

# 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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**M**edical 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  $\geq 1$  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
Rusmusen 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  $\leq 1$  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 cho-

lesterol  $\times 5$  according to the Friedewald formula (5). Also, if HbA<sub>1c</sub> but not A1C data were provided, A1C was estimated by the relation between HbA<sub>1c</sub> 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:

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

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<sup>2</sup>), 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<sup>2</sup>, 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  $\geq 3$  (in this case, an LFHC diet with  $\geq 60\%$  carbohydrate and  $\leq 20\%$  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  $-1 \text{ kg/m}^2$  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  $\geq 3$ . 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  $\leq 50\%$ . 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	
	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	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 (−7.5 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 <sup>2</sup>	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 <sup>2</sup>	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												
Not 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												
C/F ratio in LFHC ≥3	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 HFHC ≤1	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 HFHC >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)
MUFA diet in HFHC diet	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)
No MUFA diet in HFHC 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)
WL diet in LFHC and HFHC diets												
No WL diet in LFHC and HFHC 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)
HFHC diets												
WL diet in LFHC and HFHC 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  $\geq 4$  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  $\geq 30\%$ . 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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