Table 3
Endpoints by glucose status

	Diet		Diet + pravastatin		Hazard ratio (95% CI)	Heterogeneity
CHD	Event (/1000 patient-years)					
DM	43	(10.9)	29	(7.5)	0.71 (0.44–1.13)	
IFG	7	(7.0)	6	(5.6)	0.89 (0.30–2.66)	
AFG	50	(10.1)	35	(7.1)	0.73 (0.47–1.13)	0.74
NFG	35	(2.7)	22	(1.8)	0.65 (0.38–1.11)	
All patients	85	(4.8)	57	(3.3)	0.70 (0.50–0.97)	
Stroke						
DM	21	(5.3)	14	(3.6)	0.70 (0.36–1.38)	
IFG	4	(4.0)	0	(0.0)	–	
AFG	25	(5.0)	14	(2.8)	0.59 (0.30–1.13)	0.68
NFG	36	(2.8)	24	(2.0)	0.70 (0.47–1.17)	
All patients	61	(3.4)	38	(2.2)	0.65 (0.43–0.97)	
CI						
DM	18	(4.5)	9	(2.3)	0.52 (0.23–1.16)	
IFG	4	(4.0)	0	(0.0)	–	
AFG	22	(4.4)	9	(1.8)	0.43 (0.20–0.93)	0.30
NFG	23	(1.8)	16	(1.3)	0.73 (0.38–1.37)	
All patients	45	(2.5)	25	(1.4)	0.58 (0.36–0.94)	
CVD						
DM	68	(17.6)	46	(12.1)	0.71 (0.49–1.03)	
IFG	12	(12.1)	6	(5.6)	0.52 (0.20–1.39)	
AFG	80	(16.5)	52	(10.7)	0.68 (0.48–0.96)	0.85
NFG	73	(5.7)	50	(4.1)	0.71 (0.50–1.02)	
All patients	153	(8.6)	102	(6.0)	0.69 (0.54–0.89)	
Total mortality						
DM	28	(6.8)	16	(4.0)	0.61 (0.33–1.12)	
IFG	1	(1.0)	4	(3.6)	4.36 (0.49–39.1)	
AFG	29	(5.7)	20	(3.9)	0.73 (0.41–1.29)	0.79
NFG	37	(2.8)	23	(1.8)	0.65 (0.39–1.10)	
All patients	66	(3.6)	43	(2.4)	0.69 (0.47–1.01)	

Hazard ratio (HR) and 95% confidence interval (95% CI) were obtained by Cox proportional hazard model, adjusted according to sex and age. Heterogeneities were compared for the abnormal fasting glucose (AFG) and normal fasting glucose (NFG).

ponents of the CVD endpoint) were also higher in DM (by 4.0 and 1.9 times, respectively) and IFG (by 2.6 and 1.4 times) than NFG. Compared with the diet group in the DM, IFG, and AFG categories, treatment with diet + pravastatin conferred a lower risk of experiencing a CVD event over 5 years of 29% ($P = 0.07$), 48% ($P = 0.19$), and 32% ($P = 0.03$), respectively. Absolute figures and event/1000 patient-years are summarized in Table 3. The CI was significantly reduced by 57% in the AFG group with diet + pravastatin group compared with the diet group ($P = 0.03$). The number needed to treat (NNT) to prevent one occurrence of CVD in AFG was 42 patients. No interaction was found between the AFG and NFG groups for CVD ($P = 0.85$), CHD ($P = 0.74$), stroke ($P = 0.68$), CI ($P = 0.30$), and total mortality ($P = 0.79$) (Table 3).

Kaplan–Meier curves for CVD, CHD, stroke, and CI in the AFG group are shown in Fig. 1. The curves begin to diverge at about 2 years for CVD, CHD, and stroke in the two treatment groups.

3.3. Safety

No significant difference was observed in the occurrence of severe adverse events, including malignant neoplasms (3.1% vs. 3.1%), elevated alanine transferase (3.0% vs. 3.7%) or elevated creatine kinase (3.3% vs. 2.9%) in AFG patients in the diet alone vs. diet + pravastatin group. No incidence of rhabdomyolysis was observed in either treatment group.

4. Discussion

Type-2 DM is a strong risk factor for the development of atherosclerotic diseases [21]. Some evidence showed that different risk factors independently and additively affect outcomes of various clinical complications in DM [22,23]. Apart from hyperglycemia, patients with type-2 DM are more likely to be obese, hypertensive, and dyslipidemic compared with non-diabetic individuals. Diabetics have more macrovascular complications (e.g., CHD, stroke, peripheral vascular disease) than non-diabetics [23]. The relationship between FPG and risk of cardiovascular disease was established by several epidemiological studies and meta-analysis of their data [24–26]. These data indicated that even pre-diabetes is associated with increased cardiovascular risk. In particular, the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) [26] showed that IFG appears to be an independent predictor

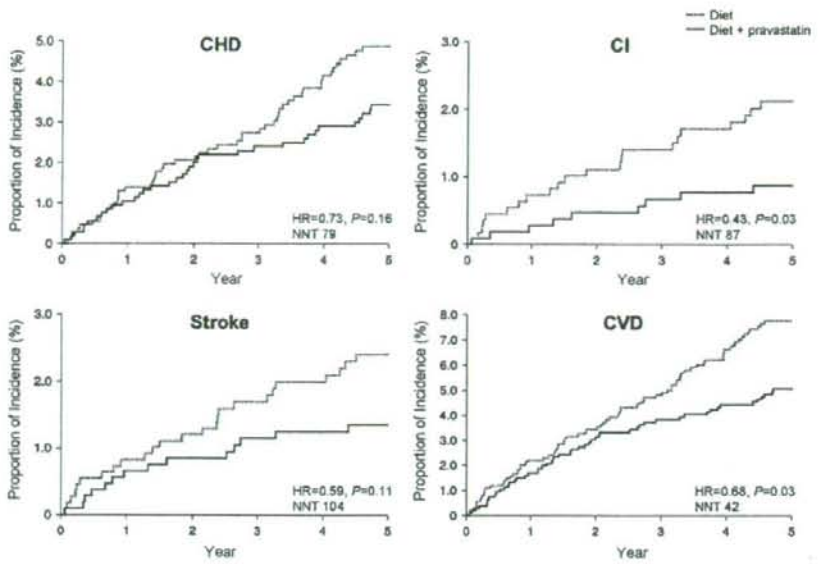

Fig. 1. Kaplan–Meier curves for CHD, stroke, CI, and CVD in the abnormal fasting glucose (AFG) group. The hazard ratio (HR) and 95% confidence interval (95% CI) were calculated by Cox proportional hazard model adjusted according to sex and age. NNT, number needed to treat.

of all-cause and CVD mortality. Therefore, the entire spectrum of abnormal fasting glucose, from IFG to established DM, must be considered to determine optimal treatment strategies to prevent CVD.

Several international landmark studies [1–5] have firmly established that lipid reduction improved CHD outcomes in at-risk subjects, including those with mild-to-moderate hypercholesterolemia, and the benefit in diabetic patients was examined in subgroup and post hoc analysis. In the primary prevention Collaborative Atorvastatin Diabetes Study (CARDS) [5], atorvastatin significantly reduced the incidence of cardiovascular events compared with placebo in diabetic patients without a history of CVD or elevated LDL-C at study entry. A significant difference in the incidence of major cardiovascular events or procedures was found with atorvastatin compared with placebo in the 2532 patients with diabetes in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) study [6]. In the Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints (ASPEN), atorvastatin compared with placebo did not significantly reduce composite endpoints such as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and revascularization in 2410 patients with type-2 DM [9]. Pravastatin compared with placebo significantly lowered the risk of a major CHD event by 24%, and any cardiovascular event (including stroke) by 21% in a subanalysis of patients with DM in the secondary prevention Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial [7]. Pravastatin substantially reduced recurrent coronary events in CHD patients with average cholesterol levels in the presence or absence of a clinical diagnosis of DM in the Cholesterol and Recurrent Events (CARE) trial [8]. The Heart Protection Study (HPS) showed that simvastatin as primary and secondary prevention significantly reduced CVD risk by about 25% in patients with DM. A significant benefit from statins was demonstrated by a meta-analysis of 90,056 patients of statins [27]. Despite sufficient data to support this evidence in Western populations with a high-risk of CVD, there are no data in low-risk populations such as the Japanese.

