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

Hirohito Sone[1,2], Sachiko Tanaka[3,4], Satoshi Iimuro[4], Koji Oida[5], Yoshimitsu Yamasaki[6], Shun Ishibashi[7], Shinichi Oikawa[8], Shigehiro Katayama[9], Hideki Ito[10], Yasuo Ohashi[4], Yasuo Akanuma[11] and Nobuhiro Yamada[2]

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

[1]Department of Lifestyle Medicine and Applied Nutrition, Ochanomizu University, Tokyo, Japan; [2]Department of Internal Medicine, University of Tsukuba Institute of Clinical Medicine, Tsukuba, Japan; [3]Laboratory of Biostatistics, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan; [4]Department of Biostatistics, University of Tokyo School of Public Health, Tokyo, Japan; [5]Fukui Chuo Clinic, Fukui, Japan; [6]Department of Internal Medicine and Therapeutics, Osaka University, Osaka, Japan; [7]Department of Endocrinology and Metabolism, Jichi Medical College, Tochigi, Japan; [8]The Third Department of Medicine, Nippon Medical School,Tokyo, Japan; [9]The Fourth Department of Medicine, Saitama Medical School, Saitama, Japan; [10]Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan; [11]The Institute for Adult Diseases Asahi Life Foundation, Tokyo, Japan. Correspondence: Nobuhiro Yamada (jdcstudy@md.tsukuba.ac.jp)

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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 ~5% 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

The Japan Diabetes Complications Study (JDCS) Group:

Primary Investigator:

Nobuhio Yamada (University of Tsukuba),

Chief in Assessment Committee:

Yasuo Akanuma (Institute for Adult Diseases Asahi Life Foundation)

Secretary General:

Hirohito Sone (Ochanomizu University).

Keita Ato, Masaaki Eto, Hiroshi Ito (Asahikawa Medical College), Azuma Kanatsuka, Naotake Hashimoto, Yasushi Saito, Kazuo Yagi, Kotaro Yokote, Kenichi Sakurai (Chiba University), Tadami Takekoshi, Takanobu Wakasugi (Fukui Prefectural Hospital), Shigetake Toyooka (Fukui Red Cross Hospital), Yukihiro Bando (Fukui Saiseikai Hospital), Tsugihiko Nakai, Koji Oida, Jinya Suzuki (Fukui University), Yasuaki Fukumoto, Seiichi Sumi (Garatia Hostiptal), Genshi Egusa, Rumi Fujikawa, Masamichi Okubo, Kiminori Yamane (Hiroshima University), Takao Koike, Narihito Yoshioka (Hokkaido University), Motonobu Anai, Ritsuko Honda, Masatoshi Kikuchi (Institute for Adult Diseases Asahi Life Foundation), Shun Ishibashi (Jichi Medical School), Masanobu Kawakami, Kazuyuki Namai, Hiroyuki Tamemoto, Hideo Toyoshima (Jichi Medical School Omiya Medical Center), Sasaki Takashi, Masami Nemoto (Jikei University), Ryuzo Kawamori, Yasushi Tanaka (Juntendo University), Toshihiko Ishida (Kagawa University), Toshihide Kawai, Izumi Takei (Keio University), Yoshikuni Fujita, Keiji Tanaka, Yoshihiro Yajima (Kitazato University), Kaku Tsuruzoe, Hideki Kishikawa, Tetsushi Toyonaga (Kumamoto University), Yoichi Imamura, Shingo Komichi, Zenji Makita, Kyohei Nonaka, Kentaro Yamada (Kurume University), Naoto Nakamura, Koji Nakano (Kyoto Prefectural University of Medicine), Toyoshi Iguchi, Hajime Nawata (Kyushu University), Yasuhisa Matsushima (Matsudo City Hospital), Hideo Takahashi (Minami Akatsuka Clinic), Hiroyuki Toyoshima (Minoh City Hospital), Shoichi Akazawa, Eiji Kawasaki, Shigenobu Nagataki (Nagasaki University), Toshio Hayashi, Nigishi Hotta, Jiro Nakamura (Nagoya University), Kentaro Doi, Yu Harano, Yasunao Yoshimasa, Hisashi Makino (National Cardiovascular Center), Yoichi Hayashi (Nihon University), Shinnichi Oikawa (Nippon Medical School), Ryuzou Abe, Hiroaki Seino, Susumu Suzuki, Daishiro Yamada (Ohta-Nishinouchi Hospital), Mitsuru Hoshi, Takao Watarai, Eiichi Imano (Osaka Koseinenkin Hospital), Masatoshi Imaizumi, Ryohei Todo (Osaka National Hospital), Keisuke Kosugi, Yasuhisa Shimizu, Yutaka Umayahara (Osaka Police Hospital), Junichiro Miyagawa, Mitsuyoshi Nanba, Kaoru Takamura, Yoshimitsu Yamasaki, Munehide Matsuhisa, Kohei Okita (Osaka University), Kazuhiro Hosokawa, Kenpei Matsuoka, Yoshihito Atsumi (Saiseikai Central Hospital), Junko Nakano, Hirotaka Umezu (Saiseikai Fukushima General Hospital), Akihiko Hoshino, Toshihiko Nishiyama, Tetsushi Nogami (Saisekai Kumamoto Hospital), Hideo Nunome (Saiseikai Mito Hospital), Shigehiro Katayama, Atsuhito Togashi (Saitama Medical College), Kenichi Yamada (Sakura National Hospital), Shinichi Araki, Atsunori Kashiwagi, Yoshihiko Nishio (Shiga University of Medical Science), Yukio Yoshimura (Shikoku University), Tatsuhide Inoue (Shizuoka General Hospital), Masafumi Kitaoka (Showa General Hospital), Toshio Kitada, Akio Shirai, Ryoichiro Watanabe (Takeda General Hospital), Takaichi Miyagawa (Tama Minami Clinic), Yoshikazu Sakamoto, Osamu Mokuta, Ryo Okazaki (Teikyo Universiy Ichihara Hospital), Kazuma Takahashi, Yasushi Ishigaki (Tohoku University), Koji Shirai,

