TABLE 3. Cox Regression Analysis of Incident Diabetic Retinopathy and Quartiles of Antioxidants, Dietary Fiber, and Potassium

	Q1[a]	Q2		Q3		Q4		Test for Trend
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	
			Vitamin C					
Median intake (min–max) (mg/day):	67.0 (12.6–86.4)	103.3 (86.5–118.8)		133.4 (119.1–152.4)		182.8 (153.1–460.4)		
FFQ								
Adjusted for risk factors[b]	1.00	1.19 (0.86–1.64)	0.31	0.73 (0.51–1.05)	0.09	0.74 (0.52–1.08)	0.12	$P = 0.02$
Further adjusted for nutrients[c]	1.00	1.07 (0.76–1.52)	0.70	0.65 (0.42–1.00)	0.05	0.62 (0.37–1.05)	0.08	$P = 0.02$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.98 (0.70–1.38)	0.92	0.90 (0.63–1.27)	0.53	0.69 (0.48–1.00)	0.05	$P = 0.04$
Further adjusted for nutrients[c,d]	1.00	0.91 (0.63–1.31)	0.62	0.84 (0.57–1.23)	0.37	0.61 (0.39–0.96)	0.03	$P = 0.03$
			Vitamin E					
Median intake (min–max) (mg/day):	6.0 (2.6–6.9)	7.7 (6.9–8.4)		9.2 (8.4–10.2)		11.4 (10.2–25.4)		
FFQ								
Adjusted for risk factors[b]	1.00	1.09 (0.79–1.52)	0.59	0.97 (0.69–1.37)	0.87	0.79 (0.55–1.13)	0.20	$P = 0.14$
Further adjusted for nutrients[c]	1.00	1.05 (0.70–1.57)	0.80	0.88 (0.52–1.48)	0.62	0.70 (0.33–1.52)	0.37	$P = 0.34$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.90 (0.64–1.26)	0.52	0.81 (0.57–1.14)	0.22	0.82 (0.58–1.17)	0.28	$P = 0.23$
Further adjusted for nutrients[c,d]	1.0	0.94 (0.64–1.36)	0.72	0.82 (0.54–1.24)	0.35	0.84 (0.51–1.40)	0.51	$P = 0.41$
			Carotene					
Median intake (min–max) (μg/day):	2,643.2 (285.2–3,485.2)	4,308.7 (3,494.3–5,216.2)		6,034.9 (5,221.5–6,912.0)		8,442.7 (6,915.7–1,9203.1)		
FFQ								
Adjusted for risk factors[b]	1.00	1.01 (0.73–1.42)	0.94	0.99 (0.71–1.38)	0.95	0.74 (0.51–1.06)	0.10	$P = 0.11$
Further adjusted for nutrients[c]	1.00	0.92 (0.64–1.33)	0.66	0.85 (0.57–1.29)	0.45	0.62 (0.35–1.10)	0.10	$P = 0.14$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	1.00 (0.73–1.38)	0.99	0.64 (0.45–0.91)	0.01	0.69 (0.49–0.98)	0.04	$P = 0.01$
Further adjusted for nutrients[c,d]	1.00	0.85 (0.61–1.20)	0.36	0.51 (0.34–0.77)	<0.01	0.52 (0.33–0.81)	<0.01	$P < 0.01$
			Retinol equivalent					
Median intake (min–max) (μg/day):	621.7 (88.9–779.4)	924.9 (782.4–1,080.0)		1,229.6 (1,080.6–1,377.7)		1,683.3 (1,377.8–4,559.6)		
FFQ								
Adjusted for risk factors[b]	1.00	0.99 (0.70–1.39)	0.94	1.08 (0.78–1.50)	0.64	0.74 (0.52–1.06)	0.10	$P = 0.19$
Further adjusted for nutrients[c]	1.00	0.85 (0.58–1.24)	0.40	0.89 (0.59–1.35)	0.58	0.57 (0.31–1.04)	0.06	$P = 0.16$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.85 (0.61–1.19)	0.35	0.75 (0.53–1.06)	0.10	0.79 (0.56–1.11)	0.18	$P = 0.14$
Further adjusted for nutrients[c,d]	1.00	0.77 (0.54–1.10)	0.15	0.66 (0.44–0.97)	0.04	0.68 (0.44–1.05)	0.08	$P = 0.07$
			Dietary fiber					
Median intake (min–max) (g/day):	9.6 (4.2–11.4)	13.0 (11.4–14.3)		15.7 (14.3–17.3)		19.7 (17.3–38.1)		
FFQ								
Adjusted for risk factors[b]	1.00	0.99 (0.71–1.39)	0.95	0.85 (0.60–1.20)	0.34	0.82 (0.57–1.18)	0.29	$P = 0.19$
Further adjusted for nutrients[c]	1.00	1.07 (0.74–1.56)	0.71	0.89 (0.57–1.40)	0.62	0.99 (0.53–1.84)	0.97	$P = 0.71$
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.89 (0.64–1.25)	0.51	0.85 (0.61–1.20)	0.37	0.74 (0.52–1.06)	0.10	$P = 0.11$
Further adjusted for nutrients[c,d]	1.00	0.86 (0.60–1.23)	0.41	0.76 (0.50–1.16)	0.20	0.63 (0.38–1.03)	0.07	$P = 0.07$
			Potassium					
Median intake (min–max) (mg/day):	1977.1 (1,051.9–2,293.3)	2,521.5 (2298.1–2,754.8)		2,997.1 (2,756.5–3,257.6)		3,710.8 (3,258.5–7,249.5)		
FFQ								
Adjusted for risk factors[b]	1.00	1.48 (1.06–2.05)	0.02	0.94 (0.66–1.34)	0.73	0.84 (0.58–1.22)	0.36	$P = 0.09$
Further adjusted for nutrients[c]	1.00	1.36 (0.94–1.97)	0.10	0.83 (0.53–1.31)	0.43	0.72 (0.38–1.38)	0.33	$P = 0.16$

