First-Phase Insulin Secretion Restoration and Differential Response to Glucose Load Depending on the Route of Administration in Type 2 Diabetic Subjects After Bariatric Surgery

Serenella Salinari, dsc[1]
Alessandro Bertuzzi, dsc[2]
Simone Asnaghi, msc[1]
Caterina Guidone, md[3]
Melania Manco, md[4]
Geltrude Mingrone, md, phd[3]

OBJECTIVE — The purpose of this study was to elucidate the mechanisms of diabetes reversibility after malabsorptive bariatric surgery.

RESEARCH DESIGN AND METHODS — Peripheral insulin sensitivity and β-cell function after either intravenous (IVGTT) or oral glucose tolerance (OGTT) tests and minimal model analysis were assessed in nine obese, type 2 diabetic subjects before and 1 month after biliopancreatic diversion and compared with those in six normal-weight control subjects. Insulin-dependent whole-body glucose disposal was measured by the euglycemic clamp, and glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) were also measured.

RESULTS — The first phase of insulin secretion after the IVGTT was fully normalized after the operation. The disposition index from OGTT data was increased about 10-fold and became similar to the values found in control subjects, and the disposition index from IVGTT data increased about 3.5-fold, similarly to what happened after the euglycemic clamp. The area under the curve (AUC) for GIP decreased about four times (from 3,000 ± 816 to 577 ± 155 pmol·l^{-1}·min, $P < 0.05$). On the contrary, the AUC for GLP1 almost tripled (from 150.4 ± 24.4 to 424.4 ± 64.3 pmol·l^{-1}·min, $P < 0.001$). No significant correlation was found between GIP or GLP1 percent changes and modification of the sensitivity indexes independently of the route of glucose administration.

CONCLUSIONS — Restoration of the first-phase insulin secretion and normalization of insulin sensitivity in type 2 diabetic subjects after malabsorptive bariatric surgery seem to be related to the reduction of the effect of some intestinal factor(s) resulting from intestinal bypass.

Diabetes Care 32:375–380, 2009

In 1987, Pories et al. (1) published a stunning observation that 99% of morbidly obese patients with frank type 2 diabetes or impaired glucose tolerance who had undergone Roux-en-Y gastric bypass (RYGB) became and remained euglycemic after surgery. Most interestingly, these authors reported that the patients were converted to euglycemia within 10 days, even if they had required large doses of insulin.

Subsequently, we (2,3) and other authors (4) have found that either restrictive or malabsorptive bariatric surgery is effective in improving/resolving type 2 diabetes. In particular, using the euglycemic hyperinsulinemic clamp we have demonstrated that insulin sensitivity was normalized after malabsorptive bariatric surgery in both obese type 2 diabetic (2) and obese normotolerant subjects.

We theorized that the normalization of insulin sensitivity that occurs very early after biliopancreatic diversion (BPD) before a significant weight loss can occur (2) may be dependent on the hormonal changes related to the nutrient diversion from the duodenum, the entire jejunum, and the proximal portion of the ileum. In fact, the enteroendocrine cells are largely found in these tracts of the small intestine.

Two main hypotheses have been advanced up to now to explain which part of the small intestine is implicated in the reversibility of diabetes. The first, known as the hindgut hypothesis (5), holds that diabetes control results from accelerated delivery of nutrients in the distal small intestine. The second, the so-called foregut hypothesis, states that the exclusion of duodenum and jejunum from nutrient transit might prevent the secretion of a putative signal that promotes insulin resistance (2,6). The balance between the stimulatory action on insulin secretion exerted by incretins and the anti-incretin effect might allow a finer control of the glucose disposal.

To test the hypothesis that an imbalance in the release of intestinal hormone(s) can determine insulin resistance and that after BPD secretion of intestinal hormone(s) is reduced, allowing normalization of insulin sensitivity with subsequent β-cell glucose sensitivity improvement, we assessed peripheral insulin sensitivity and β-cell function after either an intravenous or oral glucose tolerance test in nine obese, type 2 diabetic subjects compared with those in six normal-weight age- and sex-matched control subjects. To further support our results, insulin-dependent whole-body glucose disposal was also measured by the euglycemic clamp.