Yoh Miyashita (Toho University Sakura Hospital), Akira Tanaka (Tokyo Medical and Dental University), Yoshiaki Fujita (Tokyo Metropolitan Institute of Gerontology), Hideki Ito (Tokyo Metroporitan Geriatric Hospital) Reiko Kawahara, Yasue Omori, Asako Sato (Tokyo Women's Medical University), Toshio Murase, Mitsuhiko Noda, Masato Odawara Yasumichi Mori (Toranomon Hospital), Masashi Kobayashi, Masaharu Urakaze (Toyama University), Takashi Kadowaki, Yasuo Ohashi, Junichi Osuga, Yasuyoshi Ouchi (University of Tokyo), Kamejiro Yamashita (University of Tsukuba), Ryo Kawasaki, Hidetoshi Yamashita (Yamagata University), Hisahiko Sekihara, Yasuo Terauchi (Yokohama City University), Tetsuo Nishikawa (Yokohama Rosai Hospital), Hiroto Furuta, Kishio Nanjo (Wakayama Medical University).

Influence of Fat and Carbohydrate Proportions on the Metabolic Profile in Patients With Type 2 Diabetes: A Meta-Analysis

SATORU KODAMA, MD, PHD[1]
KAZUMI SAITO, MD, PHD[1]
SHIRO TANAKA, PHD[2]
MIHO MAKI, MS[1]
YOKO YACHI, RD[1]
MUTSUMI SATO, RD[1]
AYUMI SUGAWARA, RD[1]
KUMIKO TOTSUKA, RD[1]
HITOSHI SHIMANO, MD, PHD[3]
YASUO OHASHI, PHD[2]
NOBUHIRO YAMADA, MD, PHD[3]
HIROHITO SONE, MD, PHD, FACP[1]

OBJECTIVE — The effects of dietary macronutrient composition on metabolic profiles in patients with type 2 diabetes have been inconsistent. This meta-analysis aimed to elucidate the effect of replacing dietary fat with carbohydrate on glucose and lipid parameters in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We searched for randomized trials that investigated the effects of two kinds of prescribed diets (a low-fat, high-carbohydrate [LFHC] diet and a high-fat, low-carbohydrate [HFLC] diet); in these studies, energy and protein intake did not differ significantly between the two dietary groups. Nineteen studies that included 306 patients met our inclusion criteria. Median diet composition of carbohydrate/fat in the LFHC and HFLC diets was 58%/24% and 40%/40%, respectively.

RESULTS — Changes in values for A1C, fasting plasma glucose (FPG), and total and LDL cholesterol did not differ significantly between the LFHC and HFLC groups. However, the LFHC diet significantly increased fasting insulin and triglycerides by 8% ($P = 0.02$) and 13% ($P < 0.001$), respectively, and lowered HDL cholesterol by 6% ($P < 0.001$) compared with the HFLC diet. There were positive associations among the magnitude of changes in FPG, fasting insulin, and triglycerides for the diets analyzed. However, stratified analysis indicated that the increase in triglycerides was insignificant when accompanied by energy intake restriction.

CONCLUSIONS — Our findings suggested that replacing fat with carbohydrate could deteriorate insulin resistance while the adverse effect on triglycerides from the LFHC diet could be avoided by restricting energy intake to a degree sufficient for the attainment of weight reduction.

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Medical nutrition therapy (MNT) is the most important aspect of diabetes treatment (1). Optimizing energy intake and macronutrient composition are especially major topics in MNT. Whereas it is well-known that caloric restriction is essential for the achievement of good glycemic and lipid profiles, mainly through weight loss, the optimal dietary macronutrient composition for patients with type 2 diabetes remains controversial.

Since a high-protein diet is not recommended for diabetic patients because of the risk of nephropathy (1), macronutrient composition is mainly regulated by the carbohydrate-to-fat (C/F) ratio. Conventionally, restricting fat intake has been promoted to decrease energy intake and reduce weight (2). However, a low-fat diet, inevitably accompanied by high carbohydrate intake, may increase postprandial plasma glucose, insulin, and triglyceride levels (1). Therefore, the benefit of raising the dietary C/F ratio on metabolic control in type 2 diabetes has not been established. The effects of a low-fat, high-carbohydrate (LFHC) diet or a high-fat, low-carbohydrate (HFLC) diet in which total energy and protein intake are consistent in patients with type 2 diabetes have often been compared. The aim of this meta-analysis is to systematically compare the effects of LFHC and HFLC diets on glucose and lipid control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— We searched MEDLINE (between 1966 and 2007) and the Cochrane Library Central Registry of Controlled Trials (between 1984 and 2007) for relevant publications using the following medical subject heading terms: diabetes and (food or diet). We examined reference lists of those publications to identify additional studies suitable for our purpose. We restricted the search to randomized controlled trials published in English. We searched for studies of the effects of two kinds of prescribed diets differing according to proportions of carbohydrate and fat under conditions that the prescribed total energy and protein intake did not differ significantly between groups of patients with type 2 diabetes. Trials in patients with type 1 diabetes were excluded. We designated one diet as the LFHC diet, which was defined as having a relatively high C/F ratio, and the other as the HFLC diet, which had a relatively low C/F ratio. As shown in detail in Table 1, in examining these studies, we found that the C/F ratio ranged from 0.60 to 1.56 for the HFLC diets and from 1.67 to 7.30 for the LFHC diets.

