Original Article

Mechanisms of Recovery From Type 2 Diabetes After Malabsorptive Bariatric Surgery

Caterina Guidone,[1] Melania Manco,[1] Elena Valera-Mora,[1] Amerigo Iaconelli,[1] Donatella Gniuli,[1] Andrea Mari,[2] Giuseppe Nanni,[3] Marco Castagneto,[3] Menotti Calvani,[1] and Geltrude Mingrone[1]

Currently, there are no data in the literature regarding the pathophysiological mechanisms involved in the rapid resolution of type 2 diabetes after bariatric surgery, which was reported as an additional benefit of the surgical treatment for morbid obesity. With this question in mind, insulin sensitivity, using euglycemic-hyperinsulinemic clamp, and insulin secretion, by the C-peptide deconvolution method after an oral glucose load, together with the circulating levels of intestinal incretins and adipocytokines, have been studied in 10 diabetic morbidly obese subjects before and shortly after biliopancreatic diversion (BPD) to avoid the weight loss interference. Diabetes disappeared 1 week after BPD, while insulin sensitivity (32.96 ± 4.3 to 65.73 ± 3.22 μmol · kg fat-free mass^{-1} · min^{-1} at 1 week and to 64.73 ± 3.42 μmol · kg fat-free mass^{-1} · min^{-1} at 4 weeks; $P < 0.0001$) was fully normalized. Fasting insulin secretion rate (148.16 ± 20.07 to 70.0.2 ± 8.14 and 83.24 ± 8.28 pmol/min per m^2; $P < 0.01$) and total insulin output (43.76 ± 4.07 to 25.48 ± 1.69 and 30.50 ± 4.71 nmol/m^2; $P < 0.05$) dramatically decreased, while a significant improvement in β-cell glucose sensitivity was observed. Both fasting and glucose-stimulated gastrointestinal polypeptide (13.40 ± 1.99 to 6.58 ± 1.72 pmol/l at 1 week and 5.83 ± 0.80 pmol/l at 4 weeks) significantly ($P < 0.001$) decreased, while glucagon-like peptide 1 significantly increased (1.75 ± 0.16 to 3.42 ± 0.41 pmol/l at 1 week and 3.62 ± 0.21 pmol/l at 4 weeks; $P < 0.001$). BPD determines a prompt reversibility of type 2 diabetes by normalizing peripheral insulin sensitivity and enhancing β-cell sensitivity to glucose, these changes occurring very early after the operation. This operation may affect the enteroinsular axis function by diverting nutrients away from the proximal gastrointestinal tract and by delivering incompletely digested nutrients to the ileum. *Diabetes* 55:2025–2031, 2006

From the Department of Internal Medicine, Catholic University, School of Medicine, Rome, Italy; the [2]Metabolic Modeling Unit, Institute of Biomedical Engineering, National Research Council, Padova, Italy; and the [3]Department of Surgery, CNR Centro di Fisiopatologia dello Shock, Catholic University, School of Medicine, Rome, Italy.

Address correspondence and reprint requests to Prof. Geltrude Mingrone, Dipartimento di Medicina Interna, Catholic University, Largo A. Gemelli, 8, 00168 Rome, Italy. E-mail: gmingrone@rm.unicatt.it.

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AUC, area under the curve; BPD, biliopancreatic diversion; FFM, fat-free mass; GIP, gastrointestinal polypeptide; GLP-1, glucagon-like peptide 1; OGTT, oral glucose tolerance test.

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Resolution of type 2 diabetes has been observed as an additional benefit of surgical treatment for morbid obesity (1). After the Greenville gastric bypass operation, 88.7% of 515 morbidly obese patients became and have remained euglycemic, and only 5.8% patients remained diabetic (2). The Swedish Obese Subjects Intervention Study (3), where the effect of bariatric surgery was compared with that of conventional medical treatment of obesity in a large sample of 1,690 obese subjects, showed that the 2-year incidence of diabetes in the surgical arm was 0% compared with 16% in the control group. Furthermore, clinical remission of type 2 diabetes occurred in 83% of 192 severely obese patients with type 2 diabetes who underwent laparoscopic Roux-en-Y gastric bypass, while a significant improvement was observed in the remaining 17%. Noticeably, this study found that a shorter history of diabetes and milder disease was associated with an increased likelihood of remission (4).

In a recent systematic review and meta-analysis of the data reported in the literature on bariatric surgery, Buchwald et al. (5) found a gradation of effects on the resolution of diabetes from 98.9% for biliopancreatic diversion (BPD) or duodenal switch technique to 83.7% for gastric bypass to 71.6% for gastroplasty and to 47.9% for gastric banding. However, up to now, there is a lack of prospective studies showing the relative merits of gastric restrictive or malabsorptive procedures for those patients with diabetes.

It should be emphasized that in these subjects, glycemic control often occurs long before a significant weight loss (6), and bariatric surgery is also effective in curing diabetes in normal-weight subjects (7), suggesting that the control of diabetes may be a direct effect of the operations rather than a secondary outcome of the weight loss. Pories and Albrecht (8) have suggested that the rapidity of the correction to euglycemia, usually a matter of days, might be the result of the exclusion of food from the intestinal transit, resulting in a secondary alteration in incretin signals from the antrum, duodenum, and proximal jejunum to the pancreatic islets.

