Differential effects of saturated and monounsaturated fats on postprandial lipemia and glucagon-like peptide 1 responses in patients with type 2 diabetes[1–3]

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ABSTRACT

Background: Postprandial lipemia is important in the development of coronary artery disease because of elevated postprandial triacylglycerol-rich plasma lipoproteins and suppressed HDL-cholesterol concentrations. We showed in healthy subjects a possible association between postprandial lipid metabolism and the responses of the duodenal incretin hormones glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide after meals rich in saturated and monounsaturated fatty acids (oleic acid), respectively.

Objective: The objective was to compare the postprandial responses (8 h) of glucose, insulin, fatty acids, triacylglycerol, gastric inhibitory polypeptide, and GLP-1 to saturated- and monounsaturated-rich test meals.

Design: Twelve overweight patients with type 2 diabetes ingested 3 meals randomly: an energy-free soup with 50 g carbohydrate (control meal), the control meal plus 100 g butter, and the control meal plus 80 g olive oil. Triacylglycerol responses were measured in total plasma and in a chylomicron-rich and a chylomicron-poor fraction.

Results: No significant differences in the glucose, insulin, or fatty acid responses to the 2 fat-rich meals were seen. The plasma triacylglycerol and chylomicron triacylglycerol responses were highest after the butter meal. HDL-cholesterol concentrations decreased significantly after the butter meal but did not change significantly after the olive oil meal. GLP-1 responses were highest after the olive oil meal.

Conclusions: Olive oil induced lower triacylglycerol concentrations and higher HDL-cholesterol concentrations than did butter, without eliciting significant changes in glucose, insulin, or fatty acids. Furthermore, olive oil induced higher concentrations of GLP-1, which may indicate a relation between fatty acid composition, incretin responses, and triacylglycerol metabolism postprandially in patients with type 2 diabetes. *Am J Clin Nutr* 2003;77:605–11.

KEY WORDS Saturated fat, monounsaturated fat, glucagon-like peptide 1, GLP-1, postprandial lipemia, triacylglycerol, olive oil, type 2 diabetes, gastric inhibitory polypeptide, coronary artery disease

INTRODUCTION

A high consumption of fat, especially saturated fat, increases the risk of coronary artery disease (CAD), which is the main cause of early death in patients with type 2 diabetes.

Type 2 diabetes is a central component of the metabolic syndrome, which consists of a cluster of risk factors for CAD: type 2 diabetes, abdominal obesity, insulin resistance, hypertension, and dyslipoproteinemia with elevated triacylglycerol and low HDL-cholesterol concentrations. Postprandial lipoproteins are thought to be particularly atherogenic (1–3), and an abnormal metabolism of postprandial lipoproteins is a common finding in type 2 diabetes (4–6). Thus, patients with type 2 diabetes have higher postprandial triacylglycerol concentrations than do nondiabetic persons when carefully matched for fasting plasma triacylglycerol concentrations (7). Consequently, the exaggerated postprandial triacylglycerol responses may, at least in part, be responsible for the increased morbidity from CAD in type 2 diabetes. Furthermore, postprandial lipemia determines plasma HDL-cholesterol concentrations (8). The negative correlation between HDL cholesterol and CAD seems to originate in the highly positive correlation between postprandial triacylglycerol concentrations and CAD (9).

The fatty acid composition of the diet influences postprandial lipid responses. In patients with type 2 diabetes (10), we showed that butter, compared with olive oil, augmented postprandial fatty acid and triacylglycerol responses when fat was consumed with carbohydrates. Interestingly, we found in healthy subjects indications of a linkage between the fatty acid composition of the diet and the postprandial incretin [eg, glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP)] and triacylglycerol responses (11). Similar studies have not been done in patients with type 2 diabetes. We compared the in vivo acute postprandial lipid and lipoprotein responses to and investigated the possible differences in GIP and GLP-1 responses to the ingestion of butter and olive oil in patients with type 2 diabetes.

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[2] Supported by grants from the Danish Research Council, the Danish Diabetes Association, the Institute of Experimental Clinical Research, Aarhus University, the Eli Lilly Diabetes Research Foundation, The Novo Nordisk Research Foundation Committee, Johannes & Desiré Ydes Fond, and the Novo Nordisk Foundation.