Among the studies identified, we included only randomized controlled trials with measurements of fasting plasma glucose (FPG) and fasting insulin and intervention periods of ≥1 week. Both parallel-group and crossover designs

From the [1]Department of Lifestyle Medicine and Applied Nutrition, Ochanomizu University, Tokyo, Japan; the [2]Department of Biostatistic, Epidemiology and Preventive Health Sciences, University of Tokyo, Tokyo, Japan; and [3]Endocrinology and Metabolism, University of Tsukuba, Tsukuba, Japan.
Corresponding author: Hirohito Sone, sone.hirohito@ocha.ac.jp.
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Table 1—*Descriptive statistics of studies included in the meta-analysis*

	Intervention period (weeks)	Dropout (%)	LFHC		HFLC		Age (years)	Men (%)	BMI	Using antihyperglycemia agents (%)	Diabetes duration (years)
			n	C/F/P (%)	*n*	C/F/P (%)					
Campbell et al. (1994; ref. 13)	2	N/A	10	55/22/23	10	40/37/23	55	100	26.5	10	5
Chen et al. (1995; ref. 14)	6	N/A	9	55/30/15	9	40/45/15	49	67	27.5	N/A	N/A
Coulston et al. (1989; ref. 15)	6	0	8	60/20/20	8	40/40/20	66	63	25.5	75	N/A
Fuh et al. (1990; ref. 16)	2	N/A	11	60/20/20	11	40/40/20	58	100	25.8	100	N/A
Garg et al. (1992; ref. 17)	3	N/A	8	60/25/15	8	35/50/15	63	100	30	0	N/A
Garg et al. (1994; ref. 18)	6	0	42	55/30/15	42	40/45/15	58	79	28.1	100	N/A
Heilbronn et al. (1999a; ref. 19)	12	17	12	73/10/17	10	50/32/18	58	27	32.9	58	5
Heilbronn et al. (1999b; ref. 19)	12	15	12	73/10/17	13	50/32/18	58	20	33.1	52	6
Lovejoy et al. (2002a; ref. 20)	4	12	30	58/27/15	30	46/39/15	54	43	33	47	N/A
Lovejoy et al. (2002b; ref. 20)	4	12	30	58/27/15	30	46/39/15	54	43	33	47	N/A
Luscombe et al. (1999; ref. 21)	4	25	21	53/21/26	21	42/35/23	57	67	30.4	76	6
Miyashita et al. (2004; ref. 22)	4	N/A	11	63/10/27	11	40/35/25	52	73	27	0	N/A
Parillo et al. (1992; ref. 23)	2	0	10	60/20/20	10	40/40/20	53	70	26.7	50	8
Parillo et al. (1996a; ref. 24)	2	0	9	60/20/20	9	40/40/20	48	N/A	24.7	0	6
Parillo et al. (1996b; ref. 24)	2	0	9	60/20/20	9	40/40/20	50	N/A	24.6	100	8
Rodriguez-Villar et al. (2000; ref. 25)	6	25	12	55/30/15	12	45/40/15	N/A	N/A	27.9	N/A	6
Rodriguez-Villar et al. (2004; ref. 26)	6	15	22	55/30/15	22	45/40/15	61	54	28.3	N/A	N/A
Rusmussen et al. (1994; refs. 27, 28)	3	N/A	15	50/30/20	15	30/50/20	57	67	27	47	6
Sestoft et al. (1985; ref. 29)	1.4	N/A	8	50/30/20	8	42/36/22	48	50	22.7	0	5
Simpson et al. (1982; ref. 30)	4	N/A	10	60/22/18	10	35/47/18	58	N/A	26.2	80	6
Storm et al. (1997a; ref. 31)	3	0	15	50/30/20	15	40/45/15	53	53	29.7	73	6
Storm et al. (1997b; ref. 31)	3	0	15	50/30/20	15	40/45/15	53	53	29.7	73	6
Median	4	6	12	58/24/20	12	40/40/20	55	65	27.7	52	6
Minimum	1.4	0	8		8		48	20	22.7	0	5
Maximum	12	25	42		42		66	100	33.1	100	8

C/F/P, proportion of carbohydrate/fat/protein to total energy of the prescribed diet; N/A, not assessed.

were included. Studies that included an intervention with a change in the content or quality of carbohydrate such as an increase in fiber and whole grains were excluded because such diets are high in fiber, which in itself ameliorates glycemia and lipemia regardless of changes in the C/F ratio (3,4). Studies of very-low-calorie or enteral (not oral) diets and those in which the dosage of hypoglycemic agents was changed during the intervention period were also excluded. One of three reviewers extracted all studies that met the eligibility criteria, and a second reviewed all extracted data. When necessary, disagreement was resolved by discussion with a third author.