From the [1]Department of Systems Analysis and Informatics, University of Rome "La Sapienza," Rome, Italy; [2]Institute of Systems Analysis and Computer Science, Consiglio Nazionale delle Ricerche, Rome, Italy; [3]Institute of Internal Medicine, Catholic University, School of Medicine, Rome, Italy; and [4]Liver Unit, Bambino Gesù Hospital and Research Institute, Rome, Italy.
Corresponding author: Serenella Salinari, salinari@dis.uniroma1.it.
Received 15 July 2008 and accepted 19 November 2008.
Published ahead of print at http://care.diabetesjournals.org on 25 November 2008. DOI: 10.2337/dc08-1314.

RESEARCH DESIGN AND METHODS

— Nine (five women and four men) morbidly obese (BMI 51.7 ± 8.1 kg/m^2, age 41 ± 9 years [mean ± SD]), type 2 diabetic patients and six normotolerant (according to the American Diabetes Association criteria [7]) sex- and age-matched volunteers (three women and three men, BMI 24.6 ± 1.3 kg/m^2, age 39 ± 7 years) were studied. The patients were all characterized as having type 2 diabetes according to the American Diabetes Association criteria. A1C ranged from 7.5 to 9.5%.

At the time of the baseline study, all subjects were consuming a diet with the following average composition: 60% carbohydrate, 30% fat, and 10% protein (~1 g/kg body weight). This dietary regimen was maintained for 1 week before the study. In all patients, an oral glucose tolerance test (OGTT), an intravenous glucose tolerance test (IVGTT), and a euglycemic hyperinsulinemic clamp (EHC) were randomly performed within 1 month before surgery and 1 month after surgery. The healthy volunteers also underwent the same tests. All patients received the same parenteral nutrition regimen (~7,100 kJ/day) during the first 6 days after surgery; then they were free to consume a normal diet.

The study protocol was approved by the institutional ethics committee of the Catholic University of Rome. The nature and purpose of the study were carefully explained to all subjects before they provided their written consent to participate.

Body composition

On a separate day, total body water (TBW) was determined using 0.19 MBq ^3H_2O in 5 ml of saline administered as an intravenous bolus injection. Blood samples were drawn before and 3 h after the injection. Radioactivity was determined in duplicate on 0.5 ml plasma in a β-scintillation counter (model 1600TR; Canberra-Packard, Meriden, CT). Corrections were made for nonaqueous hydrogen exchange. Water density at body temperature was assumed to be 0.99371 kg/l. TBW (kilograms) was computed as ^3H_2O dilution space (liters) × 0.95 × 0.99371. Fat-free mass (FFM) was obtained by dividing TBW by 0.732 (8).

OGTT

After an overnight fast, a standard 75-g OGTT was performed in each patient at baseline and within 1 month after surgery as well as in each volunteer, with blood sampling at 0, 30, 60, 90, 120, 150, 180, and 240 min. Samples were placed in chilled tubes, and plasma was separated within 20 min and stored at −70°C.

IVGTT

An IVGTT was performed preoperatively and within 1 month postoperatively. At 8:00–9:00 A.M., after a 12-h overnight fast, an intravenous catheter was placed in one antecubital vein and an intravenous bolus of 0.33 g glucose/kg body weight as 50% water solution was injected in the contralateral antecubital vein. Blood samples were obtained at −15, −5, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 25, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, 180, and 240 min relative to the start of dextrose injection. Samples were placed in chilled tubes, and plasma was separated within 20 min and stored at −70°C.

EHC

Peripheral insulin sensitivity was evaluated by the EHC (9) at baseline and within 4 weeks after surgery. After a cannula was inserted in a dorsal hand vein for sampling arterialized venous blood and another in the antecubital fossa of the contralateral arm for infusions, the subjects rested in the supine position for at least 1 h. They were placed with one hand warmed in a heated-air box set at 60°C to obtain arterialized blood samples. Insulin sensitivity, as the total insulin-mediated glucose uptake, was determined during a primed constant infusion of insulin at the rate of 6 pmol · min^{-1} · kg^{-1}. To maintain the glycemia in a normal range, rapid insulin and potassium phosphate in saline were infused overnight before BPD. The plasma glucose concentration was clamped at 5.1 ± 0.5 mmol/l (mean ± SD) before and at 3.9 ± 0.4 mmol/l after BPD, respectively, throughout the insulin infusion by means of a variable glucose infusion and blood glucose determinations every 5 min. Insulin sensitivity was determined during the last 40 min of the clamp by computing the whole-body glucose uptake (micromoles per minute per kilogram of FFM) or the clearance rate (milliliters per minute per kilogram of FFM) during steady-state euglycemic hyperinsulinemia.

