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Original article

Incretin effects, gastric emptying and insulin responses to low oral glucose loads in patients after gastric bypass and lean and obese controls

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Abstract

Background: After laparoscopic Roux-en-Y gastric bypass (LRYGB), many patients suffer from dumping syndrome. Oral glucose tolerance tests are usually carried out with 50–75 g of glucose. The aim of this study was to examine whether minimal glucose loads of 10 g and 25 g induce a reliable secretion of satiation peptides without dumping symptoms after LRYGB. In addition, lean and obese controls were examined.

Objective: The objective of this study was to determine the effects of low oral glucose loads on incretin release and gastric emptying.

Setting: All surgical procedures were performed by the same surgeon (RP) at the St. Claraspital Basel in Switzerland. Oral glucose challenges were carried out at the University Hospital of Basel (Phase 1 Research Unit).

Methods: Eight patients 10 ± .4 weeks after LRYGB (PostOP; body mass index [BMI]: 38.6 kg/m^2 ± 1.7) as well as 12 lean controls (LC; BMI: 21.8 kg/m^2 ± .6) and 12 obese controls (OC; BMI 38.7 kg/m^2 ± 1.3) received 10 g and 25 g of oral glucose. We examined clinical signs of dumping syndrome; plasma glucose, insulin, glucagon-like peptide 1, glucose-dependent insulinotropic peptide, and peptide tyrosine tyrosine concentrations; and gastric emptying with a ^{13}C-sodium acetate breath test.

Results: No signs of dumping were seen in PostOP. Compared with OC, LC showed lower fasting glucose, insulin, and C-peptide, and lower homeostasis model assessment (HOMA) and AUC-180 for insulin and C-peptide. In PostOP, fasting insulin, HOMA and AUC-180 for insulin was lower and no difference was found in fasting C-peptide or AUC-180 for C-peptide compared to OC. There was no significant difference in fasting glucose, insulin, C-peptide, HOMA and AUC-180 for insulin in PostOP compared to LC, but AUC-180 for C-peptide was higher in PostOP. AUC-60 for gut hormones was similar in OC and LC and higher in PostOP compared to OC or LC. gastric emptying was slower in LC and OC compared with PostOP.

Conclusion: After LRYGB, 25 g oral glucose is well tolerated and leads to reliable secretion of gut hormones. Fasting glucose, insulin and C-peptide are normalized, while glucagon-like peptide 1, glucose-dependent insulinotropic peptide and peptide tyrosine tyrosine are overcorrected. Pouch emptying is accelerated after LRYGB. (Surg Obes Relat Dis 2016;12:1320–1328.)

Keywords: Obesity; Bariatric surgery; Oral glucose tolerance test; Gastric emptying; Incretins

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After Roux-en-Y gastric bypass (RYGB), many patients suffer from early and/or late dumping syndrome as a reaction to carbohydrate-rich meals. *Early dumping* is

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caused by faster nutrition release to the intestine, which leads to osmotically-driven fluid shifts from the blood to the lumen and, thus, vasomotor symptoms. The marked increased secretion of gastrointestinal hormones, such as glucagon-like peptide 1 (GLP-1), after RYGB probably contributes to early dumping [1]. *Late dumping* occurs 1–3 hours after eating and is caused by hyperinsulinemia and is therefore characterized by symptoms of hypoglycemia-like weakness, sweating, and dizziness. But how much glucose is too much? A clear threshold above which symptoms of dumping syndrome are to be expected is missing in the literature. Oral glucose tolerance tests in non-operated patients are usually carried out with 75 g of glucose. For stimulation of incretin release with glucose, glucose loads of 50–75 g are most commonly used. From practical experience, we know that patients after gastric bypass do not always tolerate glucose loads commonly used in an oral glucose tolerance test (OGTT). To study incretin and gut hormone release—for example, GLP-1—a minimal delivery of 2 kcal/min solution into the intestine is needed. However, as gastric emptying (or rather pouch emptying) is accelerated after RYGB, we hypothesized that less glucose is necessary to reach this threshold of 2 kcal/min.

The aim of this study was therefore to examine whether minimal glucose loads of 10 g and 25 g induce a reliable secretion of incretin and satiation peptides without dumping symptoms in patients after gastric bypass.

