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Effects of Fat on Gastric Emptying of and the Glycemic, Insulin, and Incretin Responses to a Carbohydrate Meal in Type 2 Diabetes

Diana Gentilcore, Reawika Chaikomin, Karen L. Jones, Antonietta Russo, Christine Feinle-Bisset, Judith M. Wishart, Christopher K. Rayner, and Michael Horowitz

University of Adelaide, Department of Medicine, Royal Adelaide Hospital, Adelaide, South Australia 5000, Australia

Context: Gastric emptying (GE) is a major determinant of postprandial glycemia. Because the presence of fat in the small intestine inhibits GE, ingestion of fat may attenuate the glycemic response to carbohydrate.

Objective: The objective of this study was to evaluate the effect of patterns of fat consumption on GE and glucose, insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) concentrations after a carbohydrate meal in type 2 diabetes.

Design: This was a randomized, cross-over study in which GE of a radioisotopically labeled potato meal was measured on 3 d.

Setting: The study was performed at the Royal Adelaide Hospital.

Patients: Six males with type 2 diabetes were studied.

Intervention: Subjects ingested 1) 30 ml water 30 min before the mashed potato (water), 2) 30 ml olive oil 30 min before the mashed potato (oil), or 3) 30 ml water 30 min before the mashed potato meal that contained 30 ml olive oil (water and oil).

Main Outcome Measures: GE, blood glucose, plasma insulin, GLP-1, and GIP concentrations were the main outcome measures.

Results: GE was much slower with oil compared with both water ($P < 0.0001$) and water and oil ($P < 0.05$) and was slower after water and oil compared with water ($P < 0.01$). The postprandial rise in blood glucose was markedly delayed ($P = 0.03$), and peak glucose occurred later ($P = 0.04$) with oil compared with the two other meals. The rises in insulin and GIP were attenuated ($P < 0.0001$), whereas the GLP-1 response was greater ($P = 0.0001$), after oil.

Conclusions: Ingestion of fat before a carbohydrate meal markedly slows GE and attenuates the postprandial rises in glucose, insulin, and GIP, but stimulates GLP-1, in type 2 diabetes. **(*J Clin Endocrinol Metab* 91: 2062–2067, 2006)**

IT HAS BEEN recognized, albeit only relatively recently, that humans are predominantly in the postprandial, rather than fasted, state (1) simply because the rate at which nutrients, including glucose, are delivered from the stomach into the small intestine in healthy subjects approximates 2–4 kcal/min (8.4–16.8 kJ/min) after an initial emptying phase that may be slightly faster (2, 3). Hence, it is not surprising that postprandial glycemia is probably the major determinant of overall glycemia, as assessed by glycated hemoglobin (4), the traditional marker for the development and progression of diabetic macrovascular complications. The extent of postprandial glycemic excursions probably represents an independent risk factor for macrovascular disease even in individuals who do not have diabetes (5). Accordingly, there is substantial interest in dietary and pharmacological [*e.g.* short-acting insulin analogs, α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) and its analogs, and pramlintide] strategies directed at the control of postprandial blood glucose excursions, particularly in type 2 diabetes (5, 6).

Gastric emptying is a major determinant of postprandial glycemia, as attested to by the relationship between the rise in blood glucose after oral carbohydrate with gastric emptying (6–9) and the effects of modulation of gastric emptying on postprandial glucose and insulin concentrations (8, 10–14). Even minor variations in the initial rate of small intestinal carbohydrate delivery may have major effects on the glycemic response (15, 16). Enteral administration of glucose also stimulates the secretion of the incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP); the incretin effect accounts for approximately 50% of the rise in plasma insulin after oral glucose (17). Hence, interventions that result in slowing of gastric emptying have the potential to improve postprandial glycemic control (6) and may be more effective if incretin hormone secretion is also stimulated.