Up to now, no data are reported in the literature regarding the pathophysiological mechanisms involved in the rapid resolution of diabetes after malabsorptive bariatric surgery, like BPD. With the purpose of providing additional evidence on this topic and in order to avoid the interference due to weight loss, we have studied 10 obese, diabetic subjects both before and shortly after BPD, i.e., 1 and 4 weeks after surgery. Insulin sensitivity was mea-

sured using the euglycemic-hyperinsulinemic clamp, and insulin secretion was derived by the C-peptide deconvolution method after a standard oral glucose load, and, in addition, circulating levels of intestinal incretins and adipocytokines were obtained.

RESEARCH DESIGN AND METHODS

Ten morbidly obese women (BMI 54.55 ± 3.75 kg/m^2), affected by type 2 diabetes, undergoing BPD were studied. The onset of diabetes dated 1–3 years, and the average HbA_{1c} was 8.5 ± 1.2%. Patients were restudied at 1 and 4 weeks after surgery.

BPD. This malabsorptive surgical procedure (9) consists of a distal gastric resection with stapled closure of the duodenal stump. The residual volume of the stomach is ~400 ml. The small bowel is transected at 2.5 m from the ileo-caecal valve, and its distal end is anastomosed to the remaining stomach. The proximal end of the ileum, comprising the remaining small bowel carrying the bilio-pancreatic juice and excluded from food transit, is anastomosed in an end-to-side fashion to the bowel 50 cm proximal to the ileo-caecal valve. Consequently, the total length of absorbing bowel is brought to 250 cm, the final 50 cm of which (the so-called common channel) represents the site where ingested food and bilio-pancreatic juices mix. Immediately after BPD and until they restarted eating on the 6th day after the operation, the patients received 1,800 kcal (60% glucose, 25% fat as soybean emulsion, and 15% amino acids) as parenteral nutrition.

Body composition. Body weight was measured to the nearest 0.1 kg with a beam scale and height to the nearest 0.5 cm using a stadiometer (Holatin, Crosswell, Wales, U.K.). Total body water was determined using 0.19 Bq of tritiated water in 5 ml of saline solution 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 of plasma using a β-scintillation counter (model 1600TR; Canberra-Packard, Meriden, CT). Corrections were made (5%) for nonaqueous hydrogen exchange; water density at body temperature was assumed to be 0.99371 kg/l. Total body water (kilograms) was computed as ^3H_2O dilution space (liters) × 0.95 × 0.99371. The within-subject coefficient of variation (CV) for this method is 1.5%. Fat-free mass (FFM) in kilograms was obtained by dividing the total body water by 0.732 (10). Fat mass was then calculated as the difference between body weight and FFM.

Oral glucose tolerance test. A standard 75-g oral glucose tolerance test (OGTT) was performed in each patient at baseline and at 1 and 4 weeks after surgery, with blood sampling at 0, 30, 60, 90, 120, and 180 min.

Euglycemic-hyperinsulinemic clamp. Peripheral insulin sensitivity was evaluated by the euglycemic-hyperinsulinemic technique (11) at baseline and at 1 and 4 weeks after surgery. After inserting a cannula 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 (M value, in μmol · min^{-1} · kg FFM^{-1}) was determined during a primed constant infusion of insulin (at the rate of 6 pmol · min^{-1} · kg^{-1}). The fasting plasma glucose concentration was maintained throughout the insulin infusion by means of a variable glucose infusion and blood glucose determinations every 5 min.

Insulin action was expressed as the whole-body glucose disposal rate during steady-state euglycemic hyperinsulinemia. Glucose disposal (M value) was calculated from the exogenous glucose infusion rate during the last 40 min of the 2-h clamp after correction for changes in glucose concentration in a total distribution volume of 250 ml/kg. Whole-body glucose disposal was normalized per kilogram of FFM (m/kg$_{FFM}$). Insulin clearance rate (ml/min) was calculated as insulin infusion rate (pmol/min) divided by plasma insulin concentration (pmol/ml). The clearance values were then normalized by the body surface area.

β-Cell function was assessed using a model describing the relationship between insulin secretion and glucose concentration, which has been previously illustrated in detail (12,13). The characteristic parameter of the dose response is the mean slope within the observed glucose range, denoted as β-cell glucose sensitivity. The dose response is modulated by a potentiation factor, which accounts for several potentiating factors (prolonged exposure to hyperglycemia, nonglucose substrates, gastrointestinal hormones, in particular gastrointestinal polypeptide [GIP] and glucagon-like peptide 1 [GLP-1], and neurotransmitters). The potentiation factor is set to be a positive function of time and to average one during the experiment. Thus, it expresses a relative potentiation of the secretory response to glucose.

