Predictors of weight loss and reversal of comorbidities in malabsorptive bariatric surgery[1–3]

Maria E Valera-Mora, Benedetta Simeoni, Lucilla Gagliardi, Antonino Scarfone, Giuseppe Nanni, Marco Castagneto, Melania Manco, Geltrude Mingrone, and Ele Ferrannini

ABSTRACT

Background: Cardiovascular and metabolic comorbidities are dramatically increased in severe obesity, a condition highly resistant to nonsurgical therapy.

Objective: The objective was to identify predictors of weight loss and reversal of comorbidity in obese patients undergoing malabsorptive bariatric surgery.

Design: Morbidly obese men and women ($n = 107$) were studied before and 2 y after biliopancreatic diversion (BPD). Body composition, serum lipid profile, oral glucose tolerance, and blood pressure were measured. Insulin sensitivity was determined by use of a euglycemic clamp. The length of the small intestine was measured during surgery.

Results: Intestinal length was 671 ± 99 cm, and the residual absorbing intestine after BPD ranged from 54% to 24% of initial length. Patients lost an average of 36% of their initial weight, with ≈50% of them reaching a body mass index (in kg/m^2) < 30. Serum cholesterol decreased (from 4.58 ± 1.11 to 3.34 ± 0.73 mmol/L; $P < 0.0001$), as did serum triacylglycerols (from 1.52 ± 0.59 to 0.88 ± 0.35 mmol/L; $P < 0.0001$), whereas insulin sensitivity rose 150% (from 26 ± 4 to 64 ± 11 μmol · min^{-1} · kg fat-free mass^{-1}; $P < 0.0001$). Diabetes (in 23% of patients before surgery) and hypertension (in 83%) were reduced (by 88% and 96%, respectively) after surgery. In a multivariate model (including sex, age, intestinal length, presence of diabetes, insulin sensitivity, and initial fat mass), age and diabetes were independent, negative predictors of weight loss, whereas initial fat mass was a strong positive predictor ($r^2 = 0.51$).

Conclusions: Two years after BPD in morbidly obese patients, comorbidities are largely corrected and insulin resistance is fully reversed despite persistent obesity. Initial fat mass, but not residual intestinal length, is the strongest predictor of weight loss after BPD. *Am J Clin Nutr* 2005;81:1292–7.

KEY WORDS Morbid obesity, bariatric surgery, weight loss, biliopancreatic diversion, insulin resistance

INTRODUCTION

Obese adults generally show a clustering of cardiovascular disease (CVD) risk factors; compared with their less severely obese counterparts, morbidly obese patients have a disproportionately high rate of mortality and morbidity (1–7). The health risk associated with obesity, including type 2 diabetes, hypertension, and coronary artery disease, increases exponentially as excess body weight reaches and exceeds 45 kg (8). In a Veterans Administration study of 200 morbidly obese men aged 23–70 y with an average weight of 144 kg, mortality was increased 12-fold in the 25–34-year age group and 6-fold in the 35–44-year age group. During a follow-up period of only 7 y, 50 subjects from the original cohort had died (9).

The failure of conventional intervention (ie, diet, exercise, behavior modification) to treat morbid obesity successfully has generated increasing interest in bariatric surgery (10, 11). The preliminary report of the 1991 National Institute of Health Consensus Conference (8) made a recommendation for surgery in those patients with a body mass index (BMI; in kg/m^2) > 40 who exhibit a strong desire for substantial weight loss to improve quality of life. In certain instances, less severely obese subjects (those with a BMI between 35 and 40) may also be considered for surgery. Included in that category are patients with high-risk comorbid conditions such as life-threatening cardiopulmonary problems, severe diabetes mellitus, or obesity-related physical problems that interfere with lifestyle.

Two general approaches are available to the surgical treatment of morbid obesity: restriction of food intake (mainly vertical banded gastroplasty and gastrointestinal bypass) and induced malabsorption (mainly biliopancreatic diversion; BPD). Operations that produce malabsorption rely on decreasing the absorptive surface of the small intestine and reliably produce rapid weight loss. BPD combines moderate volume restriction and severe lipid malabsorption to induce weight loss. BPD usually permits substantial decrements in body weight, but the variability in achieved weight is large (12, 13).

