Orlistat Augments Postprandial Increases in Glucagon-like Peptide 1 in Obese Type 2 Diabetic Patients

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OBJECTIVE — Orlistat leads to improved glycemic control in obese type 2 diabetic patients, which is attributed to decreased insulin resistance associated with weight loss. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are gut hormones that are secreted in response to food intake, and they both stimulate insulin secretion. Orlistat decreases fat absorption and increases intestinal fat content, which may lead to increased secretion of these peptides. In this pilot study, we tested the hypothesis that increased levels of these intestinal hormones may be involved in the improvement of postprandial hyperglycemia observed previously with orlistat in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — A total of 29 type 2 diabetic patients, who were not taking insulin or α-glucosidase inhibitors, were enrolled in the study. On a crossover and single-blind design, after an overnight fasting, the patients received 120-mg orlistat or placebo capsules, followed by a standard 600-kcal mixed meal that contained 38% fat. At baseline and 60 min after the meal, blood samples were obtained for the measurement of GLP-1, GIP, insulin, C-peptide, triglycerides, free fatty acids, and glucose.

RESULTS — All measured parameters increased significantly in response to the mixed meal compared with baseline, both with orlistat or placebo. When compared with the placebo, the orlistat administration resulted in a significantly enhanced postprandial increase in GLP-1 and C-peptide levels and attenuated the postprandial rise in glucose and triglycerides.

CONCLUSIONS — The results of this study suggest that apart from decreasing insulin resistance as a result of weight loss, orlistat may increase postprandial GLP-1 levels, thereby enhancing the insulin secretory response to the meal and blunting the postprandial rise in glucose in type 2 diabetic patients. Increased GLP-1 levels, which lead to decreased food intake, may also contribute to the weight loss that is associated with the use of this drug.

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In normal humans, meal ingestion leads to secretion of gut hormones, which regulate gastric and intestinal motility, absorption of the nutrients, and energy storage (1). Among these gut hormones, the most important and well studied are the glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (gastric inhibitory peptide [GIP]). Both GLP-1 and GIP are potent stimulators of insulin secretion and promote expansion of pancreatic islet β-cell mass (1). GLP-1 also inhibits gastric emptying and glucagon secretion and suppresses appetite (1). In type 2 diabetes, basal and postprandial GIP levels are normal (2), but there seems to be a resistance to the action of GIP (3). On the other hand, in patients with type 2 diabetes or in individuals with impaired glucose tolerance, postprandial levels of GLP-1 were found to be lower than that of normal subjects (2,4). GLP-1 is secreted in two active forms, namely GLP-1 (7-36) amide and GLP-1 (7-37), which are equally potent in terms of stimulation of insulin secretion (5). Administration of GLP-1 or its agonists has been studied with considerable success in improving metabolic control in type 2 diabetic patients (6–8). GIP is predominantly released from the proximal small intestinal K-cells and GLP-1 from more distally located L-cells (1). Ingestion of a meal rich in fats and complex carbohydrates stimulates secretion of both GIP and GLP-1 (9,10). This, in turn, leads to increased insulin secretion, thus attenuating postprandial increases in blood glucose levels.

Orlistat, a gastrointestinal lipase inhibitor drug, has been used effectively and safely in the treatment of obesity (11). By inhibiting lipases, orlistat reduces the absorption of dietary fats by ~30% (12). In obese type 2 diabetic patients, orlistat treatment is associated with weight loss and improved glycemic control in the long term (13). In type 2 diabetic patients, orlistat also attenuates postprandial increases in triglycerides, remnant-like particles, cholesterol, and free fatty acids (14). The antihyperglycemic effect of orlistat has been attributed to weight loss–associated decrease in insulin resistance (13). However, clinical observations suggest that the improvement in postprandial glucose levels with orlistat is greater in magnitude than could be expected from the decrease in body weight. A hypothetical mechanism could be that orlistat enhances postprandial secretion of certain incretins, particularly GLP-1, due to increased delivery of fats to the distal ileum

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Abbreviations: GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1.