In the present post hoc analysis of the MEGA Study, a significant reduction in CVD risk (32%) was found in patients with AFG with diet + pravastatin treatment. This relative risk reduction is consistent with the results from the CARDS trial (32%), subanalysis of the LIPID study (23%), and the CARE study (25%), despite the low-dose of pravastatin. A lower incidence was found for CHD (27%), stroke (41%), and total mortality (27%) with diet + pravastatin compared with diet therapy. The difference was not statistically significant, but CHD, stroke, and total mortality were reduced by 27%, 41%, and 27%, respectively, in the AFG group with diet + pravastatin treatment compared with the diet alone group. In the DM and IFG groups, a risk reduction of 11%–48% was observed for CHD, stroke, and CI, although they did not reach statistical significance. They did not reach statistical significance probably because of the small number of events in the study; these reductions are in accordance with results from other comparable studies. The results of this subanalysis suggest that pravastatin has a beneficial effect in preventing CVD in individuals with AFG in Japan, similar

to the results in Western populations. These results probably apply to other Asian populations of the same race. The NNT to prevent one CVD is 42 with AFG. This small NNT underscores the particular benefit of pravastatin in patients with AFG to prevent cardiovascular events, despite a proportionally lower prevalence of CVD in Japan.

Risk reduction was found in patients with IFG. Although this did not reach statistical significance, hazard ratios were very similar to the results of the DM subanalysis of the LIPID trial [7], indicating that diet + pravastatin is beneficial in preventing CVD events in the early phase of impaired glucose regulation, regardless of a prior history of CVD.

No significant difference in severe adverse events (including occurrence of cancer) was found between the two treatment groups or across the glucose strata, confirming the safety and tolerability of pravastatin in these groups. Although it did not reach statistical significance, hemorrhagic stroke was observed more in the diet + pravastatin group (2 in diet alone vs. 5 in diet + pravastatin) in the AFG group, which occurred primarily in the first 2 years of the study. Determining a specific effect from pravastatin treatment on hemorrhagic stroke was difficult because events were few, and because pravastatin did not have this effect in the NFG group, in which there were fewer hemorrhagic strokes compared with diet alone (18 events vs. 12 events, respectively).

Subanalyses of the West of Scotland Coronary Prevention Study (WOSCOPS) [15] have suggested that randomized assignment to pravastatin was a significant baseline predictor for future DM ($P < 0.05$), with a 30% reduction in developing DM. Subanalyses of the LIPID study suggested that pravastatin may play a part in preventing new-onset DM [7]. In the present study, the incidence of DM in those who were not diabetic at baseline was not different between the diet alone and diet + pravastatin groups, and FPG and HbA1c did not differ before or after pravastatin treatment. This result in the present subanalysis is consistent with reports from several small trials, and an epidemiological study indicated [28] no changes in glycemic control with pravastatin treatment.

Type-2 DM and IFG are associated with a strong risk for developing CVD in patients with hyperlipidemia, based on the present subanalysis from the MEGA Study. The small study population calls for careful interpretation, but these results are in accordance with those reported from Western studies, despite a regimen with a lower dose of pravastatin. Although no beneficial effect of pravastatin was found on new-onset DM or glycemic control in the present study, pravastatin did not worsen glycemic control. We showed that long-term treatment with diet + low-dose pravastatin reduces the risk of CVD across the full spectrum of abnormal fasting glucose in Japan in the setting of primary prevention, with a good safety and tolerability profile. The results of this study suggest the importance of statin therapy in subjects with hypercholesterolemia and AFG. It also suggests that the effect of low-dose statin therapy is considerable for primary prevention, even in AFG in low-risk populations.

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Waist Circumference as a Cardiovascular and Metabolic Risk in Japanese Patients With Type 2 Diabetes

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Excess waist circumference (WC) is a frequently used indicator of abdominal obesity and/or cardiovascular disease (CVD) risk. Nonetheless, search of the literature revealed no prospective studies on the association between WC and CVD events in diabetic patients. In this study, the clinical significance and implications of WC as a cardiovascular and metabolic risk indicator was prospectively investigated in Japanese patients with type 2 diabetes. For this purpose, baseline data on WC, hypertension, and dyslipidemia were collected and subsequent CVD (coronary heart disease and stroke) events during the following 8 years were studied in 1,424 Japanese type 2 diabetic patients, and the cross-sectional/longitudinal associations between WC and CVD risk factors/events were analyzed. Mean WC levels were significantly increased according to the number of coexisting risk factors. However, no significant difference in mean WC between subgroups with and without CVD events was noted, and excess WC alone was not predictive of subsequent CVD events either in male or female subjects even after adjustment for age, smoking, hypertension, and dyslipidemia. In female patients, excess WC (≥80 cm) was predictive of CVD events only with the coexistence of hypertension. In Japanese diabetic patients, excess WC alone, although a good marker for clustering of CVD risk factors, did not raise the risk of CVD events unless accompanied by hypertension in female patients. Further investigations are necessary before WC as a risk factor can be utilized in clinical settings for the management of diabetes in this population.

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INTRODUCTION

Waist circumference (WC) is a simple and widely used indicator of abdominal adiposity and the risk of cardiovascular disease (CVD) (1), and, thus, has been adopted in most definitions of metabolic syndrome (MetS) (2–4). However, prospective studies of the relationship between WC and CVD events *per se* have been performed mostly in white populations (5– 10). Moreover, we are not aware of studies that are specific to diabetic subjects.

The incidence and characteristics of CVD are known to be quite different between Asians and whites (11) or between diabetic and nondiabetic subjects. In particular, the importance of central obesity in the diabetic population has hardly been examined. Therefore, a prospective study is needed on the clinical significance of WC in relation to CVD in Asian diabetic subjects, who comprise more than one-third of the global diabetic population (12).

In previous studies (13,14), we examined the diagnosis of MetS as a predictor of CVD and found that MetS, as defined by the International Diabetes Federation (IDF) (2), has lower predictability for future CVD events than that according to the World Health Organization (WHO) (15) and National Cholesterol Education Program/Adult Treatment Panel III (16) in Japanese patients with type 2 diabetes. Since IDF criteria (2) include excess WC as a mandatory component for the diagnosis of MetS and the criteria of the other two organizations do not, it is possible that the lower prognostic power of IDF criteria is derived from mandatory inclusion of WC. In

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this study, we undertook a detailed evaluation of the significance of WC in cardiovascular and metabolic risk in Japanese patients with type 2 diabetes.