The interaction of nutrients with the small intestine plays the dominant role in the regulation of gastric emptying (2, 18, 19); the extent of small intestinal feedback is related to the length and possibly the region of small intestine exposed to nutrient (18). Of the macronutrients, fat generates the most potent feedback, primarily because of its high caloric density and possibly because its absorption rate is relatively slower (20). In healthy young subjects, when fat is incorporated either into a carbohydrate-containing drink (21) or a solid meal (12) or is administered directly into the small intestine (22), gastric emptying is slowed, and the blood glucose and insulin responses are attenuated (12, 22). Fat also stimulates GLP-1 (23) and, possibly to a lesser extent, GIP (24) secretion.

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Abbreviations: GE, Gastric emptying; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; T50, 50% emptying time.

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The slowing of gastric emptying (10, 13, 25, 26) and the stimulation of GLP-1 and GIP (23) are dependent on the digestion of fat to fatty acids. Accordingly, acute administration of the lipase inhibitor, orlistat, accelerates gastric emptying of carbohydrate-containing meals that have a high fat content (10, 13) while attenuating the incretin and exacerbating the glycemic responses (10, 13).

Despite the theoretical benefits of fat on postprandial glycemia, its effects on gastric emptying and the blood glucose and incretin responses to carbohydrate in type 2 diabetes to our knowledge have not been evaluated. Given that 1) fat digestion is required to inhibit gastric emptying (10, 13, 25, 26) and stimulate incretin hormones (23); 2) the slowing of gastric emptying by fat is dependent on the length of small intestine exposed to lipolytic products (18); and 3) intracellular and homogenized fat empty from the stomach with other meal components (27, 28); the effects of fat on the glycemic response to oral carbohydrate were likely to be greater if the fat was consumed by itself and before, rather than with, a carbohydrate-containing meal. In this study we evaluated both the effects and the timing of fat consumption on gastric emptying, blood glucose, and plasma insulin, GLP-1, and GIP concentrations after a carbohydrate meal in patients with type 2 diabetes.

Subjects and Methods

Subjects

Six males with type 2 diabetes, diagnosed by World Health Organization criteria and managed by diet alone (median age, 56 yr; range, 46–65 yr; median body mass index, 26.1 kg/m^2; range, 21.9–28.9), were recruited by advertisement. None had a history of significant gastrointestinal, respiratory, renal, hepatic, or cardiac disease; chronic alcohol abuse; or epilepsy, was a smoker, or was taking medication known to influence blood pressure or gastrointestinal function. The mean duration of known diabetes was 2.6 ± 1.4 yr, and glycated hemoglobin at the time of the study was 6.2 ± 0.3% (normal, <6.0).

The study protocol was approved by the research ethics committee of the Royal Adelaide Hospital, and each subject provided written informed consent before inclusion in the study. All experiments were carried out in accordance with the Declaration of Helsinki.

Protocol

Each subject was studied on three occasions, each separated by at least 7 d, in random order. On each day, subjects attended the Department of Nuclear Medicine, Positron Emission Tomography, and Bone Densitometry at 0830 h after an overnight fast (14 h for solids; 12 h for liquids) (3). A cannula was placed in a right antecubital vein for blood sampling, and subjects were seated with their back against a γ-camera. Concurrent measurements of gastric emptying, blood glucose, and plasma insulin, GIP, and GLP-1 concentrations were performed after ingestion, on 3 separate days of 1) 30 ml water, 30 min before a mashed potato meal (water); 2) 30 ml olive oil (Faulding Healthcare Pty. Ltd., Rydalmere, Australia) 30 min before a mashed potato meal (oil); and 3) 30 ml water 30 min before a mashed potato meal that contained 30 ml olive oil (water and oil). Each meal consisted of 65 g powdered potato (Deb Instant Mashed Potato, Continental Brand Foods, Epping, Australia), reconstituted with 250 ml water and 20 g glucose and labeled with 20 MBq [^{99m}Tc]sulfur colloid (13). The energy content of the potato was 1263 kJ (total carbohydrate, 61 g), and the olive oil contained 1010 kJ (*i.e.* 27.3 g). Subjects consumed the meal between −5 and 0 min; 0 min was considered the time of meal completion. The olive oil or water was swallowed as one mouthful at −30 min. At 210 min, the iv cannula was removed, and the subject was allowed to leave the laboratory. On 1 of the 3 d, cardiovascular autonomic nerve function was evaluated after completion of the gastric emptying measurements (3).