The model parameters were estimated from glucose and C-peptide concentration by regularized least squares, as previously described (14,15). Regularization involves the choice of smoothing factors that were selected to obtain glucose and C-peptide model residuals with SDs close to the expected measurement error (~1% for glucose and ~4% for C-peptide). As we have previously shown (14), this parameter estimation procedure resulted in reasonable reproducibility of the parameter estimates. CVs were 16% for insulin secretion at fixed glucose concentration, 24% for glucose sensitivity, and 52% for rate sensitivity.

Basal and total insulin secretion during the OGTT were calculated from the estimated model parameters. Total insulin secretion was calculated as the integral over the first 2 h of the OGTT, in both the 2- and 3-h OGTT protocols. Insulin secretion was expressed in picomoles per minute per meters squared of body surface area.

Analytical methods. Blood samples were drawn into EDTA-evacuated tubes, with the addition of 30 μl (10 μl per milliliter of blood) of dipeptidyl peptidase IV inhibitor (LC0014; Linco, St. Charles, MO). The plasma was immediately separated by centrifugation at 4°C and stored at −80°C until assay. These samples were not thawed until hormone assays were performed.

Plasma glucose was measured by the glucose oxidase method (Beckman, Fullerton, CA). Plasma insulin was assayed by microparticle enzyme immunoassay (Abbott, Pasadena, CA) with a sensitivity of 1 μU/ml and an intra-assay 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 inter- and intra-assay CVs of 3.3–5.7 and 4.6–5.3, respectively. Plasma adiponectin levels were measured using radioimmunoassay (Linco) with a sensitivity of 1 μg/ml and an intra-assay CV of 6.2%. Plasma leptin was assayed by radioimmunoassay for human leptin (Phoenix Pharmaceuticals, Phoenix, AZ). Intra- and interassay CVs were 4.2 and 4.5%, respectively. The sensitivity of the method was 0.5 ng/ml. Immunoreactive GIP levels were determined using 0.1 ml plasma in a human GIP RIA kit (Peninsula Laboratories, Belmont, CA). Intra-assay variation was <6% and interassay variation was ~8 and 12% for 20 and 80 pmol/l standards, respectively.

GLP-1(7–36)amide/(7–37) was measured by a GLP-1 (active) enzyme-linked immunoassay kit (Linco). This assay was based on a monoclonal antibody fixed in a coated microwell plate that binds the NH_2-terminal region of active GLP-1. The concentration of active GLP-1 is proportional to the fluorescence generated by umbelliferone, which is produced by the reaction between alkaline phosphatase (conjugated with anti–GLP-1 monoclonal antibodies) and methyl umbelliferyl phosphate. The lowest reported detection limit is 2 pmol/l; the reported within-assay CV is 8% at low and high concentrations (range 4–76 pmol/l), and the between-assay CV is 12% at 4–8 pmol/l and 7% at 28–76 pmol/l. Assay cross-reactivity is 100% for GLP-1(7–36)amide and GLP-1(7–37), but it is not detectable for GLP-1(9–36)amide, GLP-2, and glucagon.

Statistical analysis. Data are reported as means ± SE, unless otherwise specified. Data analyses were performed with SPSS statistical software (SPSS, Chicago, IL). Two-sided $P < 0.05$ was regarded as significant. The Wilcoxon's signed-rank test was performed to compare data from the same subjects before and after BPD, and the P values were adjusted using the Bonferroni method. The distribution of the residuals, testing for normality, and checking the linearity assumptions in the model were done by means of standard scatter plots. The areas under the curve (AUCs) of the hormone time courses were calculated using the trapezoidal rule.

Predictors of glucose and insulin sensitivity changes were tested using the Spearman correlation. Multiple linear regression was then used to fit models to predict glucose and insulin sensitivity changes after BPD. Predictor variables considered for these models included weight, insulin, leptin, GIP, and GLP-1 plasma levels. Variables were allowed to enter the models if significant at the <0.05 probability level.

RESULTS

Effect on weight loss and body composition. A nonsignificant average weight loss of 6.04 ± 1.27 kg was reached 1 week after BPD; while 4 weeks after the operation, the weight decrease was of borderline significance (15.5 ± 2.28 kg, $P = 0.051$) (Table 1). Fat mass decrease accounted for 72.6 ± 9.5% and FFM for 27.4 ± 9.5% of the weight lost at 1 week; while at 4 weeks, fat mass loss was 74.2 ± 5.9% and FFM loss was 25.7 ± 5.9%.

Effect on diabetes. A full reversion of diabetes was observed after BPD, since fasting plasma glucose as well as glycemia 2 h after OGTT were in the normal range 1 and 4 weeks after the operation.

Glucose, hormones, and adipocytokines. Data relative to the levels of glucose, insulin, C-peptide, incretins, and

TABLE 1
Anthropometric characteristics of the subjects

	Before BPD	1 week after BPD	4 weeks after BPD
n	10	10	10
Age (years)	51.0 ± 3.7	51.0 ± 3.7	51.0 ± 3.7
Weight (kg)	151.59 ± 13.10	146.75 ± 14.21	137.52 ± 14.0
BMI (kg/m^2)	54.55 ± 3.75	52.66 ± 4.01	48.89 ± 3.55
FFM (kg)	78.05 ± 9.41	77.65 ± 10.59	74.21 ± 8.84
Fat mass (kg)	73.54 ± 5.18	69.10 ± 5.51	61.70 ± 6.04

Data are means ± SE. No statistical difference was observed between preopertation and postoperation groups, either at 1 week or at 4 weeks following the operation.

adipocytokines both at fast and during OGTT, expressed as AUC values, are summarized in Table 2.