(*Continued*)

TABLE 3. (Continued)

	Q1[a]	Q2		Q3		Q4		Test for Trend
	HR	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	
FFQ and 24-hour dietary recall								
Adjusted for risk factors[b,d]	1.00	0.98 (0.70–1.38)	0.90	0.88 (0.62–1.24)	0.47	0.86 (0.60–1.22)	0.39	$P = 0.31$
Further adjusted for nutrients[c,d]	1.00	0.98 (0.67–1.41)	0.90	0.87 (0.57–1.33)	0.51	0.82 (0.49–1.38)	0.45	$P = 0.39$

[a]Reference category.
[b]Adjusted for age, sex, body mass index, HbA_{1C}, diabetes duration, treatment by insulin or oral hypoglycemic agents, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, triglycerides, current smoker, alcohol intake, and physical activity.
[c]Further adjusted for total energy intake, proportions of carbohydrate, saturated fatty acids, n-6 polyunsaturated fatty acids, and n-3 polyunsaturated fatty acids, cholesterol, and sodium.
[d]Dietary intakes were estimated by the average of FFQ and 24-hour DR.

understood. In this 8-year follow-up study of patients with type 2 diabetes in Japan, those who consumed an average of 253 g of fruit per day had a 50% lower risk of incident retinopathy compared with those consuming an average of 23 g/day. HbA_{1C}, BMI, triglycerides, and SBP were well controlled over 8 years even in the fourth quartile. This is the first report of a follow-up study on the temporal associations between antioxidants, dietary fiber, and potassium and incident diabetic retinopathy, which previously has been examined only cross-sectionally.[12–15] Decreasing trends in HRs were noted for vitamin C and carotene.

The mechanisms whereby fruits exert preventive effects on diabetic retinopathy are not entirely clear, but our data suggest the potential involvement of vitamin C, carotene, retinol equivalent, and dietary fiber. A high-fruit-vegetable intervention is known to increase carotene and vitamin C levels in plasma.[24] However, a previous systematic review found no clear association between vitamin C and E and prevalent diabetic retinopathy.[12] Our findings are not consistent with these results. This may reflect the cross-sectional design of those previous studies, which limits the ability to establish a temporal relationship and may suggest that it takes several years for antioxidants to have an effect on diabetic retinopathy. Another possibility is that the preventive effects of fruits are mediated through glycemic control. Fruits are low-glycemic-index foods rich in dietary fiber, which can slow glucose response after ingestion.[18] Our findings also suggest that dietary fiber might reduce damage to the retina caused by glucose.