Measurements

Gastric emptying and intragastric meal distribution. Radioisotopic data were acquired for 180 min (60-sec frames for the first 60 min and 3-min frames thereafter) (3). Data were corrected for subject movement, radionuclide decay, and γ-ray attenuation (29). Regions of interest were drawn around the total stomach, which was subsequently divided into proximal and distal regions, and gastric emptying curves (expressed as percent retention over time) were derived (3). The lag phase was defined visually as the time before any radioactivity had entered the proximal small intestine (29). The amount of the meal remaining in the total, proximal, and distal stomach at 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min was calculated, and the 50% emptying time (T50) was determined (29). For the water and oil and the water meals, the emptying rate for both the total meal (*i.e.* mashed potato and oil for water and oil, and mashed potato alone for water) and the carbohydrate component (*i.e.* only the mashed potato for water and oil) was also calculated as kilojoules on the basis of the T50.

Blood glucose, plasma insulin, GLP-1, and GIP concentrations. Venous blood samples (~15 ml) were obtained immediately before ingestion of the water or oil at −30 min, before the commencement of the meal at −7 min, and then at 15-min intervals after meal completion until 210 min. Blood glucose concentrations were determined immediately using a portable blood glucose meter (Medisense Companion 2 Meter, Medisense, Inc., Waltham, MA) (7). The peak blood glucose was defined as the greatest increment above baseline. Blood samples for plasma insulin, GIP, and GLP-1 were collected in ice-chilled EDTA-treated tubes containing 400 kIU aprotinin (Trasylol, Bayer Australia Ltd., Pymble, Australia)/ml blood. Peak insulin was defined as the greatest increment above baseline. For both blood glucose and plasma insulin, the rate of increase between −7 min and peak levels was also calculated. Plasma was stored at −70 C for subsequent analysis, and measurements were performed on blood samples obtained at −30, −7, 15, 30, 45, 60, 90, 120, 150, 180, and 210 min. Plasma insulin was measured by ELISA (Diagnostic Systems Laboratories, Inc., Webster, TX; sensitivity of the assay, 0.26 mU/liter; intraassay coefficient of variation, 2.6%; interassay coefficient of variation, 6.2%) (16). Total plasma GIP was measured by RIA; the minimum detectable limit was 2 pmol/liter, and both intra- and interassay coefficients of variation were 15% (16). Total plasma GLP-1 was measured by RIA; the minimum detectable limit was 1.5 pmol/liter, the intraassay coefficient of variation was 17%, and the interassay coefficient of variation was 18% (16).

Cardiovascular autonomic function

Autonomic nerve function was evaluated using standardized cardiovascular reflex tests (3). Parasympathetic function was evaluated by the variation (R-R interval) in the heart rate during deep breathing and the heart rate response to standing (30:15); sympathetic function was determined by the fall in systolic blood pressure in response to standing. Each test result was scored according to age-adjusted predefined criteria as: 0 = normal, 1 = borderline, and 2 = abnormal, for a total maximum score of 6. A score of 3 or higher indicated autonomic dysfunction (3).

Statistical analysis

Data were evaluated using mixed model, repeated measures, two-way ANOVA with *post hoc* comparisons in the event of a treatment × time interaction. Relationships between variables were assessed using linear regression analysis. All analyses were performed using StatView (version 5.0, Abacus Concepts, Inc., Berkeley, CA) and SuperANOVA (version 1.11, Abacus Concepts, Inc.). Data are shown as the mean ± SEM; $P < 0.05$ was considered significant in all analyses.

Results

All subjects tolerated the study well. The median score for autonomic nerve dysfunction was 1.7 (range, 0–4); one of the six subjects had definite autonomic dysfunction.

