Lipid, Glycemic, and Insulin Responses to Meals Rich in Saturated, *cis*-Monounsaturated, and Polyunsaturated (n-3 and n-6) Fatty Acids in Subjects With Type 2 Diabetes

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OBJECTIVE — The recommendations for dietary fats in patients with type 2 diabetes are based largely on the impact of fatty acids on fasting serum lipid and glucose concentrations. How fatty acids affect postprandial insulin, glucose, and triglyceride concentrations, however, remains unclear. The objective of this study was to study the effect of fatty acids on postprandial insulin, glucose, and triglyceride responses.

RESEARCH DESIGN AND METHODS — Test meals rich in palmitic acid, linoleic acid, oleic acid, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and containing 1,000 kcal each were administered in a randomized crossover design to 11 type 2 diabetic subjects. Serum insulin, glucose, and triglyceride concentrations were measured for 360 min. All subjects received an isoenergetic diet of constant composition throughout the study.

RESULTS — According to repeated-measures ANOVA, the insulin ($P = 0.0002$) but not glucose ($P = 0.10$) response was significantly different between meals. The insulin response was lower to meals rich in oleic acid or EPA and DHA than to meals rich in palmitic acid or linoleic acid ($P < 0.01$). The triglyceride response did not reach statistical significance ($P = 0.06$) but tended to be lower with EPA and DHA than with the other fatty acids. Similar trends were seen for area under the curve (AUC) and incremental AUC for serum insulin and triglycerides, but the differences were not significant.

CONCLUSIONS — In comparison with palmitic acid and linoleic acid, oleic acid or EPA and DHA may modestly lower insulin response in patients with type 2 diabetes without deteriorating the glucose response. EPA and DHA may also reduce the triglyceride response.

Diabetes Care 30:2993–2998, 2007

The dietary recommendations for fatty acid intakes to manage dyslipidemia and glycemia in patients with type 2 diabetes are largely based on the findings from studies on the impact of fatty acids on fasting serum lipid and glucose concentrations (1). How the different types of fatty acids affect postprandial lipid, glucose, and insulin concentrations, however, is not clearly understood. This information is important because most individuals in Western countries are in a postprandial state for most of the day (2,3). Postprandial triglyceride concentrations are associated with cardiovascular disease (CVD) (4,5), and this fact may be even more relevant in patients with type 2 diabetes, given that these individuals have higher postprandial triglyceride responses than individuals without type 2 diabetes (6,7), even when baseline triglyceride concentrations are normal (7). How the different types of fatty acids affect postprandial glucose and insulin response also needs to be further examined especially because poor glycemic control is linked to diabetes complications including CVD, and hyperinsulinemia is a risk factor for CVD (1).

The acute effect of different types of fats on postprandial insulin response in subjects with type 2 diabetes has been examined in only two studies (8,9). These studies compared meals rich in butter and olive oil and reported no difference in insulin levels. Studies in subjects without diabetes showed either no difference in insulin response to meals rich in saturated, monounsaturated, or polyunsaturated (n-3 or n-6) fatty acids (10–18) or a higher insulin response to meals rich in eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or linoleic acid than to a meal rich in beef fat (19). A possible explanation in part for the results of the latter study (19) may be that the meals rich in polyunsaturated fatty acids contained about 10% more carbohydrate, a determinant of postprandial insulin response (3), than the meal rich in beef fat.

Three studies have looked at the acute effect of different fatty acids on postprandial glucose response in subjects with type 2 diabetes and either showed no differences in glucose response to meals rich in butter and olive oil (9) and to meals rich in oleic acid and oleic acid plus EPA and DHA (20) or showed a lower glucose

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Received for publication 29 May 2007 and accepted in revised form 29 August 2007.

Published ahead of print at http://care.diabetesjournals.org on 5 September 2007. DOI: 10.2337/dc07-1026. Clinical trial reg. no. NCT00479791, clinicaltrials.gov.