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Received February 27, 2002.

Accepted for publication May 24, 2002.

SUBJECTS AND METHODS

Subjects

Twelve patients (5 women and 7 men) with type 2 diabetes were recruited from our outpatient clinic. The patients were aged 64 ± 4 y ($\bar{x}$ ± SD), were overweight [body weight: 81.9 ± 17.6 kg; body mass index (in kg/m^2): 27.9 ± 5.3], had a waist circumference of 97.4 ± 12.9 cm, and had a glycated hemoglobin value of 6.9 ± 0.8% (normal range: 3.5–5.5%). All patients had the diabetes diagnosis for ≥ 1 y (3.9 ± 1.6 y). All participants were treated with diet; 10 of the patients were treated with sulfonylurea; none were treated with insulin or any other prescribed medicine, including lipid-lowering drugs. The patients were all nonsmokers. The study was approved by the local ethical committee of Aarhus County, Denmark.

Study design

The patients participated 3 times with intervals of ≥ 1 wk. During the preceding 24 h, the patients ingested high-carbohydrate food (bread, rice, potato, whole grains, and vegetables) delivered by the dietitian. The amounts of food corresponded to the patients' individual energy requirements, which were estimated with the Harris-Benedict equation with adjustments for physical activity (12). The patients were instructed to standardize and minimize their physical activity on the study mornings, ie, get dressed without washing, take a bus to the experimental setting, and be seated immediately on arrival at 0700. On arrival, a catheter was placed in an antecubital vein, and the patients rested for 30 min. Basal blood samples were drawn and then the test meal was ingested. During the subsequent 8 h, blood samples were drawn regularly for the measurement of glucose, insulin, fatty acids, cholesterol, triacylglycerol, GIP, and GLP-1. Plasma was immediately separated by centrifugation (26 000 × *g*, 30 min, 25 °C) and kept frozen at −20 °C, except for the GIP and GLP-1 samples, which were stored at −80 °C until analyzed.

Test meal

In randomized order, the patients consumed *1*) an energy-free soup with 50 g carbohydrate as white bread (control meal), *2*) the control meal plus 100 g butter, and *3*) the control meal plus 80 g olive oil. The apparent discrepancy in the amounts of the given fats was due to the 20% water content of the butter. The manufacturers provided the nutrient contents of the unsalted butter and olive oil. The olive oil contained predominantly monounsaturated fat (74%) and the butter contained mainly saturated fat (72%). The unmelted butter or olive oil was added to the hot soup, which was stirred until the butter was dissolved. Sliced, raw leek was added to mask both the appearance and the taste. The patients were unable to distinguish between the 2 soups. The test meals were ingested within 10 min and were served with 250 mL tap water. The patients were instructed to wipe the inside of the soup plate with some of the white bread and then to eat the bread to ensure the intake of all the fat in the test meal. The energy content of the fat-rich meals was 4200 kJ and of the test meal 1090 kJ.

Separation of chylomicron-rich and chylomicron-poor plasma

To separate the lipoproteins, the plasma samples were subjected to a single ultracentrifugation step to divide the sample into a chylomicron-rich and a chylomicron-poor fraction. Plasma (4 mL) was overlayered with 2 mL of a solution with a density of 1.006 g/mL in a Quick-seal tube (no. 344619; Beckman Instruments, Palo Alto, CA) and was centrifuged in an Sw 50.3-Ti fixed-angle rotor (Beckman Instruments) for 30 min at 26 000 × *g* for 30 min at 25 °C. The tubes were sliced 4 mL from the bottom in a Beckman slicer, and the chylomicron-rich supernatant fluid (Svedberg flotation >1000) was removed and brought to a final volume of 4 mL with saline. The infranatant fluid, ie, the chylomicron-poor fraction, contains the plasma proteins and remaining lipoproteins; thus, the triacylglycerol concentration may be allocated to the chylomicrons in the chylomicron-rich fraction and to the VLDL, intermediate-density lipoprotein, and chylomicron remnants in the chylomicron-poor fraction. Triacylglycerol and cholesterol concentrations were measured in plasma and in both fractions, whereas HDL cholesterol was measured only in the chylomicron-poor fraction.