One week after BPD, fasting plasma glucose, leptin, and GIP significantly decreased; while fasting GLP-1 significantly increased and adiponectin did not change significantly. Four weeks after BPD, fasting plasma glucose was further reduced, although not significantly, while fasting plasma insulin and C-peptide significantly dropped; GIP and GLP-1 levels did not change significantly.

The AUC of glucose, insulin, C-peptide, and GIP circulating levels after the OGTT significantly decreased 1 week after BPD, but the further decrease at 4 weeks was not statistically significant. In contrast, the GLP-1 AUC significantly increased 1 week following surgery, but at 4 weeks the further increase was not significant. The time courses of plasma glucose, insulin, GIP, and GLP-1 during the OGTT, before and after BPD, are reported in Fig. 1. The time course of GLP-1 was relatively flat either before or after BPD.

Insulin sensitivity. Insulin sensitivity significantly ($P < 0.0001$) increased from 32.96 ± 4.30 to 65.73 ± 3.22 μmol · kg FFM^{-1} · min^{-1} 1 week after BPD and remained stable 3 weeks later (64.73 ± 3.42 μmol · kg FFM^{-1} · min^{-1}) at levels even higher than those reported in lean control subjects (15). No statistical difference was observed among steady-state plasma insulin levels during the clamps performed at different times (Table 3).

The insulin clearance, measured at euglycemic-hyperinsulinemic clamp steady state, did not significantly change before and after BPD (971.69 ± 40.92 ml/min before BPD vs. 952.25 ± 37.63 ml/min 1 week after BPD vs. 974.63 ± 48.57 ml/min 4 weeks after BPD).

Insulin secretion and β-cell sensitivity. Following surgery, fasting insulin secretion rate and total insulin output decreased, while a significant improvement in β-cell glucose sensitivity was observed, as shown in Table 3. The rate sensitivity, which is related to the first phase of insulin secretion, halved, while the potentiation, which also includes the effect of gastrointestinal hormones GIP and GLP1, was unchanged. Figure 2 reports the plot of total insulin output during the OGTT against insulin sensitivity in morbidly obese subjects before BPD and 1 and 4 weeks after. The following equations are of the fittings of the experimental data in Fig. 2: $y = 75.38e^{-0.0175x}$ before BPD; $y = 233.29e^{-0.037x}$ 1 week after BPD; and $y = 364.73e^{-0.0418x}$ 4 weeks after BPD.

It is clear from the above equations that not only the *y*-intercept value increases but the slope is also steeper after the bariatric operation, with the highest value being reached 4 weeks following BPD. These findings, which are used in the mathematical model to estimate the β-cell sensitivity, indicate that similar variation in insulin sensitivity produces a higher insulin secretion, which progressively increases over time from the operation.

Correlations. The cumulative fasting glucose percentage variation from baseline (1 week plus 4 weeks changes) was significantly related to the changes in fasting GIP levels (Fig. 3). As shown in Table 4, we were able to find significant positive metabolic-hormonal correlations between changes in AUC of glucose and GIP, glucose and insulin, GIP and GLP-1, and leptin and insulin. Finally, no significant correlation was observed between weight loss and leptin percentage decrease. Changes in adiponectin did not correlate with any other variable.

Multivariate analysis. In a multivariate model (R^2 of the general equation = 0.57 and $P = 0.04$.) with percent variation of weight, fasting GIP, GLP-1, insulin, and leptin levels as dependent variables, the best predictor of the changes in fasting glucose was the percent GIP variation ($P = 0.0011$). None of the dependent variables (namely changes in weight, fasting GIP, GLP-1, insulin, and leptin concentrations) significantly predicted the insulin-mediated glucose uptake modifications.

TABLE 2
Circulating levels of glucose, insulin, C-peptide, adipocytokines, and incretins after either an overnight fast and an OGTT, as AUC, in morbidly obese subjects before BPD and 1 week and 4 weeks after BPD

	Before BPD	1 week after BPD	4 weeks after BPD
	10	10	10
Fasting glucose (mmol/l)	7.79 ± 0.10	5.92 ± 0.42*	4.78 ± 0.12*
Fasting insulin (pmol/l)	135.72 ± 18.23	107.8 ± 15.99	69.04 ± 4.31†
Fasting C-peptide (nmol/l)	1.40 ± 0.13	1.05 ± 0.10	1.00 ± 0.08‡
Fasting leptin (ng/ml)	51.59 ± 6.38	38.56 ± 7.49*	31.03 ± 3.73
Fasting adiponectin (μ g/ml)	7.67 ± 0.82	8.49 ± 0.82	6.71 ± 0.36
Fasting GIP (pmol/l)	13.40 ± 1.99	6.58 ± 1.72§	5.83 ± 0.80§
Fasting GLP-1 (pmol/l)	1.75 ± 0.16	3.42 ± 0.41§	3.62 ± 0.21§
Glucose AUC (mmol/l)	1,704.52 ± 91.36	1,146.47 ± 88.52*	1,079.02 ± 47.13*
Insulin AUC (pmol/l)	96,390.90 ± 12681.51	53,414.30 ± 8617.14§	24,776.00 ± 2249.24*
C-peptide AUC (nmol/l)	589.89 ± 50.72	337.77 ± 52.38†	289.36 ± 24.87*
GIP AUC (pmol/l)	3,297.00 ± 440.60	1,775.70 ± 189.76§	1,874.00 ± 169.60§
GLP-1 AUC (pmol/l)	388.04 ± 23.40	700.14 ± 84.71†	721.46 ± 26.70*