METHODS AND PROCEDURES

The Japan Diabetes Complications Study is a multicenter prospective study of Japanese patients with type 2 diabetes (17–20). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1c} levels of >6.5% were recruited from 59 institutes specializing in diabetes care. The eligibility criteria for participating patients have been described previously (17). Of the 2,205 patients, the present study focused on the 1,424 patients (771 men and 653 women) analyzed previously (13,14), who had no history of CVD but had a complete set of data including those parameters necessary to satisfy the WHO (15) and National Cholesterol Education Program (16) criteria for the definition of MetS at baseline. Baseline characteristics of the patients analyzed are shown in **Table 1**. In terms of representativeness of the 1,424 patients among the 2,205 patients, comparison between the 1,424 patients and the remaining patients (i.e., 781 patients) showed that only two of the parameters listed in **Table 1** differed significantly between these two groups as determined by the *t*-test. These two exceptions were fasting plasma glucose and HbA_{1c}, which were slightly but significantly higher in the 1,424 patients than in the 781 patients (159 ± 44 mg/dl vs. 154 ± 40 mg/dl, $P = 0.006$, and 7.8 ± 1.4 vs. 7.6 ± 1.2%, $P = 0.006$, respectively). The protocol of the Japan Diabetes Complications Study received ethical approval from the institutional review boards of all of the participating institutes and all of the study participants gave written informed consent.

Baseline WC was analyzed with baseline presence of hypertension and dyslipidemia. Also evaluated was the association of baseline WC with future CVD events (fatal/nonfatal coronary heart disease (CHD) and stroke) during an 8-year period. Thresholds for individual risk factors were adopted from the Japanese definition of MetS (3), which was close to that of IDF (2). Since all of the subjects in this study had diabetes mellitus, three criteria other than an elevated fasting plasma glucose level (>110 mg/dl) were used: (i) excess WC (male ≥85 cm, female ≥90 cm), (ii) hypertension (systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg), and (iii) dyslipidemia (triglyceride ≥150 mg/dl and/or high-density lipoprotein cholesterol <40 mg/dl). Subjects using agents for hypertension and hyperlipidemia were considered to have those risk factors. The alternative WC cutoff values for Asians in general as decided by the WHO (male ≥90 cm, female ≥80 cm) (2,4) were also used for additional evaluation.

Patients were assessed for CHD and stroke at baseline and yearly thereafter. In all subjects, a 12-lead electrocardiogram was recorded at each assessment. Both fatal/nonfatal CHD and stroke events identified during follow-up were certified by at least two members of the experts' committee who were masked as to risk factor status of the patient and the other member's diagnosis. In terms of CHD, myocardial infarction was defined in accordance with the criteria of the WHO Monitoring of Trends and Determinants in Cardiovascular Disease (21), and angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by use of nitroglycerine as validated by exercise-positive electrocardiogram and/or angiography.

Stroke events were defined as a constellation of focal or global neurological deficits that were sudden or rapid in onset and for which there was no apparent cause other than a vascular accident on the basis of a detailed history, neurologic examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria (22). No cases of asymptomatic lesions detected by brain imaging (i.e., silent infarction) were included. Only "first-ever" CHD or stroke events during the study period were counted for the analysis and if a patient had both CHD and stroke events, then each event was counted separately.

Measurement of WC was at the level of the umbilicus. Information regarding cigarette smoking was collected using a standardized questionnaire. All laboratory tests were undertaken using the standard methods of each participating institute, apart from the HbA_{1c} assays that used a common standard, with 5.8% as the upper normal limit. Plasma low-density lipoprotein cholesterol was calculated using Friedwald's equation, except where triglycerides exceeded 400 mg/dl, in which case the low-density lipoprotein cholesterol data were treated as "missing." Data are presented as means ± s.d. or as a proportion unless otherwise specified. WC in each group was assessed by Wilcoxon's rank sum test. Cox regression analysis was used to calculate the age-adjusted hazard ratio and 95% confidence intervals of risk factors for CVD. The SAS software package (version 9.0; SAS Institute, Cary, NC) was used for all analyses. $P < 0.05$ was considered to be significant.

RESULTS

WC was associated with a number of CVD risk factors but not with future CVD events

We first determined mean WC values with 95% confidence intervals in groups of patients stratified according to the number of risk factors at baseline (**Table 2**). In both men and women, WC significantly increased in a stepwise manner beginning with those with no risk factors to those with two risk factors. Differences in mean WC levels did not differ significantly between groups with 0 vs. 1 or 2 risk factors, as well as groups with 0 or 1 vs. 2 risk factors. Then, we compared

Table 1 Baseline characteristics of patients analyzed

	Men	Women
Number of patients (%)	771	653
Age (years)	58.2 ± 7.4	58.7 ± 7.4
Diabetes duration (years)	10.9 ± 7.6	10.1 ± 6.7
BMI (kg/m^2)	22.9 ± 2.6	23.4 ± 3.3
Waist circumference (cm)	82.3 ± 7.7	76.5 ± 9.8
Waist-to-hip ratio	0.89 ± 0.07	0.83 ± 0.08
Blood pressure (mm Hg)	132 ± 16/78 ± 10	132 ± 17/76 ± 10
HbA_{1c} (%)	7.61 ± 1.36	8.05 ± 1.45
Fasting plasma glucose[a] (mmol/l)	8.3 (7.2, 10.0)	8.6 (7.3, 10.2)
Fasting plasma insulin[a] (pmol/l)[c]	6.2 (0.5, 1.9)	7.1 (0.5, 1.9)
Serum LDL cholesterol (mmol/l)	3.03 ± 0.86	3.38 ± 0.82
Serum HDL cholesterol (mmol/l)	1.34 ± 0.39	1.47 ± 0.44
Serum triglycerides[b] (mmol/l)	1.39 (0.75)	1.29 (0.72)
Current smoker (%)	43.9	8.7
OHA (without insulin) use (%)	72	77
Insulin (with or without OHA) use (%)	16	20
Medication for hypertension (%)	22	29
Medication for hyperlipidemia (%)	15	35

Data are presented as mean ± s.d.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; OHA, oral hypoglycemic agents.
[a]Median (IQR). [b]Geometric mean (1 s.d.). [c]Patients on insulin therapy were excluded.

Table 2 Mean waist circumference (WC) with 95% confidence intervals (CI) in Japanese patients with type 2 diabetes stratified according to the number of risk factors (i.e., hypertension and/or dyslipidemia) at baseline

				Model 1		Model 2	
	Number of CVD risk factors		No. patients	Mean WC (95% CI)	*P* value	Mean WC (95% CI)	*P* value
Men	0 vs. 1 vs. 2	0	181	78.8 (77.7–79.8)*	<0.0001	78.7 (77.6–79.8)*	<0.0001
		1	399	82.5 (81.7–83.2)*		82.4 (81.6–83.2)*	
		2	191	85.2 (84.1–86.2)*		85.5 (84.4–86.6)*	
	0 vs. ≥1	0	181	78.8 (77.7–79.9)	<0.0001	78.7 (77.6–79.8)	<0.0001
		≥1	590	83.3 (82.7–83.9)		83.4 (82.8–84.0)	
	1≤ vs. 2	1≤	580	81.3 (80.7–81.9)	<0.0001	81.2 (80.6–81.9)	<0.0001
		2	191	85.2 (84.1–86.2)		85.5 (84.4–86.6)	
Women	0 vs. 1 vs. 2	0	153	72.9 (71.4–74.5)**	<0.0001	72.1 (70.1–74.0)**	<0.0001
		1	354	77.0 (76.0–78.0)**		76.5 (75.0–78.1)**	
		2	146	78.9 (77.4–80.5)**		78.4 (76.5–80.3)**	
	0 vs. ≥1	0	153	72.9 (71.4–74.5)	<0.0001	72.0 (70.2–74.2)	<0.0001
		≥1	500	77.6 (76.7–78.4)		77.2 (75.8–78.6)	
	1≤ vs. 2	1≤	507	75.8 (74.9–76.6)	0.0008	75.2 (73.8–76.7)	0.0013
		2	146	78.9 (77.3–80.5)		78.4 (76.5–80.3)	

Model 1, adjusted by age; model 2, adjusted by age and smoking status; *P* values were calculated by ANOVA.
CVD, cardiovascular disease.
*Significant differences existed between all three groups. **significant differences existed between 0 vs. 1 and 0 vs. 2 by Tukey's multiple comparison test. Significant trend ($P < 0.0001$) also existed for both men* and women**.