Analyses

Plasma glucose was measured with a glucose oxidase method (CV: 3.8%). Serum insulin was measured by enzyme-linked immunosorbent assay (CV: 1.7%) (13). Triacylglycerol, cholesterol (HDL cholesterol in the chylomicron-poor fraction only, after precipitation of apolipoprotein B–containing lipoproteins with phosphotungstic acid), and fatty acids were measured by standard enzymatic colorimetric assays with the use of commercial kits [Waco Chemicals (Neuss, Germany) and Boehringer Mannheim (Mannheim, Germany)]. GIP was measured by radioimmunoassay with the use of the antiserum R65, monoiodinated human GIP, and human GIP for standards after extraction of the peptide from plasma according to a previously described method (14). The sensitivity and detection limits of the assay are ≈1 pmol/L. The assay is highly specific for GIP and does not cross-react with the 8-kDa immunoreactive component of unknown nature cross-reacting in most GIP assays. Plasma concentrations of GLP-1 were measured as previously described (15) against standards of synthetic GLP-1 7–36 amide (proglucagon 78–106 amide) (16) with the use of antiserum code no. 89390, which can be used at a final dilution of 1:250 000 and endows the assay with a detection limit of 1 pmol/L and has an intraassay CV < 5% at 20 pmol/L. This antiserum is highly specific for the COOH-terminus of proglucagon 78–107 amide and reacts neither with glycine-extended GLP-1 (proglucagon 78–108) nor with proglucagon 78–106. Thus, it mainly reacts with GLP-1 of intestinal origin (17). Before the analysis, plasma was extracted with ethanol (70%, vol:vol) (16).

Statistical analysis

The results are expressed as means ± SDs from individually analyzed results from all 12 participants. The response data are given as peak nadir concentrations and as incremental areas above baseline (18). The data presented were all tested for normality of distribution. Comparisons between results from the 3 meals were made by analysis of variance (repeated measures) followed by Tukey's test (SIGMASTAT for WINDOWS; SPSS Inc, Chicago). A P value < 0.05 was considered statistically significant.

RESULTS

All participants completed the study and ingested the test meals with no problems. No significant differences in the fasting concentrations of glucose, insulin, fatty acids, triacylglycerol (plasma and both fractions), or plasma HDL cholesterol, GLP-1, or GIP were observed. No significant weight changes were observed

TABLE 1
Metabolic responses in patients with type 2 diabetes to meals of soup plus 50 g carbohydrate (control meal), the control meal plus 80 g olive oil, and the control meal plus 100 g butter[1]

	Control	Olive oil	Butter	P^2
Fasting blood glucose (mmol/L)	7.8 ± 2.3	7.4 ± 2.2	7.8 ± 2.3	0.52
Blood glucose area (mmol·480 min/L)	377.4 ± 208.4[a]	270.3 ± 166.5[b]	297.0 ± 151.5[a,b]	<0.05
Fasting insulin (pmol/L)	36.6 ± 26.9	33.5 ± 30.2	40.6 ± 29.7	0.10
Insulin area (pmol·480 min/L)	6179 ± 3865[a]	12579 ± 10534[b]	11247 ± 6729[b]	0.005
Fasting fatty acids (mmol/L)	0.79 ± 0.31	0.78 ± 0.22	0.77 ± 0.18	0.52
Nadir fatty acids (mmol/L)	0.21 ± 0.10[a]	0.38 ± 0.20[b]	0.42 ± 0.19[b]	<0.001
GLP-1 (pmol·480 min/L)	746 ± 488[a]	5071 ± 2871[b]	4274 ± 3361[c]	<0.001
GIP (pmol·480 min/L)	4876 ± 1794[a]	18026 ± 5799[a]	14659 ± 6617[b]	<0.001

[1] $\bar{x}$ ± SD; n = 12. GLP-1, glucagon-like peptide 1; GIP, gastric inhibitory polypeptide. Means in a row with different superscript letters are significantly different, $P < 0.05$.
[2] ANOVA.

during the study period (baseline weight: 81.9 ± 17.6 kg; end weight: 80.7 ± 15.9 kg).