Gastric emptying

Total stomach. Gastric emptying commenced after a short lag phase; the latter was longer when oil was consumed before the

meal (water, 4.8 ± 2.5 min; oil, 11.2 ± 3.3 min; water and oil, 4.3 ± 2.2 min; $P = 0.007$). After the lag phase, emptying approximated a linear pattern for water and oil and a monoexponential pattern for oil and for water. There was a treatment × time effect ($P = 0.0001$) for gastric emptying on the 3 study days. Gastric emptying was slower between 15 and 180 min with oil than with water ($P < 0.0001$), between 15 and 165 min with oil when compared with water and oil ($P < 0.05$), and between 30 and 180 min with water and oil compared with water ($P < 0.01$). The T50 was longer for oil than either water ($P = 0.002$) or water and oil ($P = 0.02$; T50 water, 43.0 ± 2.4 min; oil, 107.3 ± 16.9 min; water and oil, 66.2 ± 9.9 min; Fig. 1A). Gastric emptying of both the oil and carbohydrate for water and for water and oil meals (expressed as kilojoules per min on the basis of the T50) was not different at 14.9 ± 0.9 and 18.9 ± 2.5 kJ/min (water *vs.* water and oil), respectively. In contrast, the rate of emptying of carbohydrate alone was less with water and oil (10.5 ± 1.4 kJ/min) than with water (14.9 ± 0.9 kJ/min; $P = 0.02$). In the one subject with autonomic neuropathy, gastric emptying of all three meals was within the range observed in the remainder of the group.

Intragastric distribution. There was a modest increase in meal retention in the proximal stomach between 0 and 150 min with oil compared with water ($P < 0.05$), between 0 and 60 min with oil compared with water and oil ($P < 0.01$), and at 0 and between 30 and 135 min after water compared with water and oil ($P < 0.05$; Fig. 1B). In contrast, there was a marked increase in meal retention in the distal stomach between 15 and 180 min with oil compared with water ($P < 0.05$) and between 0 and 180 min with oil compared with water and oil ($P < 0.05$). At 0 min and between 90 and 120 min, meal retention in the distal stomach was greater after water and oil than after water ($P \leq 0.05$; Fig. 1C).

Blood glucose and plasma insulin, GLP-1, and GIP concentrations

There was no significant difference in baseline (*i.e.* −30 min) blood glucose (6.7 ± 0.3 *vs.* 7.1 ± 0.4 *vs.* 7.4 ± 0.4 mmol/liter), plasma insulin (10.2 ± 1.8 *vs.* 10.0 ± 1.8 *vs.* 13.0 ± 0.7 mU/liter), plasma GIP (13.5 ± 3.5 *vs.* 11.2 ± 3.3 *vs.* 11.9 ± 2.1 pmol/liter), or plasma GLP-1 (9.2 ± 1.5 *vs.* 8.0 ± 1.5 *vs.* 7.1 ± 2.0 pmol/liter) between the 3 d (water *vs.* oil *vs.* water and oil, respectively). Similarly, there was no difference in blood levels at −7 min or any significant change between −30 and −7 min (data not shown).

There was a significant treatment × time effect ($P = 0.0001$) for blood glucose, and whereas there was a postprandial rise in blood glucose on all days ($P < 0.0001$), this was significant from 30 min after both water ($P = 0.0001$) and water and oil ($P = 0.04$) and was substantially later at 75 min ($P = 0.03$) after oil. Between 30 and 105 min, blood glucose concentrations were less ($P < 0.01$), and between 165 and 210 min, they were greater ($P < 0.01$), with oil compared with both water and water and oil. Blood glucose concentrations were less between 45 and 60 min ($P < 0.05$) and were greater at 150 min ($P < 0.05$) with water and oil compared with water. Although there was no significant difference in peak blood glucose concentrations (14.0 ± 0.9, 13.2 ± 0.7, and 12.8 ± 0.9 mmol/liter for water, oil, and water and oil, respectively; $P = 0.28$), peak blood glucose tended ($P = 0.07$) to be less with water and oil than with water. The time of peak blood glucose was much later for oil (140 ± 19 min) compared with water (75 ± 7 min; $P = 0.005$) and water and oil (98 ± 6 min; $P = 0.04$). The rate of increase in plasma blood glucose was different on the 3 d ($P = 0.001$) and was slower for oil ($P = 0.0005$) and water and oil ($P = 0.003$) compared with water (0.10 ± 0.0, 0.05 ± 0.0, and 0.06 ± 0.0 mmol/liter·min for water, oil, and water and oil, respectively). At 210 min, blood glucose was higher than at baseline (*i.e.* −30 min) with oil ($P = 0.03$), but not with water ($P = 0.38$) and water and oil ($P = 0.84$; Fig. 2A).

