The Importance of Caloric Restriction in the Early Improvements in Insulin Sensitivity After Roux-en-Y Gastric Bypass Surgery

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OBJECTIVE — Many of the metabolic benefits of Roux-en-Y gastric bypass (RYGB) occur before weight loss. In this study we investigated the influence of caloric restriction on the improvements in the metabolic responses that occur within the 1st week after RYGB.

RESEARCH METHODS AND DESIGN — A mixed meal was administered to nine subjects before and after RYGB (average 4 ± 0.5 days) and to nine matched, obese subjects before and after 4 days of the post-RYGB diet.

RESULTS — Weight loss in both groups was minimal; the RYGB subjects lost 1.4 ± 5.3 kg ($P = 0.46$) vs. 2.2 ± 1.0 kg ($P = 0.004$) in the calorically restricted group. Insulin resistance (homeostasis model assessment of insulin resistance) improved with both RYGB (5.0 ± 3.1 to 3.3 ± 2.1; $P = 0.03$) and caloric restriction (4.8 ± 4.1 to 3.6 ± 4.1; $P = 0.004$). The insulin response to a mixed meal was blunted in both the RYGB and caloric restriction groups (113 ± 67 to 65 ± 33 and 85 ± 59 to 65 ± 56 nmol · l^{-1} · min^{-1}, respectively; $P < 0.05$) without a change in the glucose response. Glucagon-like peptide 1 levels increased (9.2 ± 8.6 to 12.2 ± 5.5 pg · l^{-1} · min^{-1}; $P = 0.04$) and peaked higher (45.2 ± 37.3 to 84.8 ± 33.0 pg/ml; $P = 0.01$) in response to a mixed meal after RYGB, but incretin responses were not altered after caloric restriction.

CONCLUSIONS — These data suggest that an improvement in insulin resistance in the 1st week after RYGB is primarily due to caloric restriction, and the enhanced incretin response after RYGB does not improve postprandial glucose homeostasis during this time.

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Bariatric surgical procedures achieve a large and sustained improvement in insulin sensitivity and a high resolution rate in type 2 diabetes. The metabolic benefits of Roux-en-Y gastric bypass surgery (RYGB) are observed very early and precede substantial weight loss (1). It has been proposed that the long-term improvements are related to a reduction in fat mass (2); however, the mechanisms for the early improvements remain uncertain. The surgical bypass of the foregut and/or rapid nutrient exposure of the distal gut alters enterokine release, which has been proposed to result in metabolic improvements (3) and in particular glucose homeostasis. However, caloric restriction in the absence of weight loss has metabolic benefits (4) and could also contribute to the early improvements in glucose homeostasis.

The incretins, namely glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), are gut hormones that contribute to postprandial insulin secretion (5). RYGB augments GLP-1 secretion, whereas its impact on GIP is less consistent (3). In contrast, bariatric procedures that induce weight loss by caloric restriction in the absence of intestinal bypass, such as adjustable gastric banding, do not alter postprandial incretin levels (3). Ghrelin is another enterokine that has a primary role in appetite stimulation but also has glucose and insulin modulatory effects (6). The presence of an acyl group is considered necessary for biological activity of ghrelin, although the desacyl form probably has biological functions as well (7). Ghrelin levels are abnormally low in obese individuals and remain suppressed after RYGB, whereas weight loss by diet enhances ghrelin levels (8). Leptin and adiponectin, adipocyte-derived hormones, are thought to be mediators of weight-related improvements in insulin resistance. The concentrations of these hormones are aberrant in obesity and normalize after RYGB. A recent study indicated that >5% weight loss by consumption of a hypocaloric diet (~40% energy restriction) is required to favorably change circulating adipokines and metabolic parameters (9).

A limited number of reports have directly compared the contribution of duodenal bypass versus caloric restriction on enterokine responses and hormone levels after RYGB (10–12). These studies all incorporated moderate weight loss (~10 kg) and were conducted 2–4 weeks postoperatively. In the present study, we compared the immediate, weight loss–independent effects of RYGB and caloric restriction on fasting hormone levels and meal-stimulated enterokine release. RYGB were evaluated within the 1st week after surgery, and a matched group of subjects were evaluated after 4 days of the equivalent post–bariatric surgery diet.