Extracted data included features of the study design (i.e., crossover or parallel design and presence of a washout period), intervention periods, characteristics of patients (mean age, BMI, percent men, and percent those using hypoglycemia agents). Other extracted data regarded the characteristics of each diet, such as macronutrient composition; a weight-loss diet, which was defined as caloric restriction resulting in weight reduction; a weight-maintenance diet, which was defined by a weight change of ≤1 kg during the intervention period, and a monounsaturated fat (MUFA) diet within the HFLC-diet group, which was defined as the addition of MUFA to the HFLC diet. We also extracted baseline and final means and statistical dispersions of each group for the following metabolic profiles: A1C, FPG, fasting insulin, total cholesterol, fasting triglycerides, LDL cholesterol, HDL cholesterol, and 2-h postprandial levels of glucose and insulin. If VLDL cholesterol but not triglyceride data were provided, the triglyceride value was calculated by multiplying VLDL cholesterol × 5 according to the Friedewald formula (5). Also, if HbA_1 but not A1C data were provided, A1C was estimated by the relation between HbA_1 and A1C concentrations according to the methodology of Kilpatrick et al. (6). If necessary, measures of means and dispersion were approximated from figures in the articles using an image scanner (CanoScan LiDE 500F [resolution 600 dpi]; Canon, Tokyo, Japan). Study quality was assessed according to the scale described by Jadad et al. (7), with each included trial evaluated according to randomization, double blinding, withdrawals, and dropouts.

The effect on each metabolic profile, which is expressed as the mean difference between LFHC- and HFLC-diet groups in individual studies, was calculated by subtracting the change from baseline to final values in the HFLC-diet group from that in the LFHC-diet group. The SE of the

change from baseline values was directly extracted from the reported data or estimated from the SEs of the baseline and final values in the LFHC- and HFLC-diet groups, assuming a correlation of 0.5 between the baseline and final measures within each group, according to the formula of Follmann et al. (8), as follows:

$$\sqrt{(SE_{baseline})^2 + (SE_{final})^2 - 2 \times 0.5 \times (SE_{baseline}) \times (SE_{final})}$$

We chose the percent change from baseline values because the mean baseline and final values in patients in each study were highly skewed. To estimate percent change, we divided each change from baseline values and its SE by the baseline value. When no baseline value was reported, as in some crossover studies, we summarized the intervention effect by the ratio of the difference in final values between LFHC- and HFLC-diet groups to the final value in the HFLC-diet group and assumed that the baseline SE was equal to the final SE. This method of estimating percent change has limitations, especially in studies without washout periods. Therefore, we performed a sensitivity analysis to examine the effect of these studies on the results.

All percent changes were firstly pooled with a fixed-effects model (9). For each outcome measure, influence analysis was conducted to detect an outlier (i.e., a single estimate with an extreme result), which influenced overall outcome. Study heterogeneity was statistically assessed by Q statistics (9). If heterogeneity was significant, the percent changes were secondarily re-pooled with a random-effects model (9). Publication bias was assessed using two formal methods: Begg's test (10) and Egger's test (11). The trim-and-fill technique (12) was used to investigate the impact of any suggested bias.

We also calculated the weighted mean difference (WMD) in individual trials by multiplying each percent change by the inverse of its SE squared. We ecologically examined the mutual association among each metabolic effect of the LFHC diet compared with the HFLC diet by Spearman's correlation analyses among WMDs.

To investigate the effect of study characteristics, stratified analyses were performed for the following possible confounders: study design (i.e., whether each trial used a crossover design and, if so, whether the trial had a washout period or data on baseline values), intervention period (<4 vs. ≥4 weeks), percent the study of female sex (<50 or ≥50%), mean age (<55 vs. ≥55 years), BMI (<28 vs. ≥28 kg/m^2), percentage using hypoglycemia agents (zero vs. above zero), C/F ratio in the LFHC (>3 vs. ≤3) and HFLC (>1 vs. ≤1) groups, prescription of the MUFA diet (yes vs. no), and prescription of a weight-loss or weight-maintenance diet. We additionally conducted linear multivariable regression analyses to determine whether the characteristics of the patients were independent predictors that influenced the effect of the LFHC diet versus that of the HFLC diet. In this analysis, age, BMI, and the carbohydrate proportion in the LFHC and HFLC diets were entered as continuous variables. A P value of ≤0.05 was considered statistically significant. All analyses were performed with STATA software version 10 (STATA Corporation, College Station, TX).

RESULTS

Descriptive statistics on studies included in the meta-analysis (Table 1)

Of 2,203 potentially relevant publications based on search terms and 22 references obtained from manual searches, 19 (13–31) met the inclusion criteria. Four articles (19,20,24,31) included two trials in one study, and two articles (27,28) used the same cohort. Finally, 22 trials (306 patients) were included in our analyses. Studies included in the current analysis had intervention periods ranging from 10 days to 6 weeks and patient numbers ranging from 8 to 42. Means ± between-study SDs for the mean study characteristics from 22 trials were as follows: age 55 ± 5 years, percent men 63 ± 23, BMI 28 ± 3 kg/m^2, percent using hypoglycemia agents 52 ± 31, and diabetes duration 6 ± 1 years.