There was a prompt rise in plasma insulin on the 3 d ($P < 0.0001$). This was significant from 15 min after water ($P = 0.04$), 30 min after water and oil ($P = 0.001$), and 60 min after oil ($P = 0.05$). There was a significant treatment × time effect ($P = 0.0001$) for plasma insulin on the 3 d; between 30 and 120 min, plasma insulin was much lower with oil compared with water ($P = 0.05$) and water and oil ($P < 0.01$). In contrast, plasma insulin was greater ($P < 0.01$) between 180 and 210 min with oil compared with water and greater ($P = 0.003$) at 210 min with oil compared with water and oil. At 150 min, plasma insulin was less ($P = 0.05$) with water compared with water and oil. There was no difference in peak plasma insulin concentrations (72.0 ± 13.3, 69.1 ± 10.5, and 70.9 ± 10.6 mU/liter for water, oil, and water and oil, respectively; $P = 0.89$), but the time of peak plasma insulin was much later for

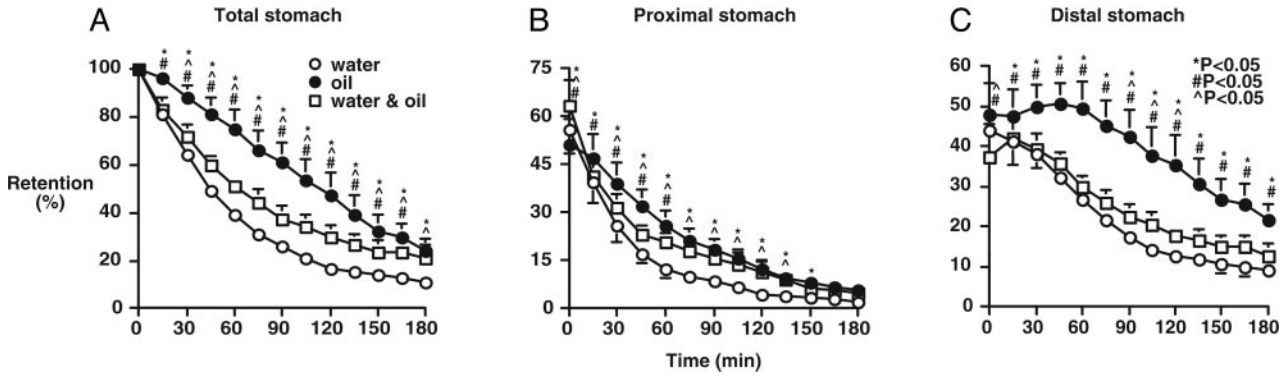

FIG. 1. Gastric emptying (A) and intragastric distribution [proximal stomach (B) and distal stomach (C)] of a mashed potato meal when 30 ml olive oil was consumed before the meal (oil), 30 ml water was consumed before the meal (water), or 30 ml water was consumed before a meal that also contained 30 ml olive oil (water and oil) in type 2 patients. Data are the mean ± SEM. *, $P < 0.05$, oil *vs.* water; #, $P < 0.05$, oil *vs.* water and oil; ^, $P < 0.05$, water *vs.* water and oil.