Blood glucose, insulin, incretin hormone, and fatty acid responses

The responses of glucose, insulin, incretin hormones, and fatty acids to the test meals are shown in **Table 1**. The postprandial responses of glucose, insulin, and fatty acids are shown in **Figure 1** as well. The lowest fatty acid concentration was found after the control meal. The highest glucose concentration (12.8 ± 3.9 mmol/L) was also found after the control meal (olive oil meal: 9.9 ± 3.5 mmol/L; butter meal: 11.2 ± 2.8 mmol/L; P = 0.016). Olive oil induced significantly lower incremental glucose areas than did the control meal, whereas no significant differences in fat-induced insulin areas were seen. The control meal induced lower nadir fatty acid concentrations compared with the fat meals.

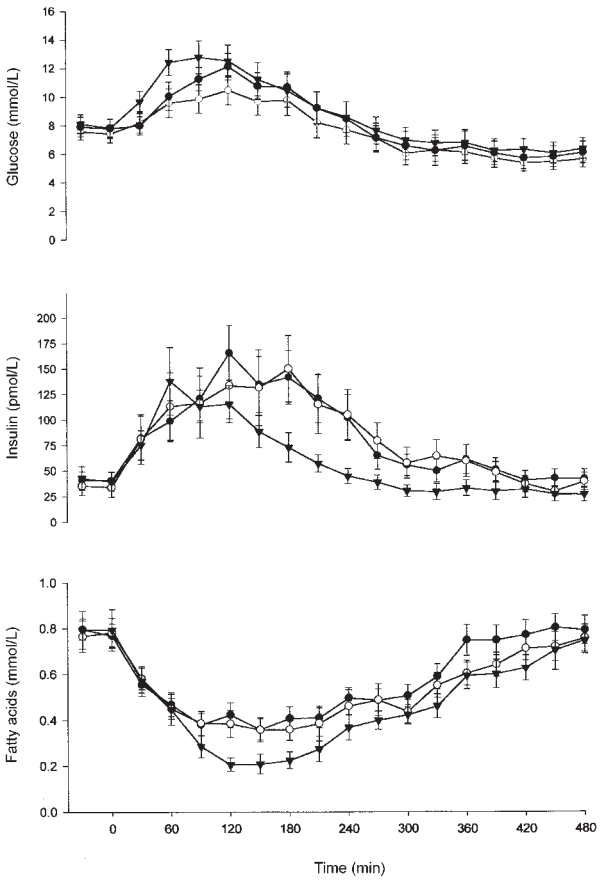

FIGURE 1. Mean (± SE) responses of glucose, insulin, and fatty acid concentrations in 12 patients with type 2 diabetes to a control meal of soup plus 50 g carbohydrates (▼), the control meal plus 80 g olive oil (○), and the control meal plus 100 g butter (●).

No significant differences in the time courses of the glucose, insulin, and fatty acid responses were found between the 2 fat-rich meals (Figure 1), whereas both glucose and insulin responses tended to peak earlier after ingestion of the control meal. No significant differences in the insulinogenic indexes [insulin:glucose area under the curve (AUC)] were found between the 3 test meals.

Lipid responses

The postprandial triacylglycerol responses are given in **Figure 2**. After the control meal, no significant increase in triacylglycerol was seen in either the plasma or in the chylomicron-rich or chylomicron-poor fraction. The butter meal caused a significant increase in plasma triacylglycerol concentrations and in the chylomicron-rich fraction during the initial 3 h. In contrast, no significant changes in plasma triacylglycerol concentrations or in the chylomicron-poor fraction were seen after the olive oil meal. Compared with the control meal, the olive oil meal induced significantly higher triacylglycerol concentrations in the chylomicron-rich fraction but lower concentrations than did the butter meal at 360 min. As shown on the right side of Figure 2, the incremental AUCs above baseline of plasma triacylglycerol after the butter meal were significantly higher than those after the olive oil and control meals. The chylomicron-rich triacylglycerol AUC was not significantly different in response to the 2 fat-rich meals but was significantly higher than the response to the control meal. No significant differences in triacylglycerol AUCs were found in the chylomicron-poor fractions.