BPD

This malabsorptive surgical procedure (2) consists of an ~60% distal gastric resection with stapled closure of the duodenal stump. The residual volume of the stomach is about 300 ml. The small bowel is transected at 2.5 m from the ileocecal valve, and its distal end is anastomosed to the remaining stomach. The proximal end of the ileum, comprising the remaining small bowel (involved in carrying biliopancreatic juice but excluded from food transit), is anastomosed in an end-to-side fashion to the bowel, 50 cm proximal to the ileocecal valve. Consequently, the total length of absorbing bowel is reduced to 250 cm, the final 50 cm of which, the so-called common channel, represents the site where ingested food and biliopancreatic juices mix.

Analytical procedures

Plasma glucose was measured by the glucose oxidase technique on a Beckman glucose analyzer (Beckman, Fullerton, CA). Plasma insulin was assayed by a microparticle enzyme immunoassay (Abbott, Pasadena, CA) with sensitivity of 1 μU/ml and intra-assay coefficient of variation (CV) of 6.6%. C-peptide was assayed by radioimmunoassay (MYRIA; Technogenetics, Milan, Italy); this assay has a minimal detectable concentration of 17 pmol/l and intra-assay and inter-assay CVs of 3.3–5.7 and 4.6–5.3%, respectively.

Total glucose-dependent insulinotropic polypeptide (GIP) was measured by ELISA (Linco). The assay is 100% specific for GIP 1–42 and GIP 3–42 and does not cross-react with glucagon-like peptide (GLP)-1, GLP-2, oxyntomodulin, or glucagon. The intra-assay and inter-assay CVs were 3.0–8.8 and 1.8–6.1%, respectively. Active GLP-1, an indicator of potential action, was measured by ELISA (Linco). The intra-assay and inter-assay CVs were 3–7 and 7–8%, respectively. The assay is 100% specific for GLP-1(7–36) and GLP-1(7–37) and does not react with GLP-1(9–36), glucagon, or GLP-2.

Mathematical model

The OGTT and IVGTT minimal models (10) were used to compute the insulin sensitivity (S_I). The indexes of β-cell sensitivity to glucose for the IVGTT (the first-phase β-cell sensitivity, Φ_1, and the second-phase sensitivity, Φ_2) and for the OGTT (the dynamic β-cell sensitivity, Φ_d, the static sensitivity, Φ_s, and the total sensitivity, Φ) were computed by the C-peptide minimal model as proposed by Toffolo et al. (11) and Breda et al. (12). The disposition index (DI) was computed as $\Phi \times S_I$. The model parameters were estimated by minimization of a weighted least-squares index using a constrained

Levenberg-Marquardt minimization routine of the MATLAB library. The standard errors of the estimates of individual parameters were evaluated by the Jackknife method (3), and the coefficients of variation were found to be <20%.

Statistics

All of the data are expressed as means ± SEM unless otherwise specified. The Wilcoxon paired-sample test and ANOVA for repeated measurements, followed by the Tukey test, were used for intragroup and intergroup comparisons, respectively. Two-sided $P < 0.05$ was considered significant. Nonparametric Spearman correlations (SPSS for Windows version 10) were used to assess linear relationships between single variables.

RESULTS — A small, but significant, weight loss (from 153.1 ± 34.2 to 143.5 ± 32.8 kg [mean ± SD], $P < 0.01$) was observed 1 month after BPD.