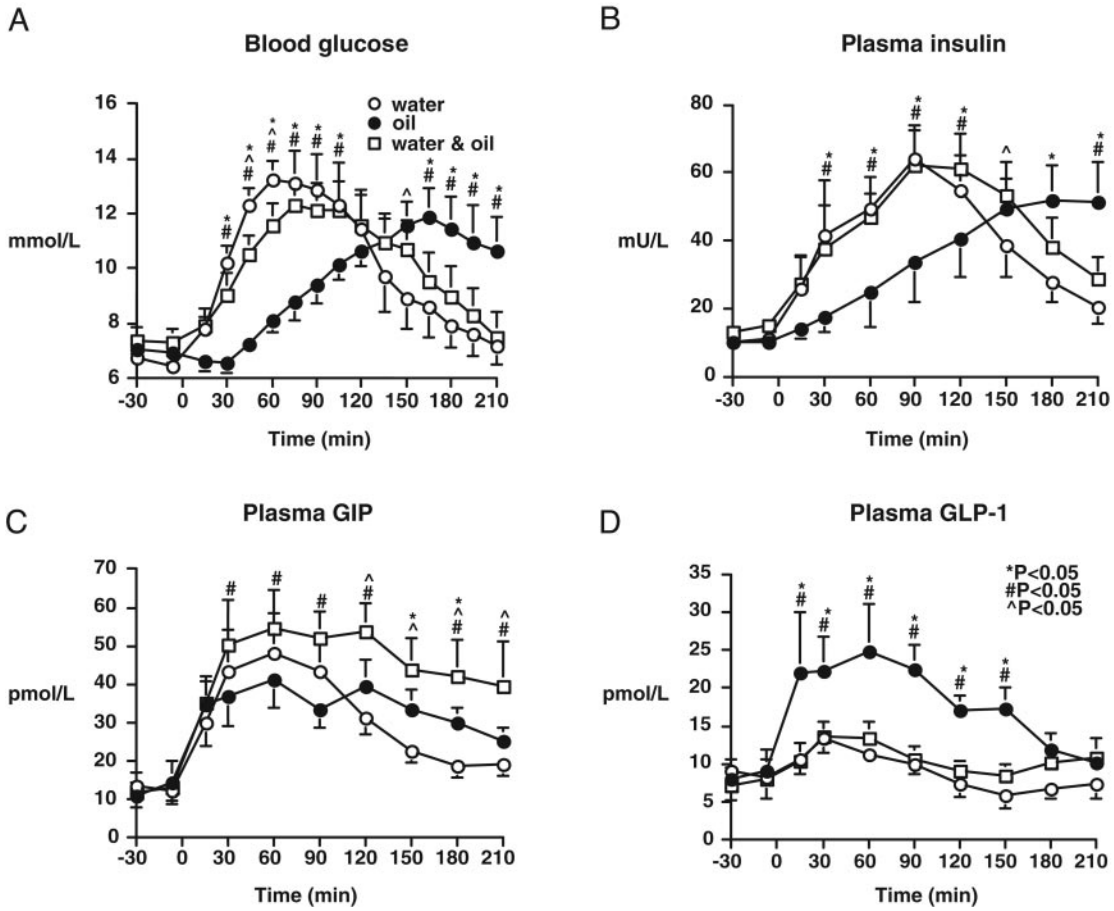

FIG. 2. Blood glucose concentrations (A), plasma insulin concentrations (B), plasma GIP concentrations (C), and plasma GLP-1 concentrations (D) after ingestion of a mashed potato meal when either 30 ml olive oil was consumed before the meal (oil), 30 ml water was consumed before the meal (water), or 30 ml water was consumed before a meal that also contained 30 ml olive oil (water and oil) in type 2 patients. Data are the mean ± SEM. *, $P < 0.05$, oil *vs.* water; #, $P < 0.05$, oil *vs.* water and oil; ^, $P < 0.05$, water *vs.* water and oil.

oil (160 ± 15 min) than for water (85 ± 14 min; $P = 0.0001$) and water and oil (90 ± 17 min; $P = 0.0002$). The rate of increase in plasma insulin was not significantly different for the 3 d (0.37 ± 0.1, 1.0 ± 0.5, and 0.88 ± 0.4 mU/liter·min for water, oil, and water and oil, respectively ($P = 0.19$). At 210 min, plasma insulin was markedly higher than baseline with oil ($P = 0.01$) and higher with water ($P = 0.02$), but not with water and oil ($P = 0.08$; Fig. 2B).