Guidelines for diabetic patients in the United States,[3–5] Europe,[6] and Canada[7] (but not in Japan)[11] recommend a diet rich in fruits. Fruits and vegetables have a variety of beneficial effects; the Dietary Approaches to Stop Hypertension diet lowers blood pressure,[8] and increased fruit-vegetable intake reduces the incidence of stroke,[9] coronary heart disease,[10] and cancer.[25] Our findings support guidelines in Western countries encouraging diabetics to consume a diet rich in fruits,[3–7] in addition to those benefits already shown. However, this is a single observational study; randomized trials would be needed to establish the clinical benefit of high-fruit diet for reducing incident diabetic retinopathy.

Determining a tentative goal of fruit intake to achieve clinical benefit in preventing diabetic retinopathy is a difficult task, but it is notable that the association between fruit intake and incident diabetic retinopathy was in the range of amounts commonly consumed. The average intake in the fourth quartile was 253 g/day, which is approximately one fruit serving (eg, one apple or two bananas). This is twice the average intake for Japanese adults in the National Health and Nutrition Survey[26] and achieving such intake would be a realistic goal. It is also important that most patients in the larger study had a "low-fat energy-restricted diet." The proportion of protein, fat, and carbohydrate consumption met the Western guidelines,[5–7] which recommended carbohydrate intake from 45 to 65%, fat intake less than 35%, and protein intake from 10 to 20%. Unexpectedly, there was no increasing trend in BMI and triglycerides even in the fourth quartile (Figure 2), although patients consumed more energy than in the lower quartiles by 100 to 200 kcal (Table 1). The European Prospective Investigation into Cancer and Nutrition study recently reported that increasing baseline fruit-vegetable intake while keeping total energy intake constant did not substantially influence midterm weight change.[27] These data suggest that the benefits of consuming fruits up to 250 g/day outweigh the potential impact on weight control under a low-fat energy-restricted diet. The possible benefits of antioxidant supplements would be difficult to assess, based on our data, given the fact that micronutrients are highly correlated with each other and difficult to isolate in preventive effects of fruits.

These findings must be interpreted in the context of study limitations. First, the potential for bias, such as measurement errors in dietary assessments, confounding factors, and informative censoring, cannot be ruled out entirely. For example, use of vitamin supplements was assessed only by 24-hour dietary records, and intake of vitamins C and E and carotene could be underestimated. We believe, however, that measurement error and the possibility of unmeasured confounders were minimized by the use of two instruments for dietary assessment and by the comprehensive lifestyle survey of diet, physical activity, and smoking status. Second, as an observational study rather than a randomized trial, it is impossible to conclude whether

medical nutritional treatment encouraging fruits would reduce incident retinopathy in clinical practice. Another limitation is the accuracy of diabetic retinopathy staging based on clinical diagnosis compared with staging based on seven-field stereo fundus photography. Finally, our results may not be generally applicable to populations with different genetic or lifestyle factors. Fruits commonly consumed in Japan include pome fruits (apples, Japanese pears, and Japanese persimmons), citrus fruits (oranges, grapefruits, and lemons), drupes (peaches, cherries, and Japanese apricots), berries (strawberries, blueberries, and grapes), bananas, watermelon, and other melons; people in other locations may consume different types of fruits. Moreover, as we previously reported, BMI and body weight are markedly different between patients in Japan and Western countries, although energy intakes were similar.[28] Verifying our findings in studies of different ethnic populations would be useful.

These limitations notwithstanding, we conclude that increased fruit intake within the range commonly consumed is associated with reduced incident diabetic retinopathy. Further randomized trials are needed to clarify whether medical nutritional treatment that encourages consumption of fruits reduces incident retinopathy in the management of diabetes.