RESEARCH DESIGN AND METHODS

— RYBG subjects were recruited from the Center for Surgical Weight Loss at Vanderbilt University Medical Center after approval for surgery. Diet control were matched to the surgery group (Table 1) for age ($P = 0.37$), weight ($P = 0.09$), diabetes status and duration ($P = 0.80$), and A1C ($P = 0.56$). All subjects provided written, informed

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Table 1—*Baseline subject characteristics*

	RYGB	Diet
n	9	9
Age (years)	41.1 ± 11.5	46.6 ± 6.7
Sex (male/female)	3/6	2/7
Weight (kg)	153.2 ± 32.2	127.0 ± 36.5
Type 2 diabetes (yes/no)	5/4	4/5
Diabetes duration (years)	3.7 ± 4.7	2.6 ± 1.5
A1C (%)	6.5 ± 1.3	6.2 ± 1.0

Data are means ± SD or count. All comparisons between groups were nonsignificant ($P > 0.05$).

consent to participate in the study. The study protocol was approved by the Vanderbilt University Institutional Review Board.

Subjects were studied at baseline and then after RYGB (surgery group) or after caloric restriction (diet group). After the baseline study, subjects in the surgery group underwent either open or laparoscopic RYGB (13). The average time for the postoperative study was 4 ± 0.5 days (range 2–7 days). The diet group was studied after 4 days of caloric restriction that replicated the post-RYGB diet. The diet consisted of 2.5 liters of fluid/day for 3 days; the 1st day included water only, followed by water and sugar-free clear liquids (e.g., gelatin, juices, and/or broths equivalent to 200–300 kcal/day) on days 2 and 3. For each study visit, subjects were admitted after a 12-h overnight fast for measurement of fasting and meal-induced metabolic and hormonal responses. Blood samples were collected from a heated forearm vein at 0700 h (time 0), immediately after completion of a meal (time 20), and every subsequent hour for 4 h. Subjects were asked to take 15–20 min to complete the meal to account for the reduced stomach capacity after RYGB. The meal was a standardized 250-kcal liquid mixed-meal containing 40 g carbohydrates, 6 g fat, and 9 g protein (8 oz of Ensure).

Sample collection and analysis

Blood was collected in chilled EDTA tubes and immediately centrifuged, and plasma was stored at −80°C until analysis. Glucose was measured via the glucose oxidase method (Beckman glucose analyzer). The plasma designated for GLP-1 measurement was supplemented with aprotinin (1,000 kIU/ml) and dipeptidyl peptidase 4 inhibitor (20 μl/ml plasma). Plasma designated for acylated ghrelin measurement was treated with 1 N hydrochloric acid (50 μl/ml plasma) and phenylmethylsulfonyl fluoride (0.1 mg/ml plasma). Plasma insulin, leptin, adiponectin, and active GLP-1 were measured using multiplex immunoassays (Luminex xMAP). Total (acylated and desacyl) and acylated ghrelin were determined by radioimmunoassay. Plasma concentrations of total GIP were measured by enzyme-linked radioimmunoassay. A1C was assayed using high-pressure liquid chromatography.

Calculations

The homeostasis model assessment of insulin resistance index (HOMA-IR) is derived from the inverse of insulin sensitivity based on Levy's nonlinear computer model (14). Total area under the curve (AUC) was calculated according to the trapezoidal rule in GraphPad Prism (version 5.02).

Statistical analyses

The Wilcoxon signed rank test was performed to compare data from the same subjects. The nonparametric Mann-Whitney test was used for comparisons between RYGB and diet groups. All analyses were performed in R 2.6.2 (www.r-project.org). Data are means ± SD, except for graphs which are presented as means ± SEM.

RESULTS

Weight loss

RYGB subjects lost 1.4 ± 5.3 kg or 1.0 ± 3.4% of initial body weight ($P = 0.46$) in the 1st week postoperatively. Caloric-restricted control subjects lost 2.2 ± 1.0 kg or 2.2 ± 1.0% of initial body weight ($P = 0.004$). Comparison of the weight changes with RYGB and diet was not significant ($P = 0.09$) (Table 2).