Table 3 Mean waist circumference (WC) with 95% confidence intervals (CI) in Japanese patients with type 2 diabetes stratified according to CVD events during follow-up

				Model 1		Model 2		Model 3	
	CVD event		No. patients	Mean WC (95% CI)	*P* value	Mean WC (95% CI)	*P* value	Mean WC (95% CI)	*P* value
Men	CHD	–	703	82.2 (81.6–82.8)	0.616	82.2 (81.6–82.8)	0.609	82.4 (81.7–83.0)	0.777
		+	42	82.7 (80.9–84.5)		82.7 (80.9–84.5)		82.1 (80.4–83.8)	
	Stroke	–	738	82.3 (81.7–82.8)	0.962	82.3 (81.7–82.8)	0.936	82.4 (81.8–83.0)	0.619
		+	33	82.2 (79.6–84.8)		82.1 (79.5–84.8)		81.7 (79.1–84.3)	
	CHD and/or stroke	–	673	82.2 (81.7–82.8)	0.523	82.2 (81.6–82.8)	0.513	82.3 (81.7–83.0)	0.956
		+	72	83.0 (80.7–85.3)		83.0 (80.7–85.4)		82.3 (80.0–84.5)	
Women	CHD	–	618	76.3 (75.5–77.1)	0.131	76.0 (74.6–77.4)	0.197	75.6 (74.2–77.1)	0.269
		+	20	78.6 (75.7–81.4)		78.0 (74.9–81.2)		77.4 (74.3–80.5)	
	Stroke	–	627	76.4 (75.6–77.1)	0.237	76.0 (74.6–77.4)	0.297	75.7 (74.3–77.1)	0.400
		+	26	78.7 (74.9–82.5)		78.2 (74.1–82.2)		77.4 (73.4–81.4)	
	CHD and/or stroke	–	593	76.4 (75.6–77.2)	0.523	76.1 (74.7–77.5)	0.611	75.8 (74.4–77.2)	0.696
		+	45	77.8 (73.5–82.1)		77.3 (72.6–82.0)		76.7 (72.1–81.2)	

Model 1, adjusted by age; model 2, adjusted by age and smoking status; model 3, adjusted by age, smoking status, hypertension, and dyslipidemia. *P* values were calculated by ANOVA.
CHD, coronary heart disease; CVD, cardiovascular disease.

mean WC in groups stratified according to whether CVD events (CHD and/or stroke) occurred during the 8-year follow-up period (**Table 3**). However, unlike groups stratified by baseline risk factors (**Table 2**), mean WC values did not differ significantly between either male or female groups with and without CVD events (**Table 3**). These relationships between WC and the number of risk factors or between WC and CVD events were not altered even after adjustment for age, smoking, (**Tables 2** and **3**) and existence of hypertension and dyslipidemia (**Table 3**). The relationships between WC and CHD events were not changed regardless of inclusion or exclusion of subjects with asymptomatic myocardial infarction, which accounted for 5 of 42 men and 3 of 20 women (data not shown).

Table 4 Hazard ratio (HR) of those who have each risk factor compared to those who do not (as a categorical variable)

		Model 1		Model 2	
	(Yes vs. no, no = reference)	HR	*P* value	HR	*P* value
Men	Hypertension	1.34 (0.79–2.27)	0.28	1.30 (0.76–2.22)	0.35
	Dyslipidemia	**1.93 (1.21–3.07)**	**0.006**	**1.90 (1.18–3.07)**	**0.009**
	High WC (by Japanese cutoff, i.e., > 85 cm)	1.32 (0.83–2.12)	0.24	1.07 (0.65–1.74)	0.80
	High WC (by Asian cutoff, i.e., >90 cm)	1.32 (0.75–2.31)	0.33	1.09 (0.62–1.93)	0.76
Women	Hypertension	1.06 (0.53–2.14)	0.86	0.96 (0.47–1.96)	0.91
	Dyslipidemia	1.58 (0.84–2.96)	0.16	1.47 (0.77–2.79)	0.24
	High WC (by Japanese cutoff, i.e.,, > 90 cm)	0.92 (0.33–2.60)	0.88	0.84 (0.29–2.38)	0.74
	High WC (by Asian cutoff, i.e., >80 cm)	1.68 (0.91–3.11)	0.099	1.52 (0.81–2.85)	0.19

HR of each of the various risk factors for cardiovascular disease events (coronary heart disease and/or stroke) in Japanese patients with type 2 diabetes calculated by the Cox regression analysis. Statistically significant ($P < 0.05$) values are shown in boldface. Model 1, adjusted by age and smoking status; model 2, adjusted by age, smoking status, hypertension, and dyslipidemia. Adjustment by hypertension or dyslipidemia was performed in cases when either or both of these two parameters were not used (e.g., when calculating odds ratio of hypertension, only age, smoking status, and dyslipidemia were used for adjustment).
WC, waist circumference.

Table 5 Hazard ratio (HR) of having every 1 s.d. higher value of each risk factor (ss continuous variable)

		Model 1		Model 2	
	(Per 1 s.d. increase of each value)	HR	*P* value	HR	*P* value
Men	Systolic blood pressure	1.26 (0.99–1.60)	0.051	1.25 (0.98–1.59)	0.077
	Diastolic blood pressure	**1.28 (1.00–1.64)**	**0.046**	1.25 (097–1.61)	0.091
	Triglycerides	**1.32 (1.08–1.61)**	**0.007**	**1.29 (1.05–1.59)**	**0.015**
	HDL cholesterol	0.43 (0.18–1.05)	0.065	0.43 (0.18–1.07)	0.069
	HbA_{1c}	**1.37 (1.12–1.67)**	**0.002**	**1.37 (1.11–1.68)**	**0.004**
	WC	1.09 (0.86–1.37)	0.49	0.94 (0.73–1.21)	0.62
Women	Systolic blood pressure	**1.40 (1.02–1.92)**	**0.038**	1.37 (1.00–1.89)	0.051
	Diastolic blood pressure	1.18 (0.89–1.58)	0.26	1.14 (0.85–1.53)	0.40
	Triglycerides	1.09 (0.82–1.43)	0.55	1.02 (0.77–1.37)	0.88
	HDL cholesterol	0.55 (0.17–1.71)	0.30	0.61 (0.19–2.00)	0.41
	HbA_{1c}	1.29 (0.97–1.72)	0.086	1.32 (0.98–1.77)	0.072
	WC	1.21 (0.90–1.63)	0.21	1.15 (0.84–1.57)	0.40

HR of each of the various risk factors for cardiovascular disease events (coronary heart disease and/or stroke) in Japanese patients with type 2 diabetes calculated by the Cox regression analysis. Statistically significant ($P < 0.05$) values are shown in boldface. Model 1, adjusted by age and smoking status; model 2, adjusted by age, smoking status, hypertension, and dyslipidemia. Adjustment by hypertension or dyslipidemia was performed in cases when either or both of these two parameters were not used (e.g., when calculating odds ratio of hypertension, only age, smoking status, and dyslipidemia were used for adjustment).
HDL, high-density lipoprotein; WC, waist circumference.