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

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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

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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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研究報告書
日本人の食事摂取基準の策定に資する代謝性疾患の栄養評価に関する研究

糖尿病の予防のための栄養摂基準の策定

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【研究要旨】
2型糖尿病は、糖尿病の予防には、肥満の是正が第一義的な意味を有する。そのためには、総エネルギーの適正化を中心とする生活習慣の是正が重要であり、体重の減少にともなって糖尿病の発症リスクは低減する。総エネルギーとは無関係に、消化性炭水化物摂取量のみの減量によって体重が減少する、あるいは血糖コントロールやインスリン抵抗性が改善することを示すエビデンスはない。摂取エネルギー量は、身体活動レベルと体重に基づいて設定するが、日本人ではBMIと糖尿病発症率は連続的な関係を示し、糖尿病予防のためのBMIについて安全域を規定することはできない。炭水化物摂取量の多寡と糖尿病の発症リスクとの関係は不明であるが、糖尿病が心血管疾患と慢性腎臓病のリスクになることから、脂質ならびにたんぱく質摂取比率の制約を受けるため、炭水化物摂取比率は50-60%エネルギーとすることが妥当である。目安量を150g/日とするが、インスリン不足状態におけるRDAを規定するための科学的根拠は、充分ではない。穀物由来の食物繊維は、糖尿病の発症リスクを低減するが、Glycemic Indexの多寡と糖尿病発症リスクとの関係は明らかではない。糖尿病では、食物繊維は20g/日以上摂取することを目安とする。総脂質摂取量は必ずしも糖尿病発症リスクを増加させないが、糖尿病が心血管疾患の高いリスクとなることから、総脂質摂取比率は25%エネルギー未満とする。動物性脂肪の摂取はリスクを増大し、飽和脂肪酸の制限と多価不飽和脂肪酸の増加は、糖尿病発症リスクを低減する。また、多価不飽和脂肪酸は、血糖の是正にも寄与する。n-3系脂肪酸摂取は、アジア人では糖尿病発症リスクを低減する可能性がある。脂質栄養には、脂肪酸組成への配慮が必須である。たんぱく質が糖尿病腎症のない糖尿病において、腎症発症リスクになるとする明らかな根拠はない。しかし、日本人を含む調査によれば、たんぱく質摂取量の過剰摂取が糖尿病や心血管疾患の発症リスク増加につながる可能性がある。特に、20%を超す高たんぱく食については、安全性が確認されていない。

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A. 背景と目的

近年の2型糖尿病の増加は、我が国おける医療上の大きな課題となっている。糖尿病は生活習慣病の代表的疾患であり、特に内臓脂肪型肥満の増加により、インスリン抵抗性を主体とした欧米型の糖尿病が増数していることは、日本人の食生活の変化に原因があると考えられている。糖尿病では、食事療法を治療に基

本としている。食事療法の目的は、総エネルギーの適正化と栄養素組成のバランスを図り、糖尿病の病態の基軸となるインスリン分泌不全を補完し、インスリン抵抗性を是正することによって、代謝状態の改善をもたらすことにある。一方、糖尿病は動脈硬化性疾患や慢性腎臓病などの慢性疾患の基盤となることから、それぞれの疾患の進行抑制のための栄養学的制約をうけることになる。

本研究では、かかる背景から糖尿病の予防に資する栄養摂取量にあり方について、国内外の文献を収集し、現時点における指針を定めることを目指した。

B. 方法

総エネルギー、炭水化物、脂質、たんぱく質と糖尿病をkey wordとして、PubMedを中心として文献検索を行った。この中で、肥満の是正、糖尿病の1次予防と栄養摂取量との関係を検討した観察研究ならびに介入研究、およびそのメタ解析を取り上げた。これらをreviewし、総エネルギーと各栄養素についての基準の策定を試みた。基準値の推算に至らなかったものについては、記述するにとどめた。

C. 結果

1.概念と定義

糖尿病は、インスリン作用の不足に基づく慢性の高血糖状態を主徴とする代謝症候群である。この疾患群の共通の特徴はインスリン効果の不足であり、それによって糖、脂質、蛋白質を含むほとんどすべての代謝系に異常をきたす。インスリンの効果が不足する機序には、インスリンの供給不全（絶対的ないし相対的）とインスリンが作用する臓器（細胞）におけるインスリン感受性の低下（インスリン抵抗性）とがある。インスリンの供給不全は膵β細胞におけるインスリン分泌能の機能不全、インスリン抵抗性は内臓脂肪型肥満が病態の基盤をなすと考えられている。糖尿病の原因は多様であり、その発症には遺伝因子と環境因子がともに関与する。

