる[5]．つまり転倒は，高齢者の自立を損なう疾患として極めてその意義は重く，転倒リスクの評価，予防介入が必要である．

近年，糖尿病が転倒の独立した危険因子であることを示す報告が集積されている．糖尿病が転倒のリスクとなる原因として，糖尿病の合併症-末梢神経症，心血管疾患，視力障害，認知障害や低血糖などの関与が想定されるが，その機序について一定のコンセンサスは得られていない．わが国の高齢者糖尿病における転倒の実態調査は，ほとんど行われていないのが現状であろう．そこで本稿では糖尿病と転倒との関連について，これまでの海外の知見を紹介したい．なお転倒リスクの評価，予防については，他稿を参考にされたい．

糖尿病と転倒との関連

これまで，歩行・バランスの障害，視力障害，多剤服用などは転倒の危険因子として広く認知されているのに対して，糖尿病はあまり知られていない．糖尿病は，糖尿病性末梢神経症，網膜症，自律神経障害，心不全や関節症，足病変，低血糖など，転倒に関連する因子を多く有しており，転倒が多いことが想定されてきた．近年，糖尿病は転倒の独立した危険因子であることを示す知見が蓄積されている[6-10,13,14,17,20,21]．

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