WC was not an independent risk factor for CVD in diabetic patients

The above results led us to further investigate the individual hazard ratio for WC in comparison with other risk factors when expressed as categorical (**Table 4**) or continuous (**Table 5**) variables. Although hypertension, dyslipidemia, and glycemia in men and hypertension in women had a significantly elevated hazard ratio, the hazard ratio for WC, either as a categorical (**Table 4**) or as a continuous (**Table 5**) variable, was not significantly elevated. Then, we determined whether WC could have a potential interaction between hypertension and dyslipidemia, or both by calculating the hazard ratio adjusted by either of these potential confounders, replacing each with the other. However, we did not find any significantly elevated hazard ratio even after that calculation (data not shown).

Results of subgroup analysis of participants categorized according to the presence of hypertension and/or dyslipidemia are shown in **Table 4**. Only in female patients did those with hypertension demonstrate a significantly elevated hazard ratio in accordance with excess WC as defined by the Asian cutoff (i.e., 80 cm) or per 1 s.d. Hazard ratios were not significantly elevated in male subjects in any category regardless of whether they had hypertension and/or dyslipidemia.

DISCUSSION

The current results shown in **Table 2** are partially concordant with results of a cross-sectional study by Tseng (23) showing that excess WC is strongly associated with clustering of cardiovascular risk factors in East Asian patients with type 2 diabetes. Nevertheless, according to our current results shown

in **Table 3**, this positive relationship could not be used for the prediction of future CVD events. Although to the best of our knowledge no study has evaluated WC and its association with the baseline presence of CVD risk factors and future incidence of CVD in the same cohort, the results shown in this study clearly demonstrate a vast discrepancy between cross-sectional and longitudinal results for this topic. These discrepancies are somewhat understandable as the majority of the current WC cutoff values, including the Japanese (24) and Asian (25) values, were not determined based on prospective data on CVD events (26) but on the presence of cardiovascular risk factor(s), which are only surrogate markers for CVD events.

However, it was also reported that clustering of cardiovascular risk factors increased the risk of events even in subjects with diabetes (27). A possible explanation for the apparent contradictory results shown here that WC was not a predictor of CVD events, despite being a good marker for risk factor clustering, is that excess WC alone might not be predictive in these patients without the presence of other risk factors. This hypothesis is partially supported by our results shown in **Table 6** that excess WC was predictive only with coexisting hypertension in women with diabetes. Another interpretation is that the risk factors that tend to be clustered with an enlarged WC might be insufficient to significantly raise the risk of CVD events. Although we mostly used only the CVD risk factors adopted in the MetS definitions in this study, existing definitions of MetS have been shown to be quite poor predictors of future CVD events in patients with type 2 diagnosis, as recently reported by us (13,14) as well as by the United Kingdom Prospective Diabetes Study (28). Therefore, other risk factors such as diabetes duration, status of glycemic control or low-density lipoprotein– cholesterol level, smoking habits or the presence of atrial fibrillation, which do not have close associations with WC *per se*, also have potent effects (29,30). Actually, the status of glycemic control as expressed by HbA_{1c} values was a significant risk factor in men (**Table 5**).

Another possible explanation for the contradiction is that a longer period of observation than ours might be necessary for CVD events to occur or that diabetes *per se* might impact on body composition. Finally, another possibility is that WC might not be a good indicator of visceral adiposity in diabetic patients and that other methods of assessment such as computed tomography or magnetic resonance imaging might be better. In addition, it should be considered whether this result was obtained by chance; therefore, further investigations are necessary.

This is a primary prevention study of macrovascular complications of diabetes and our patients had no baseline CVD even though the mean duration of diabetes was 10 years. Although such patients might be considered quite unusual in Europe or in the United States, patients with diabetes of a rather long duration but without CVD are common in Japan because the incidence of CVD is markedly lower in East Asian countries than in Europe or in the United States (31). In fact, only ~3% of patients with a 10-year history of type 2 diabetes in Japan have CHD in their history (32). Moreover, although the mean WC in our patients is much lower than in European or American patients with type 2 diabetes, the mean WC in our cohort is almost identical to that reported in the Japanese general population (33,34). In fact, as we have reported previously (18), Japanese diabetic patients, in general, are not obese compared to the general population, which is an important characteristic of patients with diabetes in Japan. In addition, thresholds of WC appropriate for diagnosis of MetS are also reportedly much lower in Japanese compared with white patients (35);

Table 6 Hazard ratio (HR) of having larger waist circumference (WC; as a categorical or a continuous variable) for cardiovascular disease events (coronary heart disease and/or stroke) according to patients subgrouped by existence of hypertension and/or dyslipidemia

	Hypertension		Dyslipidemia	No. patients	(1) WC ≥ 85 cm (vs. WC < 85 cm)	*P* value	(2) WC ≥ 90 cm (vs. WC < 90 cm)	*P* value	(3) per 1 s.d. increase in WC	*P* value
Men	–		–	181	0.74 (0.16–3.33)	0.69	NA		0.88 (0.51–1.50)	0.63
	+		–	303	0.86 (0.35–2.08)	0.73	1.21 (0.45–3.25)	0.71	0.93 (0.61–1.40)	0.72
	–		+	96	2.31 (0.55–9.68)	0.25	1.51 (0.30–7.54)	0.62	1.02 (0.48–2.16)	0.96
	+	and	+	191	1.27 (0.60–2.72)	0.53	1.42 (0.64–3.14)	0.39	1.18 (0.77–1.80)	0.44
	+	or	+	590	1.34 (0.80–2.24)	0.26	1.44 (0.81–2.55)	0.22	0.88 (0.51–1.50)	0.63
	Hypertension		**Dyslipidemia**	**No. patients**	**(1) WC ≥ 90 cm (vs. WC < 90 cm)**	***P* value**	**(2) WC ≥ 80 cm (vs. WC < 80 cm)**	***P* value**	**(3) per 1 s.d. increase in WC**	***P* value**
Women	–		–	153	1.10 (0.84–1.44)	0.47	NA		0.64 (0.22–1.91)	0.43
	+		–	303	2.49 (0.90–6.85)	0.078	**2.41 (0.99–5.82)**	**0.050**	**1.56 (1.04–2.32)**	**0.031**
	–		+	51	NA		1.57 (0.25–9.86)	0.63	0.87 (0.30–2.52)	0.79
	+	and	+	146	NA		1.43 (0.47–4.39)	0.53	0.94 (0.54–1.62)	0.82
	+	or	+	500	NA		**1.93 (1.02–3.64)**	**0.042**	1.26 (0.94–1.70)	0.13

HRs were calculated in three ways, i.e., HR of those whose WC was equal to or greater than cutoffs by (1) Japanese or (2) Asian criteria, compared to those whose WC was less than those cutoffs (as a categorical variable); or (3) HR of having every 1 s.d. larger WC (as a continuous variable). Statistically significant ($P < 0.05$) values are shown in boldface.
NA, could not analyze due to small numbers of events.

however, even a small increase in WC is predictive of a substantial increase in the risk for CVD in other East Asian countries (36).

It is widely accepted that WC cutoff values should be modified in consideration of ethnicity (26,37,38). However, even using ethnic-specific (either for Japanese or Asians) cutoffs, WC alone was not a significant risk factor for CVD events in both male and female patients with type 2 diabetes (13,14), which is inconsistent with previously reported prospective results in the general population or in mainly nondiabetic populations (5–10,39,40). It is speculated that diabetes itself could greatly enhance the CVD risk, thus mask the influence of coexisting excess WC. If so, clinical significance of excess WC in predicting CVD might need to be modified according to diabetes status.

The current study has several strengths and limitations. Strengths include the multicentered setting and prospective design, which enabled us to assess the predictability of a CVD event *per se*. A limitation is that the results may only be applicable to Japanese patients with type 2 diabetes. Further investigations are necessary in non-Asian diabetic patients. In addition, the combination of WC plus other indices of obesity such as BMI (41,42) should be examined in the future in diabetic subjects because the significance of those combinations differs between studies in chiefly nondiabetic subjects (43–46). However, there is increasing evidence that the significance of BMI alone is relatively limited (47).

In conclusion, despite the fact that WC is a good marker for clustering of CVD risk factors, a high WC value alone is not sufficient to raise the risk of CVD events significantly and is not an independent risk factor in Japanese diabetic patients. Further investigations are necessary before WC as a risk factor can be utilized in clinical settings for the management of diabetes in this population.

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DISCLOSURE

The authors declared no conflict of interest.

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APPENDIX

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Cross-sectional association between BMI, glycemic control and energy intake in Japanese patients with type 2 diabetes Analysis from the Japan Diabetes Complications Study

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Abstract

Although, weight loss is associated with improved glycemic control in diabetic patients, the relationships between patient weight, daily energy intake (EI), and glycemic or other control status have been poorly investigated. Baseline characteristics of the Japan Diabetes Complications Study, a representative cohort of Japanese diabetic patients, were used for quartile analysis stratified according to patient body mass index (BMI) and EI. Despite a 1.4-fold discrepancy in BMI between the highest and the lowest quartiles, no significant linear trend in HbA_{1C} levels or EI between quartiles was seen, although, waist/hip ratio, blood pressure, total cholesterol and triglycerides increased and HDL cholesterol decreased with the increase in BMI. Quartile analysis, according to EI, revealed a 1.8-fold elevation in EI between the lowest and the highest quartile. Nevertheless, the differences in patient BMI between the lowest and the highest quartile were no more than 3% and there were no significant linear trends among the four quartiles in most parameters including HbA_{1C}, blood pressure, serum lipids. These results revealed only very limited cross-sectional correlations among BMI, EI and other parameters suggesting that it is necessary to consider much wider variations in ideal weight and optimal dietary prescription when making assessments of diabetic patients.

Keywords: Body mass index; Energy intake; Glycemic control; Japan Diabetes Complications Study (JDCS)

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1. Introduction

Obesity increases morbidity and mortality in patients with type 2 diabetes and short-term studies have demonstrated that even moderate weight reduction through diet and/or exercise can improve patient hyperglycemia [1–3]. However, the few long-term cohort studies on the effects of weight loss on glycemic control in diabetic patients produced inconsistent results [2–5]. It has been speculated that the inconsistencies may have arisen from the confounding effects of other influences on body weight, such as the disease process itself or the medications used [6,7]. Even the detailed cross-sectional relationships between body weight and glycemic control indices in type 2 diabetic patients have been poorly investigated in large-scale settings, and the clinical utility of patient body weight and energy intake data has yet to be fully evaluated. To deepen our understanding of obesity in diabetic patients, further analysis of patient data obtained from the Japan Diabetes Complications Study (JDCS) was performed to clarify the cross-sectional relationships between obesity, energy intake and diabetes control status within a single ethnic group.

2. Patients and methods

The JDCS is a nationwide prospective study of the characteristics of 2205 Japanese patients with type 2 diabetes aged between 40 and 70 years old at registration [8–12]. All patients had been previously diagnosed with type 2 diabetes, having glycohaemoglobin A_{1C} levels of more than 6.5%. Patients with impaired glucose tolerance were not included in this study. Other characteristics of the patients and details of the protocol were described previously [8]. The protocol received ethical approval from the committee of the Ministry of Health and Welfare, Japan and written informed consent was obtained from all patients enrolled. From the study cohort, we analysed the baseline data from 1637 patients who completed a baseline dietary survey, comprised of food records and a food frequency questionnaire (FFQ). Daily energy intake (EI) was adjusted for height and a height-adjusted EI was calculated from the residuals (plus total mean) of a simple regression model of EI on height [13]. Exercise amount (content and frequency) was determined by questionnaire and expressed in kilocalories of energy expenditure per day. Glycohemoglobin A_{1C} assays were standardized with 5.8% as the upper normal limit. All other laboratory tests were determined by standard methods in each clinic. Statistical analyses of male and female data were carried out separately using the SAS software package version 8.0. A p value of less than 0.05 was considered significant.

3. Results

The results, according to quartile of BMI, are shown in Table 1. Despite a 1.4-fold discrepancy in BMI between the highest (BMI-Q4) and the lowest (BMI-Q1) quartiles, no significant linear trend in glycohemoglobin A_{1C} levels between quartiles was seen in either men or women. There was no clear tendency in fasting plasma glucose in BMI-Q2, -Q3 and -Q4, although, it was significantly lower in BMI-Q1. Thus, BMI and glycemic control had only a very modest cross-sectional correlation in these patients. The lack of a significant linear trend in EI, as well as the very minor differences in fat intake and exercise activity between these four categories, indicated that these factors were insufficient to explain the differences in patient BMI. Furthermore, the highest BMI seen in BMI-Q4 was not due to pharmacological treatment because the proportion of patients on insulin therapy was markedly lower than that of the patients in BMI-Q1.

Waist circumference and waist/hip ratio increased in parallel with BMI (Table 1). Blood pressure, total cholesterol and triglycerides increased and HDL cholesterol decreased with the increase in BMI despite the increased frequency of antihypertensive and anti-dyslipidemia medication use, and most of the cardiovascular risk factors that comprise the metabolic syndrome were shown to be significantly elevated with increased BMI.

Quartile analysis according to EI (height-adjusted) (Table 2) revealed a 1.8-fold elevation in EI (i.e. nearly 1000 kcal/day) between the lowest (EI-Q1) and the highest (EI-Q4) quartile, in parallel with a 2-fold increase in fat intake. Nevertheless, the differences in patient BMI between EI-Q1 and -Q4 were no more than 3% (i.e. approximately 2 kg), which supports the previously noted poor correlation between EI and BMI. Furthermore, unlike the BMI categorization (Table 1), there were no significant linear trends in waist size, glycohemoglobin A_{1C}, fasting plasma insulin, blood pressure, serum lipids among the four quartiles, nor any specific trends in exercise activity or pharmacological therapeutic contents (Table 2).

4. Discussion

A common preconception is that patients with higher energy intake are more obese. However, previous population-based studies of mostly non-diabetic subjects revealed a rather inverse correlation between weight and energy intake [13,14], while among European or East Asian patients with established type

Table 1
Baseline characteristics of Japanese patients with type 2 diabetes ($N = 1637$) in the Japan Diabetes Complications Study (JDCS) stratified into quartiles according to their BMI (i.e. BMI-Q1 at lowest and BMI-Q4 at highest)