The aim of the present study was to identify factors that may predict individual weight loss in a large cohort of severely obese subjects with significant comorbidities undergoing BPD. In particular, we examined the effect of the residual absorbing intestinal length and insulin resistance on degree of weight loss and reversal of comorbidities.

[1] From the Departments of Internal Medicine (MEV-M, BS, LG, AS, MM, and GM) and General Surgery (GN, MC) and CNR (GM), Catholic University of Rome, Rome, Italy, and the Department of Medicine and CNR Institute of Clinical Physiology, University of Pisa School of Medicine, Pisa, Italy (EF).

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[3] Address reprint requests to E Ferrannini, Department of Internal Medicine, Via Roma, 67, 56100 Pisa, Italy. E-mail: ferranni@ifc.cnr.it.

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SUBJECTS AND METHODS

Study subjects

The study population consisted of 107 morbidly obese subjects (85 women and 22 men). The average age of the subjects was 37 ± 10 y ($\bar{x}$± SD).

Experimental protocol

Medical history, physical examination, and routine laboratory analyses were performed at the screening visit. On this occasion, the medical implications as well as treatment options were discussed with the patient. If appropriate, entry into the study was offered, and the informed consent was signed.

Blood pressure was measured 3 times after 5 min of rest, while the participant was sitting quietly. The mean of the second and the third reading was recorded. World Health Organization (WHO) criteria (14) were used for the classification of hypertension [normal = 1, systolic blood pressure (BP) < 130 mm Hg and diastolic BP < 85 mm Hg; borderline = 2, systolic BP 140–149 mm Hg and diastolic BP 90–99 mm Hg; mild = 3, systolic BP 149–159 mm Hg and diastolic BP 90–99 mm Hg; moderate = 4, systolic BP 160–179 mm Hg and diastolic BP 100–109 mm Hg; and severe = 5, systolic BP ≥ 180 mm Hg and diastolic BP ≥ 110 mm Hg]. Subjects were considered diabetic if fasting plasma glucose was ≥7 mmol/L or if 2-h plasma glucose was ≥11.1 mmol/L on the oral glucose tolerance test (15) or if they were on antidiabetic drugs. WHO criteria were used to define hypercholesterolemia (total cholesterol ≥ 5.17 mmol/L) and hypertriglyceridemia (serum triacylglycerols ≥ 1.92 mmol/L) (16); dyslipidemia was defined as the presence of hypercholesterolemia or hypertriglyceridemia.

The metabolic studies and body composition measurement (described in Body composition) were repeated 2 y after treatment, when patients had reached a stable weight (±1 kg over 6 mo). The study was approved by the Institutional Review Board of the Catholic University of Rome.

Body composition

We used a beam scale (Wunder SA.BI. srl, Milano, Italy) to measure body weight to the nearest 0.1 kg and a stadiometer (Holatin; Crosswell, Wales, United Kingdom) to measure height to the nearest 0.5 cm. Total body water was determined with the use of 0.19 Bq ^3H_2O in 5 mL saline solution administered as an intravenous bolus. Blood samples were drawn before and 3 h after the tracer dose. We used a β-scintillation counter (Canberra-Packard, Model 1600TR; Meriden, CT) to count radioactivity in duplicate on 0.5 mL plasma. Correction was made (5%) for nonaqueous hydrogen exchange, and water density at body temperature was assumed to be 0.99371 kg/L. Thus, total body water (in kg) was computed as the ^3H_2O dilution space × 0.95 × 0.99371. The intraindividual day-to-day CV reported for this method is 1.5% (17).

