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Original article

Long-term effects of Roux-en-Y gastric bypass on postprandial plasma lipid and bile acids kinetics in female non diabetic subjects: A cross-sectional pilot study

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SUMMARY

Background and aims: Formerly obese patients having undergone Roux-en-Y gastric bypass (RYGB) display both an accelerated digestion and absorption of carbohydrate and an increased plasma glucose clearance rate after meal ingestion. How RYGB effects postprandial kinetics of dietary lipids has yet not been investigated.

Methods: Plasma triglyceride (TG), apoB48, total apoB, bile acids (BA), fibroblast growth factor 19 (FGF19), and cholecystokinin (CCK) were measured in post-absorptive conditions and over 4-h following the ingestion of a mixed test meal in a cross-sectional, pilot study involving 11 formerly obese female patients 33.8 ± 16.4 months after RYGB surgery and in 11 weight- and age-matched female control participants.

Results: Compared to controls, RYGB patients had faster (254 ± 14 vs. 327 ± 7 min, $p < 0.05$) and lower (0.14 ± 0.04 vs. 0.35 ± 0.07 mM, $p < 0.05$) peak TG responses, but their peak apoB48 responses tended to be higher (2692 ± 336 vs. 1841 ± 228 ng/ml, $p = 0.09$). Their postprandial total BA concentrations were significantly increased and peaked earlier after meal ingestion than in controls. Their FGF19 and CCK concentrations also peaked earlier and to a higher value.

Conclusions: The early postprandial apoB48 and BA responses indicate that RYGB accelerated the rate of dietary lipid absorption. The lower postprandial peak TG strongly suggests that the RYGB simultaneously increased the clearance of TG-rich lipoproteins.

Clinical trial registration: NCT01891591.

1. Introduction

Roux-en-Y Gastric Bypass (RYGB) is a widely used procedure for the surgical treatment of severe obesity. In Switzerland, where obesity prevalence rate is about 9% (http://www.oecd.org/health/obesity-update.htm, released 27 May 2014), it was recently estimated that about 2566 bariatric surgery procedures (0.03% of the Swiss population) were performed yearly, of which 1991 RYGB procedures [1].RYGP results in a rapid improvement of blood glucose control and insulin resistance in obese patients with type 2 diabetes mellitus. This may be due to the rapid delivery of ingested carbohydrates to distal portions of the small intestine and the colon, which is associated with an enhanced secretion of GLP-1, a potentiation of insulin secretion, and an increase in glucose metabolic clearance [2,3]. Beside improving glucose homeostasis, RYGB is also associated with an improved plasma lipid profile in

Abbreviations: RYGB, Roux-en-Y-gastric bypass; TG, triglycerides; ApoB, apolipoprotein B; VLDL, very low density lipoprotein; C4, 7-alpha hydroxy 4-cholesten-3 one; BA, bile acids.

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dyslipidemic obese patients [4,5]. We hypothesized that RYGP also resulted in an accelerated delivery of lipids to distal small intestine, and that the enhanced fat absorption triggered an increased metabolic clearance of plasma triglycerides (TG). Consistent with an accelerated postprandial lipid metabolism, several studies have reported increased postprandial bile acids (BA) and of fibroblast growth factor 19 (FGF19) concentrations after gastric bypass [6,7].

In order to gain further insights into the effects of RYGB on postprandial lipid and BA metabolism, we carried out a cross-sectional pilot study in formerly obese women who had undergone RYGB 33.8 ± 16.4 months earlier, and in weight- and age-matched non-operated women. We monitored their total plasma TG, total apoprotein B (apoBtot), and apolipoprotein B48 (apoB48) concentrations after an overnight fast and over 4 h after ingestion of a mixed test meal. Plasma concentration of 7alpha-hydroxy-4-cholesten-3-one (C4) was measured as a marker of BA synthesis [8]. Plasma cholecystokinin (CCK) and FGF19 concentrations were also measured since these two gut-related peptides are key regulators of bile synthesis, secretion and storage [9].

2. Methods

2.1. Subjects

Eleven formerly obese, weight-stable non-diabetic female patients having had RYGB for the treatment of their obesity 33.8 ± 16.4 months earlier (mean age: 35.1 ± 1.4y, BMI: 28.3 ± 1.4 kg/m^2, fat mass: 34.9 ± 2.2%) were included in the study. Their pre-surgery BMI had been 44.3 ± 1.2 kg/m^2, and their mean weight loss since surgery was 43.1 ± 1.9 kg, corresponding to 36.5 ± 1.9% of their initial weight. Eleven non-operated weight- and age-matched women (mean age: 33.4 ± 1.4y, BMI: 28.4 ± 1.3 kg/m^2, fat mass: 34.4 ± 2.7%) were included as controls. The primary endpoint of the study was the investigation of EEG responses elicited by the sight of food items varying in energy density (to be reported elsewhere). The study was registered under NCT01891591 in the clinicaltrial.gov database.