The OGTT glucose incremental area under the curve (ΔAUC) significantly ($P < 0.02$) decreased after BPD from 0.74 ± 0.08 to 0.22 ± 0.04 × 10^3 mmol/l · min, becoming not statistically different from that of control subjects. Insulin ΔAUC decreased from 3.83 ± 0.99 to 1.01 ± 0.28 × 10^4 pmol · l^{-1} · min ($P < 0.02$), reaching a value comparable to that of healthy control subjects (NS). Finally, the C-peptide ΔAUC declined from 2.48 ± 0.35 to 1.10 ± 0.34 × 10^2 nmol/l · min ($P < 0.02$); its value in control subjects was 1.71 ± 0.36 × 10^2 nmol/l · min (NS).

In the IVGTT also, the ΔAUC of glucose significantly decreased from 0.63 ± 0.08 to 0.51 ± 0.06 × 10^3 mmol · l^{-1} min ($P < 0.05$) (control subjects 0.31 ± 0.02 × 10^3 mmol · l^{-1} · min, NS). Similarly, insulin ΔAUC decreased from 3.66 ± 0.65 to 1.90 ± 0.27 × 10^4 pmol · l^{-1} · min ($P < 0.02$) (control subjects 0.50 ± 0.06 × 10^4 pmol · l^{-1} · min). C-peptide ΔAUC did not change significantly (from 1.63 ± 0.28 to 1.54 ± 0.50 × 10^2 nmol · l^{-1} · min, NS); however, the latter was not statistically dissimilar from that in control subjects (0.85 ± 0.16 × 10^2 nmol · l^{-1} · min, NS), probably as a consequence of a rather large SEM.

The estimates of the indexes computed by the oral and intravenous mathematical models are reported in Table 1. The first phase of insulin secretion was fully normalized after BPD, as shown in Table 1 by the marked increase of the Φ_1 index. Figure 1 shows the recovery of the first phase of the insulin secretion rate in the IVGTT. The dynamic sensitivity index also showed a tendency to increase after BPD.

Before BPD, the insulin sensitivity determined by the OGTT was significantly smaller than that found by the IVGTT or the euglycemic clamp (Table 1), with the M value increasing from 27.7 ± 6.4 to 77.9 ± 20.0 μmol · kg_{FFM}^{-1} · min^{-1} after BPD ($P < 0.0001$). However, 1 month after BPD, insulin sensitivity reached values comparable to those found in control subjects, independently of the glucose administration route. In particular, a threefold increase in the insulin sensitivity estimated by either the IVGTT minimal model or the EHC was observed, whereas the same index computed by the OGTT minimal model was raised six times ($P < 0.05$). The DI, calculated by the OGTT, was increased ~10-fold and became similar to the values found in control subjects, whereas the DI calculated by the IVGTT increased about 3.5 times.

Table 1—*Estimates of the indexes computed by the oral and the intravenous mathematical models*

	Control subjects	Diabetic subjects before BPD	Diabetic subjects after BPD
Indexes OGTT			
$S_I \times 10^2$ (ml · min^{-1} · kg_{FFM}^{-1} · $pmol^{-1}$ · l)	2.70 ± 0.98	0.64 ± 0.19	3.60 ± 0.97*
$S_{I\,post}/S_{I\,pre}$			6.3 ± 3.1
$\Phi_d \times 10^{-9}$	500 ± 140	203 ± 144	480 ± 365
$\Phi_s \times 10^{-9}$ (min^{-1})	39.2 ± 20.8	23.0 ± 10.0	32.0 ± 16.0
$\Phi \times 10^{-9}$ (min^{-1})	47.7 ± 24.3	25.9 ± 11.2	37.7 ± 12.0#
AUC_{ISR} (nmol · m^{-2})	33.4 ± 12.8	62.3 ± 28.4	37.2 ± 13.3¶
DI × 10^{-14} (dl · min^{-2} · kg_{FFM}^{-1} · $pmol^{-1}$ · l)	1,197 ± 599	148 ± 51	1,227 ± 276¶
Indexes IVGTT			
$S_I \times 10^2$ (ml · min^{-1} · kg_{FFM}^{-1} · $pmol^{-1}$ · l)	2.10 ± 0.80	1.04 ± 0.28	2.70 ± 0.60§
$S_{I\,post}/S_{I\,pre}$			2.7 ± 1.1
$\Phi_1 \times 10^{-9}$	242 ± 199	27.9 ± 17.1	164 ± 119§
$\Phi_2 \times 10^{-9}$ (min^{-1})	10.2 ± 2.9	10.0 ± 4.8	12.5 ± 8.5
$\Phi \times 10^{-9}$ (min^{-1})	16.6 ± 5.3	10.8 ± 5.2	16.5 ± 9.5#
AUC_{ISR} (nmol · m^{-2})	23.9 ± 3.7	43.9 ± 22.8	41.9 ± 21.7
DI × 10^{-14} (dl · min^{-2} · kg_{FFM}^{-1} · $pmol^{-1}$ · l)	341 ± 124	118 ± 78	453 ± 318§
Indexes EHC			
$S_I \times 10^2$ (ml · min^{-1} · kg_{FFM}^{-1} · $pmol^{-1}$ · l)		1.4 ± 0.7	4.5 ± 1.5
$S_{I\,post}/S_{I\,pre}$			3.5 ± 1.2