Ten studies (15,18–21,23–26,31) described the number of dropouts, and nine (13,14,16,17,22,27–30) did not. The dropout rate ranged from 0 to 25%. None of the 19 articles described methods of randomization, which led to a low quality score for the trial. A crossover design was used in 17 studies (13–18,20,21,23–31) (with 19 trials), whereas a parallel design was used in two studies (19,22) with three trials. Median carbohydrate/fat proportion of total energy (C/F ratio) in the LFHC and HFLC diets was 58%/24% (2.4) and 40%/40% (1.0), respectively. Three studies (19,22,26) with 4 trials prescribed a weight-loss diet, and 11 studies (13,14,17–19,21,23–25,27,28) with 11 trials provided a MUFA diet to the HFLC-diet group.

Overall effects of the LFHC diet compared with those of the HFLC diet on metabolic outcomes and study heterogeneity

Table 2 provides a summary of pooled estimates of various outcome measures. There were no significant differences in the reduction in A1C, total cholesterol, and LDL cholesterol between the LFHC and HFLC diets. However, the LFHC diet produced significant increases in fasting insulin and triglycerides levels of 8.4% ($P = 0.02$) and 13.4% ($P < 0.001$), respectively, and a significant reduction in HDL cholesterol compared with that associated with the HFLC diet. Two-h glucose and insulin values were higher in the LFHC-diet group than in the HFLC-diet group by 10.3% ($P < 0.001$) and 12.8% ($P < 0.001$), respectively.

Influence analyses indicated that there were a few outliers for percent change in total (22), HDL (22), and LDL (29) cholesterol (see online appendix Tables A1 and A2, available at http://care.diabetesjournals.org/cgi/content/full/dc08-1716/DC1). When these trials were omitted from the analyses, percent change in total cholesterol, HDL cholesterol, and LDL cholesterol significantly changed from −0.0% (95% CI −2.1 to 2.0) to −1.6% (−4.5 to 1.3; $P = 0.03$), from −10.4% (−12.2 to −8.6) to −5.6% (−2.9 to −8.4; $P < 0.001$), and from −3.0% (−6.3 to 0.4) to −0.1% (−4.1 to 3.8; $P = 0.001$), respectively. These outlying trials comprised a large part of study heterogeneity in percent change in total, HDL, and LDL cholesterol (22.2, 59.1, and 53.0%, respectively.) Therefore, they were excluded from the following analyses for the outcome that they affected. After omission of these outliers, there was no evidence of significant study heterogeneity ($P > 0.4$ for all outcomes).

Relationships among the magnitude of effects on metabolic profiles

Ecological analyses showed trends indicating that the WMD in FPG was positively associated with that in fasting insulin ($r = 0.45$; $P = 0.04$) and triglycerides ($r = 0.59$; $P = 0.004$) and that the WMD in fasting insulin and triglycerides was mutually associated ($r = 0.43$; $P = 0.04$). These associations remained signif-

Table 2—*Overall percent changes resulting from LFHC versus HFLC diet on metabolic profiles and data on publication bias and their likely effect on the estimates*

	A1C	FPG	2-h glucose	Fasting insulin	2-h fasting insulin	Total cholesterol	Triglycerides	HDL cholesterol	LDL cholesterol
Trials (*n*)	10	22	10	22	9	20	22	20	16
Overall percent change	−1.5	0.3	10.3	8.4	12.8	1.6	13.4	−5.6	0.1
95% CI	−5.3 to 2.3	−2.8 to 3.4	6.7–13.9	1.3–15.6	5.2–20.4	−1.3 to 4.5	7.1–19.8	−8.4 to −2.9	−3.8 to 4.1
P	0.70	0.87	<0.001	0.02	<0.001	0.27	<0.001	<0.001	0.94
Publication bias									
Begg's	0.80	0.82	0.25	0.30	0.40	0.85	0.48	0.75	0.86
Egger's	0.47	0.30	0.12	0.13	0.16	0.26	0.75	0.08	0.92
Trim and fill									
Fill*								7	
Adjusted†								−7.6	
95% CI								−10.2 to −5.0	

*Studies (*n*) added by the trim-and-fill method. †Percent change after adjustment for publication bias by the trim-and-fill method. Begg's, Begg's adjusted rank correlation test; Egger's, Egger's regression asymmetry test.

icant after adjustment for whether a weight-loss diet was prescribed (FPG vs. fasting insulin, $r = 0.58$ and $P = 0.004$; FPG vs. triglycerides, $r = 0.44$ and $P = 0.04$; and fasting insulin vs. triglycerides, $r = 0.44$ and $P = 0.04$).

Test of publication bias

Table 2 also shows data on publication bias and its likely effect on estimates of outcome according to the trim-and-fill method (12). There was a relatively strong suspicion of publication bias for HDL cholesterol (Egger's test, $P = 0.08$ for HDL cholesterol; recommended level of significance, $P \leq 0.10$ [32]). According to results of the compensatory trim-and-fill method, the effect of publication bias would slightly underestimate the adverse effect of the LFHC diet.

Sensitivity analysis

Results of our stratified analysis to detect characteristics of studies and patients included in our analyses that might have modulated study outcomes are shown in Table 3. Of the 17 studies with a crossover design, 9 with 10 trials (14–16,21,23–26,29) did not include a washout period, which could lead to an underestimation due to a carryover effect (33). Moreover, none of these studies had baseline data. However, the effect of these nine studies on results was not significant for any of the measures.

The elevation in fasting insulin was remarkable (17.1%; $P = 0.001$) in LFHC diets with a C/F ratio ≥3 (in this case, an LFHC diet with ≥60% carbohydrate and ≤20% fat of total energy) while the C/F ratio in the LFHC diet did not influence triglycerides. There was a greater elevation in triglycerides (21.0%; $P<0.001$) with the LFHC diet when the LFHC diet and MUFA diet were compared; i.e., MUFA was replaced with carbohydrate. However, the magnitude of the elevation in fasting insulin did not differ between the MUFA diet and non-MUFA diet (i.e., regardless of dietary fat quality). Whereas a larger elevation in triglycerides was observed in trials limited to weight-maintenance diets, the LFHC diet did not significantly elevate triglycerides compared with the HFLC diet when only trials with weight-loss diets were examined (i.e., diets for weight loss) ($P = 0.48$).

The elevation in fasting insulin was greater in younger and leaner patients in response to the LFHC diet compared with that in response to the HFLC diet. Moreover, mean age and BMI were independent predictors of percent change in fasting insulin. Multiple regression analysis indicated that every −1 kg/m^2 of BMI and −1 year of age were independently associated with a greater elevation in fasting insulin by 2.6% ($P = 0.002$) and 1.7% ($P = 0.005$), respectively. For patients not taking antihyperglycemic drugs, the LFHC diet could be more harmful for fasting insulin than the HFLC diet. However, because only a few studies included patients not receiving antihyperglycemic drugs, the results should perhaps be interpreted with caution.

CONCLUSIONS — Although central to MNT, the influences of various dietary C/F ratios on glycemic control and lipid profiles in patients with type 2 diabetes have not been systematically reviewed. Our meta-analysis is the first to quantify the effect of the LFHC diet compared with that of the HFLC diet on each metabolic outcome.

Our results fundamentally support current dietary guidelines (1) stating that replacing fat with carbohydrate significantly elevates postprandial glucose and insulin levels when total energy intake is consistent. We additionally found that the LFHC diet significantly elevated fasting insulin compared with the HFLC diet, with marked elevations noted when the C/F ratio was ≥3. Moreover, there were significantly positive relationships among the change in FPG and the magnitude of the elevation in fasting insulin and triglycerides, independent of energy restriction for weight control.

Postprandial hyperglycemia with postprandial hyperinsulinemia and failure to maintain glucose homeostasis are often clustered in insulin-resistant individuals, who are representative of those with type 2 diabetes (34). This suggests that an LFHC diet is unfavorable compared with an HFLC diet for insulin-resistant patients, at least when energy intake is consistent. However, our findings do not support the benefit of an extremely high-fat diet because the carbohydrate proportion in the HFLC diets included in our analyses was ≤50%. Moreover, we cannot comment on the possible benefit of a high-carbohydrate diet with a high-fiber component because we excluded studies investigating the effect of such a diet. Moreover, there is concern that increased fat intake ad libitum may promote weight gain (35). It is worth repeating that total caloric intake and nu-

Table 3—*Stratified analysis to examine the effects of characteristics of studies and patients on each metabolic profile*