The plasma cholesterol and HDL-cholesterol responses in the chylomicron-poor fraction are given in **Figure 3**. Compared with baseline, the olive oil meal induced a significant suppression of plasma cholesterol concentrations after the initial 2 h, whereas no significant changes were found after the 2 other test meals. After the butter meal, HDL-cholesterol concentrations decreased but did not reach baseline concentrations during the 8-h test period. HDL-cholesterol concentrations were practically unchanged after the

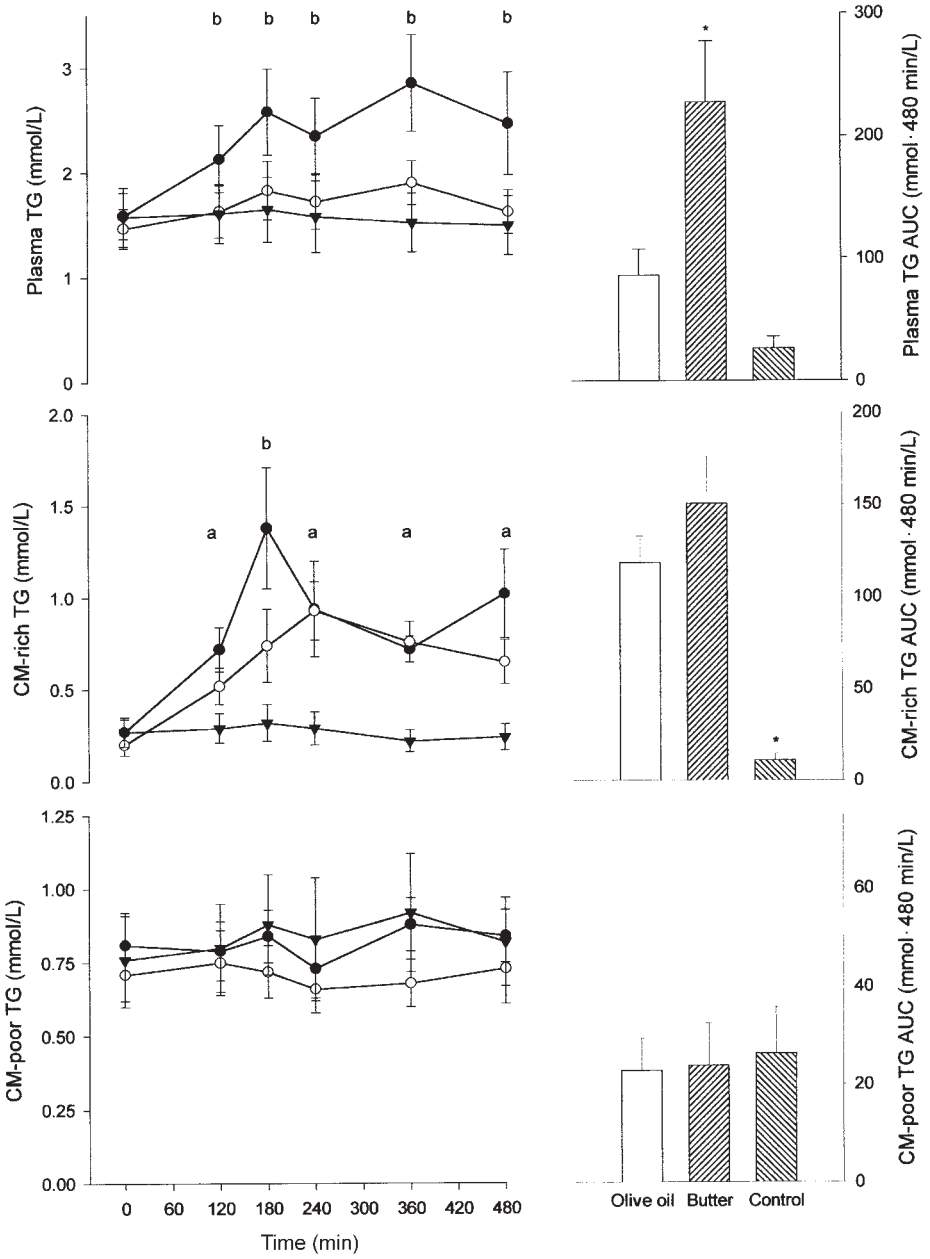

FIGURE 2. Mean (±SE) responses of triacylglycerol (TG) in plasma, the chylomicron (CM)-rich fraction, and the CM-poor fraction in 12 patients with type 2 diabetes to a control meal of soup plus 50 g carbohydrates (▼), the control meal plus 80 g olive oil (○), and the control meal plus 100 g butter (●). The corresponding areas under the curve (AUC) are also shown. Repeated-measures ANOVA and Tukey's test: [a]control meal significantly different from the butter and olive oil meals, $P < 0.05$; [b]butter meal significantly different from the control and olive oil meals, $P < 0.05$; [*]significantly different from the other 2 meals, $P < 0.05$.

olive oil meal and were significantly higher than after the butter meal 4 h postprandially.