Data are means ± SD. OGTT (after/before): *$P < 0.005$; #$P < 0.05$; ¶$P < 0.02$. Diabetic subjects after BPD/control subjects: NS. IVGTT (after/before): §$P < 0.01$; #$P < 0.05$. Diabetic subjects after BPD/control subjects: NS. EHC: S_I before BPD is significantly different from S_I (OGTT) ($P < 0.001$). S_I (OGTT) and S_I (IVGTT) before BPD are significantly different ($P < 0.05$); S_I (EHC), S_I (OGTT), and S_I (IVGTT) after BPD are not significantly different.

The time courses of GIP and GLP-1 during the OGTT are reported in Fig. 2. GIP peaked earlier after than before BPD, i.e., 30 min compared with 60 min. The ΔAUC_{GIP} (mean ± SEM) decreased about four times, from 3,000 ± 816 pmol · l^{-1} · min preoperatively to 577 ± 155 pmol · l^{-1} · min postoperatively ($P < 0.05$). On the contrary, the ΔAUC_{GLP1} was almost tripled, from 150 ± 24 to 424 ± 64 pmol · l^{-1} · min ($P < 0.001$). The ΔAUC of both GLP1 and GIP in control subjects (392 ± 11 and 983 ± 77 pmol · l^{-1} · min, respectively) were not statistically different from the values observed in diabetic patients after BPD.

No significant correlation was found between the percent change in the AUCs of GIP and GLP-1 and the modification of the oral sensitivity index.

CONCLUSIONS — The principal findings of our study are that *1*) the first-phase insulin secretion was restored 1 month after BPD (Φ_1), *2*) the β-cell glucose sensitivity was fully normalized, *3*)

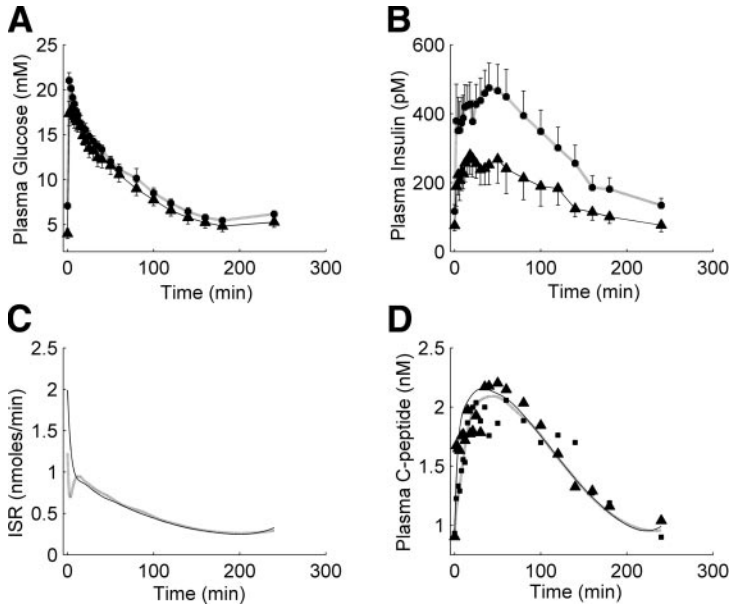

Figure 1— *IVGTT data (mean ± SEM). Glucose* (A) *and insulin* (B) *plasma concentrations before (gray shaded line) and after (solid line) BPD. Insulin secretion rate (ISR)* (C) *and C-peptide data points with the fitting curves superimposed* (D)*. Before BPD: gray shaded lines and* ■*; after BPD: solid lines and* ▲*. Because of the overlapping of SEM bars, only mean values of C-peptide data are reported.*

the DI was normalized thanks to the normalization of insulin sensitivity and the consequent reduced requirement of insulin secretion, and *4*) the increase in the insulin sensitivity estimated by the OGTT minimal model was larger than that estimated by the IVGTT minimal model.