2.病態の分類

現在、糖尿病は成因（発症機序）と病態（病期）によって分類がなされている。成因分類の上では、大きく1型と2型を分けている。1型糖尿病は、主に自己免疫によって膵β細胞の破壊を生じ、インスリンの欠乏をきたして発症する糖尿病である。2型糖尿病は、インスリン分泌低下をきたす複数の遺伝因子に、過食、運動不足などの生活習慣に起因する内臓脂肪型肥満が加わり、インスリン作用の需要と供給のバランスの破綻を生じ、糖尿病を発症する。糖尿病の成因が何であっても、発病過程では種々の病態を経て進展し、治療によっても変化する可能性がある。そこで、病態（病期）による分類が設定されている（1）。成因とは別に、インスリン作用不足の程度によって、インスリン治療が生命維持に必須であるインスリン依存状態とそうでない非依存状態に分け、ふたつの基軸から適切な治療の選択を目指しているのである。

3.発症予防と重症化予防の基本的な考え方と食事の関連

2型糖尿病における食事療法は、総エネルギー摂取量の適正化によって肥満を解消し、インスリン分泌不全を補完し、インスリン抵抗性を改善する。すなわち、インスリン作用からみた需要と供給のバランスをとることによって、高血糖のみならず糖尿病の種々の病態を是正することを目的としている。インスリンの作用は糖代謝のみならず、脂質ならびに蛋白質代謝など多岐に及んでおり、これらは相互に密接な連関をもつことから、食事療法を実践するにあたっては、個々の病態に合わせ、高血糖のみならず、あらゆる側面からその妥当性が検

証されなければならない。さらに、長期にわたる継続を可能にするためには、安全性とともに我が国の食文化あるいは患者の嗜好性に対する配慮が必須である。諸外国においても、生活習慣の介入による肥満の是正を重要視し、そのために総エネルギーを調整し、合併症に対する配慮の上で三大栄養素のバランスを図ることが推奨されている。しかし、各栄養素についての推定必要量の規定はあっても、相互の関係に基づく適正比率を定めるための十分なエビデンスには乏しい。このため、三大栄養素のバランスの目安は健常人の平均摂取量に基づいているのが現状であるが、糖尿病では動脈硬化性疾患や糖尿病腎症など種々の臓器障害を合併することから、予防のためのそれぞれの食事療法が設定されており、その中で栄養素摂取比率を勘案することが求められている。

我が国における２型糖尿病の増加は、戦後の生活習慣の変化に起因している。特に、食生活の欧米化が、内臓脂肪型肥満をきたし、インスリン抵抗性を主病態とする糖尿病が増加していることは、衆目の一致するところである。糖尿病の予防には、肥満の是正が第一義的な意味を有する。そのためには、総エネルギーの適正化を中心とする生活習慣の是正が重要であり、体重の減少にともなって糖尿病の発症リスクは低減する。我が国の２型糖尿病の発症時におけるBMI は欧米に比較して低いが、それでもBMIの増加とともに糖尿病の発症リスクは連続的に増加し、安全域となるBMIは存在しない。これは、日本人を含むアジア人では、内臓脂肪を蓄積しやすく、体質的に規定されたインスリン分泌能とのバランスが早期に破綻し、糖尿病を発症すると理解されている。総エネルギー量は身体活動レベルと体重に基づいて算定するが、糖尿病の予防ならびに発症後の管理にあたって目指すBMIは個々に設定されるべきであり、その評価に基づいて総エネルギー量を勘案することが望まれる。

体重の減少のために、特定の栄養素の減量が有効であることを示すエビデンスはない。特に、消化性炭水化物摂取量のみの減量によって体重が減少することはなく、血糖コントロールやインスリン抵抗性の改善についても、根拠となる研究結果はえられていない。食事療法の効果は、様々な栄養素の相互の関係において評価すべきものであって、特定の栄養素の効果のみを抽出することは困難である。

炭水化物摂取量の多寡と糖尿病の発症リスクとの関係は不明であるが、糖尿病が心血管疾患と慢性腎臓病のリスクになることから、脂質ならびにたんぱく質摂取比率の制約を受けるため、炭水化物摂取比率は50-60％エネルギーとすることが妥当である (2)。目安量を150g/日とするが、インスリン不足状態における RDA を規定するための科学的根拠は、充分ではない。穀物由来の食物繊維は、糖尿病のリスクを低減するが、Glycemic Index の多寡と糖尿病との関係を示す根拠はない。糖尿病では、食物繊維は 20g/日以上摂取することを目安とする。