	FPG		Fasting insulin		Triglycerides		Total cholesterol		HDL cholesterol		LDL cholesterol	
	N	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)	*N*	Percent change (95% CI)
Study with washout period or baseline data												
Neither*	10	0.9 (−4.6 to 6.3)	10	9.0 (−1.7 to 19.7)	10	18.2 (7.3–29.1)	9	0.7 (−4.2 to 5.5)	9	−6.8 (−10.3 to −3.2)	5	−0.7 (−8 to 6.6)
Others†	12	0.0 (−3.8 to 3.7)	12	8.0 (−1.6 to 17.6)		11.0 (3.2–18.8)	11	2.2 (−1.5 to 5.8)	11	−4.0 (−8.2 to 0.3)	11	0.5 (−4.2 to 5.1)
Period <4 weeks	10	1.3 (−2.9 to 5.5)	10	15.2 (3.1–27.3)	10	15.8 (4.9–26.6)	10	1.7 (−3 to 6.4)	10	−7.3 (−10.9 to −3.6)	6	0.8 (−7.5 to 9.1)
Period ≥4 weeks	12	−1 (−5.5 to 3.6)	12	4.9 (−3.9 to 13.7)	12	12.2 (4.4–20)	10	1.6 (−2.1 to 5.3)	10	−3.6 (−7.7 to 0.6)	10	0.0 (−4.5 to 4.4)
<50% of subjects female	13	0.4 (−3.3 to 4.1)	13	6.2 (−3.4 to 15.9)	13	13.7 (5.8–21.6)	11	2 (−1.8 to 5.9)	11	−3.4 (−8.1 to 1.2)	10	0.6 (−4.6 to 5.8)
≥50% of subjects female	5	1.6 (−4.6 to 7.8)	5	11.5 (−0.1 to 23.2)	5	15.1 (2.8–27.3)	5	1.8 (−3.8 to 7.4)	5	−7.4 (−11 to −3.7)	4	−0.5 (−7 to 6.1)
Mean age <55 years	10	−0.2 (−4.1 to 3.7)	10	17.2 (6.7–27.8)‡	10	12.7 (4.6–20.8)	8	1.2 (−3.9 to 6.2)	8	−5.8 (−9.2 to −2.4)	4	−0.6 (−7.5 to 6.3)
Mean age ≥55 years	11	1.2 (−3.9 to 6.4)	11	1.7 (−8.2 to 11.7)‡	11	15.1 (4.5–25.7)	11	1.9 (−1.7 to 5.5)	11	−5.6 (−10.3 to −0.8)	11	0.7 (−4.2 to 5.5)
BMI <28.0 kg/m^2	12	1.9 (−2.8 to 6.6)	12	18.2 (7.6–28.8)‡	12	12.5 (4.6–20.4)	10	1.2 (−3.5 to 5.8)	10	−7.8 (−11.6 to −4.1)	6	−0.9 (−8.6 to 6.9)
BMI ≥28.0 kg/m^2	10	−1 (−5.1 to 3.1)	10	0.3 (−9.4 to 9.9)‡	10	15.1 (4.6–25.7)	10	1.9 (−1.8 to 5.6)	10	−3.1 (−7.1 to 0.9)	10	0.5 (−4.1 to 5)
Taking hypoglycemic agents	18	−0.6 (−4.1 to 2.9)	18	4.4 (−3.8 to 12.7)§	18	15.4 (6.9–23.8)	17	1.5 (−1.5 to 4.6)	17	−3.1 (−6.6 to 0.4)	15	0.1 (−3.8 to 4.1)
Not taking hypoglycemic agents	4	2.9 (−3.3 to 9.1)	4	20.7 (6.3–35.1)§	4	10.9 (1.4–20.5)	3	2.6 (−6.7 to 11.8)	3	−9.4 (−13.7 to −5.1)	1	0 (−31.8 to 31.8)
C/F ratio in LFHC ≥3	8	0.5 (−5.5 to 6.5)	8	17.1 (5.7–28.6)§	8	9.3 (−0.9 to 19.4)	7	−0.1 (−5.4 to 5.1)	7	−4.6 (−10.9 to 1.6)	4	−3.1 (−11.4 to 5.2)
C/F ratio in LFHC <3	14	0.2 (−3.4 to 3.8)	14	2.9 (−6.2 to 12.1)§	14	16 (8–24.1)	13	2.4 (−1.1 to 5.9)	13	−5.9 (−8.9 to −2.8)	12	1.1 (−3.4 to 5.5)
C/F ratio in HFLC ≤1	12	0.2 (−3.8 to 4.2)	12	8.1 (−4 to 20.2)	12	18.7 (8.3–29.1)	11	1.2 (−2.7 to 5)	11	−4.2 (−9.1 to 0.6)	8	−0.6 (−6.4 to 5.2)
C/F ratio in HFLC >1	10	0.4 (−4.5 to 5.2)	10	8.6 (−0.2 to 17.5)	10	10.4 (2.4–18.3)	9	2.2 (−2.2 to 6.6)	9	−6.3 (−9.6 to −3)	8	0.8 (−4.5 to 6.1)
MUFA diet in HFLC diet	11	1.9 (−3.9 to 7.7)	11	5.2 (−4.9 to 15.2)	11	21.0 (10.2–31.7)§	10	3.1 (−1.1 to 7.2)	10	−4.3 (−9.4 to 0.8)	7	2.8 (−3.4 to 8.9)
No MUFA diet in HFLC diet	11	−0.4 (−4.0 to 3.3)	11	11.8 (1.7–22)	11	9.4 (1.6–17.2)§	10	0.2 (−3.8 to 4.3)	10	−6.2 (−9.4 to −3)	9	−1.6 (−6.7 to 3.4)
WL diet in LFHC and HFLC diets	4	−2.1 (−9.6 to 5.5)	4	12.5 (−1 to 25.9)	4	4.0 (−7.1 to 15.2)‡	3	1.3 (−6 to 8.5)	3	−3.9 (−12.4 to 4.6)	3	1.9 (−7.4 to 11.2)
No WL diet in LFHC and HFLC diets	18	0.7 (−2.7 to 4.1)	18	6.9 (−1.5 to 15.3)	18	17.9 (10.2–25.5)‡	17	1.7 (−1.5 to 4.9)	17	−5.8 (−8.7 to −3)	13	−0.2 (−4.6 to 4.1)

*Studies having neither a washout period nor baseline data. †Parallel study design or cross-sectional design studies that have a washout period and/or baseline data. ‡$P < 0.01$; §$P < 0.05$. WL diet, energy intake restricted for weight loss.

tritional content must be appropriate for metabolic control regardless of macronutrient proportions (1).

Changes in FPG and A1C did not differ between the two diets despite significant elevations in 2-h and fasting insulin with the LFHC diet. One possible explanation is that the elevation in postprandial glucose level was overcompensated for by increased insulin secretion. However, only three studies concurrently assessed A1C, fasting insulin, and FPG values, with an intervention period of, at most, 6 weeks. Therefore, we could not conclude whether the elevation in postprandial glucose and insulin level achieved by raising the dietary C/F ratio leads to the deterioration of glycemic control represented by elevations in FPG and A1C.

A previous meta-analysis suggested that replacing carbohydrate with MUFA reduced fasting triglycerides in patients with type 2 diabetes on weight-maintenance diets (36); this was supported by our results. However, it is uncertain whether the effect on triglycerides was caused by the C/F ratio or the ratio of energy from MUFA to total energy. Moreover, whether the effect of this replacement was independent of that of a weight-loss diet has not been investigated. According to our stratified analyses, no dose-response relationship between the C/F ratio in the LFHC diet and the elevation in triglycerides was indicated, although replacement of the MUFA diet with the LFHC diet induced a greater elevation in triglycerides. Moreover, the LFHC diet did not significantly elevate triglycerides compared with the HFLC diet when a weight-loss diet was prescribed. Therefore, controlling total caloric intake and the quality of dietary fat appear to be more important than carbohydrate and fat composition in improving triglycerides levels. In other words, these findings suggest that a high-carbohydrate diet has little harmful effect on triglycerides levels if such a diet provides sufficient energy restriction for weight control.