2.2. Surgical procedure

The surgical procedure has been described in detail elsewhere [10]. Briefly, the stomach was divided just below the cardia to form a proximal gastric pouch of approximately 10–15 mL while preserving the integrity of the vagus nerve. The jejunum was then divided between 30 and 50 cm from the angle of Treitz. The Roux limb was brought close to the gastric pouch in a retrocolic and retrogastric fashion. The anastomosis between the gastric pouch and the Roux limb was performed with a 21-mm circular stapler, and the jejuno-jejunostomy was performed side-to-side with a linear stapler. The proximal end of the Roux limb was staple-closed with the same instrument. The length of the Roux-en-Y limb was determined according to the patient's BMI: 100 cm up to a BMI of 48 and 150 cm with a BMI greater than 48. Cholecystectomy was performed in eight out of the eleven participants to prevent the development of gallstones during rapid weight loss.

2.3. Study design and protocol

The study was designed as an unblinded, cross-sectional case-control study. Each participant was studied at one single occasion after an overnight fast and over 4 h following ingestion of a standardized breakfast containing 25% of daily energy requirements (calculated as Basal energy expenditure according to Harris and Benedikt equation time a physical activity factor of 1.5), and composed of 50% carbohydrate, 35% fat lipids, and 15% proteins.

Plasma glucose, triglycerides (TG), nonesterified fatty acids (NEFAs), total cholesterol and HDL-cholesterol concentrations were measured by enzymatic methods (Randox Laboratory Ltd, Cumlin, U.K). Plasma insulin, GLP-1, (Millipore, Billerica, MA), fibroblast growth factor 19 (FGF19; R&D Systems Europe Ltd, Abingdon, UK) and cholecystokinin (CCK; Euro-Diagnostica, Malmö, Sweden) were assessed by radioimmunoassays. ApoBtot concentrations were measured by ELISA, using a kit from R&D Systems Europe Ltd, Abingdon, UK, and apoB48 concentrations (ApoB48) were measured using a kit from Shibayagi, Shibukawa, Japan. Total plasma BA concentrations were measured with an enzyme-linked immunosorbent assay kit (Randox Laboratories, Crumlin, United Kingdom). Individual BA and 7-alpha hydroxy 4-cholesten-3 one (C4) concentrations were measured by gas chromatography–mass spectroscopy (GC–MS) [11,12].

2.4. Statistical analyses

All statistical analyses were performed by using STATA version 10 (Stata Corp, College Station, TX, USA)). Data are presented as means ± SEM. Global comparisons of concentrations of each measured hormone and substrate were done by two-way ANOVAs, with time as within-subject variable and participant group (RYGB patients vs. controls) as between-subject factor. The mean peak response of each metabolic variable was obtained by averaging the maximal individual concentrations observed after meal ingestion minus Basal, pre-meal concentrations. The mean peak time for each variable was calculated by averaging the individual times corresponding to peak values. For each metabolic variable, between-group differences in fasting values, peak responses, and peak times were assessed by two-tailed unpaired *t*-tests. Differences were considered significant when p was ≤ 0.05.

3. Results

3.1. Fasting metabolic variables

Fasting plasma glucose and NEFA were not different in RYGB patients and controls (Figs. 1 and 2), but fasting plasma insulin (RYGB: 10.6 ± 0.4 mU/L vs. controls: 14.8 ± 1.4 mU/L $p < 0.01$) and TG (RYGB: 0.85 ± 0.05 mM vs. controls: 1.18 ± 0.07 mM, $p < 0.01$) concentrations were significantly lower (Figs. 1 and 2), and insulin sensitivity estimated from HOMA-IR index was higher in RYGB (3.3 ± 1.1) compared to controls (2.3 ± 0.3, $p < 0.01$). Fasting CCK concentrations (RYGB: 0.4 ± 0.0 pM vs. controls: 0.5 ± 0.0 pM, $p = 0.01$) were significant lower in RYGB patients compared to matched subjects ($p < 0.01$, and $p < 0.05$ respectively), while fasting GIP and GLP-1 (Fig. 1) concentrations showed no significant differences.

Fasting concentrations of BA and FGF19 (Fig. 3) were significantly increased in RYGB. Fasting total cholesterol (RYGB: 3.8 ± 0.4 mM vs. controls: 5.2 ± 0.5 mM, $p < 0.01$) and LDL-cholesterol (RYGB: 2.5 ± 0.5 mM vs. controls: 3.9 ± 0.6 mM, $p < 0.01$) were significantly lower in RYGB group; HDL-cholesterol (RYGB: 1.1 ± 0.2 mM vs. controls: 1.0 ± 0.2 mM, $p = 0.09$), ApoB48, and C4 (Fig. 2) concentrations were not significantly different in the two groups.

3.2. Postprandial metabolism

Compared to controls, ingestion of the test meal elicited higher peak responses for glucose, insulin, GLP1, GIP, CCK, and FGF19 (Figs. 1 and 3 and Table 1) in RYGB patients. Peak responses were also increased for total, secondary, and conjugated BA, but not for free BA (Fig. 2, Tables 1 and 2). The ratios of cholic