There was a prompt rise in plasma GIP on the 3 d ($P < 0.0001$), which was significant from 15 min, and a significant treatment × time effect ($P = 0.004$). Plasma GIP concentrations were less ($P < 0.05$) between 30 and 120 min and between 180 and 210 min with oil compared with water and oil. Between 150 and 180 min, plasma GIP was greater ($P < 0.05$) with oil compared with water. Plasma GIP was less ($P < 0.001$) between 120 and 210 min with water compared with water and oil. At 210 min, plasma GIP was higher than baseline ($P \leq 0.05$) after all three meals (Fig. 2C).

There was a rise in plasma GLP-1 on the 3 d ($P = 0.0002$), which was rapid after oil ($P = 0.0001$), *i.e.* significant from 15 min. There was a significant treatment × time effect ($P = 0.05$) for plasma GLP-1 on the 3 d, so that plasma GLP-1 was much greater between 15 and 150 min with oil compared with both water ($P < 0.05$) and water and oil ($P < 0.05$). There was no significant difference in plasma GLP-1 concentrations with water compared with water and oil. At 210 min, plasma GLP-1 concentrations were not significantly different from baseline after any of the meals (Fig. 2D).

Relationships between blood glucose, plasma insulin, GLP-1, and GIP concentrations and gastric emptying

When data from the 3 study days were pooled, the magnitude of the postprandial rise in blood glucose from baseline was inversely related to the T50 (*e.g.* at 60 min: $r = -0.80$; $P < 0.0001$; Fig. 3; at 90 min: $r = -0.71$; $P < 0.0009$). There were no significant relationships between gastric emptying and plasma insulin, GIP, or GLP-1.

Discussion

This study establishes that in type 2 diabetic patients managed by diet, ingestion of a relatively small amount of olive oil as a preload 30 min before a carbohydrate meal markedly slows gastric emptying; affects intragastric meal distribution; delays the postprandial rises in blood glucose, plasma insulin, and GIP; and stimulates the secretion of GLP-1. In contrast, the effects of including the same amount of oil in an identical carbohydrate meal on gastric emptying and on gly-

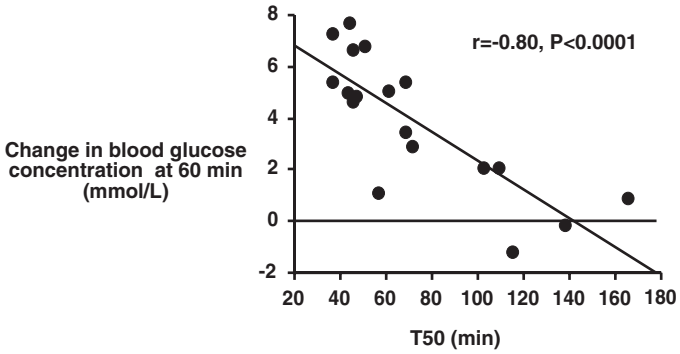

FIG. 3. Relationship between the change in blood glucose concentration from baseline at 60 min after all three meals (*i.e.* water, oil, and water and oil) and the gastric T50.

cemic and incretin responses were relatively modest. These observations are consistent with the concept, initially suggested by Cunningham and Read (12), that the effects of fat on gastric emptying and glycemia will be dependent on whether fat is given independently of carbohydrate or mixed with it, and have significant implications for dietary strategies to minimize postprandial glycemic excursions in type 2 and possibly type 1 diabetes.

The slowing of gastric emptying (10, 13, 25, 26), the stimulation of a number of gut hormones (including GLP-1, GIP, peptide YY, cholecystokinin, and pancreatic polypeptide) (23, 30), and the suppression of ghrelin (30) by fat are dependent on lipolysis of triglycerides to fatty acids. We reasoned that the magnitude of the slowing of gastric emptying was likely to be greater when oil was given before, rather than with, a carbohydrate-containing meal, given that it takes some time (~30–40 min) for small intestinal feedback mechanisms induced by fat to become established (19, 23, 30, 31) (probably reflecting the time required to generate sufficient fatty acids to induce these responses), and administration of oil before a meal ensures that it would empty from the stomach preferentially, so that both digested and nondigested fat would be in the small intestine when the remainder of the meal is consumed and the caudal spread of oil and lipolytic products facilitated. It would be expected that at the time of ingestion of the meal approximately 40% of the oil preload would have emptied from the stomach (28, 32). The slowing of gastric emptying by the oil preload was associated with changes in intragastric meal distribution, with increased retention in both the proximal and distal stomach. Intragastric meal distribution may influence gastrointestinal symptoms and appetite; in healthy subjects, the perception of fullness is greater, and energy intake less, when antral volume is relatively greater (33). The slowing of gastric emptying induced by incorporation of fat into the meal was much less marked and was attributable to the higher energy density, as attested to by the comparable emptying rates of the meals with and without oil, when expressed as kilojoules per minute. It is appropriate to note that when oil is consumed concurrently, but not mixed with, a meal consumed in the seated or erect posture, it layers on top of other meal components because of its lower density (28, 34) and would be expected to have little effect on gastric emptying of carbohydrate.