Abbreviations: AUC, area under the curve; iAUC, incremental AUC; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Fatty acid composition of the various test oils*

	Fatty acids (%)					
	Saturated		*Cis*-mono-unsaturated	Polyunsaturated		
	Medium chain	Long chain	n-9	n-6	n-3	Others
Palm oil	0.1	51.3	38.9	9.6	0.2	0
Olive oil	0	13.8	77.1	8.3	0.6	0.2
Safflower oil	0	6.5	15.0	78.0	0	0.5
Salmon oil	0	17.6	29.4	2.3	38.6	12.1

response to a meal rich in butter compared with a meal rich in olive oil (8). A majority of the studies in subjects without diabetes showed no difference in glucose response to meals rich in different fatty acids (10–15,18,21). Gatti et al. (16), however, found a lower glucose response to meals rich in olive oil than to meals rich in corn oil or butter, and Lardinois et al. (19) found a higher glucose response to a meal rich in fish compared with a meal rich in corn oil or beef in individuals without diabetes.

The number of studies examining the acute effect of meals on postprandial triglyceride response in type 2 diabetic subjects is also limited. West et al. (20) reported a lower triglyceride response to a meal rich in both oleic acid and EPA and DHA compared with a meal rich in just oleic acid but only in subjects with high triglyceride concentrations. This difference may be due to decreased chylomicron production or secretion (22) and reduced synthesis of VLDLs (23) associated with very long-chain n-3 fatty acids. Comparison of meals rich in butter and olive oil in subjects with type 2 diabetes revealed either no difference (8) or a higher triglyceride response to the meal rich in butter (9). The results from studies in subjects without diabetes have also been controversial, with some studies showing no difference in postprandial triglyceride response to different fatty acids (11–15,21,24–27) and others showing either a lower response to meals rich in n-3 (17), n-6 (10), and n-9 (10,18) fatty acids or a higher response to n-6 (28,29) and n-9 (28,29) fatty acids compared with responses to saturated fatty acids.

Possible reasons for the conflicting results could be the fact that the order in which the meals were tested was not randomized in a number of studies (13, 14,19,24), and in several studies a constant background diet was not provided (10–17,19–21,24,27,28). It has been reported that the fats and carbohydrates in the daily diet may influence the postprandial response to a meal (3,30). In addition, some researchers limited the energy content of the test meal (300–500 kcal) (16,19) and the time during which the response was measured (180 min) (16,19,26), and these limitations may make it difficult to detect significant differences between the different test meals. The controversial results may also be due to the use of butter as a source of saturated fat (8–10,16,18,21,25). Nearly 15% of the saturated fat content in butter is accounted for by medium-chain fatty acids known to improve insulin sensitivity and glycemic control (31).

The above studies have a number of design issues, which make it difficult to clearly interpret the results. Also, there is a paucity of data in patients with type 2 diabetes. We addressed these issues in our study in which we compared the postprandial triglyceride, glucose, and insulin response to meals rich in palmitic acid, oleic acid, linoleic acid, and EPA and DHA in subjects with type 2 diabetes. The postprandial response was measured for 360 min, and the meals were administered in a randomized crossover design. Each test meal was designed to provide 1,000 kcal, and the percent energy from carbohydrate, protein, and fat was held constant. In addition, the subjects were fed an isoenergetic diet of constant composition throughout the study. We hypothesized that there will be no difference in postprandial insulin and glucose response to meals rich in different fatty acids. The secondary hypothesis was that the postprandial triglyceride response will be lower to meals rich in very long-chain n-3 fatty acids compared with the other fatty acids.

RESEARCH DESIGN AND METHODS

— Eleven men with type 2 diabetes who had fasting blood glucose concentrations <200 mg/dl and were not receiving insulin therapy were studied at the General Clinical Research Center of the University of Texas Southwestern Medical Center at Dallas. The protocol was approved by the University of Texas Southwestern Institutional Review Board, and each participant gave informed consent. Mean ± SD age was 54.6 ± 12.2 years, and mean BMI was 33.2 ± 3.7 kg/m^2. Six of the subjects were non-Hispanic whites, three were African American, and one each was Asian and Hispanic. None of the subjects had thyroid, renal, or hepatic disease, uncontrolled hypertension, anemia, or a history of ketosis.

All subjects received an isoenergetic diet of constant composition throughout the study duration of 12–15 days. The subjects were instructed to maintain a constant level of physical activity.