The association of β-cell dysfunction with insulin resistance represents the main pathophysiological defect responsible for the development of type 2 diabetes. The β-cell function in type 2 diabetes is characterized by a progressive decline, from a net reduction to the disappearance of the first phase of glucose-induced insulin secretion to the impairment of the second-phase insulin secretion. The early insulin response disappears, even in the early stages of the disease, when fasting glucose concentrations are only slightly higher than normal. This defect is important because first-phase insulin secretion seems to have the greatest impact on postprandial plasma glucose excursions (13), determining postmeal hyperglycemia.

Actually, the causes of this β-cell dysfunction are not completely known. Autopsy studies have shown that <20–50% of the β-cells may have been lost after many years of disease (14). However, there is experimental evidence that a 65% partial pancreatectomy in dogs reduces the maximum secretive pancreatic insulin response, but that the residual pancreatic β-cells become more sensitive to glucose, thus providing partial compensation (15). Therefore, Porte and Kahn (16) noted that "the loss of β-cell function is disproportionately more important than the degree of β-cell loss." Furthermore, there is more recent evidence from the autopsy of type 2 diabetic patients that the β-cell mass is not significantly diminished in most patients and that β-cells maintain active insulin gene transcription and translation even in amyloid-containing islets. This finding suggests that the main defect resides in an abnormal coupling of insulin secretion to glycemia (17).

It is interesting to note that in the present investigation the first-phase insulin secretion impairment was reversible after BPD, when the body weight was reduced only on the order of ~6%. Briatore et al. (18) have recently reported that the acute insulin response (AIR) after IVGTT was significantly increased after BPD in morbidly obese, type 2 diabetic subjects. However, being based on insulin concentration, AIR does not correspond directly to the first phase of insulin secretion, as it also reflects the hepatic insulin extraction. Because the hepatic extraction differs depending on the pattern and amount of insulin release, AIR does not provide an independent assessment of insulin secretion. Furthermore, insulin clearance appeared to be significantly reduced before BPD, according to recently published findings (19).

Recently, Henquin et al. (20) clearly showed that the first-phase insulin secretion, which was absent in vivo in mice with a double knockout for islet antigen 2 and 2β (21), was fully restored in the islets of the same animals studied in vitro. Thus, these authors (20) suggested the existence of factors, extrinsic to the islets, that can inhibit the in vivo insulin response to an intraperitoneal glucose challenge. In analogy with the hypothesis of Henquin et al. (20), we suggest that a "factor" inhibiting insulin secretion can be produced in the small intestine and that the intestinal bypass, as occurs in BPD, can reduce/suppress its synthesis and/or delivery into the circulatory stream, allowing the restoration of the first-phase insulin secretion.

It has been shown that a 3-h synthetic GLP-1 infusion in type 2 diabetic individuals was able to increase the AIR after an IVGTT from 197 ± 97 to 1,141 ± 409 pmol · l^{-1} · min, which, however, was still seven times lower than the levels reached in healthy control subjects (22). The corresponding circulating levels of GLP1 were on the order of 40–50 pmol/l. In our series, the