Fasting measures of insulin resistance

Within 1 week after RYGB, fasting glucose levels were similar to preoperative levels (−6%; $P = 0.14$); however, a decrease in insulin levels was observed (−25%; $P = 0.04$). HOMA-IR also decreased by 25% ($P = 0.03$). Diet control subjects exhibited a disparate decrease in glucose levels (−20%; $P = 0.004$) but a similar decrease in fasting insulin levels (−27%; $P = 0.07$) and improvement in the HOMA-IR index (−30%; $P = 0.004$). Changes in HOMA-IR with RYGB and diet were not different ($P = 0.45$) (Table 2).

Fasting levels of enterokines and adipokines

Fasting plasma levels of GLP-1 and GIP were not altered either by RYGB ($P = 0.65$ and 0.16, respectively) or after caloric restriction ($P = 0.73$ and 0.13, respectively). On the other hand, there were decreases in the fasting levels of acylated (−21%; $P = 0.03$) and total ghrelin (−20%; $P = 0.05$) after RYGB, with no changes in the caloric-restricted group

Table 2—*Early effects of RYGB and short-term diet restriction on body weight and fasting metabolic parameters*

	Before RYGB	After RYGB	Before diet	After diet
Weight (kg)	153.2 ± 32.2	151.8 ± 33.1	127.0 ± 36.5	124.2 ± 36.5*
BMI (kg/m^2)	51.9 ± 6.0	51.4 ± 6.6	44.2 ± 9.9	43.2 ± 10.0*
Glucose (mmol/l)	6.4 ± 1.5	6.0 ± 1.8	6.8 ± 1.8	5.4 ± 1.1*
Insulin (pmol/l)	236 ± 159	155 ± 102*	220 ± 196	178 ± 217
HOMA-IR	5.0 ± 3.1	3.3 ± 2.1*	4.8 ± 4.1	3.6 ± 4.1*
GLP-1 (pg/ml)	34.9 ± 32.4	36.5 ± 32.6	39.4 ± 14.9	39.3 ± 32.8
GIP (pg/ml)	58.0 ± 31.6	42.4 ± 21.1	53.3 ± 29.0	33.7 ± 25.5
Leptin (ng/ml)	72.4 ± 15.3	49.5 ± 15.1*	61.1 ± 30.6	38.0 ± 21.9
Adiponectin (μg/ml)	7.3 ± 3.0	6.4 ± 2.0	4.5 ± 2.6	4.7 ± 2.6
Acylated ghrelin (pg/ml)	68.2 ± 33.6	48.5 ± 26.9*	34.7 ± 23.5	26.1 ± 20.2
Total ghrelin (pg/ml)	585 ± 272	414 ± 107	623 ± 205	559 ± 268

Data are means ± SD. *$P < 0.05$ compared with baseline within each group (RYGB or Diet).

($P > 0.2$). The fasting levels of leptin declined 1 week after RYGB (−31%; $P = 0.004$) and after caloric restriction (−26%; $P = 0.05$), whereas adiponectin levels were not altered in either group ($P > 0.1$) (Table 2).

Metabolic response to a mixed meal

RYGB did not result in differences in the glucose AUC ($P = 0.13$) or peak glucose levels ($P = 0.21$) achieved after a mixed meal. The insulin response was reduced after RYGB, evidenced by decreases in AUC ($P = 0.004$) and peak levels of insulin ($P = 0.02$). Conversely, there were increases in the AUC ($P = 0.04$) and peak ($P = 0.01$) GLP-1 levels postoperatively. Whereas the AUC and peak levels of GIP were not altered in response to a mixed meal after RYGB, the peak in GIP occurred earlier. Despite a decrease in the AUC and nadir for total ghrelin in the early postoperative period ($P = 0.004$ for both), ghrelin remained at fasting levels throughout the study (Fig. 1, Table 3).

The subjects who underwent caloric restriction similar to that for the subjects undergoing RYGB displayed similar changes in meal-stimulated glucose and insulin release after the diet; the AUC ($P = 0.13$) and peak ($P = 0.34$) glucose concentrations did not change and the AUC ($P = 0.02$) and peak ($P = 0.04$) insulin concentrations decreased. Although the AUC for insulin was decreased in both the RYGB and diet groups, the change in the RYGB group was greater ($P = 0.04$). Caloric restriction alone did not induce any changes in enterokine responses to a mixed meal (all $P > 0.05$), with the exception of a decreased nadir in ghrelin release after diet ($P = 0.05$). Interestingly, caloric restriction altered the pattern of ghrelin release. At baseline, ghrelin levels did not vary after the mixed meal similar to that in the RYGB subjects; however, after the diet, ghrelin release was suppressed after the mixed meal followed by a steady increase in ghrelin release above fasting levels.

CONCLUSIONS — It is well established that RYGB is effective in improving insulin resistance and ameliorating type 2 diabetes. The beneficial metabolic effects of RYGB were initially attributed to the substantial weight reduction achieved with surgery; however, subsequent investigations revealed an improvement in insulin sensitivity at 6 days after RYGB without appreciable weight loss (15). We have confirmed these findings by demon-

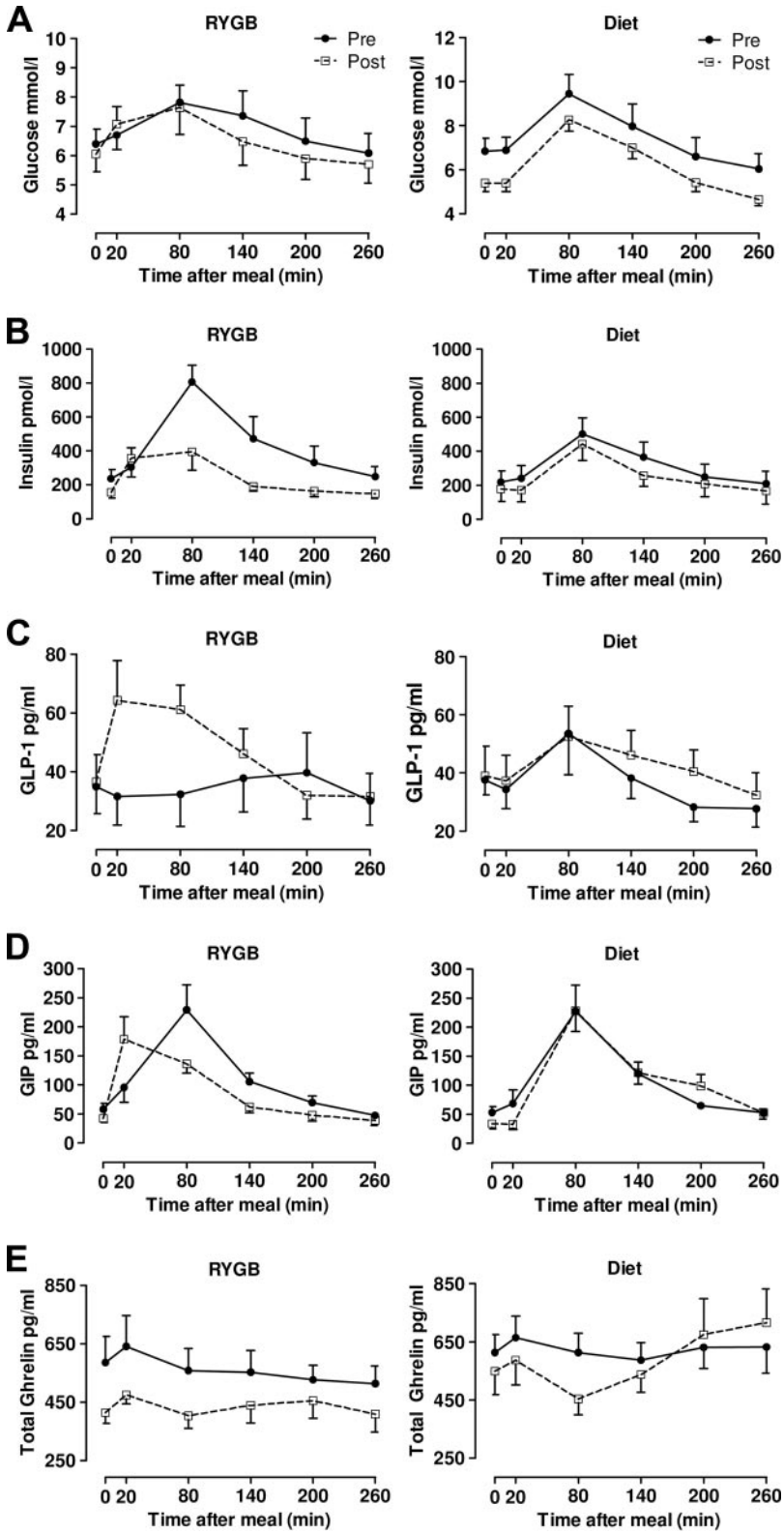

Figure 1—*Metabolic responses during a mixed-meal before and after RYGB and diet. Blood was drawn before (time 0), immediately after the ingestion of a mixed-meal (time 20), and every subsequent hour for 4 h. Plasma levels of glucose* (A)*, insulin* (B)*, GLP-1* (C)*, GIP* (D)*, and total ghrelin* (E) *were measured at each time point at baseline* (●) *and 4 days after RYGB* (□) *or 3 days after a post–bariatric surgery diet* (□)*. Data are means ± SEM.*

Table 3—*Metabolic responses to a mixed-meal before and after RYGB and diet*

	Before RYGB	After RYGB	Before diet	After diet
Glucose AUC (mmol · l^{-1} · min^{-1})	1,829 ± 510	1,714 ± 568	1,966 ± 641	1,637 ± 297
Peak glucose (mmol/l)	8.4 ± 2.1	7.9 ± 2.5	9.4 ± 2.6	8.2 ± 1.5
Insulin AUC (mmol · l^{-1} · min^{-1})	113 ± 67	65 ± 33*	85 ± 59	65 ± 56*
Peak insulin (pmol/l)	742 ± 347	485 ± 307*	532 ± 287	406 ± 307*
GLP-1 AUC (pg · l^{-1} · min^{-1})	9.2 ± 8.4	12.2 ± 5.5*	10.2 ± 5.9	11.6 ± 6.4
Peak GLP-1 (pg/ml)	45.2 ± 37.3	84.8 ± 33.0*	58.8 ± 43.2	57.2 ± 28.4
GIP AUC (pg · l^{-1} · min^{-1})	28.7 ± 12.3	23.5 ± 8.6	29.5 ± 13.5	30.1 ± 13.8
Peak GIP (pg/ml)	227 ± 115	193 ± 111	235 ± 128	228 ± 105
Ghrelin AUC (pg · l^{-1} · min^{-1})	145 ± 53	112 ± 36*	162 ± 58	142 ± 52
Nadir ghrelin (pg/ml)	456 ± 165	341 ± 84*	543 ± 217	393 ± 201

Data are means ± SD. *$P < 0.05$ compared with baseline within each group (RYGB and diet).

strating a 25% improvement in insulin sensitivity (HOMA-IR) within 1 week after RYGB before any apparent weight loss. Interestingly, obese subjects, albeit with a nonsignificantly lower body weight, who consumed a post–bariatric surgery liquid diet for 4 days replicated the improved insulin sensitivity observed in the RYGB subjects. The parallel improvements occurred with minimal noticeable differences in weight loss between the two groups. HOMA-IR is a fasting measure of whole-body insulin resistance that has been shown to correlate with other dynamic measures of insulin sensitivity in obese subjects, such as the hyperinsulinemic-euglycemic clamp (16). Such studies suggest that a short duration, very-low-calorie diet can reduce hepatic glucose production (17) and improve skeletal muscle insulin sensitivity (4). Our data demonstrate that the improvement in insulin sensitivity, as measured by HOMA-IR, precedes appreciable weight loss and is largely achieved with caloric restriction. However, we must consider the possibility that the immediate improvements in insulin sensitivity after RYGB could have been blunted consequent to the associated stress/inflammatory responses of surgery, thus masking a greater improvement in insulin sensitivity with RYGB than with caloric restriction.

Fasting levels of GLP-1 have been reported to remain stable 2–10 weeks after RYGB (1,11,18,19), consistent with our current observations within the 1st postoperative week. Our data show increases in peak GLP-1 levels and total GLP-1 release after ingestion of a mixed meal 1 week after RYGB, in agreement with previous short-term follow-up investigations (11,19–21). This increase in GLP-1 could not be attributed to the restrictive nature of the surgical procedure, because the caloric-restricted diet group did not show enhanced an GLP-1 release in response to the mixed meal. The findings with GIP are novel; GIP is released sooner but not to a greater extent with a meal within the 1st week after RYGB. Laferrère et al. (11) and Campos et al. (10) compared incretin levels in two groups of subjects after a 10-kg weight loss via RYGB or diet and reported an increase in GLP-1 only after RYGB; their findings for GIP were disparate, with one reporting an increase (11) and the other reporting no change (10). Our results, however, show altered incretin release after RYGB before substantial weight loss. The proposed mechanism of enhanced incretin release after RYGB is most likely related to the increased and more rapid nutrient stimulus to the intestinal neuroendocrine cells.

The effects of the changes in incretin levels on the improved metabolic responses after RYGB remain controversial. In our study, the observed increase in GLP-1 and shift to an earlier GIP peak within 1 week after RYGB was accompanied by improved insulin sensitivity, whereas the improvement in insulin sensitivity after caloric restriction occurred without alterations in either GLP-1 or GIP. Thus, the improvements in insulin sensitivity in our study are unlikely to be due to altered incretin-induced insulin release but rather to the caloric restriction. In fact, in both surgical and caloric-restricted diet groups we observed similar decreases in insulin release (Fig. 1) accompanied by improved insulin sensitivity. These findings contrast with previous reports of either no early changes in insulin release (10) or an increase in insulin release (11) after RYGB. The discrepancy with our findings may be related to the associated losses (10 kg) in body weight in these studies (10,11). In addition, GLP-1 could exert extrapancreatic effects on improving insulin sensitivity (22), which in our RYGB group could have been blunted as a result of the associated inflammatory responses immediately after surgery. Lastly, perhaps the improved GLP-1 response in the 1st week after RYGB is not robust enough to elicit increased insulin secretion and glucose-lowering effects and may take longer to exert such effects.

Levels of the orexiogenic hormone ghrelin are diminished in obesity (23), perhaps indicating a positive energy balance. The short-term effect of RYGB on fasting total ghrelin is controversial. We observed 20% decreases in fasting levels of acylated and total ghrelin within 1 week after RYGB; these are consistent with previously reported decreases in fasting total ghrelin at 6 weeks (24) but different from another report showing no change 1 month after RYGB (12). Whether the decreased levels of acylated and total ghrelin levels play a role in the improvement in insulin sensitivity after RYGB remains to be determined. Vestergaard et al. (6) demonstrated that exogenous infusion of a pharmacological dose of acyl-ghrelin acutely induced insulin resistance independent of growth hormone and cortisol.

Alterations in adipokines, such as leptin and adiponectin, after RYGB have been attributed to fat mass loss and are responsible for the long-term improvements in insulin resistance (2). The similarities in the decrease in plasma leptin in the RYGB and diet groups suggest that this immediate change in leptin after surgery can be accounted for by caloric restriction. A similar finding was reported 1 month after RYGB and diet, coinciding with a 10-kg weight loss (12). The stable adiponectin concentrations during caloric restriction via RYGB and diet could indicate dissociation in the regulation of these two adipokines between nutrient exposure and fat mass.

In summary, our present data suggest that caloric restriction without substantial weight loss is of primary importance in the rapid improvement of insulin sensitivity within the 1st week after RYGB. Early alterations in the incretin response can be attributed to the surgery; however, the enhanced incretin response does not seem to have any additional benefit beyond caloric restriction on glucose homeostasis and insulin sensitivity. It is important to note that our cohorts of obese subjects were balanced for type 2

diabetes, and the measured parameters were similar at baseline (except for HOMA-IR, which was higher in the subjects with type 2 diabetes) and changed similarly after intervention. Further investigations in the immediate postoperative period with more dynamic measures of insulin resistance are also warranted to determine the mechanisms/site of improved insulin sensitivity, along with a direct assessment of the incretin effect on insulin production.

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