At intervals of 3–4 days, after an overnight fast, each subject consumed a mixed test meal on four occasions in a randomized manner. The type of fat in the test meal varied on each occasion, and the meal was rich in palmitic acid, oleic acid, linoleic acid, or EPA and DHA.

Daily diet and test meals

Daily energy intake of the subjects was estimated using the Harris Benedict equation (32). The subjects received an isoenergetic background diet containing 15% of total energy as protein, 35% as fat, and 50% as carbohydrate throughout the study period, which started 3–4 days before the first test meal was evaluated. The subjects picked up their daily meals every 3–4 days from the General Clinical Research Center metabolic kitchen. Energy intake was adjusted to maintain a constant body weight. Alcohol was not allowed during the entire study period. Coffee was limited to one serving of reconstituted freeze-dried coffee (2 g dry coffee) at breakfast, and tea was limited to one serving of reconstituted instant tea at lunch and one at dinner. Sugar-free soft drinks were allowed but only as a replacement for tea. No deviations from the above guidelines were reported.

Each test meal provided 1,000 kcal with 15% energy as protein, 35% as carbohydrate, and 50% as fat. The test meals contained farina, egg substitute, ham with 5% fat, white bread, skim milk, orange juice, and 51 g of test oil. The test meals rich in palmitic acid, oleic acid, linoleic acid, and EPA and DHA were made using palm oil, olive oil, safflower oil, and

salmon oil, respectively. The fat content of the four test oils is shown in Table 1.

Meal tolerance test

The meal tolerance test was conducted after a 12-h overnight fast. An intravenous cannula was placed in a forearm vein for blood sampling. After collection of three baseline blood samples at −30, −15, and 0 min, patients were asked to consume the test meal in a 15-min period, and blood was collected every 30 min for the next 360 min for measurement of plasma glucose, insulin, and triglyceride concentrations.

Biochemical analysis

Plasma glucose concentrations were assayed by the glucose oxidase method (Beckman Glucose Analyzer; Beckman Instruments, Fullerton, CA). Plasma insulin concentrations were measured using a radioimmunoassay kit (Linco Research, St. Louis, MO). Plasma triglycerides were measured enzymatically (Sigma Diagnostics, St. Louis, MO).

Statistical methods

A repeated-measures ANOVA model was used to assess the effect of the different meals on plasma glucose, insulin, and triglyceride responses after log transformations. The main effects and meal × time interaction effects were evaluated. Pairwise contrasts were made by comparing the least-square mean estimates, and *P* values were adjusted for multiple comparisons using the Bonferroni Holm method (33). Repeated-measures ANOVA was also used to compare the effect of the meals following rank transformation of the glucose, insulin, and triglyceride response values after subtraction of the respective baseline values. Peak response and peak time were compared across meals by a single-factor repeated-measures ANOVA model.

Area under the curve (AUC) and incremental AUC (iAUC), i.e., the area above baseline, were calculated using the trapezoidal rule. The respective natural log values were compared by a single-factor repeated-measures ANOVA model.

Similar trends were seen even after we adjusted our analyses for treatment with lipid- or glucose-lowering medications or excluded the four men who were receiving one of these medications. All statistical analyses were performed using SAS (version 9.13; SAS Institute, Cary, NC).

RESULTS — Body weight was maintained throughout the study period with the carefully controlled isoenergetic background diet of constant composition. According to the repeated-measures ANOVA test after log transformation, the postprandial insulin response (Fig. 1*A*) was significantly different among the various meals ($P = 0.0002$), whereas the postprandial glucose (Fig. 1*C*) and triglyceride (Fig. 1*E*) responses did not differ significantly by the type of meal given ($P = 0.10$ and $P = 0.06$, respectively). Post hoc analyses, adjusted for multiple comparisons, showed that the insulin response was significantly higher to the meal rich in palmitic acid than to the meals rich in oleic acid ($P = 0.002$) or EPA and DHA ($P = 0.002$) and to the meal rich in linoleic acid than to the meals rich in oleic acid ($P = 0.007$) or EPA and DHA ($P = 0.006$). There was no difference in insulin response between meals rich in oleic acid and EPA and DHA and between meals rich in palmitic acid and linoleic acid. The meal × time interaction was not significant, indicating that the peak insulin concentration was reached at around the same time across meals and that the difference in the insulin response to the meals was due to the difference in the magnitude of the response. There was no difference in peak time ($P = 0.62$), which was reached at ~60 min for each meal. Peak insulin concentration was significantly different ($P = 0.01$) by meals (Fig. 1*A*). It was higher after the meal rich in linoleic acid than after the meals rich in oleic acid ($P = 0.04$) or EPA and DHA ($P = 0.02$) and not different between the meals rich in oleic acid and EPA and DHA or between the meals rich in palmitic acid and the other fatty acids.