Data are means ± SE. Significant differences were observed only between pre- and postoperation groups. *$P < 0.0001$; †$P < 0.001$; ‡$P < 0.05$; §$P < 0.01$.

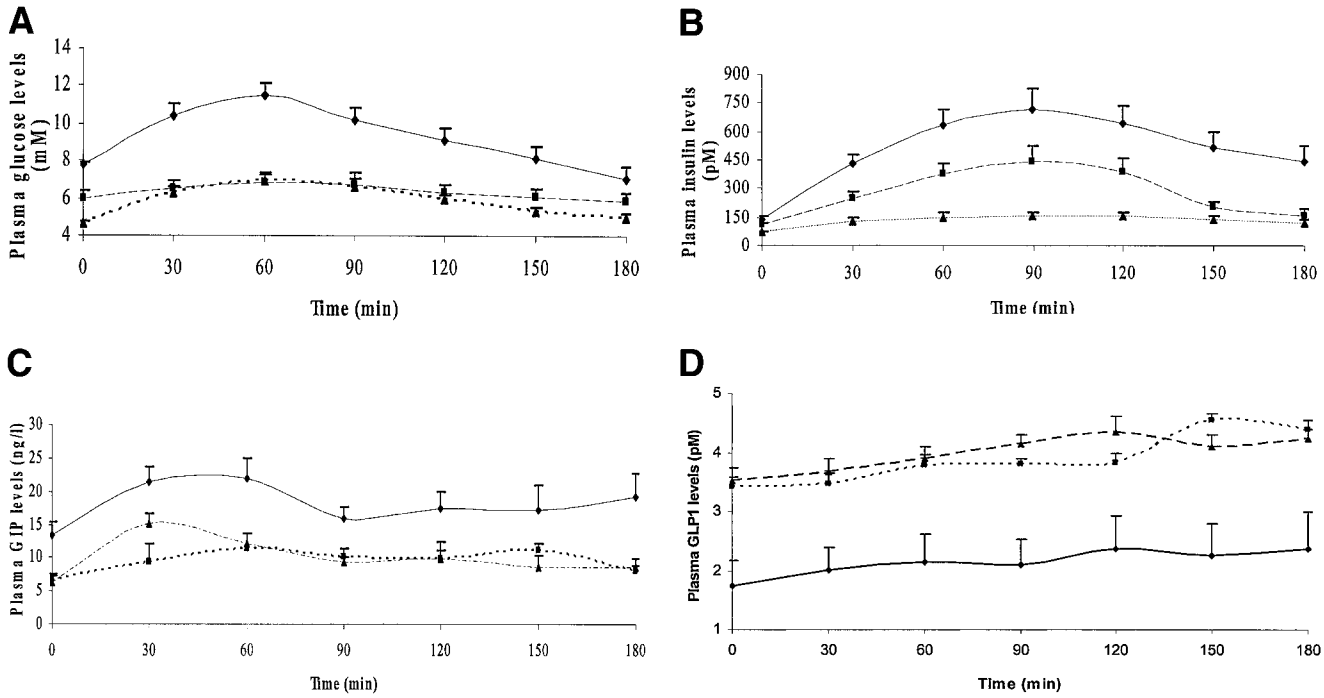

FIG. 1. Time courses of plasma glucose, insulin, GIP, and GLP-1 after OGTT before and after BPD. Solid line, before BPD; dashed line, 1 week after BPD; dotted line, 4 weeks after BPD. Data are expressed as means ± SE.

DISCUSSION

The main findings of the present investigation are that very early (at 1 and 4 weeks) after BPD, when no significant changes in body weight occurred, the patients experienced the following:

1) Complete reversion of frank type 2 diabetes
2) Full normalization of the insulin-mediated whole-body glucose uptake
3) Net improvement of the β-cell glucose sensitivity
4) Significant decrease of GIP plasma concentration both at fast and after OGTT
5) Significant increase of GLP-1 plasma levels both at fast and after OGTT
6) Significant reduction of the circulating levels of leptin either at fast and after OGTT

Diabetes reversal. Under conditions of stress or acute illness, such as cardiovascular events, surgery, infections, or stroke, insulin therapy is generally required in subjects affected by type 2 diabetes either because of the worsening of insulin resistance or because of frank diabetes decompensation (16). In contrast, our patients had a complete resolution of type 2 diabetes shortly after surgery, when their weight was not significantly changed.