	Men ($N = 891$)						Women ($N = 746$)					
	Total	BMI-Q1 ($N = 221$)	BMI-Q2 ($N = 223$)	BMI-Q3 ($N = 215$)	BMI-Q4 ($N = 232$)	[a]P values	Total	BMI-Q1 ($N = 180$)	BMI-Q2 ($N = 190$)	BMI-Q3 ($N = 189$)	BMI-Q4 ($N = 187$)	[a]P values
BMI (kg/m^2)	22.7 (2.6)	19.4 (1.1)	21.7 (0.5)	23.5 (0.5)	26.1 (1.4)		23.3 (3.3)	19.2 (1.3)	22.0 (0.6)	24.1 (0.7)	27.7 (1.9)	
Weight (kg)	62.2 (8.7)	53.0 (5.0)	59.3 (4.5)	64.3 (5.3)	71.7 (6.1)	<0.0001	54.3 (8.5)	44.7 (4.0)	51.8 (3.6)	56.2 (3.9)	64.4 (6.2)	<0.0001
Age (years)	58.4 (7.3)	59.5 (7.0)	59.0 (6.8)	58.1 (7.3)	57.2 (8.0)	0.0005	58.8 (7.3)	58.8 (7.2)	59.4 (7.1)	58.9 (7.0)	58.3 (7.9)	0.4808
Diabetes duration (years)	11.3 (7.4)	12.4 (7.5)	11.9 (7.3)	11.2 (7.6)	9.9 (7.1)	0.0002	10.2 (6.7)	11.6 (7.7)	11.4 (6.8)	9.4 (5.8)	8.6 (5.9)	<0.0001
Waist circumference (cm)	82.1 (7.9)	74.4 (5.8)	79.8 (4.4)	83.6 (5.4)	90.0 (5.9)	<0.0001	76.6 (9.5)	67.6 (6.5)	74.2 (6.7)	78.4 (6.1)	86.2 (7.8)	<0.0001
Waist/hip ratio	0.89 (0.06)	0.85 (0.06)	0.88 (0.05)	0.89 (0.06)	0.93 (0.06)	<0.0001	0.83 (0.07)	0.79 (0.07)	0.83 (0.07)	0.84 (0.06)	0.88 (0.07)	<0.0001
Systolic blood pressure (mmHg)	131 (16)	128 (18)	129 (15)	133 (15)	135 (15)	<0.0001	132 (16)	126 (16)	132 (16)	134 (16)	134 (16)	<0.0001
Diastolic blood pressure (mmHg)	77 (10)	75 (10)	76 (10)	78 (9)	80 (10)	<0.0001	76 (9.9)	73 (9)	75 (10)	78 (9)	78 (10)	<0.0001
Glycohaemoglobin A_{1c} (%)	7.59 (1.33)	7.57 (1.40)	7.70 (1.39)	7.54 (1.30)	7.55 (1.22)	0.6102	8.00 (1.39)	7.89 (1.19)	8.15 (1.53)	7.95 (1.26)	8.02 (1.54)	0.6896
	148	146	153	150	150		155	144	157	157	157	
Fasting plasma glucose[b] (mmol/L)	(130, 178)	(121, 168)	(133, 182)	(130, 175)	(128, 191)	0.0088	(132, 182)	(124, 175)	(133, 182)	(135, 184)	(137, 186)	0.0019
Fasting plasma insulin[c] (pmol/L)[d]	6.0 (0.5, 2.0)	4.3 (0.5, 2.0)	5.0 (0.5, 1.8)	6.2 (0.5, 1.8)	9.2 (0.5, 1.8)	<0.0001	7.0 (0.5, 2.0)	4.7 (0.5, 2.0)	6.5 (0.5, 1.7)	8.5 (0.5, 1.8)	9.0 (0.5, 2.0)	<0.0001
Serum total cholesterol (mmol/L)	193 (35)	184 (34)	194 (32)	201 (37)	194 (34)	0.0004	209 (34)	203 (31)	208 (33)	212 (36)	213 (33)	0.0010
Serum HDL cholesterol (mmol/L)	53 (17)	58 (19)	53 (15)	51 (15)	47 (15)	<0.0001	57 (17)	65 (20)	58 (17)	52 (14)	53 (12)	<0.0001
	109	90	102	116	132		101	78	96	117	119	
Serum triglycerides[b] (mmol/L)	(53, 150)	(57, 140)	(54, 148)	(52, 154)	(54, 147)	<0.0001	(52, 151)	(54, 148)	(54, 149)	(53, 152)	(56, 143)	<0.0001
Daily energy intake, height-adjusted (kcal/day)	1817 (45)	1814 (45)	1815 (45)	1817 (49)	1820 (43)	0.1624	1642 (60)	1640 (60)	1649 (56)	1639 (61)	1639 (63)	0.5394
Fat intake (g/day)	54.3 (17.1)	53.4 (16.1)	54.3 (17.9)	55.0 (18.2)	54.7 (16.3)	0.3904	53.2 (18.8)	51.5 (17.1)	51.5 (18.2)	54.3 (19.0)	55.1 (20.5)	0.0278
	163	170	156	179	147		127	113	151	140	125	
Exercise activity[b] (kcal/day)	(55, 354)	(59, 302)	(52, 316)	(64, 393)	(34, 355)	0.0304	(34, 256)	(39, 233)	(50, 259)	(25, 319)	(26, 247)	0.0683
Oral hypoglycaemic reagents: OHA (without insulin) use (%)	60.0	53.4	61.8	61.9	62.9	0.0520[e]	61.0	59.4	65.8	59.3	59.4	0.6558[e]
Insulin (with or without OHA) use (%)	17.2	25.3	17.5	13.5	12.5	0.0002[e]	21.6	27.2	22.6	20.1	16.6	0.0112[e]
Medication for hypertension (%)	23.8	17.9	22.2	28.3	31.6	0.0012[e]	30.5	12.8	20.7	32.6	33.9	<0.0001[e]
Medication for hyperlipidemia (%)	16.4	15.1	19.9	29.4	35.6	<0.0001[e]	33.8	17.9	21.8	32.1	28.2	0.0006[e]

Values are mean (S.D.).
[a] Analysis of variance with contrast test for linear trend.
[b] Median (IQR).
[c] Geometric mean (1 S.D.).
[d] Patients with insulin therapy were excluded.
[e] Mantel test.

Table 2
Baseline characteristics of Japanese patients with type 2 diabetes ($N = 1637$) in the Japan Diabetes Complications Study (JDCS) stratified into quartiles according to their daily energy intake (EI) (height-adjusted) (i.e. EI-Q1 at lowest and EI-Q4 at highest)