Repeated-measures ANOVA following rank transformation after subtraction of the baseline values showed a significantly different effect of the meals on the postprandial triglyceride ($P = 0.004$) and insulin ($P = 0.006$) responses but not on the glucose ($P = 0.58$) response. Post hoc analyses, adjusted for multiple comparisons, showed that the insulin response was higher to the meals rich in linoleic acid than to the meals rich in oleic acid ($P = 0.05$) or EPA and DHA ($P = 0.02$) and also higher to the meal rich in palmitic acid compared with EPA and DHA ($P = 0.05$). The postprandial triglyceride response tended to be lower after the meals rich in EPA and DHA than after the meals rich in other fatty acids, but the difference was significant only between EPA and DHA and oleic acid ($P = 0.003$). Because the triglyceride response was delayed by 120 min, we conducted an additional analysis after excluding the postprandial data obtained during the first 120 min and found that the response was significantly higher after the meal rich in oleic acid than after the other meals. However, because the study was designed to look at the postprandial response for 360 min and because the typical response lasts for >120 min, our focus will be on the entire postprandial period.

AUC for insulin (Fig. 1*B*) was higher for meals rich in palmitic acid or linoleic acid than for meals rich in EPA and DHA or oleic acid, and that for triglycerides (Fig. 1*F*) tended to be lower for the meal rich in EPA and DHA than for the other meals, but the differences did not reach statistical significance. AUC for glucose (Fig. 1*D*) did not differ by meals. Similar results were seen for iAUC (data not shown).

CONCLUSIONS — We examined the effects of different fatty acids on postprandial triglyceride, glucose, and insulin concentrations in subjects with type 2 diabetes. According to repeated-measures ANOVA, the insulin response was significantly different by the type of fatty acid consumed. It was significantly higher in response to the meals rich in palmitic acid or linoleic acid than to meals rich in oleic acid or EPA and DHA. A similar trend was seen for AUC and iAUC, but the differences did not reach statistical significance possibly because of the small sample size. These results contradict most of the earlier studies that showed no difference in insulin response to meals rich in different types of fatty acids in subjects with (8,9) or without (10–18) diabetes.

A possible mechanism for the insulin response observed in our study is the different insulinotropic potency of the different fatty acids. Stein et al. (34) studied the influence of fatty acids on insulin secretion in the perfused rat pancreas and found that glucose-stimulated insulin release was higher with palmitic acid than with oleic acid, which in turn was higher than that with linoleic acid. Although we also found an increased postprandial insulin response with palmitic acid compared with oleic acid, our observation of higher insulin response to linoleic acid than to oleic acid is not consistent with the data of Stein et al. (34). Holness et al. (35) reported that acute replacement of some dietary saturated fatty acids with