総脂質摂取量は必ずしも糖尿病発症リスクを増加させないが、糖尿病が心血管疾患の高いリスクとなることから、総脂質摂取比率は25%エネルギー未満とする。動物性脂肪の摂取はリスクを増大し、飽和脂肪酸の制限と多価不飽和脂肪酸の増加は、糖尿病発症リスクを低減する。また、多価不飽和脂肪酸は、血糖の是正にも寄与する。n-3系脂肪酸摂取は、アジア人では糖尿病発症リスクを低減する可能性がある。脂質栄養には、脂肪酸組成への配慮が必須である。

たんぱく質が糖尿病腎症のない糖尿病において、糖尿病腎症の発症リスクになると

する明らかな根拠はない。しかし、日本人を含む調査によれば、たんぱく質摂取量の過剰摂取が糖尿病や心血管疾患の発症リスク増加につながる可能性がある。特に、20%を超す高たんぱく食については、安全性が確認されていない。

栄養素の摂取比率は、個人の嗜好性ひいては地域の食文化を反映している。食事療法を長く継続するためには、個々の食習慣を尊重しながら、柔軟な対応をしなければならない。一方、糖尿病が心血管疾患や慢性腎臓病など、多臓器の障害を引き起こす重要な基盤病態であり、その増加が我が国の疾患構造を大きな変貌させている事実に鑑み、各栄養素に推奨される摂取比率は、量的にも質的にも制約を受けることを忘れてはならない。それぞれの患者のリスクを評価し、医学的祖語のない範囲で、食を楽しむことを最も優先させるべきである。

(1) 総エネルギー

2型糖尿病の予防には、肥満の是正が重要な意義をもち、そのためには総エネルギーの適正化を中心とする生活習慣の介入が有効である。米国で行われた生活介入研究DPP(Diabetes Prevention Program)では、3年間で5%の体重の低下は、糖尿病の発症を55%抑制したとしている(3)。英国で行われたIGTを対象とした研究では、平均3.1年間の観察において、生活介入群で55%の糖尿病発症リスクの低減を認め、体重の減少、身体活動の増加、食事の改善が糖尿病の発症抑制に関係していたと報じている(4)。これらのことから、米国糖尿病の食事療法に関するガイドラインでも、総エネルギーの適正化による肥満の是正が糖尿病の予防と管理には最も重要だとし、体重を7%減量することを薦めている(5)。日本人を含むアジア人においても、BMIの増加は2型糖尿病の発症リスクになる。しかし、BMIと糖尿病有病率の関係には人種差があり、アジア人ではBMIが20を超えれば、BMIの増加とともに糖尿病の有病率が増し、この関係は白人に較べて顕著であって、いわゆる閾値は認められない(6)。これは、アジア人のβ細胞機能の予備力が低いことと、ならびに低いBMIであっても内臓脂肪の蓄積を生じやすいことが関係しているのかもしれない(7)。従って、2型糖尿病の予防のための適正なBMIを特定することはできない。しかし、日本人の糖尿病においても、体重の減少が代謝パラメーターの改善に寄与することは確認されている(8)。必要エネルギー量は、基礎代謝量と身体活動レベルから算出される推定エネルギー必要量をもとに設定するが、現実的には標準体重と労作量から計算される量を目安とし、代謝パラメーターを評価しながら個々の適正体重を決めることが勧められる。ただし、2型糖尿病において総エネルギー制限と活動性の増加による体重減少と血糖コントロールが、心血管疾患の抑制につながるか否かについて、明確な証拠はない。最近、米国で発表されたLook AHEAD研究は、5,145例の2型糖尿病を、総エネルギー制限と活動量の増加を中心とする介入群と非加入群の2群に分け、9.6年間の追跡調査を行った。介入群では、有意の体重の減量とHbA1cの低下を示したのにも関わらず、両群間の心血管疾患の累積発症率に差異は認められなかったとしている(9)。