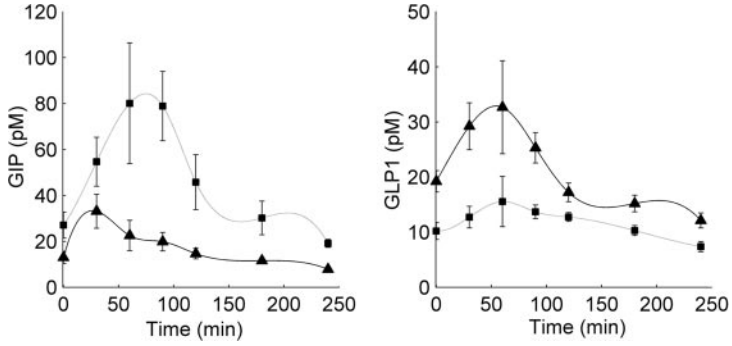

Figure 2— *GIP and GLP-1 concentrations during OGTT in diabetic patients before (■) and after (▲) BPD.*

first-phase insulin secretion was normalized, whereas the circulating GLP1 reached levels of about 35 pmol/l, suggesting that other mechanisms, such as the presence of still unrecognized intestinal factor/s can play a role in normalizing insulin secretion.

This very factor, or even another factor secreted by the small intestine, may also determine the insulin resistance. In fact, insulin sensitivity was fully normalized after BPD when a small but significant weight loss was achieved. In support of this hypothesis, we have found that the insulin-mediated glucose uptake was significantly higher after BPD when the glucose load was administered orally instead of intravenously. Dalla Man et al. (23) have shown that insulin action on glucose disposal estimated by the oral minimal model (S_I*) was almost identical to that measured by a euglycemic hyperinsulinemic clamp ($S_I{}^{*clamp}$), suggesting that the glucose disposal component of the oral glucose minimal model was well described. Therefore, at least in healthy control subjects, the OGTT minimal model of glucose kinetics provides estimates of insulin action equivalent to those with the euglycemic clamp. This observation reinforces our findings that after BPD insulin sensitivity increases much more after an oral than an intravenous glucose challenge. Furthermore, insulin resistance before bariatric surgery was much higher after an oral than after an intravenous glucose load. Therefore, the anatomical changes induced by the operation led to a complete inversion of the insulin sensitivity response, depending on the route of glucose administration.

To our knowledge, very few data are found in the literature for insulin sensitivity after RYGB, and these were measured mostly by empirical methods and thus are not easily comparable to the present results. We reported previously (24) that insulin-mediated glucose uptake, measured by the EHC, did not change significantly after RYGB, whereas it was dramatically increased after BPD in normotolerant, morbidly obese patients, becoming even higher than that reported in healthy subjects. Burstein et al. (25) observed a significant increase in the glucose metabolic clearance rate, from a mean baseline value of 3.0 ± 1.6 to 6.7 ± 3.9 ml · kg^{-1} · min^{-1} after RYGB ($P < 0.02$), which, however, as noted by the authors, was not completely reversed to normality.

We note that the GLP-1 plasma concentration was increased about threefold after BPD; however, neither the changes in GLP-1 plasma levels nor those in GIP explained the normalization of insulin sensitivity. This fact might suggest the existence of other intestinal factors in the control of insulin action in peripheral tissues, whose secretion is inhibited by surgery-induced nutrient diversion.

In summary, restoration of first-phase insulin secretion as well as normalization of the insulin sensitivity in type 2 diabetic subjects after malabsorptive bariatric surgery seems to be related to a reduction in the effect of some intestinal factor(s) as a consequence of intestinal bypass.

Acknowledgments— No potential conflicts of interest relevant to this article were reported.