Metabolic studies

A 75-g oral glucose tolerance test was performed after an overnight fast at 0800. Blood samples were drawn at 0 and 120 min from an antecubital vein. Insulin sensitivity was measured by the euglycemic hyperinsulinemic clamp technique, as previously described (18). Briefly, after inserting a cannula into a dorsal hand vein for blood sampling and another cannula into a contralateral antecubital vein for infusions, the subjects rested in a supine position for at least 1 h with the cannulated hand placed in a heated (60 °C) box to obtain arterialized blood samples. Insulin sensitivity, as the whole-body insulin-mediated glucose disposal (also termed M value), was determined during a primed-constant infusion of insulin (at the rate of 240 pmol · min^{-1} · m^{-2}). The plasma glucose concentration was maintained throughout the period of insulin infusion by means of a variable glucose infusion and blood glucose determinations every 5 min. Whole-body insulin-mediated glucose disposal was calculated during the last 40-min period of insulin infusion and was expressed as μmol · min^{-1} · kg fat-free $mass^{-1}$ (18).

Analytic methods

Plasma glucose concentrations were measured by a glucose oxidase method with an automated analyzer (Beckman Instruments, Fullerton, CA). Plasma immunoreactive insulin was assayed by microparticle enzyme immunoassay (Abbott, Pasadena, CA). Serum cholesterol and triacylglycerol measurements were performed by standard enzymatic colorimetric methods. Serum concentrations of albumin were assayed by a quantitative, colorimetric method.

Biliopancreatic diversion

All patients underwent a BPD diversion according to Scopinaro's gastric resection with a Roux gastroenteroanastomosis. This procedure consists of ≈60% distal gastric resection with stapled closure of the duodenal stump. The residual volume of the stomach is ≈300 mL. The small bowel is divided at 250 cm 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 carrying the biliopancreatic juice and 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 in all cases (so-called alimentary tract); the final 50 cm, or common channel, represents the site where ingested food and biliopancreatic juices mix. Intestinal length was measured by the same surgeon during the intervention.

Statistical analysis

Data are given as means ± SDs. Clustering of CVD risk factors was defined as the number of prevalent conditions (hypertension, hyperlipidemia, or diabetes) for each subject, with a range of none to all 3 of these conditions. Proportions were compared by McNemar test. Mean values of continuous variables before and after surgery in women and men were compared by two-way analysis of variance for repeated measures. Simple and multiple linear regression analyses were used to identify predictors of weight loss; the coefficient of determination (r^2) was used as a measure of goodness of fit of the generated equation. A two-tailed P value < 0.05 was considered statistically significant. For all statistical analyses, we used the software package JMP (version 3.1; SAS Institute, Madison, WI).

RESULTS

Anthropometric variables

Two years after BPD, the patients had lost an average of 36% of their initial body weight, with a 50% reduction in fat mass and

TABLE 1
Anthropometric characteristics and length of the absorbing portion of the small intestine in women and men before and after biliopancreatic diversion (BPD)[1]

	Women (n = 85)	Men (n = 22)
Weight (kg)[2]		
Before BPD	129 ± 25	150 ± 18
After BPD[3]	84 ± 18	95 ± 16
BMI (kg/m^2)		
Before BPD	48.9 ± 8.8	48.1 ± 6.1
After BPD[3]	31.8 ± 7.1	30.5 ± 5.0
Fat-free mass (kg)		
Before BPD	88 ± 13	96 ± 14
After BPD[3]	62 ± 12	67 ± 13
Fat mass (kg)		
Before BPD	41 ± 24	54 ± 22
After BPD[3]	22 ± 14	28 ± 16
Intestinal length (cm)		
Before BPD	647 ± 74	773 ± 114[4]
After BPD	250	250

[1] All values are $\bar{x}$ ± SD.
[2] Significant interaction with sex, $P < 0.03$ (two-way ANOVA for repeated measures).
[3] Significantly different from before BPD, $P < 0.0001$.
[4] Significantly different from men, $P < 0.0001$.

a 30% decrease in fat-free mass (**Table 1**). Of the weight lost, 58% was fat-free mass. Women lost less weight than men (women: 46 ± 19 kg; men: 55 ± 12 kg; $P = 0.01$). Serum albumin did not change significantly after BPD (from 45.0 ± 4.5 to 42.4 ± 4.9 g/L).