GIP and GLP-1 responses

During the initial 6 h, the GLP-1 response to the control meal was significantly lower than that to the 2 fat-rich meals (**Figure 4**). For the whole 8-h test period, olive oil induced significantly larger incremental GLP-1 responses than did the butter and control meals, which also differed significantly (Table 1). The GIP responses to the olive oil and butter meals were not significantly different over the whole 8-h period (Figure 4); however, both responses were significantly higher than those to the control meal (Table 1).

DISCUSSION

In the current study, we investigated the effects of saturated fat– and monounsaturated fat–rich meals on postprandial lipemia and incretins in patients with type 2 diabetes. The results indicate that the consumption of saturated and monounsaturated fats with

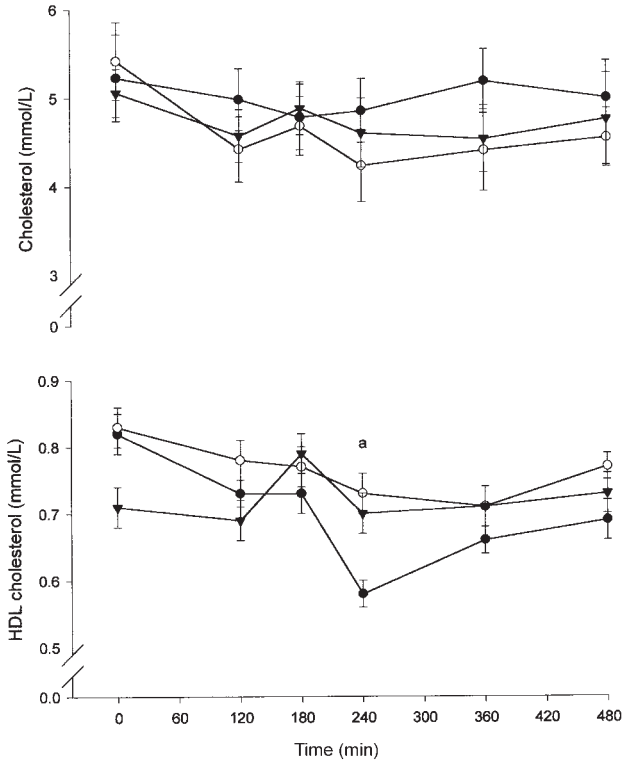

FIGURE 3. Mean (±SE) responses of plasma cholesterol and HDL-cholesterol concentrations in 12 patients with type 2 diabetes to a control meal of soup plus 50 g carbohydrates (▼), the control meal plus 80 g olive oil (○), and the control meal plus 100 g butter (●). [a]Olive oil meal significantly different from the butter meal, $P < 0.05$ (repeated-measures ANOVA and Tukey's test).