(2) 炭水化物摂取量および%エネルギー比

炭水化物の摂取量と糖尿病の発症率との関係を検討した例はほとんどなく、両者の関係は不明である。最近、英国でなされたコホート研究では、炭水化物摂取量と糖尿病の発症数との関係が検討されているが、炭水化物摂取量と糖尿病の発症率には関係がなく、果糖の摂取量が糖尿病のリスクを

増したとしている (10)。一方、メタ解析によって、総炭水化物摂取量が糖尿病の発症リスク増加につながる(RR=1.11)とする報告もみられる (11)。２型糖尿病の血糖コントロールに対して、消化性炭水化物の制限が及ぼす効果については議論がなされている。もともと、一日の炭水化物摂取量が100g 以下とする炭水化物制限が、肥満の是正に有効だとする研究結果から、糖尿病治療における炭水化物制限の有用性が注目された。しかし、その後のメタ解析では、炭水化物制限の体重減少効果は１年以内の短期的なものであり、その原因として、症例数が少ないことや高い脱落率があげられている (12)。また、炭水化物の制限とともに総エネルギー摂取量が減じており、体重減少効果が炭水化物の制限のみによってもたらされたとは結論できない。2008 年に発表された DIRECT 研究は、脂質栄養を中心に総エネルギーを制限した群、総エネルギーを制限し、地中海食とした群、エネルギーをフリーとし、炭水化物を 40%エネルギーに制限した 3 群を設定し、その後 2 年間の体重の変化を追跡したところ、脂質制限群に比較して、地中海食と炭水化物制限食で有意に体重減少効果が優っていたと報告している (13)。しかし、炭水化物制限群でも、総エネルギーは他の群同様に低下しており、体重減量効果が総エネルギーとは無関係に、炭水化物の制限のみによると解釈はできない。一方、炭水化物の摂取比率が低く、たんぱく質の摂取比率の高い集団では、心血管疾患発症率ならびに総死亡率が高かったことが報告されている (14,15)。

2012 年に炭水化物制限の糖尿病状態に対する systematic review が発表されているが、現時点ではどのレベルの炭水化物制限であっても、高血糖ならびにインスリン抵抗性の改善に有効であるとする明確な根拠は見出せないとしている (16)。また、炭水化物摂取比率は、糖尿病が心血管疾患ならびに慢性腎臓病のリスクになることから、脂質およびたんぱく質の摂取比率にも制約を受けることを忘れてはならない。これらの知見を踏まえ、日本糖尿病学会は、「糖尿病の食事療法に関する声明」の中で、炭水化物摂取比率を 50-60%エネルギーとし、一日摂取量 150g/日以上を目安量にすることを勧めている (1)。この数値は、現時点では妥当なものといえる。しかし、糖尿病症例における炭水化物の至適摂取量は、身体活動量やインスリン作用の良否によって異なり、一意に目標量を規定することは困難である。合併症や薬物療法などの制約がなければ、柔軟な対応をしてもよい。今後も科学的検証が必要である。

(3) Glycemic Index(GI)ならびに食物繊維

GI と糖尿病発症率に関する従来の検討は、GI あるいは Glycemic Load (GL)の高値と糖尿病発症率が相関するとするもの(17, 18)と相関を否定するもの(19)が、拮抗する形になっており、諸外国のガイドラインにおける記載にも違いがみられ、現時点では衆目の一致には至っていないと解釈せざるをえない。

食物繊維については、穀物の食物繊維が糖尿病発症リスクを低減するとする報告が多くみられるが (20, 21, 22)、他の食物繊維との関係は明らかではない。また、食物繊維の研究は、他の栄養素を絡めた形で検討されている場合が多く、糖尿病発症に関わる繊維の種類あるいは量を特定することは困難であるが、穀物繊維を中心にその摂取を促すことは妥当と考えられる。健常人の摂取量が 17-19g/日であることを勘案し、糖尿病における目標量を 20g/日とする。