Metabolic variables

Fasting serum cholesterol concentrations decreased from 4.58 ± 1.11 to 3.34 ± 0.73 mmol/L ($P < 0.0001$). Similarly, serum triacylglycerol concentrations declined from 1.52 ± 0.59 to 0.88 ± 0.35 mmol/L ($P < 0.0001$). Blood pressure was also significantly ($P < 0.001$) reduced in both men and women. Before surgery, 83% of the patients (22 men and 67 women) had borderline to severe hypertension; 2 y after surgery, blood pressure values were in the normal range in 96% of the patients, whereas the remaining 4% showed only mild hypertension not requiring the use of drugs. Before BPD, 23% of the patients (6 men and 19 women) had overt diabetes as shown by fasting or 2-h plasma glucose concentrations; after surgery, 88% of the diabetic subjects (4 men and 18 women) had regained normal glucose

TABLE 2
Prevalence of cardiovascular disease risk factors before and after biliopancreatic diversion (BPD)

	Men (n = 22)		Women (n = 85)	
No. of risk factors	Before BPD	After BPD	Before BPD	After BPD
	%		%	
One	73	14[1]	69	8[1]
Two	18	5	21	1[1]
Three	9	0	7	0[1]
One + two + three	100	19[1]	97	9[1]

[1] Significantly different from before BPD, $P \leq 0.05$ (McNemar test).

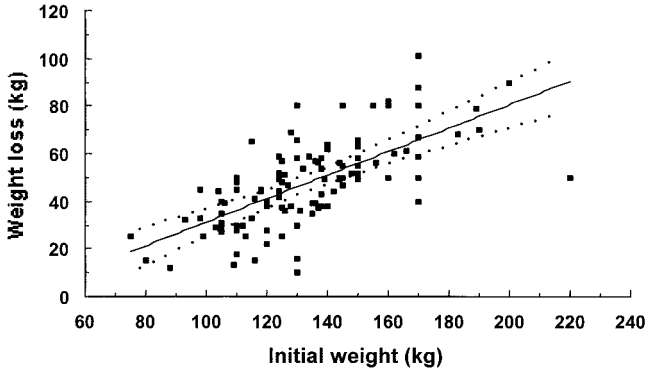

FIGURE 1. Dependence of achieved weight loss 2 y after surgery on initial body weight in 107 morbidly obese patients undergoing biliopancreatic diversion. The solid line is the line of best fit; the dotted lines are its 95% confidence bands. Equation: $y = -18 + 0.5x$; $r = 0.68$, $P < 0.0001$.

tolerance, whereas the 2 men and 1 woman who remained diabetic were in good glycemic control (glycated hemoglobin ≤ 7%) on diet treatment alone. Clustering of CVD risk factors (diabetes, hypertension, dyslipidemia) was not different in men and women before BPD (**Table 2**). After BPD, a drastic decrease was observed in prevalence of single or combined CVD risk factors.

Insulin sensitivity

Two years after BPD, insulin sensitivity increased by 150% (from 26 ± 4 to 64 ± 11 μmol · min^{-1} · kg fat-free mass^{-1}; $P <$