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

Table 1—*Fasting and 60-min postprandial values in mixed meal tests using placebo or orlistat*

	Placebo		Orlistat	
Parameter	Fasting	Postprandial	Fasting	Postprandial
Serum glucose (mmol/l)	6.2 ± 0.16	10.7 ± 0.4*	6.3 ± 0.19	9.57 ± 0.3*†
Serum triglycerides (mmol/l)	1.4 ± 0.08	1.78 ± 0.1*	1.46 ± 0.1	1.6 ± 0.1*†
Serum free fatty acids (mg/l)	57 ± 7	107 ± 8.8*	58 ± 8	104 ± 8*
Serum insulin (pmol/ml)	80.3 ± 9.3	423 ± 54.5*	81.7 ± 9.3	486 ± 46*
Serum C-peptide (pmol/ml)	1.7 ± 0.12	3.2 ± 0.19*	1.7 ± 0.1	4 ± 0.29*†
Plasma GIP (pmol/l)	1.6 ± 0.2	17.8 ± 1.4*	2.3 ± 0.41	16.1 ± 1.3*
Plasma GLP-1 (pmol/l)	2.4 ± 0.5	3.49 ± 0.5*	1.94 ± 0.3	4.8 ± 0.5*†

Data are means ± SE. $N = 29$. *Significant difference in fasting versus postprandial values; †significant difference with orlistat versus with placebo.

as a result of inhibition of lipase proximally. If so, such an action of orlistat could lead to suppressed appetite and decreased food intake, as well as improvement in meal-stimulated insulin release. We tested this hypothesis in a single-blind crossover study in a sample of obese type 2 diabetic subjects who took orlistat on a single occasion and placebo on another occasion before ingesting a standardized mixed meal. Our results indicate that stimulation of GLP-1 may indeed play a role in the improvement of postprandial glucose levels observed with orlistat in patients with diabetes.

RESEARCH DESIGN AND METHODS

— Twenty-nine type 2 diabetic patients, 24 women and 5 men, with a mean age of 54.9 ± 10.4 years (range 38–70), a diabetes duration of 2.8 ± 2.7 years, and an HbA_{1c} of 7.4 ± 0.9% were included in the study. All subjects were overweight or obese, with a mean BMI of 31.0 ± 4.1 kg/m^2 and waist circumference 106 ± 8.1 cm. Patients with previously documented diabetes complications or cardiovascular disease were excluded. Twelve patients were receiving diet-only therapy, 3 were receiving metformin, 4 were receiving sulfonylureas, and 10 were receiving combination therapy with metformin and a sulfonylurea. Insulin-treated patients were excluded so that the subjects would have relatively preserved β-cell function. Patients on an α-glucosidase inhibitor were also excluded to avoid potential interference with gastrointestinal function. The local ethics committee of Cerrahpasa Medical School approved the protocol; all subjects gave their written informed consent at the time of enrollment.

Each subject underwent two identical mixed meal tests during the morning hours at least 1 week apart. All drugs were withdrawn 24 h before each study, and the subjects fasted for at least 12 h overnight. Before each test, an antecubital vein was catheterized, and a baseline fasting blood sample (one plain tube and one tube containing EDTA) was obtained. Then, in random order, each subject took by mouth either a capsule containing 120 mg of orlistat (Xenical; F. Hoffmann, La Roche, Basel, Switzerland) or an identical-looking placebo capsule; the subject did not know the contents of the capsule. Right after swallowing the capsule, >15 min, the subject ate a breakfast meal comprising 600 kcal, 38% fat, 50% carbohydrates, and 12% proteins. A second blood sample was obtained 60 min after the commencement of the meal, at which time the test ended. Blood samples were kept on ice until the time of processing. The plain tubes were centrifuged at 4,000*g* for 10 min, and the serum was analyzed on the same day for glucose, triglycerides, free fatty acids, insulin, and C-peptide. EDTA tubes were centrifuged at 1,600*g* for 15 min, and the plasma was separated and stored at −70°C until the time of the assays for GLP-1 and GIP.