In a recent review regarding the effects of bariatric surgery on type 2 diabetes, Greenway et al. (17) pointed out that "the exact mechanism for the dramatic effect of surgical procedures for obesity on type 2 diabetes remains unknown." Among the possible hypotheses on the mechanisms responsible for the reversion of diabetes, they examined the different effects of weight reduction, of the decreased caloric intake, and of the exclusion to food transit of the hormonally active foregut.

It is undoubted that the surgical exclusion of a large part of the small intestine from nutrient transit may play a relevant role in the resolution of diabetes. BPD operation consists of a partial gastrectomy, which leaves behind a 200- to 500-ml–sized upper stomach (400 ml in our series). This is connected to the distal 250 cm of small intestine,

TABLE 3
Insulin mediated, whole-body glucose uptake, steady-state plasma insulin during the euglycemic-hyperinsulinemic clamp, insulin secretion at fast and after an OGTT, β-cell glucose sensitivity, β-cell sensitivity rate, and potentiation in morbidly obese subjects before and 1 and 4 weeks after BPD

	Before BPD	1 week after BPD	4 weeks after BPD
n	10	10	10
FFM (m/kg$_{FFM}$) (μm · kg$_{FFM}^{-1}$ · min^{-1})	32.96 ± 4.30	65.73 ± 3.22*	64.73 ± 3.42*
Plasma insulin levels during clamp steady state (pmol/l)	520.20 ± 20.16	528.00 ± 24.23	520.80 ± 22.85
Fasting insulin secretion (pmol/ min per m^2)	148.16 ± 20.07	70.00.2 ± 8.14†	83.24 ± 8.28†
Total insulin output (nmol/m^2)	43.76 ± 4.07	25.48 ± 1.69‡	30.50 ± 4.71‡
β-Cell glucose sensitivity (pmol/min per m^2 per mmol/l)	29.61 ± 4.21	73.73 ± 4.01‡	60.99 ± 5.44‡
Rate of sensitivity (nmol/m^2 per mmol/l)	0.84 ± 0.06	0.44 ± 0.09	0.48 ± 0.09
Potentiation ratio (fold)	1.29 ± 0.15	1.95 ± 0.21	1.16 ± 0.20

Data are means ± SE. Significant differences were observed only between pre- and postoperation groups. *$P < 0.0001$; †$P < 0.01$; ‡$P < 0.05$.

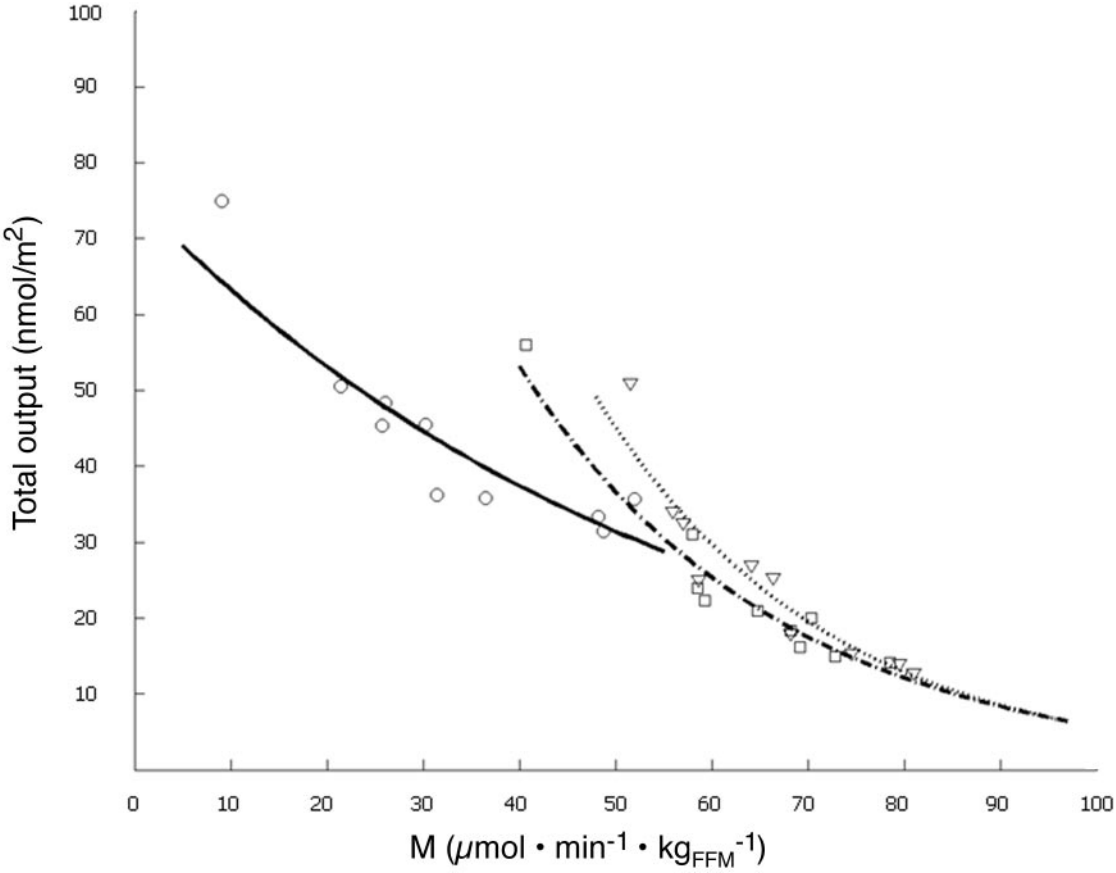

FIG. 2. Curvilinear reciprocal relationship between total insulin delivery and insulin resistance (as measured by the euglycemic clamp technique) in the groups of subjects. Solid line and ○, before BPD; dashed line and □, 1 week after BPD; dotted line and △, 4 weeks after BPD.