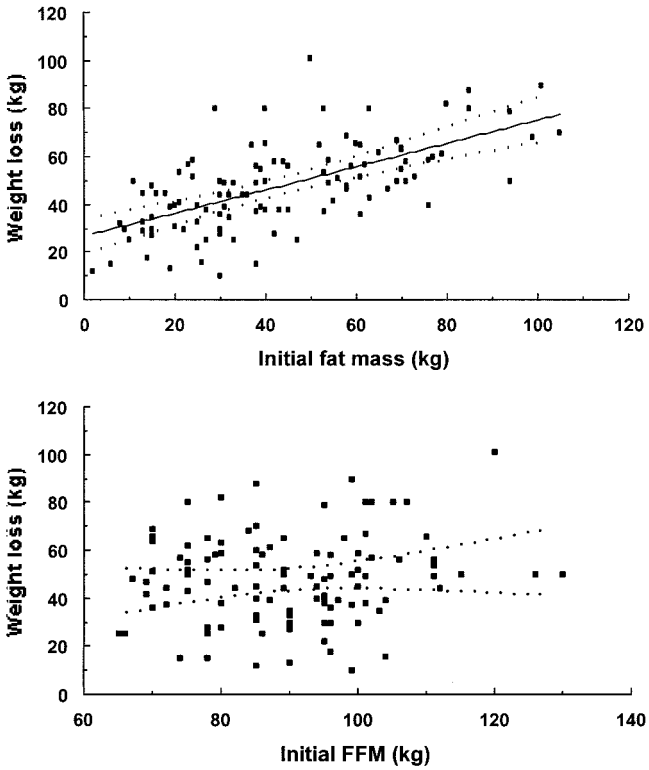

FIGURE 2. Dependence of achieved weight loss 2 y after surgery on initial fat mass (equation: $y = 27 + 0.5x$; $r = 0.64$, $P < 0.0001$.) or initial fat-free mass (FFM; $r = 0.14$, NS) in 107 morbidly obese patients undergoing biliopancreatic diversion. The solid line is the line of best fit; the dotted lines are its 95% confidence bands.

TABLE 3
Multiple regression analysis of weight loss (in kg)[1]

	β	PCC	P
Model 1			
Sex (women or men)	−0.53	0.03	NS
Age (10 y)	−3.34	0.26	<0.01
Diabetes (yes or no)	−3.13	0.20	<0.05
Initial insulin sensitivity	−0.82	0.20	0.05
Initial weight (kg)	0.44	0.57	<0.0001
Model 2			
Sex (women or men)	−0.62	0.04	NS
Age (10 y)	−3.07	0.24	<0.02
Diabetes (yes or no)	−3.27	0.21	<0.04
Initial insulin sensitivity	−0.17	0.03	NS
Initial fat-free mass (kg)	0.32	0.28	0.004
Initial fat mass (kg)	0.53	0.50	<0.0001

[1] β, regression coefficient; PCC, partial correlation coefficient.

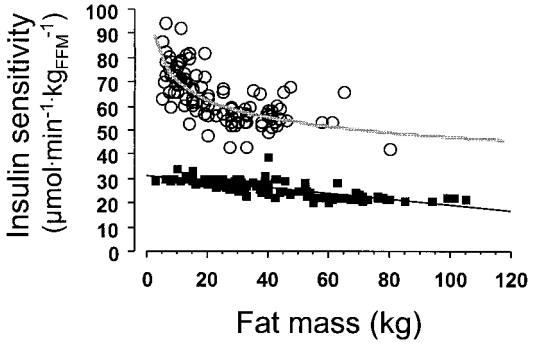

FIGURE 3. Relation between insulin sensitivity and total fat mass before (○) and 2 y after (■) biliopancreatic diversion. FFM, fat-free mass. The fitting function is a straight line before surgery ($y = 31 - 0.12x$; $r = 0.79$, $P < 0.0001$) and a power function after surgery ($y = 105x^{-0.18}$; $r = 0.72$, $P < 0.0001$). Note the complete separation of the 2 curves.

0.0001). Insulin sensitivity reached values similar to those reported for healthy lean subjects (19).

Intestinal length

The length of the intestine, as measured at surgery, showed a large interindividual variability (from a minimum of 460 to a maximum of 1050 cm; 671 ± 99 cm). Intestinal length was significantly greater in men than in women ($P < 0.0001$; Table 1).

Predictors of weight loss

In univariate association, weight loss was positively related to initial weight ($\rho = 0.71$, $P < 0.0001$) (**Figure 1**) and initial fat mass ($\rho = 0.64$, $P < 0.0001$) (**Figure 2**) and was negatively related to insulin sensitivity ($\rho = -0.45$, $P < 0.0001$). Age, diabetes, and insulin sensitivity were independent, negative predictors of weight loss in a multivariate model ($r^2 = 0.51$) that included sex, age, presence of diabetes, insulin sensitivity, and initial body weight, whereas initial body weight was a strong positive predictor (**Table 3**). By replacing initial weight with initial fat-free mass and initial fat mass, insulin sensitivity was no longer a significant predictor, and both initial fat mass and fat-free mass were independent positive predictors of weight loss. The use of attained weight instead of weight loss did not change the pattern of associations. The reciprocal relation between insulin sensitivity and fat mass was significantly different before from after surgery ($P < 0.0001$) (**Figure 3**).