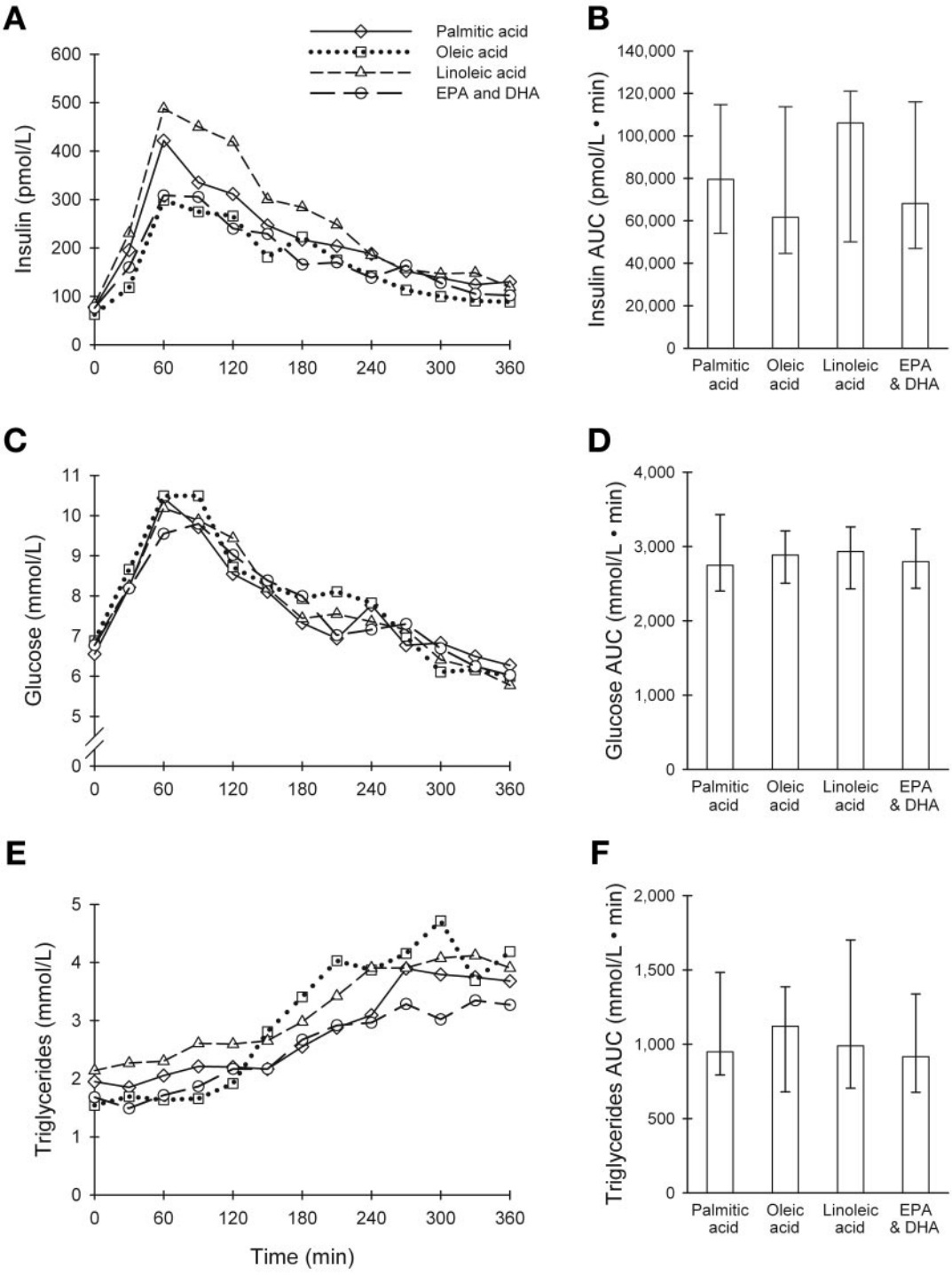

Figure 1— *Postprandial insulin, glucose, and triglyceride responses to meals. Shown are median values for postprandial insulin* (A)*, glucose* (C)*, and triglyceride* (E) *responses to meals rich in palmitic acid (◇), oleic acid (□), linoleic acid (△), and EPA and DHA (○). The baseline values are the means of the values collected at −30, −15, and 0 min. To convert insulin values from picomoles per liter to microunits per milliliter, divide by 6.0; to convert glucose and triglyceride values from millimoles per liter to milligrams per deciliter, divide by 0.05551 and 0.01129, respectively. Also shown are AUC values (medians and 25th and 75th percentiles) for insulin* (B)*, glucose* (D)*, and triglycerides* (F) *for different meals.*

EPA and DHA, in rats made insulin resistant by high–saturated fat feeding for 4 weeks, reversed insulin hypersecretion in vivo and during glucose perifusion of isolated islets. The lowered insulin secretion, however, was not accompanied by improved insulin action, and glucose tolerance was adversely affected. In our study, the insulin-lowering effect of EPA and DHA and oleic acid was not associated with deterioration in glucose tolerance, as indicated by the lack of difference in postprandial glucose response to the different fatty acids, and may suggest an increase in insulin sensitivity. In our study, we did not observe an improvement in insulin sensitivity after the meal rich in linoleic acid compared with that after the meal

rich in palmitic acid. This finding conflicts with data from a 5-week study (36) in which improved insulin sensitivity was reported with a diet rich in linoleic acid compared with a diet rich in palmitic acid. Energy intake in the latter study, however, was lower during the linoleic acid–rich phase compared with the other diet phase, which may partly explain the results.

