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Surgery for Obesity and Related Diseases 10 (2014) 1–8

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Changes in post-prandial glucose and pancreatic hormones, and steady-state insulin and free fatty acids after gastric bypass surgery

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Received March 9, 2013; accepted July 15, 2013

Abstract

Background: Changes in the multiple mechanisms that regulate glucose metabolism after gastric bypass (RYGB) are still being unveiled. The objective of this study was to compare the changes of glucose and pancreatic hormones [C-peptide, glucagon, and pancreatic polypeptide (PP)] during a meal tolerance test (MTT) and steady-state insulin and free fatty acid (FFA) concentrations during euglycemic–hyperinsulinemic clamp 14 days and 6 months after RYGB in morbidly obese nondiabetic patients.

Methods: Two groups were studied at baseline and at 14 days: the RYGB followed by caloric restriction group (RYGB, n = 12) and the equivalent caloric restriction alone group (Diet, n = 10), to control for energy intake and weight loss. The RYGB group was studied again at 6 months to assess the changes after substantial weight loss. During MTT, the early and overall changes in glucose and pancreatic hormone concentrations were determined, and during the clamp, steady-state insulin and FFA concentrations were assessed.

Results: After 14 days, RYGB patients had enhanced postprandial glucose, C-peptide, and glucagon responses, and decreased postprandial PP concentrations. Steady-state insulin concentrations were decreased at 14 days only in RYGB patients, and FFA increased in both groups. Six months after RYGB and substantial weight loss, the decrease in insulin concentrations during clamp persisted, and there were further changes in postprandial glucose and glucagon responses. FFA concentrations during clamp were significantly lower at 6 months, relative to presurgical values.

Conclusions: In morbidly obese nondiabetic patients, RYGB produces early changes in postmeal glucose, C-peptide, glucagon, and PP responses, and it appears to enhance insulin clearance early after RYGB and improve insulin sensitivity in adipose tissue at 6 months postsurgery. The early changes cannot be explained by caloric restriction alone. (Surg Obes Relat Dis 2014;10:1–8.)

Keywords: Gastric bypass; Gut hormones; Incretins; Insulin resistance; Free fatty acids; Insulin clearance; Hyperinsulinemic euglycemic clamp; Bariatric surgery; C-peptide; Glucagon; Glucose; Type 2 diabetes

Roux-en-Y gastric bypass (RYGB) is the most common bariatric surgical procedure used to treat morbid obesity [1] and promotes changes in the regulation of glucose metabolism [2]. In addition to improving glucose homeostasis as a

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1550-7289/14/$ – see front matter
http://dx.doi.org/10.1016/j.soard.2013.07.010

consequence of the robust weight loss that occurs with this procedure, other factors that are likely to contribute to the effects of RYGB on insulin secretion and action include the magnitude of caloric restriction, reduction in adipose tissue mass, altered gastrointestinal and pancreatic hormone responses such as changes in insulin, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), as well as changes in beta cell function, hepatic glucose metabolism and bile acids, among others [2–4]. Although previous studies have reported differences in many of these parameters after RYGB, most of these studies are cross-sectional, and few have controlled for reduced energy intake. In addition, few studies have studied the effects of surgery on postprandial glucose kinetics [5,6], glucagon [7] and pancreatic polypeptide (PP) responses [8], and insulin sensitivity of adipose tissue [9] as assessed by insulin-mediated suppression of free fatty acids (FFA). Lastly, the potential for changes of hepatic insulin clearance after RYGB has not been investigated.

The present study is a follow-up from previously published study design, patients, and other metabolic data [10], with additional analysis of the effects of RYGB on glucose, C-peptide, glucagon, and PP responses during a meal tolerance test (MTT), and steady state circulating insulin and FFA concentrations during a euglycemic–hyperinsulinemic clamp. Metabolic studies were done before and 14 days after RYGB followed by caloric restriction or equivalent caloric restriction alone, as well as 6 months after RYGB.

Methods

Morbidly obese nondiabetic patients, selected to undergo RYGB, were recruited at the University of California San Francisco's (UCSF) Bariatric Surgery Program. They met the National Institutes of Health and UCSF Bariatric Surgery Program eligibility criteria for bariatric surgery as described previously [10]. Exclusion criteria included previous weight loss, foregut and/or hindgut surgery, and diagnosis of endocrine or chronic renal disease. This project was approved by the UCSF Committee on Human Research and San Francisco General Hospital Clinical Research Center (CRC) Advisory Committee. Written consent was obtained from each participant.

Group allocation and metabolic evaluation

The 2 groups were studied at baseline and at 14 days: the RYGB followed by caloric restriction group (RYGB, n = 12) and the equivalent caloric restriction alone group (Diet, n = 10), to control for reduced energy intake and weight loss. As previously reported [10], the 2 study groups did not differ with respect to baseline demographic characteristics (female/male ratio: 9:3 RYGB, 6:4 Diet, $P = .65$; age in years 47.4 ± 8.7 RYGB, 40.2 ± 13.4 Diet, $P = .16$) and body composition (weight [kg]: 138.0 ± 21.6 RYGB, 134.7 ± 16.9 Diet, $P = .70$; BMI [kg/m^2]: 48.4 ± 6.8 RYGB, 48.3 ± 6.6 Diet, $P = .99$; percentage excess weight: 55.4 ± 6.4 RYGB, 55.3 ± 6.8 Diet, $P = .96$). Participants in both groups were markedly insulin resistant at baseline. The RYGB group was studied again at 6 months to assess the longer term changes after more substantial weight loss had occurred.

All participants underwent the same baseline metabolic evaluation (visit 1, [V1]) [10].

Meal tolerance test

On day 1, participants underwent a mixed meal tolerance test (MTT), in which they ingested a standardized 282 kcal, 100 mL liquid meal containing 50% carbohydrate, 20% protein, and 30% fat with 9.9 g of simple sugars. Participants consumed this meal within a maximum of 20 minutes. Venous blood samples were drawn at 0, +5, +15, +30, +60, +120, and +180 minutes relative to the end of the meal. The samples were processed on site and stored at −70°C for subsequent batch analysis of glucose, C-peptide, glucagon, and PP.

Euglycemic–hyperinsulinemic clamp

On day 2, after an overnight fast, whole-body insulin sensitivity and insulin and FFA concentrations were measured during the steady state interval (60–120 minutes) of a euglycemic-hyperinsulinemic clamp as described previously [10,11]. Insulin (Humulin R, Eli Lilly, Indianapolis, IN), bound to albumin, was administered intravenously at a rate of 40 mU/m^2/min for 120 minutes. Blood was drawn by intravenous catheter in a heated vein, and whole-blood glucose concentrations were measured in real time at 5-minute intervals (YSI STAT 2300 glucose analyzer, Yellow Springs, OH). Infusion of 20% dextrose was adjusted to maintain a whole-blood glucose level of 90 mg/dL.

Surgery

The participants assigned to immediate surgery were discharged from the CRC and admitted for surgery the next day. The RYGB was performed in a standardized fashion by one author (G.C.) as previously described [10]. In brief, RYGB was performed laparoscopically, a 30-mL gastric pouch created and connected to an alimentary limb of 100 cm and a biliopancreatic limb of 50 cm.

Participants were then followed as outpatients for 14 days, during which they consumed a standardized low calorie diet: Optifast HP (Novartis Nutrition Corporation), which provides 800 kcal/d (25% carbohydrate, 48% protein, and 27% fat).

Follow-up in patients undergoing diet alone

After completing the baseline evaluation and discharge from the CRC, participants assigned to the Diet group