References

1. Pories WJ, Caro JF, Flickinger EG, Meelheim HD, Swanson MS: The control of diabetes mellitus (NIDDM) in the morbidly obese with the Greenville gastric bypass. *Ann Surg* 206:316–323, 1987
2. Guidone C, Manco M, Valera-Mora E, Iaconelli A, Gniuli D, Mari A, Nanni G, Castagneto M, Calvani M, Mingrone G: Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. *Diabetes* 55:2025–2031, 2006
3. Salinari S, Bertuzzi A, Iaconelli A, Manco M, Mingrone G: Twenty-four hour insulin secretion and beta cell NEFA oxidation in type 2 diabetic, morbidly obese patients before and after bariatric surgery. *Diabetologia* 51:1276–1284, 2008
4. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K: Bariatric surgery: a systematic review and meta-analysis. *JAMA* 292:1724–1737, 2004
5. Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ: Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. *Am J Physiol Endocrinol Metab* 288:E447–E453, 2005
6. Rubino F: Is type 2 diabetes an operable intestinal disease? A provocative yet reasonable hypothesis. *Diabetes Care* 31: S290–S296, 2008
7. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 26:S5–S20, 2003
8. Sheng HP, Huggins RA: A review of body composition studies with emphasis on total body water and fat. *Am J Clin Nutr* 32: 630–647, 1979
9. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–E223, 1979
10. Caumo A, Bergman RN, Cobelli C: Insulin sensitivity from meal tolerance test in normal subjects: a minimal model index. *J Clin Endocrinol Metab* 85:4396–4402, 2000
11. Toffolo G, Cefalu WT, Cobelli C: β-Cell function during insulin-modified intravenous glucose tolerance test successfully assessed by the C-peptide minimal model. *Metabolism* 48:1162–1166, 1999
12. Breda E, Cavaghan MK, Toffolo G, Polonsky KS, Cobelli C: Oral glucose tolerance test minimal model indexes of β-cell function and insulin sensitivity. *Diabetes* 50:150–158, 2001
13. Bruce DG, Chisholm DJ, Storlien LH, Kraegen EW: Physiological importance of deficiency in early prandial insulin secretion in non-insulin-dependent diabetes. *Diabetes* 37:736–744, 1988
14. Ward WK, Bolgiano DC, McKnight B, Halter JB, Porte D Jr: Diminished B cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. *J Clin Invest* 74:1318–1328, 1984
15. Ward WK, Wallum BJ, Beard JC, Taborsky GJ Jr, Porte D Jr: Reduction of glycemic potentiation: sensitive indicator of β-cell loss in partially pancreatectomized dogs. *Diabetes* 37:723–729, 1988
16. Porte D Jr, Kahn SE: β-Cell dysfunction and failure in type 2 diabetes: potential mechanisms. *Diabetes* 50:S160–S163, 2001
17. Sempoux C, Guiot Y, Dubois D, Moulin P, Rahier J: Human type 2 diabetes: morphological evidence for abnormal β-cell function. *Diabetes* 50:S172–S177, 2001
18. Briatore L, Salani B, Andraghetti G, Danovaro C, Sferrazzo E, Scopinaro N, Adami GF, Maggi D, Cordera R: Restoration of acute insulin response in T2DM subjects 1 month after biliopancreatic diversion. *Obesity* 16:77–81, 2008
19. Kotronen A, Juurinen L, Tiikkainen M, Vehavaara S, Yki-Järvinen H: Increased liver fat, impaired insulin clearance, and hepatic and adipose tissue insulin resistance in type 2 diabetes. *Gastroenterology* 135:122–130, 2008
20. Henquin JC, Nenquin M, Szollosi A, Kubosaki A, Notkins AL: Insulin secretion in islets from mice with a double knockout for the dense core vesicle proteins islet antigen-2 (IA-2) and IA-2β. *J Endocrinol* 196:573–581, 2008
21. Kubosaki A, Nakamura S, Notkins AL: Dense core vesicle proteins IA-2 and IA-2β: metabolic alterations in double knockout mice. *Diabetes* 54: S46–S51, 2005
22. Quddusi S, Vahl TP, Hanson K, Prigeon

RL, D'Alessio DA: Differential effects of acute and extended infusions of glucagon-like peptide-1 on first- and second-phase insulin secretion in diabetic and nondiabetic humans. *Diabetes Care* 26:791–798, 2003
23. Dalla Man C, Yarasheski KE, Caumo A, Robertson H, Toffolo G, Polonsky KS, Cobelli C: Insulin sensitivity by oral glucose minimal models: validation against clamp. *Am J Physiol Endocrinol Metab* 289:E954–E959, 2005
24. Muscelli E, Mingrone G, Camastra S, Manco M, Pereira JA, Pareja JC, Ferrannini E: Differential effect of weight loss on insulin resistance in surgically treated obese patients. *Am J Med* 118:51–57, 2005
25. Burstein R, Epstein Y, Charuzi I, Suesshholz A, Karnieli E, Shapiro Y: Glucose utilization in morbidly obese subjects before and after weight loss by gastric bypass operation. *Int J Obes Relat Metab Disord* 19: 558–561, 1995