Materials and Methods

The protocol was approved by the Ethics Committee of Basel, Switzerland (EKBB: 272/05) and conducted in accordance with the principles of the Declaration of Helsinki. All patients gave written informed consent. The trial is registered in the clinical trials registry of the National Institutes of Health (NCT01851616) and was funded by the Swiss National Science Foundation (grant no. 138 157).

Between December 2012 and February 2013, 8 morbidly obese, female patients (mean body mass index [BMI]: 38.6 ± 1.7 kg/m^2, range = 32.5–46.9 kg/m^2; mean age: 35.8 ± 1.7 years, range = 23–47 years) were recruited 10 ± .4 weeks after laparoscopic bypass surgery. Exclusion criteria were: age >50 years, diabetes, smoking, substance abuse, regular intake of prokinetic drugs and a history of gastrointestinal surgery other than laparoscopic Roux-en-Y gastric bypass (LRYGB). Mean excessive BMI lost at the first visit in relation to preoperative BMI was 25.9 ± 3.6% (range = 19.0–24.6%).

Twelve lean, healthy volunteers (mean BMI: 21.8 ± .6 kg/m^2, range = 19.0–24.6 kg/m^2; 6 female and 6 male, mean age: 24.7 ± .9 years, range = 20–32 years) and 12 obese volunteers (mean BMI: 38.7 ± 1.3 kg/m^2, range = 30.5–47.8 kg/m^2; 6 female and 6 male, mean age: 28.8 years ± 2.6, range = 19–47) were recruited by word of mouth. Exclusion criteria were the same as in postoperative patients. In addition, BMI between 18 and 25 kg/m^2, respectively >30 kg/m^2, was required.

All patients were seen on 2 occasions, with an interval of 1–2 weeks. After an overnight fast, patients were admitted to our Phase 1 Research Unit at 8.30 h. Baseline heart rate and blood pressure were measured and a peripheral venous catheter was placed. After taking fasting breath and blood samples, each subject received a cup with 10 g or 25 g of glucose in 200 mL tap water and 50 mg ^{13}C-sodium acetate (for determination of gastric emptying rates). The treatment order was randomized within a subject. Patients were asked to drink the solution within 5 minutes. Throughout the test, patients remained in a sitting position in a comfortable chair. Breath samples for determination of gastric emptying rate were collected in foil bags at –1, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210 and 240 minutes. Blood samples for measurement of plasma glucose, insulin, GLP-1, and glucose-dependent insulinotropic peptide (GIP) were taken at –10, –1, 15, 30, 45, 60, 90, 120 and 180 minutes.

In all patients, gastric emptying rates were assessed using the ^{13}C-sodium acetate breath test. This test is an accurate, noninvasive, simple method without radiation exposure and represents a reliable alternative to scintigraphy, the gold standard for measuring gastric emptying [2,3]. The test solution is labeled with 50 mg ^{13}C-sodium acetate; the substrate is rapidly absorbed in the proximal small intestine, metabolized in the liver with the production of $^{13}CO_2$, which is exhaled rapidly, thus, reflecting gastric emptying of nutrients in patients with intact anatomy of the gastrointestinal tract [2,3]. Patients were asked to exhale through a mouthpiece to collect an end-expiratory breath sample into a 100 mL foil bag at certain time intervals. The $^{13}CO_2$ breath content was determined by nondispersive infrared spectroscopy using an isotope ratio mass spectrophotometer (Wagner Analysen Technik, Bremen, Germany). ^{13}C-abundance in breath is expressed as relative difference (δ ‰) from the universal reference standard (carbon from Pee Dee Belemnite limestone). ^{13}C-enrichment is defined as the difference between preprandial ^{13}C-abundance in breath and ^{13}C-abundance at the defined postprandial time points and is given in δ over basal.

Delta values were converted into atom percent excess and then into percent of administered dose of ^{13}C excreted per hour (%dose/h (%)). In this last conversion, the CO_2 production of the subjects was used, which is assumed to be 300 mmol/h multiplied by the body surface area. The body surface area was calculated by the weight-height formula of Haycock et al [4]. Whole blood and plasma glucose concentrations were measured by a commercially-available glucose oxidase method (Bayer Consumer Care AG, Basel, Switzerland). The lowest level of glucose that can be detected by this assay is .6 mmol/L. Insulin was measured with a commercially-available enzyme-linked immunosorbent assay kit (Abnova, Taipei City). The intra- and interassay coefficients of variation are below 8.1% and 8.5%. Gut