The difference in insulin response in our study may be due to secretion of incretin hormones, glucagon-like-peptide-1, and glucose-dependent insulinotropic polypeptide. However, how the incretin hormones respond to different fatty acids remains to be studied.

Our results on glucose response are similar to the results from most studies in subjects with (9,20) and without (10–15,18,21) type 2 diabetes, which showed no difference in glucose response to different fatty acids. It is important to note that although the insulin-lowering effects of EPA and DHA and oleic acid did not adversely affect glucose response, the latter remained in the diabetes range. This result indicates a need for more aggressive control of postprandial glucose levels using several treatment strategies.

According to the repeated-measures ANOVA with rank-transformed values after subtraction of the baseline values, the triglyceride response tended to be lower to the meal rich in EPA and DHA than to the other meals, but the difference was only significant between the meals rich in EPA and DHA and oleic acid. A similar, albeit not significant, trend was seen for AUC or iAUC. These results are corroborated by studies examining the acute effect of different fatty acids on postprandial triglyceride concentrations in type 2 diabetic subjects with high baseline triglyceride concentrations (20) and in individuals without diabetes (17). Other acute studies in healthy subjects (15,24), however, showed no difference in postprandial triglyceride response after meals rich in oleic acid or EPA and DHA. Our data are similar to those from a long-term intervention study (37), which showed reduced postprandial triglyceride concentrations in healthy subjects when diets rich in saturated fatty acids or monounsaturated fatty acids were supplemented with fish oil. The composition of the test meals was similar to that of the diets to which the subjects were assigned (37).

It has been reported that the postprandial triglyceride response may depend on insulin status (38). We looked at the influence of insulin resistance, estimated using the homeostasis model assessment insulin resistance calculator 2.2 (39), on triglyceride response by repeated-measures ANOVA and found no evidence of an interaction between insulin resistance status and triglyceride response to meals. Nevertheless, a larger sample may help to better examine this relationship.

Possible mechanisms by which EPA and DHA lower triglyceride levels include decreased chylomicron production or secretion (22) and reduced synthesis of hepatic VLDLs (23) seen after chronic feeding of EPA and DHA. The reduced VLDL concentrations would result in less competition for lipoprotein lipase for hydrolysis of chylomicrons. It is not known whether acute consumption of EPA and DHA would result in the above mechanisms, however.

To accurately distinguish the effect of different types of fatty acids on the postprandial responses, we tested meals that contained 1,000 kcal and 50% of energy as fat. Although these meals are more energy dense than the diet that is typically consumed by Americans (3,40), we believe that the test meal rich in oleic acid may be acceptable over the long term based on the strong adherence that we have observed in our earlier studies (3,41) testing high monounsaturated fat diets for 6–12 weeks. Whether large doses of fish oil are acceptable over the long term remains to be studied. Also, whether meals with a lower fat content would lead to reduced or similar postprandial responses compared with the meals administered in our study will require additional studies. Our test meals also contained some carbohydrate sources such as white bread, which has a high glycemic index. This should not preclude us from distinguishing the effect of the different fatty acids on postprandial response, however, because the type and amount of carbohydrate were held constant across the test meals.

In summary, our study shows that meals containing a high percentage of energy from oleic acid or EPA and DHA, the fatty acids that patients with type 2 diabetes are encouraged to consume by the American Diabetes Association (1), may be beneficial in lowering postprandial insulin response in comparison with meals rich in palmitic acid or linoleic acid with a comparable postprandial glucose response. Meals containing a high percentage of energy from EPA and DHA may also be beneficial in lowering the postprandial triglyceride response.

Acknowledgments— This study was funded by General Clinical Research Center U.S. Public Health Service Grant M01-RR00633 and by the Southwestern Medical Foundation.

Parts of this study were presented in abstract form at the 48th annual meeting of the American College of Nutrition, Orlando, Florida, 27–30 September 2007.

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