whereas the excluded small intestine carrying the bile and pancreatic secretions is connected to the alimentary channel 50 cm proximal to the ileocecal valve. Therefore, 2.5 m of ileum is transposed upward and connected to the stomach, while the duodenum, the whole jejunum, and part of the ileum are bypassed and consequently excluded from the transit of nutrients.

It is of great interest that the transposition of ileum in rats produces a metabolic and hormonal picture very similar to the one we have observed in humans after BPD. In fact, ileal transpositions in rats (18), a procedure consisting of transposing an isolated segment of the ileum to the jejunum, which results in an intestinal tract of normal length but with an alteration of the normal distribution of endocrine cells along the gut, was associated with a net increase in insulin sensitivity without any significant change in adiponectin levels but with rise of the glucose-stimulated GLP-1 and with significant lowering of plasma leptin. However, while these results were observed in rats 45 days after the operation and were ascribed to the adaptation of the ileum to an inappropriate amount and composition of the nutrient transit, in humans we demonstrated metabolic effects very early after BPD. Furthermore, the restoration of a normal insulin sensitivity, with subsequent improvement of the β-cell sensitivity, was not predicted by the variables measured. These data supports

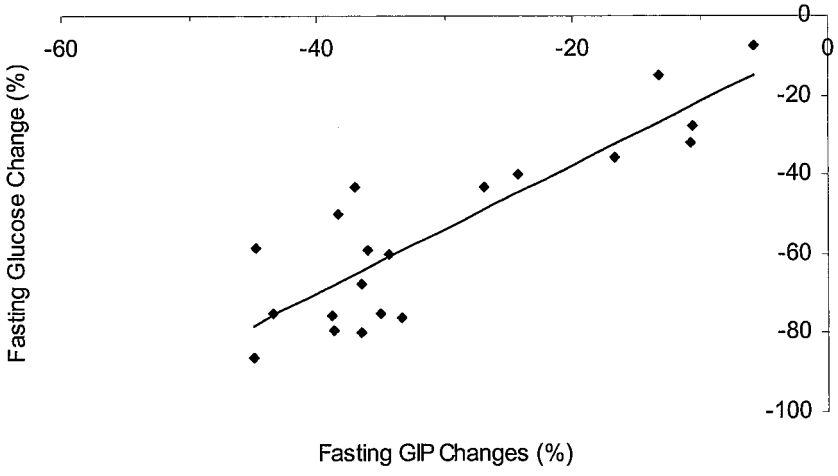

FIG. 3. Correlation between overall GIP percentage variation (1 week plus 4 weeks) and changes in glucose levels. The equation of the linear regression is fasting glucose percent variation = 1.6092 × fasting GIP percent variation − 5.4824 (R^2 = 0.75, P < 0.0001).

TABLE 4
Partial correlation coefficients between glucose AUC and hormonal AUC variables in the whole population (1 week plus 4 weeks)

	Spearman's ρ	Significance
Glucose AUC change vs. GIP AUC change	0.564	0.045
Glucose AUC change vs. insulin AUC change	0.552	0.049
GIP AUC changes vs. GLP-1 AUC changes	0.588	0.037
Leptin AUC changes vs. insulin AUC changes	0.505	0.023

the hypothesis that the exclusion of jejunum from the transit of nutrients might determine the inhibition of the secretion of one or more hormones determining insulin resistance. In fact, it is reasonable to hypothesize that if the small intestine produces hormones like GIP and GLP-1, which stimulate insulin secretion, it might also produce hormones responsible for a reduction of the insulin action on peripheral tissues.

Insulin-mediated whole-body glucose uptake. At either 1 and 4 weeks following BPD, insulin-mediated glucose disposal not only significantly increased but was even higher than the rates of glucose disposal shown in control subjects (15). There are few reports in the literature showing that in type 2 diabetic subjects' hyperglycemia improves more rapidly than loss of weight. Henry et al. (19) found that 87% reduction of hyperglycemia occurred during the first 10 days of calorie restriction. More recently, Kelley et al. (20) showed that in obese subjects with type 2 diabetes a 7-day period of calorie restriction (800 kcal/day) produced about half of the overall improvement in hepatic glucose production, insulin sensitivity, and insulin secretion with respect to that obtained after a substantial weight loss (from 92.7 ± 4.7 to 76.2 ± 2.9 kg; $P = 0.001$). However, the insulin sensitivity increase, measured by the euglycemic clamp, was in the order of 32% (from 142 ± 20 to 188 ± 17 mg/min per m^2; $P < 0.05$), while we found a 99% increase of the insulin sensitivity 1 week after BPD. Furthermore, contrary to our findings, in the study of Kelley et al. (20) neither the calorie restriction nor the weight loss produced the normalization of glucose tolerance after the OGTT, since plasma glucose levels at 120 min following the oral glucose load exceeded 200 mg/dl. Finally, Jazet et al. (21) showed that a 2-day very-low–energy diet in obese diabetic subjects lowered fasting plasma glucose via a decreased basal endogenous glucose production without an effect on glucose disposal.