Glucose was measured using the hexokinase method (Olympus OSR6121; Tokyo, Japan), triglycerides with GPO-PAP method (Olympus OSR6133), and free fatty acids with ACS-ACOD (acyl-CoA synthetase–acyl-CoA oxidase) (NEFA C; Wako, Germany). Insulin and C-peptide levels were measured using specific radioimmunoassay methods (DSL-1600 insulin [Diagnostic Systems Laboratory, Webster, TX] and BIOSOURCE 3004000/KIP0409 [Nivelles, Belgium], respectively.) GLP-1 was measured in plasma using radioimmunoassay with GLP-1 (7-37) (human) kits (Phoenix Pharmaceuticals, Belmont, CA), which does not react with inactive forms of GLP-1: GLP-1 (1-36) amide, GLP-1 (1-37), GLP-1 (9-36), and GLP-1 (9-37). GIP was also measured in plasma using radioimmunoassay with GIP kits (Phoenix Pharmaceuticals).

Statistical analyses were performed using the software package SPSS for Windows 10.0 (Seattle, WA). Paired Student's *t* testing was used to determine the significance of the differences in the results obtained with the two meal tests; $P < 0.05$ was considered significant. The data are reported as mean ± SE.

RESULTS

— As shown in Table 1, baseline values for fasting serum levels of glucose, triglycerides, free fatty acids, insulin, and C-peptide, and plasma levels of GIP and GLP-1 were similar for the two meal tests ($P > 0.05$ for all).

As expected, 1 h after a mixed meal (postprandial), the levels of all measured parameters were significantly higher than the corresponding baseline (fasting) levels, both with orlistat and placebo (Table 1). Orlistat was well tolerated in all patients; no side effects were observed. The mean postprandial increase above basal level in serum glucose was lower with orlistat than with placebo (3.2 ± 0.2 and 4.56 ± 0.41 mmol/l, respectively; $P = 0.003$) The postprandial increment above the baseline in triglyceride levels was less with orlistat (0.14 ± 0.04 mmol/l) than with placebo (0.37 ± 0.04 mmol/l; $P = 0.002$). The increases in free fatty acids were similar (46 ± 7 mg/l with orlistat and 51 ± 7 mg/l with placebo; $P = 0.45$).

The increment in plasma insulin after orlistat was only modestly higher than that seen after placebo (404 ± 42.7 and 343 ± 52.8 pmol/ml, respectively) and did not achieve statistical significance ($P = 0.249$). On the other hand, the increases in C-peptide levels above baseline were significantly greater with orlistat (2.28 ± 0.25 pmol/ml) than with placebo (1.48 ± 0.16 pmol/ml; $P = 0.004$).

The meal-induced increases in plasma levels of GIP were similar (13.8 ± 1.24 pmol/l with orlistat and 16.24 ± 1.33 pmol/l with placebo; $P = 0.072$). On the other hand, the mean postprandial increase above baseline in plasma levels of GLP-1 was greater after orlistat than after placebo (2.85 ± 0.5 and 1.04 ± 0.34 pmol/l, respectively; $P = 0.011$).

CONCLUSIONS — The principal new knowledge provided by our study is that in overweight or obese patients with type 2 diabetes, a one-time administration of orlistat augments the postprandial increase in plasma levels of GLP-1. This augmentation of meal-associated rise in plasma levels of GLP-1 very likely represents a stimulatory effect of orlistat on the secretion of GLP-1 from the L-cells located in distal ileum. Because the systemic absorption of orlistat is minimal and the likelihood of bioactive amounts of orlistat reaching the distal small bowel is small, the augmentation of the presumed secretion of GLP-1 is likely to be an indirect effect of orlistat on the L-cells. As we hypothesized at the onset of this study, the amplification of the postprandial rise in GLP-1 is likely to be the result of increased delivery of triglycerides derived from ingested fat to the region of the intestine where the L-cells reside, as triglycerides are known secretagogues for GLP-1 (9,10). However, as we have not measured GLP-1 secretion directly in response to orlistat, other mechanisms that lead to increased plasma levels of this peptide such as inhibition of the enzyme, which degrades GLP-1, could also be operative.