Our study has some limitations. First, although we omitted studies investigating the effect of high-carbohydrate diets that were also high in dietary fiber, it is possible that the additional phytochemicals (including fiber itself), which are inevitably accompanied by a substantial amount of carbohydrate, influence the metabolic effects regardless of the change in C/F ratio. Second, we assumed that energy intake from the two diet groups would be similar if a weight-maintenance diet was equal to an isocaloric diet based on evidence of the meta-analysis by Bravata et al. (37) that indicated that weight change was associated with restriction of caloric intake but not reduced carbohydrate content. However, some recent studies showed that low-carbohydrate diets resulted in greater weight loss than low-fat diets despite their similar energy content (38), as is often the case with high-fiber diets (e.g., whole grains) (39). More investigation is needed to determine whether the relationship between change in energy intake and body weight is independent of the proportions of dietary carbohydrate and fat. Third, few studies investigated long-term effects (e.g., >2 months) of changing the proportions of carbohydrate and fat on metabolic profiles in patients with type 2 diabetes. Actually, a larger elevation in fasting insulin in association with the LFHC diet was observed for an intervention period of <4 weeks compared with ≥4 weeks but without statistical significance ($P = 0.10$). Possibly, a prolonged intervention involving changes in macronutrient composition causes some adaptation of insulin metabolism. Fourth, most studies provided insufficient data about baseline glucose and lipid levels, and few focused on black or Asian patients. Therefore, the current meta-analysis provides limited suggestions on identifying patients for whom a low-fat or low-carbohydrate diet is especially effective in terms of their circumstances or metabolic profiles (1).

Future studies focused on the following are suggested: *1*) providing a possible explanation for the greater adverse effect on the fasting insulin by the LFHC diet than by the HFLC diet, especially in younger and leaner individuals; 2) identifying the long-term effect of a low-carbohydrate diet on factors other than metabolic effects (e.g., adaptation in glucose and lipid metabolism, ad libitum energy intake in patients with type 2 diabetes or obesity [40]) and the safety of such a diet (e.g., with regard to the digestive system); and 3) addressing whether a subject's medication status and the characteristics of diabetes drugs could influence the effect of changing the dietary C/F ratio in patients with type 2 diabetes.

In conclusion, replacement of dietary fat with carbohydrate is not recommended for improvement of insulin resistance in patients with type 2 diabetes under conditions whereby total energy and protein intake and the content of carbohydrate are similar and the proportion of carbohydrate to total energy is ≥30%. We found that younger and leaner patients had higher fasting insulin responses with the LFHC diet, although the biological mechanism was not fully investigated. The LFHC diet also adversely affects triglycerides and HDL cholesterol compared with the HFLC diet. However, energy restriction and dietary fat quality seemed more important for lowering the triglyceride concentration than the proportion of carbohydrate and fat.

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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

Hirohito Sone [a,b,1], Yukio Yoshimura [c,1], Sachiko Tanaka [d], Satoshi Iimuro [e], Yasuo Ohashi [e], Hideki Ito [f], Hiroaki Seino [g], Shun Ishibashi [h], Yasuo Akanuma [i], Nobuhiro Yamada [a,*]

for the Japan Diabetes Complications Study (JDCS) Group

[a] *Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan*
[b] *Department of Lifestyle Medicine and Applied Nutrition, Ochanomizu University, Japan*
[c] *Training Department of Administrative Dietician, Shikoku University, Tokushima, Japan*
[d] *Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan*
[e] *Department of Biostatistic, Epidemiology and Preventive Health Sciences, University of Tokyo, Tokyo, Japan*
[f] *Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan*
[g] *Diabetes Center, Ohta-Nishinouchi Hospital, Kohriyama, Fukushima, Japan*
[h] *Department of Endocrinology and Metabolism, Jichi Medical College, Tochigi, Japan*
[i] *The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan*

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

* Corresponding author. Fax: +81 29 853 3174.
E-mail addresses: sone.hirohito@ocha.ac.jp (H. Sone), jdcstudy@md.tsukuba.ac.jp (N. Yamada).
[1] These authors contributed equally to the study.

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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 antidyslipidemia 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 ($N = 187$)	[b]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)	0.0003	58.8 (7.3)	58.8 (7.2)	59.4 (7.1)	58.9 (7.0)	58.3 (7.9)	0.4008
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[c] (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
	149	149	149	152		160	156	152	154	
Fasting plasma glucose[b] (mmol/L)	(127, 176)	(127, 180)	(131, 181)	(132, 189)	0.0269	(129, 183)	(134, 187)	(129, 180)	(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
	112	110	104	111		97	103	100	105	
Serum triglycerides[c] (mmol/L)	(54, 150)	(55, 145)	(53, 151)	(51, 155)	0.615	(52, 153)	(51,156)	(54, 149)	(53, 150)	0.2595
	138	179	153	160		123	143	133	120	
Exercise activity (kcal/day)	(44, 303)	(67, 363)	(58, 354)	(46, 381)	0.0468	(34, 259)	(49, 289)	(25, 230)	(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.