	Men ($N = 891$)					Women ($N = 746$)				
	EI-Q1 ($N = 223$)	EI-Q2 ($N = 222$)	EI-Q3 ($N = 224$)	EI-Q4 ($N = 222$)	[a]P values	EI-Q1 ($N = 186$)	EI -Q2 ($N = 187$)	EI -Q3 ($N = 186$)	EI -Q4 ($N = 187$)	[a]P values
Daily energy intake, height-adjusted (kcal/day)	1346 (139)	1658 (73)	1920 (86)	2343 (256)		1199 (160)	1486 (60)	1716 (72)	2165 (339)	
Fat intake (g/day)	37.9 (8.7)	49.0 (10.1)	57.7 (9.9)	72.7 (15.8)	<0.0001	35.7 (8.0)	46.5 (7.9)	55.2 (8.9)	75.0 (19.3)	<0.0001
BMI (kg/m^2)	22.5 (2.5)	22.6 (2.7)	22.7 (2.8)	23.1 (2.5)	0.0165	22.9 (3.4)	23.4 (3.4)	23.0 (3.0)	23.9 (3.2)	0.0234
Weight (kg)	61.7 (8.2)	61.8 (8.6)	61.9 (8.7)	63.4 (9.1)	0.0493	53.8 (8.7)	54.4 (8.6)	53.4 (7.9)	55.9 (8.4)	0.0650
Age (year)	58.0 (7.7)	58.9 (7.4)	58.2 (6.8)	58.6 (7.5)	0.6142	58.8 (7.8)	59.4 (7.6)	59.1 (7.1)	57.9 (6.7)	0.1809
Diabetes duration (year)	11.2 (7.1)	12.1 (7.5)	11.3 (7.3)	10.9 (7.8)	0.4611	10.6 (7.1)	11.2 (7.2)	9.7 (6.4)	9.4 (6.1)	0.0163
Waist circumference (cm)	82.1 (7.3)	81.3 (8.4)	81.7 (7.7)	83.2 (8.0)	0.1039	76.5 (9.0)	76.3 (9.8)	75.6 (9.4)	78.1 (9.8)	0.1905
Waist/hip ratio	0.89 (0.06)	0.89 (0.07)	0.89 (0.06)	0.89 (0.06)	0.6375	0.84 (0.07)	0.83 (0.07)	0.83 (0.07)	0.84 (0.08)	0.8525
Systolic blood pressure (mmHg)	132 (15)	131 (17)	130 (15)	132 (16)	0.8962	131 (17)	133 (16)	131 (16)	132 (16)	0.7616
Diastolic blood pressure (mmHg)	77 (10)	78 (10)	77 (10)	77 (9)	0.7249	75 (10)	75 (10)	77 (10)	77 (10)	0.0548
Glycohaemoglobin A_{1C} (%)	7.59 (1.27)	7.45 (1.24)	7.64 (1.42)	7.67 (1.37)	0.2994	7.85 (1.17)	8.00 (1.35)	8.11 (1.52)	8.05 (1.49)	0.6896
Fasting plasma glucose[b] (mmol/L)	149 (127, 176)	149 (127, 180)	149 (131, 181)	152 (132, 189)	0.0269	160 (129, 183)	156 (134, 187)	152 (129, 180)	154 (134, 180)	0.7162
Fasting plasma insulin[c] (pmol/L)[d]	5.7 (0.5, 1.8)	6.5 (0.5, 2.0)	6.0 (0.5, 2.0)	6.0 (0.5, 2.2)	0.6003	6.7 (0.5, 2.0)	7.2 (0.5, 1.8)	6.8 (0.5, 2.0)	7.3 (0.5, 2.0)	0.4112
Serum total cholesterol (mmol/L)	192 (35)	195 (31)	191 (37)	195 (36)	0.6026	210 (35)	211 (33)	207 (34)	208 (32)	0.3835
Serum HDL cholesterol (mmol/L)	51 (16)	54 (18)	53 (16)	52 (16)	0.5414	57 (18)	58 (17)	56(15)	56 (16)	0.3274
Serum triglycerides[b] (mmol/L)	112 (54, 150)	110 (55, 145)	104 (53, 151)	111 (51, 155)	0.615	97 (52, 153)	103 (51,156)	100 (54, 149)	105 (53, 150)	0.2595
Exercise activity (kcal/day)	138 (44, 303)	179 (67, 363)	153 (58, 354)	160 (46, 381)	0.0468	123 (34, 259)	143 (49, 289)	133 (25, 230)	120 (27, 257)	0.7754
Oral hypoglycaemic reagents (without insulin) use (%)	59.6	62.2	61.6	56.8	0.5327[e]	62.9	62.0	57.0	62.0	0.6333[e]
Insulin (with or without OHA) use (%)	20.2	18.0	14.3	16.2	0.1665[e]	22.0	23.5	23.7	17.1	0.2752[e]
Medication for hypertension (%)	24.2	26.1	21.4	23.4	0.5680[e]	33.3	33.1	28.0	27.3	0.1260[e]
Medication for hyperlipidemia (%)	15.2	18.0	14.7	17.6	0.7513[e]	35.5	35.8	32.3	31.6	0.3381[e]

Values are mean (S.D.).
[a] Analysis of variance with contrast test for linear trend.
[b] Median (IQR).
[c] Geometric mean (1S.D.).
[d] Patients with insulin therapy were excluded.
[e] Extended Mantel test.

2 diabetes, almost no correlation between BMI and non-fasting blood glucose levels was found [15]. Fasting blood glucose, glycohemoglobin, EI and oral medication use were not determined simultaneously in these studies. Our analyses, while revealing that the differences in BMI or EI did not reflect the averaged glycemic control status of patients, also support the earlier studies and provide evidence of relationships between BMI and EI and parameters such as serum lipids and blood pressure. It is also clear from our analyses that it is impossible to ascertain the glycemic control status of an individual patient from a single assessment of their BMI or EI. The lack of significant differences in EI and the relatively small differences in physical activity in the face of a large discrepancy in BMI seen in our patients (Table 1) suggested that lifestyle-related factors play relatively limited roles in determining the current BMI of the patients.

Glycemic control was poorly correlated with BMI while blood pressure and serum lipids showed significant step-wise elevations with increased BMI (Table 1), despite all three parameters reportedly improving with weight loss in intervention studies of diabetic patients [1]. This suggests that the relationship between obesity and hyperglycemia is quite complex. The higher proportion of insulin therapy, and also the longer diabetes duration and the lower fasting plasma insulin levels, seen in patients in the lower BMI categories (Table 1) suggest that Japanese diabetic patients have quite limited insulin secretory capacity and are becoming obese only during the early stages of the disease. This supports previous speculation that the disease process profoundly influences the BMI of patients [4] and could also explain the much lower average BMI in Japanese patients than in white patients [9,10].

Several potential sources of bias need to be considered in interpreting our data. One is BMI-dependent underreporting of energy intake, which has been observed mainly in 24 h dietary recalls [16–18], but also in food frequency questionnaires [18]. However, we combined food recording with FFQ in our dietary survey and observed differences in energy intake (Table 2) that were much broader than the reported BMI-dependent effect (20–25% over the BMI range of approximately 10 kg/m^2) [18]. Another limitation of this study is that we only included patients who had completed a dietary survey for analysis. Neither could we discuss the role of ethnicity because comparable analyses of other ethnic groups could not be found. Such a comparison would have aided our understanding of the underlying pathophysiological relationship between energy intake and obesity in patients with type 2 diabetes and the influence of genetic background on the pathophysiology of the disease.

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Appendix A

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総　説

JDCSからみた日本人2型糖尿病患者の特徴

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Clinical Features in Japanese Patients with Type 2 Diabetes: Interim Results of Japan Diabetes Complications Study (JDCS)

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Type 2 diabetes is one of the most challenging health problems throughout the world and is increasing at an alarming rate. Most clinical evidence involved in therapeutic guidelines for diabetes is derived from European or American cohort studies, and the characteristics of diabetes in Asians, including Japanese, have been only poorly investigated to date, despite Asians constituting approximately half of the world diabetes population. The Japan Diabetes Complications Study (JDCS) is a nationwide multi-center prospective study of type 2 diabetic patients. In 1996, 2,205 patients aged 40～70 years with previously diagnosed type 2 diabetes were recruited from 59 Japanese institutes that specialize in diabetes care. Parameters related to their diet, exercise, glycemic control, diabetic complication events, dyslipidemia, hypertension, obesity and quality of life have been measured and collected every year until now. It was clarified from the interim results of JDCS that the characteristics and pathophysiological backgrounds of diabetes in East Asians were quite different from those in Caucasian subjects. Compared with Caucasian diabetic patients, the JDCS patients had a much lower body mass index (BMI). Moreover, whereas the mean BMI of Caucasian diabetic patients was higher than that reported for non-diabetics of the same ethnic origin, the mean BMI of Japanese diabetic patients was normal in comparison with the Japanese non-diabetic population. Other differences between Japanese and Caucasian patients with type 2 diabetes could be found in the incidence rate and risk factors of complications, the effects of moderate alcohol drinking on cardiovascular disease, and the clinical significance of the diagnosis of metabolic syndrome. These profound differences demonstrate the necessity for obtaining clinical evidence based on a large-scale study of East Asian patients in order to establish and provide management and care specific to this particular population.

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Key words : type 2 diabetes, diabetic complication, cardiovascular disease, risk factor, clinical evidence

1．はじめに

2型糖尿病患者は世界的に増加しており，全世界死亡の5.2％にあたる290万人分の死亡増加をもたらす深刻な問題になっている[1]。国連においても感染症以外の単独疾患としては初めて，糖尿病をターゲットとして世界を挙げて取り組む決議をし，'unite for diabetes' とい

キーワード：2型糖尿病，糖尿病合併症，心血管疾患，リスクファクター，臨床エビデンス
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