Existing knowledge on the biological actions of GLP-1 makes it reasonable to consider a role for the augmented increases in GLP-1 levels in the attenuated increases in postprandial levels of glucose observed with orlistat in our type 2 diabetic subjects. Attenuation of postprandial hyperglycemia with orlistat has been observed previously (13). We propose that GLP-1–induced enhancement of insulin secretion participates in this beneficial action of orlistat. Indeed, the postprandial increase in C-peptide levels was higher with orlistat than with placebo. The failure to observe a significant enhancement in insulin levels with orlistat could be explained by the fact that, in this pilot study, only a single postprandial blood sample was obtained at the 60-min time point, which was not sufficient to capture the cumulative response in the levels of a hormone with rapid clearance, the plasma half-life of C-peptide being 30 min and that of insulin 5 min (15). Existing information is quite convincing that GLP-1 is a secretagogue of insulin (1).

Although not a focus of our study, orlistat-induced increases in GLP-1 levels could also lead to an appetite-suppressing effect of orlistat. Unlike GLP-1, the postprandial increase in GIP levels does not seem to be affected by orlistat. The proposed mechanism of increased triglyceride load in the distal small intestine for orlistat-associated increase in GLP-1 is not likely to be operative in the proximal small intestine where GIP-secreting K-cells reside (1).

As reported previously (14) and, as would be expected from its mechanism of action, in our study, orlistat attenuated the postprandial increases in serum triglyceride levels. Postprandial hypertriglyceridemia is frequently seen in patients with type 2 diabetes and has been found to be associated with increased risk of cardiovascular events (16,17). Thus, the triglyceride-lowering effect of orlistat, in combination with its effect to attenuate postprandial hyperglycemia represent added benefits to a weight-reduction regimen that includes orlistat in obese type 2 diabetic patients. One may have expected to observe an attenuation in the postprandial increase in free fatty acids with orlistat in our study. The failure to display this effect with statistical credibility is also likely to be due to the fact that there was only a single postprandial sampling of blood in this pilot study.

Our results, as well as those reported previously on the effects of orlistat, indicate that its use in the treatment of obesity in type 2 diabetic patients, in whom weight-reduction regimens involving lifestyle changes are not effective, may have added benefits, which now also include the release of GLP-1. Orlistat is not alone among drugs that may be used in the treatment of patients with type 2 diabetes in regard to evoking an augmentation of the increase in postprandial GLP-1 levels. Metformin has been reported to increase GLP-1 levels, and this effect was attributed to the inhibition of the enzyme dipeptidyl peptidase IV, which degrades GLP-1 (18,19). Miglitol was found to enhance the postprandial GLP-1 levels and blunt appetite sensations (20). On the other hand, acarbose did not appear to influence postprandial GLP-1 levels (21).

Even though the subjects in our study were obese patients with type 2 diabetes, one may reasonably speculate that orlistat would augment the postprandial increases in GLP-1 levels also in obese individuals without diabetes. Although in nondiabetic individuals the advantage of GLP-1 as an insulin secretagogue may not be meaningful, the appetite-suppressing effect of GLP-1 is definitely desirable.

In conclusion, augmentation of the postprandial increases in plasma levels of GLP-1 may now be considered a novel mechanism of action of orlistat, thus improving the understanding of some of its actions observed clinically. In obese patients with type 2 diabetes, augmentation of postprandial levels of the insulin secretagogue GLP-1 represents an important added benefit. The results of our pilot study need to be confirmed by monitoring in greater detail the postprandial metabolic and hormonal parameters in larger groups of subjects. Whether repetitive administration of orlistat over long periods of time will continue to provide the benefit of augmented postprandial increases in GLP-1 levels also remains to be established in appropriately designed clinical trials.

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