(4) 脂質

糖尿病患者と非糖尿病対照群との比較研

究は、糖尿病症例では脂質の総摂取量、特に動物性脂質の摂取量が、糖尿病で多かったとされている (23)。しかし、前向きコホート研究では、総脂質摂取量は糖尿病発症リスクにはならない (24)あるいは BMI で調整すると関連は消失する (25)と報告されている。しかし、糖尿病が心血管疾患の高いリスクになることから、総脂質摂取比率は、25%/日未満とすることが妥当である。ただ、両研究ならびに他の多くの研究が飽和脂肪酸の摂取の糖尿病の発症リスクになり、多価不飽和脂肪酸がこれを低減するとしており (26, 27, 28)、動物性脂質の相対的な増加が、糖尿病発症リスクになるものと考えられる。また、最近のメタ解析では、不飽和多価脂肪酸の摂取量の増加は、HbA1c の低下をもたらすとしており(29)、今後の栄養摂取基準の課題は、総摂取量のみならず、脂肪酸組成にあると言える。

作今の我が国の食の問題として、魚の摂取量低下が指摘されており、n-3 系脂肪酸と糖尿病との関係が注目される。これまでの、n-3 系脂肪酸の摂取量と糖尿病発症リスクについての研究は、必ずしも一致した結果に至っていない。中国人を対象にした前向きコホート研究では、EPA、DHA 摂取量は糖尿病発症リスクに関与しなかったが、α リノレイン酸はリスクを低下させること (30)、女性において魚介類の長鎖 n-3 系脂肪酸は糖尿病発症リスクを低減すること (31)が報告されている。一方、米国で行われた調査では、n-3 系脂肪酸を 0.2g/日以上、魚を 1 日 2 回以上食べる女性は糖尿病発症リスクが増大すること (32)、オランダでの前向き観察研究では、糖尿病発症リスクに関して EPA、DHA 摂取は関係がなかったとも報告されている (33)。メタ解析の結果でも、インスリン感受性の改善はない (34)、あるいは糖尿病発症リスクに対する効果を否定するもの (35)がある反面、アシア人では魚由来 n-3 系脂肪酸は糖尿病発症リスクを低減するとするものもあり (36)、効果に人種差がある可能性を示唆している。我が国においても、糖尿病症例には魚由来 n-3 系脂肪酸の摂取を促してよい。しかし、２型糖尿病症例に EPA と DHA を投与し、心血管疾患の発症率を検討した米国の研究では、プラセボ群との間にまったく差異は認められなかった(37)。n-3 系脂肪酸の目標量の規定に足る科学的根拠は、いまだに不足していると言わざるをえない。

(5) たんぱく質

たんぱく質については、主に腎症との関係について論じられているが、腎障害のない糖
尿病にあって、たんぱく質摂取量が、腎症発症リスクを増加させるという根拠はない。しかし、前向きコホート研究では、100 g をこす赤身肉の摂取が糖尿病発症リスクを増加させることを、日本人を含めた調査によって報じている (38,39)。たんぱく質、特に動物性たんぱく質と糖尿病発症リスクとの関係を認めた研究は、最近数多く発表されており (40,41)、スウェーデンで行われた前向きコホート研究では、たんぱく質摂取比率 20%の男女と 12%にとどまったものの糖尿病発症リスクを比較すると、高たんぱく質群では HR1.27 に達したとしている (42)。たんぱく質摂取比率が 20%を超えた場合の有害事象として、糖尿病発症リスクの増加をあげることができよう。

糖尿病において関連が注目されている事象のうち、たんぱく質の過剰摂取との関係が報告されているものには、耐糖能障害のほかに、心血管疾患の増加、癌の発症率の増加、骨量の減少、BMI の増加などが挙げられる。最近の systematic review は、これらの事象とたんぱく質摂取量との関係を検討したこれまでの論文を検証し、どの事象に

ついても明らかな関連を結論することはできないとしながら、たんぱく質の摂取比率が 20%を超えた場合の安全性は確認できないと述べ、注意を喚起している(43)。我が国の糖尿病症例においても、たんぱく摂取比率は、20%未満とすることが妥当である。

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D. 結論

糖尿病の予防に資するための個々の適正な栄養素比率について、科学的に検証することは困難である。また、安全なBMIを規定することも妥当ではない。食事療法の在り方は、その国の持つ食文化を基本に、科学的に妥当な研究結果を修飾する作業を継続することが重要と結論する。

E. 研究発表

1. 論文発表

なし

2. 学会発表

なし

F. 知的所有権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし