Short-term Effects of Laparoscopic Adjustable Gastric Banding Versus Roux-en-Y Gastric Bypass

Amalia Gastaldelli,[1] Amerigo Iaconelli,[2] Melania Gaggini,[1] Maria Chiara Magnone,[3] Augusto Veneziani,[2] Francesco Rubino,[4] and Geltrude Mingrone[2,4]

Diabetes Care 2016;39:1925–1931 | DOI: 10.2337/dc15-2823

OBJECTIVE

Bariatric surgery has been shown to have important long-term metabolic effects resulting in enhanced insulin sensitivity and improved glucose tolerance in patients with type 2 diabetes. The contribution of reduced caloric intake to these beneficial effects of surgery remains unclear. The aim of this study was to compare the short-term effects (1 week) of bariatric surgical procedures with a very low caloric intake (VLCI) on insulin sensitivity (IS) and insulin secretion (ISR) in nondiabetic obese subjects.

RESEARCH DESIGN AND METHODS

Twenty obese patients without diabetes (BMI 44.2 ± 0.7 kg/m^2) were admitted to the clinic for 1 week. At baseline and 1 week after VLCI (600 kcal/day), subjects received a hyperinsulinemic-euglycemic clamp with tracer infusion to quantify endogenous glucose production (EGP), lipolysis (rate of appearance of glycerol [RaGlycerol]), peripheral insulin sensitivity (insulin-stimulated glucose disposal [M value] divided by the steady-state plasma insulin concentration [M/I]), hepatic insulin sensitivity (Hep-IS [= 1/(EGP · insulin)]), and adipose insulin sensitivity (Adipo-IS [= 1/(RaGlycerol · insulin)]). An intravenous glucose bolus was administered at the end of the insulin clamp to measure ISR and β-cell function (disposition index [DI]). Approximately 3 months later, patients were admitted for laparoscopic adjustable gastric banding (LAGB) (*n* = 10) or Roux-en-Y gastric bypass (RYGB) (*n* = 10), and were restudied 1 week after surgery under the same caloric regimen (600 kcal/day).

RESULTS

After 1 week of VLCI, patients lost 2.1 kg without significant changes in Hep-IS, Adipo-IS, M/I, or DI. RYGB and LAGB led to greater weight loss (5.5 and 5.2 kg, respectively) and to significant improvement in Hep-IS, EGP, and lipolysis. Only RYGB improved Adipo-IS and M/I. No change in ISR or DI was observed in either surgical group.

CONCLUSIONS

Bariatric surgery improves IS within 1 week. These metabolic effects were independent of caloric intake and more pronounced after RYGB compared with LAGB.

[1]Cardiometabolic Risk Laboratory, CNR Institute of Clinical Physiology, Pisa, Italy
[2]Department of Internal Medicine, Catholic University, Rome, Italy
[3]F. Hoffmann-La Roche, Ltd., Basel, Switzerland
[4]Bariatric and Metabolic Surgery, Division of Diabetes and Nutritional Sciences, King's College London, London, U.K.

Corresponding author: Amalia Gastaldelli, amalia@ifc.cnr.it.

Received 28 December 2015 and accepted 1 August 2016.

Clinical trial reg. no. NCT01063127, clinicaltrials.gov.

Bariatric surgery produces long-term improvements in both peripheral and hepatic insulin sensitivity (Hep-IS) glucose tolerance (1–5). Among surgical procedures, Roux-en-Y gastric bypass (RYGB) has been shown to be especially effective in improving insulin resistance and glucose metabolism (6–8). However, bariatric procedures are anatomically very different. Although laparoscopic adjustable gastric banding (LAGB) and sleeve gastrectomy restrict the stomach size, they do not change the intestinal anatomy. RYGB limits the gastric pouch to ~30 mL and, additionally, bypasses the duodenum and early jejunum, thus changing the pattern of food absorption as well as the food-stimulated release of gastric hormones. Bradley et al. (9,10) showed that, when matched for 20% weight loss, obese patients without diabetes undergoing RYGB, LAGB, and sleeve gastrectomy surgery showed similar metabolic improvements in insulin sensitivity and β-cell function.

The early effects of bariatric surgery on insulin sensitivity are controversial. Few studies have assessed the effect of bariatric surgery on both Hep-IS and peripheral insulin sensitivity in subjects without diabetes using the gold standard euglycemic-hyperinsulinemic clamp with isotope infusion. Bojsen-Møller et al. (8,11) demonstrated reduced basal endogenous glucose production (EGP) and improved basal Hep-IS within 1 week after RYGB surgery in obese, normal, glucose-tolerant subjects and subjects with type 2 diabetes (T2D). Dunn et al. (12) demonstrated a significant early (1 week after RYGB) improvement in Hep-IS, while peripheral insulin sensitivity was unaltered. However, these studies did not contain a control group treated with diet or a group treated with restrictive surgery alone. On the other hand, de Weijer et al. (13) observed a significant decrease in EGP but reported no changes in either Hep-IS or peripheral insulin sensitivity 2 weeks after RYGB; whereas Camastra et al. (6) failed to observe any change in the basal rate of EGP or lipolysis 2 weeks after RYGB either in patients without diabetes or in patients with T2D, although the insulin-stimulated glucose disposal value (M value) tended to be higher and the EGP value tended to be lower in the group with diabetes. Steven et al. (14) reported improvements in both peripheral and hepatic insulin resistance 8 weeks after RYGB both in patients with normal glucose tolerance (NGT) and in obese patients with T2D, and Vetter et al. (15) found that in patients with T2D, Hep-IS was significantly improved and EGP declined after RYGB compared with intensive lifestyle intervention that produced an equivalent reduction in body weight. However, this study did not evaluate the early changes in insulin sensitivity after RYGB.

All of the published studies examining the early effects of bariatric surgery on glucose homeostasis are confounded by postsurgery caloric restriction (16). Since a very low caloric intake (VLCI) improves insulin sensitivity within 2 days (17) and augments β-cell function in patients with T2D (18,19), it is difficult to separate the metabolic effects of surgery from those of caloric restriction. We hypothesized that the early effects of bariatric surgery on glucose metabolism in obese patients were independent of weight loss. The aim of the current study was to compare the short-term effects (1 week) of two different bariatric procedures (i.e., RYGB and LAGB) on insulin sensitivity and β-cell function, and to compare the results observed with those after 1 week of supervised VLCI in the same patients studied ~3 months prior to surgery.

RESEARCH DESIGN AND METHODS

Patients

We enrolled 23 morbidly obese patients without diabetes (BMI 44.1 ± 0.7 kg/m^2). Inclusion criteria were as follows: have a BMI >40 kg/m^2; willingness to undergo RYGB or LAGB; age range from 25 to 55 years; stable weight (±5 kg) for at least 6 months before the study; stable medication use; confirmed insulin resistance as assessed by the Matsuda index (20); and the absence of diabetes as determined by a screening oral glucose tolerance test. Exclusion criteria were as follows: not eligible for laparoscopic RYGB or LAGB; significant illness within 2 weeks preceding surgery; pregnancy or lactation; T2D; the presence of major cardiovascular, gastrointestinal, or respiratory disease, or any hormonal disorder; history of drug addiction and/or alcohol abuse; exercise more than three times a week; and suspected or confirmed poor compliance. Three patients were excluded, two because they did not meet the conditions described above and one because he did not undergo bariatric surgery. The protocol was approved by the ethical committee of the Catholic University-Policlinico Gemelli in Rome, and written informed consent was obtained from all subjects prior to the study. The study was registered as clinical trial reg. no. NCT01063127 (ClinicalTrials.gov).

Study Protocol

Patients were admitted to the Clinical Research Center at the University Hospital Gemelli on two occasions. During the first hospitalization, patients consumed a supervised VLCI (600 kcal/day, 2× 125 mL of Fortimel containing 300 kcal each and water and/or tea ad libitum) for 7 days. On the first and last day of VLCI, each patient underwent a measurement of insulin sensitivity, insulin secretion, and β-cell function (see below). Patients were then discharged from the hospital with nutritional counseling. Approximately 3 months later, patients were readmitted to the hospital to undergo bariatric surgery (n = 10 LAGB and n = 10 RYGB). Compliance with nutritional counseling was low since the patients regained the weight loss during VLCI and weight just before surgery was similar to weight at first hospital admission. Insulin sensitivity, insulin secretion, and β-cell function were evaluated 1 week after the surgical procedure (caloric intake after surgery was the same as during the first hospitalization; i.e., 2× 125 mL Fortimel containing 300 kcal each for a total of 600 kcal/day).

Peripheral and endogenous (hepatic) insulin sensitivity was measured with the hyperinsulinemic-euglycemic clamp (40 mU/min/m^2) with [6,6-$^2H_2$]glucose infusion (GINF). Insulin secretion was measured with a bolus of glucose (intravenous glucose tolerance test [IVGTT]) at the end of the insulin clamp (21,22). The hyperinsulinemic-euglycemic clamp (40 mU/min/m^2) was performed during the first hospital admission on day 1 (prior to VLCI) and 1 week after VLCI, and during the second hospital admission 1 week after surgery. [6,6-$^2H_2$]glucose (Cambridge Isotopes, Cambridge, MA) was infused as a primed infusion (bolus = 22 μmol/kg) − constant infusion (tracer infusion rate [INF] = 0.22 μmol/kg/min) before and until the end of the 2-h hyperinsulinemic-euglycemic clamp. During the insulin clamp, the plasma glucose concentration was clamped at 5 mmol/L with a variable infusion of 20%

glucose enriched with [6,6-$^2H_2$]glucose, using the hot-GINF approach (6,23–25). After the start of insulin infusion, the intravenous tracer INF was gradually decreased in order to maintain a constant tracer enrichment (measured as the tracer-to-tracee ratio [TTR]). Briefly, 2 g of [6,6-$^2H_2$]glucose was added to a 500-mL bottle of 20% unlabeled glucose and was infused at a variable rate (GINF) to clamp plasma glucose at 5 mmol/L. At the start of the hyperinsulinemic-euglycemic clamp (t = 0 min), the basal tracer INF was decreased by 50%, followed by further 50% decreases every 10 min until t = 30 min when the tracer infusion was discontinued (i.e., INF = 0.22 μmol/kg/min from t = −120 min to t = 0 min; INF = 0.11 μmol/kg/min from t = 0 to t = 10 min; INF = 0.05 μmol/kg/min from t = 10 to t = 20 min; INF = 0.02 μmol/kg/min from t = 20 to t = 30 min; at t = 30 min the INF was stopped). In summary, during the baseline period the tracer INF was equal to the INF, during the first 30 min of the insulin clamp the INF was equal to INF+GINF, and from t = 30 to t = 120 min the INF was equal to GINF.

At t = 120 min, insulin infusion was stopped and a bolus of unlabeled glucose (0.33 g/kg body wt) was injected intravenously (IVGTT), and blood samples were drawn after 2, 4, 6, 8, 10, 15, 20, and 30 min to measure plasma glucose, insulin, and C-peptide levels (6,22). A multiplication factor of 6.0 was used to convert insulin concentrations measured in milliunits per liter to picomoles per liter according to Robbins et al. (26).

[U-$^2H_5$]glycerol (Cambridge Isotopes, Cambridge, MA) was administered as a primed (bolus 1.5 μmol/kg) constant infusion (0.11 μmol/kg/min) for 2 h prior to the start of insulin infusion and during the 2-h insulin clamp to quantitate the rate of lipolysis, as previously described (6,27).

Calculations and Statistical Analyses

Basal EGP (primarily reflects liver) was calculated using the steady-state equation as the [6,6-$^2H_2$]glucose INF divided by plasma tracer enrichment (INF/TTR). During the clamp, Steele's non–steady-state equation was used, and EGP was calculated as the total glucose rate of appearance minus the exogenous GINF rate (6,27). Peripheral (muscle) insulin sensitivity was calculated as the rate of insulin-stimulated glucose disposal (M value) divided by the steady-state plasma insulin concentration (M/I) during the insulin clamp. Hep-IS was calculated as the inverse of the product of the basal rate of EGP and the fasting I value (I/[EGP · insulin]) (6,28–30). Peripheral lipolysis was calculated as the basal rate of appearance of glycerol (RaGlycerol) (6,27). Adipose tissue insulin sensitivity (Adipo-IS) was calculated as 1/(RaGlycerol · insulin) (28,30). This formula has also been validated after calorie restriction due to bariatric surgery (6). All metabolic fluxes were calculated both as total and normalized by body weight (6,8). We believe that total body flux rates are more appropriate since the changes in body weight early after surgery are biased by dehydration (31).

Insulin secretion rate was calculated using deconvolution of the plasma C-peptide concentration during the IVGTT according to Van Cauter et al. (32). The metabolic clearance rate of insulin (MCR-I) was calculated by dividing the insulin infusion rate during the insulin clamp by the steady-state plasma insulin concentration (80–120 min) (30). From the IVGTT data, we also calculated the acute insulin response to glucose (AIR_{cpep}) as the C-peptide area under the curve (AUC_{cpep}) from 0 to 10 min, and calculated the insulin secretion in response to glucose as $\Delta AUC_{cpep}/\Delta AUC_{glucose}$ from 0 to 30 min. β-Cell function (disposition index [DI]), was calculated as $\Delta AUC_{cpep}/\Delta AUC_{glucose} \times M/I$ (6,22).

All data represent the mean ± SE. To assess the changes compared with baseline due to VLCI or surgery, data were analyzed by paired t test for normally distributed variables and by Wilcoxon test for skewed variables using JMP 7.0 (SAS Institute). To evaluate the differences between RYGB and LAGB, data were analyzed by two-way ANOVA for normally distributed variables and by Mann-Whitney test for skewed variables.

RESULTS

Subject Characteristics

We studied 20 obese nondiabetic patients (BMI 44.2 ± 0.7 kg/m^2, age 35 ± 2 years), 7 men and 13 women. All patients did not have diabetes, but at the screening with an oral glucose tolerance test, 16 subjects had normal oral glucose tolerance (NGT according to American Diabetes Association criteria) and 4 subjects had impaired glucose tolerance. Fasting and 2-h glucose concentrations

Table 1—Metabolic changes after VLCI (600 kcal/day)

N = 20	Basal	VLCI
Weight (kg)	125.1 ± 5.0	123.0 ± 5.0*
BMI (kg/m^2)	44.2 ± 0.7	43.4 ± 0.7*
Fasting		
Glucose (mmol/L)	5.3 ± 0.1	5.3 ± 0.1
Insulin (pmol/L)	107 ± 14	102 ± 17
EGP (μmol/min)	1,013 ± 63	975 ± 50*
EGP_{BW} (μmol · min^{-1} · kg^{-1})	8.2 ± 0.4	8.0 ± 0.3
Hep-IS_{BW} (μmol^{-1} · min · kg · nmol^{-1} · L)	1.6 ± 0.2	1.9 ± 0.2
RaGlycerol (μmol · min^{-1})	363 ± 32	406 ± 55
$RaGlycerol_{BW}$ (μmol · min^{-1} · kg^{-1})	2.9 ± 0.3	3.3 ± 0.4
Adipo-IS_{BW} (μmol^{-1} · min · kg · nmol^{-1} · L)	4.6 ± 0.5	6.0 ± 1.4
Hyperinsulinemic clamp		
Glucose (mmol/L)	5.1 ± 0.1	5.2 ± 0.1
Insulin (pmol/L)	594 ± 31	617 ± 34
EGP (μmol · min^{-1})	119 ± 45	147 ± 30#
EGP_{BW} (μmol · min^{-1} · kg^{-1})	0.9 ± 0.3	1.2 ± 0.3
M (μmol · min^{-1})	1,895 ± 120	2,010 ± 148
M_{BW} (μmol min^{-1} · kg^{-1})	15.6 ± 1.1	16.7 ± 1.3
M_{BW}/I (μmol · min^{-1} · kg^{-1} · nmol^{-1} · L)	29.1 ± 2.8	31.8 ± 3.3
MCR-I clamp (mL · min^{-1} · m^{-2})	461 ± 25	446 ± 24
IVGTT		
AIR_{cpep} (nmol · L^{-1} · 10 min)	22.2 ± 2.1	21.7 ± 1.9
$\Delta AUC_{cpep}/\Delta AUC_{glucose}$ (nmol · L^{-1} · mmol^{-1} · L · 30 min)	0.187 ± 0.02	0.180 ± 0.02
ISR (nmol · min^{-1} · m^{-2} · 30 min)	12.9 ± 1.3	13.1 ± 1.4
DI (M/I · $\Delta AUC_{cpep}/\Delta AUC_{glucose}$)	5.2 ± 0.7	5.3 ± 0.7

Clamp EGP referred to the average value during the time period 80–120 min after insulin infusion. Adipo-IS = 1/(RaGlycerol · insulin); AIR = AUC_{cpep} (0–10 min); Hep-IS = 1/(EGP · insulin). BW, body weight; ISR, insulin secretion. *$P < 0.0001$ compared with basal. #$P < 0.05$ compared with basal.

were 93 ± 2 and 121 ± 6 mg/dL, respectively. The Matsuda index of insulin sensitivity was 2.1 ± 0.2, indicating severe insulin resistance. Liver enzyme levels were as follows: alanine aminotransferase 49 ± 9 mU/L; aspartate aminotransferase 33 ± 3 mU/L; and γ-glutamyl transferase 46 ± 9 mU/L. Total cholesterol level was 190 ± 7 mg/dL, HDL level was 44 ± 2 mg/dL, LDL level was 114 ± 6 mg/dL, and triglyceride level was 160 ± 18 mg/dL.

Insulin Sensitivity: VLCI Versus Surgery

After 1 week of VLCI (600 kcal/day), patients had lost ~2.1 kg. The absolute basal rate of EGP declined slightly but significantly, and the M value during the insulin clamp increased slightly but not significantly (Table 1). There were no significant improvements in lipolysis (RaGlycerol), Hep-IS, Adipo-IS, or peripheral insulin sensitivity (Table 1 and Fig. 1).

Approximately 3 months after hospitalization to undergo the VLCI, patients were readmitted to the hospital for either RYGB or LAGB. One week after surgery, body weight decreased similarly in RYGB (−5.5 ± 1.0 kg) and LAGB (−5.2 ± 0.9 kg) groups (Table 2). The absolute basal rate of EGP declined after both RYGB and LAGB, lipolysis (RaGlycerol) was significantly stimulated, and the M value during the insulin clamp increased slightly but not significantly (Table 2). Significant improvements from baseline parameters of insulin sensitivity were observed only in the RYGB group (Table 2 and Fig. 1), as follows: Hep-IS improved by 129% in the RYGB group versus 65% in the LAGB group ($P < 0.01$); peripheral insulin sensitivity (M/I) improved by 44% in the RYGB group versus 19% in the LAGB group ($P < 0.05$); Adipo-IS index significantly increased by 54% in the RYGB group versus a decrease of −8% in the LAGB group ($P < 0.05$).

Insulin Secretion and Insulin Clearance: VLCI Versus Surgery

No change was observed after VLCI or bariatric surgery in either the insulin secretion rates during the IVGTT, the AIR_{cpep}, or the incremental AUC_{cpep} normalized by glucose, and no difference was observed in the DI (Table 2 and Fig. 2). However, the plasma insulin concentrations were lower after RYGB both during the fasting state and at the end of the insulin clamp (Table 2 and Fig. 2). The insulin clearance rates (MCR-I) did not change after LAGB (MCR-I = 480 ± 44 mL · min^{-1} · m^{-2} at baseline and 478 ± 45 mL · min^{-1} · m^{-2} 1 week after surgery, $P = 0.96$; Table 2) while, after RYGB, insulin clearance increased (MCR-I = 441 ± 24 at baseline and 544 ± 24 mL · min^{-1} · m^{-2} after surgery, $P < 0.008$; Fig. 1) explaining the lower insulin concentrations.

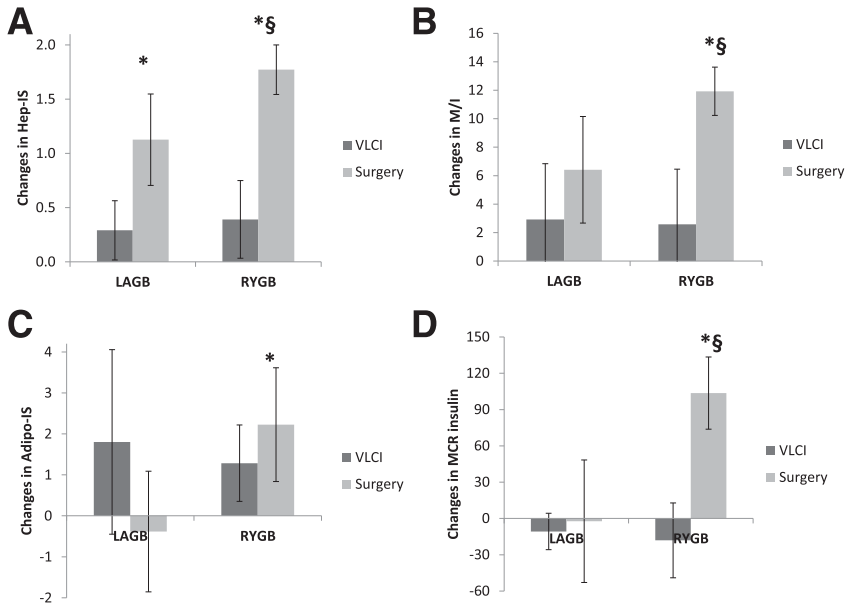

Figure 1—Metabolic changes observed after 1 week of VLCI and after 1 week of surgery (LAGB and RYGB) compared with baseline values. *A*: Changes in Hep-IS (calculated as 1/(EGP · insulin) using fasting values and expressed in micromoles per minute per kilogram per nanomoles per liter. *B*: Changes in peripheral insulin sensitivity (calculated as M/I and expressed in micromoles per minute per kilogram per nanomoles per liter). *C*: Changes in Adipo-IS (calculated as 1/(RaGlycerol · insulin) and expressed in micromoles per minute per kilogram per nanomoles per liter. *D*: Changes in insulin clearance rates (MCR-I, expressed in milliliters per minute per meter). *$P < 0.05$ vs. basal; §$P < 0.05$ vs. VLCI.

CONCLUSIONS

Previous studies have failed to distinguish the confounding effects of reduced caloric intake from those of the surgical procedure per se on the early beneficial effects on glucose metabolism. The purpose of the current study was to quantitate and compare the early (1 week) metabolic effects of two different bariatric surgical procedures (RYGB and LAGB) with those of VLCI.

To achieve this aim, we studied 20 morbidly obese patients without diabetes who had severe insulin resistance, as documented by a low Matsuda index (20). Using the hyperinsulinemic-euglycemic clamp with tracer infusion and IVGTT (6,22), we measured changes in insulin sensitivity, insulin secretion, and β-cell function after 1 week of VLCI and 1 week after bariatric surgery (either RYGB or LAGB) in the same patient. Thus, each patient served as his/her own control.

During the baseline insulin clamp, insulin suppressed basal EGP by ~90%, which is consistent with the recent results of ter Horst et al. (33). In the current study, VLCI did not enhance the suppression of EGP during the insulin clamp compared with the basal level, while EGP was significantly suppressed by both surgical procedures by ~97%. After RYGB and LAGB, but not after VCLI, basal EGP and Hep-IS were improved. RYGB, but not LAGB or VLCI, also increased peripheral insulin sensitivity and Adipo-IS. Other investigators have reported (8,12,15) an improvement in basal Hep-IS during the first weeks after RYGB. However, most of these previous studies were conducted in patients with T2D with high basal (fasting) rates of EGP, there was no control for reduced caloric intake postsurgery, and results were limited to RYGB. Patients with poorly controlled T2D have an increased rate of basal EGP, which is proportional to both the increase in

Table 2—Metabolic changes after bariatric surgery

	RYGB (n = 10)		LAGB (n = 10)	
	Basal	Postsurgery	Basal	Postsurgery
Weight (kg)	132.8 ± 8.7	127.3 ± 8.3*	117.4.±3.8	112.2 ± 3.7*
BMI (kg/m^2)	44.3 ± 1.2	42.5 ± 1.3*	44.1 ± 0.7	42.1 ± 0.7*
Fasting				
Glucose (mmol/L)	5.4 ± 0.1	5.0 ± 0.1	5.3 ± 0.1	5.2 ± 0.1
Insulin (pmol/L)	126 ± 22	63 ± 13§	88 ± 14	70 ± 10
EGP (μmol · min^{-1})	1,061 ± 111	869 ± 55*	965 ± 62	776 ± 48*
EGP_{BW} (μmol · min^{-1} · kg^{-1})	7.9 ± 0.5	6.9 ± 0.4	8.4 ± 0.7	7.0 ± 0.4
Hep-IS (μmol^{-1} · min · nmol^{-1} · L)	188 ± 49	400 ± 77§	194 ± 25	312 ± 62§
Hep-IS_{BW} (μmol^{-1} · min · kg · nmol^{-1} · L)	1.4 ± 0.4	3.2 ± 0.6 §	1.7 ± 0.2	2.8 ± 0.6*
RaGlycerol (μmol · min^{-1})	356 ± 40	448 ± 47	371 ± 51	542 ± 76
$RaGlycerol_{BW}$ (μmol · min^{-1} · kg^{-1})	2.7 ± 0.3	3.6 ± 0.4*	3.2 ± 0.4	4.9 ± 0.7*
Adipo-IS (μmol^{-1} · min · nmol^{-1} · L)	534 ± 87	794 ± 129*	587 ± 95	536 ± 153
Adipo-IS_{BW} (μmol^{-1} · min · kg · nmol^{-1} · L)	4.1 ± 0.6	6.3 ± 1.1*	5.1 ± 0.8	4.7 ± 1.2
Hyperinsulinemic clamp				
Glucose (mmol/L)	5.2 ± 0.1	5.1 ± 0.1	5.1 ± 0.1	5.1 ± 0.1
Insulin (pmol/L)	605 ± 33	489 ± 25§	583 ± 54	588 ± 54
EGP (μmol · min^{-1})	131 ± 75	39 ± 82	108 ± 54	26 ± 85
EGP_{BW} (μmol · min^{-1} · kg^{-1})	1.0 ± 0.5	0.2 ± 0.6	0.9 ± 0.5	0.3 ± 0.7
M (μmol · min^{-1})	1,887 ± 198	2,021 ± 261	1,903 ± 147	2,323 ± 276
M_{BW} (μmol · min^{-1} · kg^{-1})	14.6 ± 1.6	16.0 ± 1.9	16.6 ± 1.7	20.6 ± 2.2
M/I (μmol^{-1} · min · pmol^{-1} · L)	3.4 ± 0.5	4.9 ± 0.8*	3.6 ± 0.4	4.3 ± 0.4
M_{BW}/I (μmol^{-1} · min · kg · nmol^{-1} · L)	26.4 ± 3.7	38.3 ± 5.3*	31.8 ± 4.1	38.2 ± 3.7
MCR-I clamp (mL · min^{-1} · m^{-2})	441 ± 24	544 ± 24§#	480 ± 44	478 ± 45
IVGTT				
AIR_{cpep} (nmol · L^{-1} · 10 min)	25.1 ± 3.4	22.1 ± 3.3	19.4 ± 2.5	21.5 ± 3.1
$\Delta AUC_{cpep}/\Delta AUC_{glucose}$ (nmol · L^{-1} · mmol^{-1} · L · 30 min)	0.205 ± 0.03	0.178 ± 0.04	0.170 ± 0.03	0.170 ± 0.04
ISR (nmol · min^{-1} · m^{-2} · 30 min)	15.5 ± 2.1	12.8 ± 2.4	10.3 ± 1.1	10.8 ± 1.4
DI (M/I · $\Delta AUC_{cpep}/\Delta AUC_{glucose}$)	4.9 ± 0.7	6.2 ± 1.5	5.4 ± 1.1	5.7 ± 1.2

Clamp EGP referred to the average value during the time period 80–120 min after insulin infusion. Adipo-IS = 1/(RaGlycerol · insulin); AIR = AUC_{cpep} (0–10 min); Hep-IS = 1/(EGP · insulin). BW, body weight; ISR, insulin secretion. *$P \leq 0.05$ compared with basal. §$P \leq 0.01$ compared with basal. #$P < 0.02$ for changes from basal in RYGB vs. LAGB.

fasting hyperglycemia and to the increase in fat mass (6,34). In patients with T2D, VLCI has been shown to reduce fasting EGP by 15% within 2 days after the initiation of caloric restriction (17) at a time when changes in body weight and insulin-stimulated peripheral glucose disposal are not yet evident (17,35). In subjects without diabetes, fasting EGP is strictly regulated and maintained within normal ranges (36), whereas obese subjects often display impaired suppression of EGP during a hyperinsulinemic-euglycemic clamp (30). Therefore, it is not surprising that, after surgery, the change in fasting EGP normalized by body weight was minimal, although significant, in absolute terms. However, the improvement in the Hep-IS index was significant and independent of weight loss (Table 2).

One week after bariatric surgery, but not after VLCI, we observed a significant improvement in peripheral (primarily reflects muscle) insulin sensitivity. This result is consistent with previous studies (6,8,13) that have shown that improved insulin-mediated glucose disposal occurs within a few months after surgery. Although peripheral lipolysis has been reported to increase under conditions of caloric restriction, we observed a significant increase in lipolysis only after RYGB and LAGB, and not after VLCI. Insulin exerts its effect on the adipose tissue by suppressing lipolysis and stimulating triglyceride synthesis (6,30). The Adipo-IS index provides a measure of the antilipolytic effect of insulin (i.e., Adipo-IS) (6). We observed a significant increase in Adipo-IS only after RYGB and not after LAGB or VLCI. These results were independent of weight loss, which was similar after the two surgical procedures (LAGB −5.2 kg and RYGB −5.5 kg). This suggests that the failure of Bradley et al. (10) to observe any difference between the effect of LAGB and RYGB on insulin sensitivity and β-cell function was most likely due to the greater magnitude of weight loss (20%) in their study compared with the current study. Our results indicate that early after bariatric surgery, RYGB is more effective than a purely restrictive operation, such as LAGB, on hepatic and peripheral insulin resistance.

Our results suggest that the metabolic changes, especially those in the Hep-IS, after RYGB most likely represent a direct effect of surgery rather than an effect of low caloric intake or weight loss. The mean weight loss 1 week after surgery (−5.5 kg), although greater than that obtained after the same period with VLCI (−2.1 kg), was only 5.4% of the mean initial weight (126.5 kg).

No significant effect of either VLCI or surgery was observed on the acute insulin response during IVGTT. The lack of effect on insulin secretion should not be surprising. Although previous studies have found that both VLCI (18) and bariatric surgery (37) improve the insulin response to intravenous glucose, this effect was most evident in patients with T2D and/or only after much greater weight loss than

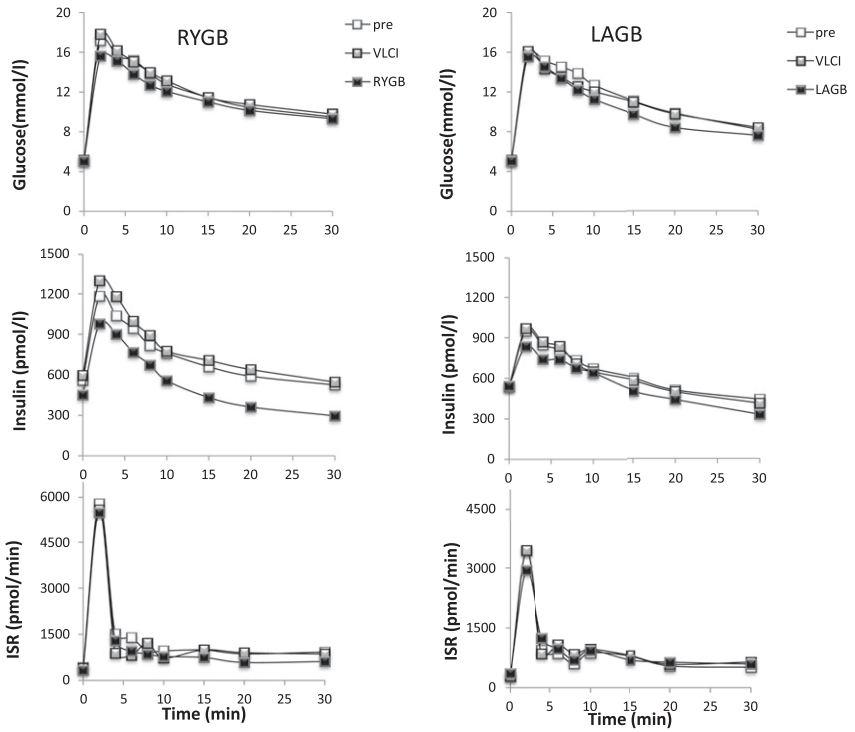

Figure 2—Glucose (top panels), insulin (middle panels), and insulin secretion rates (bottom panels) during IVGTT at baseline (white squares), after 1 week of VLCI (gray squares) and 1 week after surgery (black squares), in LAGB (left) and RYGB (right) groups.

that observed in the current study (38). The patients in the current study had near-normal glucose tolerance and insulin secretion/β-cell function and were mainly characterized by insulin resistance. Our results are in agreement with those of Martinussen et al. (37), who also failed to observe any change in the first phase of insulin secretion during an IVGTT 1 week after RYGB surgery compared with T2D, although they did observe an increase after 3 months. Our results also are consistent with those of Bojsen-Møller et al. (8) and Steven et al. (14), who showed that the early effects of bariatric surgery on insulin secretion were significant and more marked in subjects with T2D than in those with NGT.

We also observed an increase in insulin clearance (MCR-I) after RYGB that could explain the lower fasting and 2-h plasma insulin concentrations (Table 2). This result is in agreement with previous studies that observed an increase in postprandial insulin clearance within 1 week (11) or 2 weeks (13) after RYGB.

In conclusion, our results demonstrate that in obese subjects without diabetes, Hep-IS, peripheral insulin sensitivity, Adipo-IS, and insulin clearance improve early after bariatric surgery independently of the low caloric intake, but only after RYGB, and not after LAGB.

Acknowledgments. The authors thank Ralph A. DeFronzo for his useful comments in the draft of this manuscript, and all of the volunteers and staff who participated in this study.

Funding. This study was supported by an investigator-initiated and unrestricted research grant from F. Hoffmann-La Roche. A.G. received funding from the Ministry of Education, Universities, and Research (MIUR), project PREMIALE 2012.

Duality of Interest. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. A.G. and G.M. contributed to the protocol concept and design, data analysis and interpretation, and drafting of the manuscript. A.I., A.V., and F.R. contributed to carrying out the studies and participated in the discussion of the results and drafting of the manuscript. M.G. contributed to data analysis, interpretation, and drafting of the manuscript. M.C.M. contributed important intellectual content and to the critical revision of the manuscript. All authors reviewed the manuscript prior to submission. A.G. and G.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet 2015;386:964–973
2. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012; 366:1577–1585
3. Jørgensen NB, Jacobsen SH, Dirksen C, et al. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with type 2 diabetes and normal glucose tolerance. Am J Physiol Endocrinol Metab 2012;303: E122–E131
4. Camastra S, Muscelli E, Gastaldelli A, et al. Long-term effects of bariatric surgery on meal disposal and β-cell function in diabetic and nondiabetic patients. Diabetes 2013;62:3709–3717
5. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012;366:1567–1576
6. Camastra S, Gastaldelli A, Mari A, et al. Early and longer term effects of gastric bypass surgery on tissue-specific insulin sensitivity and beta cell function in morbidly obese patients with and without type 2 diabetes. Diabetologia 2011;54: 2093–2102
7. Lindegaard KK, Jorgensen NB, Just R, Heegaard PM, Madsbad S. Effects of Roux-en-Y gastric bypass on fasting and postprandial inflammation-related parameters in obese subjects with normal glucose tolerance and in obese subjects with type 2 diabetes. Diabetol Metab Syndr 2015;7:12
8. Bojsen-Møller KN, Dirksen C, Jørgensen NB, et al. Early enhancements of hepatic and later of peripheral insulin sensitivity combined with increased postprandial insulin secretion contribute to improved glycemic control after Roux-en-Y gastric bypass. Diabetes 2014;63:1725–1737
9. Bradley D, Magkos F, Eagon JC, et al. Matched weight loss induced by sleeve gastrectomy or gastric bypass similarly improves metabolic function in obese subjects. Obesity (Silver Spring) 2014;22:2026–2031
10. Bradley D, Conte C, Mittendorfer B, et al. Gastric bypass and banding equally improve insulin sensitivity and β cell function. J Clin Invest 2012;122:4667–4674
11. Bojsen-Møller KN, Dirksen C, Jørgensen NB, et al. Increased hepatic insulin clearance after Roux-en-Y gastric bypass. J Clin Endocrinol Metab 2013;98:E1066–E1071
12. Dunn JP, Abumrad NN, Breitman I, et al. Hepatic and peripheral insulin sensitivity and diabetes remission at 1 month after Roux-en-Y gastric bypass surgery in patients randomized to omentectomy. Diabetes Care 2012;35:137–142
13. de Weijer BA, Aarts E, Janssen IM, et al. Hepatic and peripheral insulin sensitivity do not improve 2 weeks after bariatric surgery. Obesity (Silver Spring) 2013;21:1143–1147
14. Steven S, Hollingsworth KG, Small PK, et al. Weight loss decreases excess pancreatic triacylglycerol specifically in type 2 diabetes. Diabetes Care 2016;39:158–165
15. Vetter ML, Wadden TA, Teff KL, et al. GLP-1 plays a limited role in improved glycemia shortly after Roux-en-Y gastric bypass: a comparison with intensive lifestyle modification. Diabetes 2015;64:434–446

16. Reed MA, Pories WJ, Chapman W, et al. Roux-en-Y gastric bypass corrects hyperinsulinemia implications for the remission of type 2 diabetes. J Clin Endocrinol Metab 2011;96:2525–2531
17. Jazet IM, Pijl H, Frölich M, Romijn JA, Meinders AE. Two days of a very low calorie diet reduces endogenous glucose production in obese type 2 diabetic patients despite the withdrawal of blood glucose-lowering therapies including insulin. Metabolism 2005;54:705–712
18. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. Diabetologia 2011;54:2506–2514
19. Jazet IM, Schaart G, Gastaldelli A, et al. Loss of 50% of excess weight using a very low energy diet improves insulin-stimulated glucose disposal and skeletal muscle insulin signalling in obese insulin-treated type 2 diabetic patients. Diabetologia 2008;51:309–319
20. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470
21. Mari A, Tura A, Natali A, et al.; RISC Investigators. Influence of hyperinsulinemia and insulin resistance on in vivo β-cell function: their role in human β-cell dysfunction. Diabetes 2011;60:3141–3147
22. Rebelos E, Muscelli E, Natali A, et al.; RISC Study Investigators. Body weight, not insulin sensitivity or secretion, may predict spontaneous weight changes in nondiabetic and prediabetic subjects: the RISC study. Diabetes 2011; 60:1938–1945
23. Fernandez M, Gastaldelli A, Triplitt C, et al. Metabolic effects of muraglitazar in type 2 diabetic subjects. Diabetes Obes Metab 2011; 13:893–902
24. Hother-Nielsen O, Henriksen JE, Holst JJ, Beck-Nielsen H. Effects of insulin on glucose turnover rates in vivo: isotope dilution versus constant specific activity technique. Metabolism 1996;45:82–91
25. Finegood DT, Bergman RN, Vranic M. Estimation of endogenous glucose production during hyperinsulinemic-euglycemic glucose clamps. Comparison of unlabeled and labeled exogenous glucose infusates. Diabetes 1987;36:914–924
26. Robbins DC, Andersen L, Bowsher R, et al. Report of the American Diabetes Association's Task Force on standardization of the insulin assay. Diabetes 1996;45:242–256
27. Gastaldelli A, Coggan AR, Wolfe RR. Assessment of methods for improving tracer estimation of non-steady-state rate of appearance. J Appl Physiol (1985) 1999;87:1813–1822
28. Gastaldelli A, Natali A, Vettor R, Corradini SG. Insulin resistance, adipose depots and gut: interactions and pathological implications. Dig Liver Dis 2010;42:310–319
29. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297–2307
30. Gastaldelli A, Cusi K, Pettiti M, et al. Relationship between hepatic/visceral fat and hepatic insulin resistance in nondiabetic and type 2 diabetic subjects. Gastroenterology 2007; 133:496–506
31. Chaston TB, Dixon JB, O'Brien PE. Changes in fat-free mass during significant weight loss: a systematic review. Int J Obes 2007;31:743–750
32. Van Cauter E, Mestrez F, Sturis J, Polonsky KS. Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 1992;41:368–377
33. ter Horst KW, Gilijamse PW, Koopman KE, et al. Insulin resistance in obesity can be reliably identified from fasting plasma insulin. Int J Obes (Lond) 2015;39:1703–1709
34. Gastaldelli A, Miyazaki Y, Pettiti M, et al. Separate contribution of diabetes, total fat mass, and fat topography to glucose production, gluconeogenesis, and glycogenolysis. J Clin Endocrinol Metab 2004;89:3914–3921
35. Christiansen MP, Linfoot PA, Neese RA, Hellerstein MK. Effect of dietary energy restriction on glucose production and substrate utilization in type 2 diabetes. Diabetes 2000;49: 1691–1699
36. Natali A, Toschi E, Camastra S, Gastaldelli A, Groop L, Ferrannini E; European Group for the Study of Insulin Resistance (EGIR). Determinants of postabsorptive endogenous glucose output in non-diabetic subjects. Diabetologia 2000;43:1266–1272
37. Martinussen C, Bojsen-Møller KN, Dirksen C, et al. Immediate enhancement of first-phase insulin secretion and unchanged glucose effectiveness in patients with type 2 diabetes after Roux-en-Y gastric bypass. Am J Physiol Endocrinol Metab 2015;308:E535–E544
38. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabtologia 2004;47:31–39