Insulin secretion. Our result confirms the impaired β-cell glucose sensitivity of morbidly obese, type 2 diabetic subjects, as previously reported in the literature (14,22,23). The impairment in β-cell sensitivity was associated with the upregulation of insulin secretion (Fig. 3), as already pointed out (23). The higher basal insulin secretory activity was related to a higher total stimulated insulin output as a consequence of the raise of the secretory system set point.

An inverse correlation between insulin sensitivity and insulin secretion was found, as shown in Fig. 3. The slope of the exponential curves after BPD was steeper than before the operation, suggesting that the pancreatic insulin secretion in response to a similar variation in insulin sensitivity was increased. In fact, β-cell glucose sensitivity significantly increased after BPD so that insulin secretion was stimulated at low circulating glucose levels. The changes observed were independent of the weight loss.

Incretin secretion. The glucoincretins, gastric inhibitory peptide and GLP-1, are intestinal peptides secreted in response to glucose or lipid intake. GIP is secreted by the K-cells, which are primarily found in the duodenum, although they are also located throughout the whole small intestine (24–26). GLP-1 is secreted by the L-cells, distributed in the highest density in the distal ileum but also found throughout the rest of the small intestine and in high density in the large intestine (27).

One cause for impaired insulin secretion is a decreased capacity of the pancreatic β-cells to produce sufficient amounts of insulin. After food intake, insulin secretion depends not only on the level of blood glucose but also on the secretion and insulinotropic effect of gut hormones, like GIP and GLP-1. Normally, the incretins GLP-1 and GIP are responsible for as much as half of the glucose-dependent insulin release after food ingestion. Pretreatment of β-cells with GLP-1 in vitro enhances their glucose sensitivity; while, in a rat model of type 2 diabetes, GLP-1 improves the glucose sensitivity of previously resistant β-cells (28), GLP-1 decreases the rate of glucose production by the liver and increases insulin production (29), being the most potent of the incretins that stimulate insulin release (30).

It is therefore very interesting that reduced GLP-1 response after food intake has been reported in obese subjects (30), while, contrary to what is observed in control subjects, in patients with type 2 diabetes, a reduced or absent incretin effect has been described (31,32). Accordingly, only a slight rise in plasma GLP-1 was recorded in our obese patients with type 2 diabetes after the OGTT.

Roux-en-Y gastric bypass, a restrictive procedure that does not involve substantial malabsorption, has been associated with greatly enhanced release of certain intestinal hormones, most prominently the products of intestinal proglucagon (33,34). Recently, Rubino et al. (35) reported that after Roux-en-Y gastric bypass, insulin as well as GIP levels decreased to normal values in obese diabetic patients, whereas GIP increased slightly but not significantly in obese nondiabetic subjects.

In our series, the increase in GLP-1 secretion might be related to an enhanced ileal L-cell activation by highly concentrated nutrients passing through the ileum, which is transposed upwards and anastomized to the gastric pouch. Previous studies (36,37) have, in fact, demonstrated that perfusion of nutrients directly in the distal gut or ileal transposition in experimental animals increases the release of GLP-1 and peptide YY.

Data on isolated intestinal tissues and dietary treatments as well as results on knockout mice strongly suggest that GIP is secreted by intestinal cells in response to glucose and lipid. However, incretin secretion can also be induced by nondigestible carbohydrates and involves the autonomic nervous system and endocrine factors such as GIP itself and cholecystokinin. It is likely that the exclusion of duodenum and jejunum from food transit may reduce GIP secretion, as observed in the present study. However, the normalization of peripheral and β-cell insulin sensitivity might play a relevant causative role in the down regulation of GIP secretion.

Leptin. One week after BPD, a 25% reduction of plasma leptin levels was observed, with a further reduction of 15%

at 4 weeks. This result might be ascribed to both calorie restriction (38) and to the rapid decline of insulin circulating levels; in fact, it has been shown that insulin controls leptin expression (39).

Conclusions. In conclusion, BPD determines a prompt reversibility of type 2 diabetes by normalizing peripheral insulin sensitivity and by enhancing β-cell sensitivity to glucose; these changes occur very early after the operation.

BPD operation may affect the enteroinsular axis by diverting nutrients away from the proximal gastrointestinal tract and by delivering incompletely digested nutrients to the ileum. This, in turn, enhances the secretion of GLP-1 in the transposed ileum, while the exclusion of the duodenum and jejunum might be responsible for the down-regulation of GIP and of other gut hormones involved in insulin sensitivity regulation.

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