Because slowing gastric emptying of carbohydrate has a profound influence on postprandial glycemia (6, 8, 14), the incretin effect is an important determinant of the postprandial insulin response (17), and fat stimulates the secretion of GLP-1 and GIP (23, 24), we reasoned that a fat preload had the potential to attenuate the glycemic response to carbohydrate. When oil was given as a preload, there was a marked delay in the onset of the postprandial rise as well as the rate of increase in blood glucose and a trend for a reduction in the peak blood glucose level. In contrast to glucose, elevations in plasma insulin, GIP, and GLP-1 occurred promptly after the three meals, presumably reflecting the emptying of the meal and, in the case of the fat preload, the stimulation of incretin hormone secretion by the presence of fat in the small intestine (23). The secretion of GIP from duodenal K cells (17) reflects the rate of carbohydrate entry into the small intestine (35), which may account for the diminished GIP response after the fat preload, but not the statistically greater GIP response to the carbohydrate meal that contained fat, for which we have no ready explanation. Because the capacity of GIP to stimulate insulin secretion is diminished in type 2 diabetes (17), and the observed differences were modest, they are unlikely to be clinically relevant. In contrast, there was a rapid and marked rise in GLP-1 immediately after the carbohydrate meal following the fat preload, which probably reflects the interaction of lipolytic products with L cells in the distal jejunum and ileum (23), although this is controversial (24). The stimulation of GLP-1 may have contributed to the reduction in glycemia by both slowing gastric emptying and stimulating insulin secretion (17, 36). However, although we cannot quantify the relative effects of slowing of gastric emptying and the incretin effect on glycemia, it is likely that the latter is of lesser importance, particularly because the glycemic response and gastric emptying were related, and plasma insulin increased, when there was a rise in plasma glucose, but a fall in plasma GLP-1.

In interpreting our observations, it should be recognized that the number of subjects studied was relatively small, and only the acute effects of modifications in fat intake were evaluated. Adaptive changes in gastrointestinal function, including gastric emptying, may occur in response to changes in dietary fat (37, 38). The energy content of the oil preload was comparable to that of the meal, and it would be of interest to evaluate the effects of smaller triglyceride loads. We studied patients with uncomplicated type 2 diabetes of short duration; long-standing type 2 diabetes is associated with a high prevalence of gastroparesis (although the relationship to upper gastrointestinal symptoms is poor) (39) and impaired insulin secretion; the effects of fat on gastric emptying and glycemia in such patients warrant evaluation. Because blood glucose levels had not returned to baseline by 210 min, we could not determine the effect on the overall glycemic (or insulinemic) response, which represents a priority for future studies, despite evidence that this is reduced by small intestinal and oral fat in healthy subjects (12, 22). Regardless of these limitations, our observations establish the capacity for the administration of a relatively small quantity of fat before a carbohydrate-containing meal to minimize glycemic excursions and potentiate GLP-1 secretion in type 2 diabetes. It would not be surprising if the dominant effect of pharmacological therapies, including GLP-1 and its analogs as well as pramlintide, on postprandial glycemia, in type 2 diabetes is also mediated by the slowing of gastric emptying (36).

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Address all correspondence and requests for reprints to: Dr. Michael Horowitz, University of Adelaide, Department of Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia 5000, Australia. E-mail: michael.horowitz@adelaide.edu.au.

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