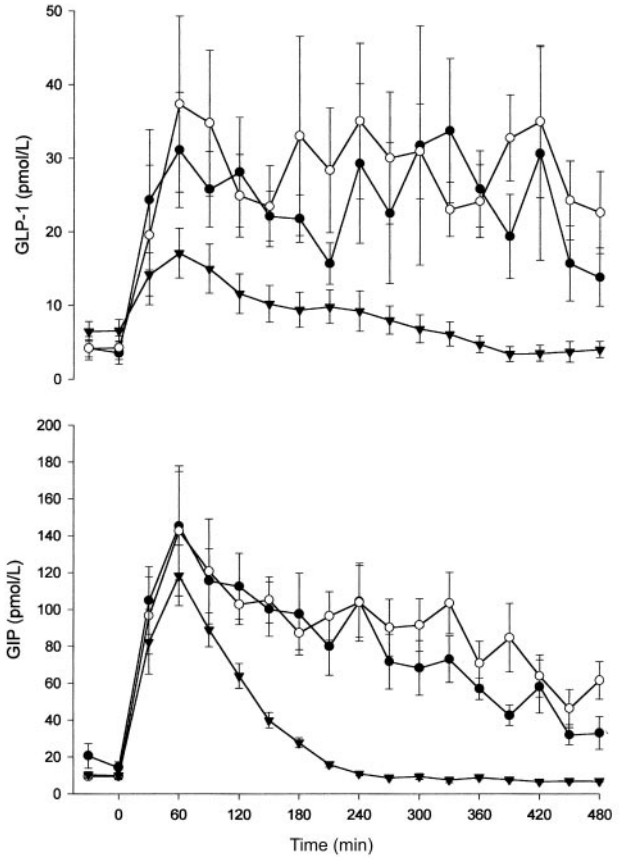

FIGURE 4. Mean (±SE) responses of glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) concentrations in 12 patients with type 2 diabetes to a control meal of soup plus 50 g carbohydrates (▼), the control meal plus 80 g olive oil (○), and the control meal plus 100 g butter (●).

carbohydrates may exert differential effects on postprandial triacylglycerol and lipoprotein metabolism and on postprandial HDL-cholesterol concentrations in patients with type 2 diabetes. A possible link between postprandial lipemia and the incretin GLP-1 was found in the patients with type 2 diabetes. Thus, olive oil induced larger GLP-1 responses during the 8-h test period than did butter.

The postprandial incremental glucose AUC after olive oil was lower than that after the control meal. However, no significant differences between the 8-h responses of glucose, insulin, or fatty acids after olive oil and butter were found. GLP-1 is being investigated as a possible treatment of hyperglycemia in type 2 diabetes (19). Preprandial injection of GLP-1 has been shown to reduce postprandial glucose excursions in patients with type 2 diabetes (20). The insulinotropic effect of GLP-1 was shown in several studies; therefore, it is puzzling that we did not find higher insulin responses to the olive oil meal than to the butter and control meals (Figure 1). GLP-1 is known to inhibit gastric emptying (21), which we did not measure directly; however, the time courses of glucose, insulin, and fatty acids in response to the 2 fat-rich meals did not differ significantly (Figure 1). The lower glucose response to the olive oil meal than to the control meal may have been a result of differential responses of GLP-1 via mechanisms other than gastric emptying rates and insulin responses.

GLP-1 responses to an oral-glucose-tolerance test were previously shown to be lower in patients with type 2 diabetes than in healthy subjects, whereas similar responses of GIP were found between these 2 groups (22). These data were corroborated by data from Vilsboll et al (23), showing that, compared with healthy subjects, type 2 diabetic patients had strongly reduced GLP-1 responses to a mixed meal but only modestly reduced GIP responses. We found significantly higher GLP-1 responses to the olive oil than to the butter meal at 8 h, whereas GIP responses did not differ significantly (Figure 4). Brynes et al (24) found no changes in GLP-1 responses in type 2 diabetic patients after the consumption of diets enriched with either monounsaturated or polyunsaturated fat for 3 wk. However, the responses measured were those to a standard test meal with a relatively low fat content (20 g) and a relatively high monounsaturated fat content (59%). Furthermore, blood samples were taken for only 3 h (24), which, relative to our study, was too short a period to determine significant differences in incretin responses. Rocca and Brubaker reported that monounsaturated fatty acids (ie, oleic acid) were strong stimulators of GLP-1 secretion both in enterocyte cultures from rats (25) and in vivo in Zucker rats (26). Approximately 90% of olive oil consists of ≥18 carbon atoms, and 74% is monounsaturated fat, whereas 72% of butter is saturated fat. Our findings are the first to suggest that monounsaturated fat is a potent stimulator of postprandial GLP-1 secretion in patients with type 2 diabetes.

The fatty acid composition of a meal may heavily influence the postprandial responses to it because the very first triacylglycerol-filled chylomicrons appearing after food intake contain the triacylglycerols from the previous meal (27). Therefore, we carefully standardized the test conditions by using carbohydrate-rich foods delivered by the dietitian for the 24 h before the test meals. The observed difference in triacylglycerol responses to olive oil and butter corroborate our previous results in type 2 diabetic subjects during 4-h study periods (10). In the current study, butter rather than olive oil induced significantly higher triacylglycerol concentrations during the 8-h test period (Figure 2), in agreement with a lower GLP-1 response (Figure 4). GLP-1 seems to not stimulate human lipolysis, either in vitro (28) or in vivo (29). Toft-Nielsen et al (30) found no influence of the subcutaneous infusion of GLP-1 on plasma concentrations of fatty acids or triacylglycerol in type 2 diabetic patients. In the current study, no difference in fatty acid responses to the fat-rich meals was observed, whereas the lowest fatty acid responses were observed after the control meal. The simultaneous increase in insulin and fatty acids after the fat-rich meals agrees with our previous findings in patients with type 2 diabetes (10), which indicates significantly lower fatty acid concentrations after a carbohydrate-rich meal than after monounsaturated fat–rich and butter-rich meals. Infusion of triacylglycerol emulsions leads to an elevated fatty acid concentration, which is related to the activity of the enzyme lipoprotein lipase (EC 3.1.1.34) (31, 32). Even during insulin infusion rates that would normally suppress fatty acids and inhibit fat oxidation, a simultaneous infusion of triacylglycerol emulsion leads to maintenance of high plasma fatty acids (33). A significant reduction in VLDL concentrations and an enlargement of LDL particle size were seen in type 2 diabetic patients treated with insulin and GLP-1 for 1 wk (20). Thus, GLP-1 may positively influence known risk factors for CAD in type 2 diabetes. In our study, olive oil reduced postprandial triacylglycerol concentrations but did not lower HDL-cholesterol concentrations, as opposed to butter (Figure 3). To our knowledge, this has not been shown previously.

We did find similar differential effects of olive oil and butter on postprandial triacylglycerol, HDL-cholesterol, glucose, and GLP-1 concentrations in healthy subjects (11). This may indicate a common link, in both healthy persons and in patients with type 2 diabetes, between the type of ingested fat and the incretin and triacylglycerol responses. The underlying mechanisms (11), however, remain to be elucidated.

We did not measure stool fat, but it seems unlikely that olive oil was absorbed to a lesser degree than was butter. Thus, Bonanome and Grundy (34) showed in healthy subjects that oleic acid was very well absorbed. Furthermore, several studies in humans showed that fecal excretion of oleic acid is $< 5\%$ (35–37), which is comparable with the excretion of linoleic acid and palmitic acid.

Olive oil induced a beneficial lipid profile, ie, lower triacylglycerol concentrations and higher HDL-cholesterol concentrations than those induced by butter, without eliciting differences in glucose, insulin, or fatty acid concentrations in patients with type 2 diabetes. Furthermore, olive oil induced higher concentrations of GLP-1, which may indicate a relation between fatty acid composition, GLP-1 responses, and triacylglycerol metabolism postprandially in type 2 diabetes.

We thank Tove Skrumsager, Kirsten Eriksen, and Hanne Mathiassen for excellent technical assistance and Eva Pedersen for dietetic assistance.

CT and HS participated in planning the study, recruiting the patients, conducting the experimental testing, analyzing the biochemical and statistical data, and writing the manuscript. JJH participated in planning the study, analyzing the biochemical data, and writing the manuscript. KH participated in planning the study and writing the manuscript. No conflicts of interest were present.

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