DISCUSSION

The patients in this series presented a high prevalence of comorbid conditions, including dyslipidemia, hypertension, type 2 diabetes, insulin resistance, and psychosocial problems, which surgery corrected almost fully. Two years after surgery, body weight was rather stable and weight loss averaged 48 kg (corresponding to 75% of the initial weight excess), which was a similar outcome to previously reported data (20). Attained BMI ranged from 19 to 62, with only ≈10% of the patients achieving a BMI ≤ 25, but ≈50% of them reached a BMI ≤ 30.

The large variability in weight loss after BPD has been observed by others (20, 21) and remains incompletely understood. Scopinaro et al (13) have postulated that weight loss depends on the changes in body composition after surgery and on an "intestinal energy transport threshold." We attempted to identify predictors of weight loss by including direct measures of insulin resistance and the length of the segment of absorbing intestine excluded by BPD. Both measures show wide interindividual variability (≈100% for both), and either one might conceivably affect weight loss. For example, more patients with insulin resistance may lose weight at a slower rate because of their defective diet-induced thermogenesis (22, 23); however, excluding a larger fraction of absorbing surface may accelerate weight loss. In contrast, we found that neither insulin resistance nor the length of excluded intestine (whether in absolute terms or as a fraction of intestinal length before surgery) was a significant predictor of weight loss at 2 y. In a multivariate model, initial body weight (in particular, initial fat mass) was the most consistent positive predictor of weight loss; age and diabetes were also independent negative predictors. Thus, older patients lost less weight (an estimated 3 kg for each 10-y increase of age) and patients with diabetes lost on average 3 kg less than nondiabetic subjects, all other factors being equal. This result can be adequately explained by the separate effect of age and diabetes on energy expenditure (24): for an equivalent energy intake, subjects with a limitation in their ability to dissipate energy will lose less weight. Quantitatively, by far the strongest predictor of weight loss was the baseline body weight, alone explaining 46% of the variability in weight loss and 48% of the attained weight. This finding can be explained as follows. The amount of absorbed calories depends both on the ingested load and on the length of the absorbing small bowel surface. Because the surgical procedure was standardized, in each patient the length of the absorbing small bowel after surgery was 250 cm (which included, as detailed before, 200 cm of the so-called alimentary tract and 50 cm of the common tract). Thus, the same absorbing surface was available for the absorption of presumably different calorie loads. If absorption is proportional to intestinal length, then the amount of absorbable calories is decreased to the same absolute level, a "floor effect." Under these conditions, the amount of unabsorbed calories solely depends on the ingested load. Before surgery, when weight was stable, energy intake must have been approximately equal to total energy expenditure and, therefore, higher in more obese subjects. It is well established that resting energy expenditure is a rather close function of fat-free mass (22, 25, 26), and in several studies it has been estimated to be similar in obese and lean subjects

when expressed per kilogram of fat-free mass (22). In our series, fat-free mass ranged from 65 to 130 kg; by assuming an average resting energy expenditure of 24 kcal/kg (22), this range of fat-free mass translates to a difference of at least 1500 kcal in daily energy intake. Restraining calorie absorption to the same absolute amount results in a larger chronic calorie deficit in the heavier individual and a larger eventual weight loss. Clearly, the composition of individual diets and diet and physical activity adaptations after surgery are likely to play an additional role in determining weight loss, presumably accounting for the unexplained variability (50%) of attained weight in our series.

It is interesting to calculate that an average weight loss of 48 kg over 2 y corresponds to a daily calorie deficit of ≈500 kcal (assuming a calorie density of 7000 kcal for a kilogram of mixed fat mass and fat-free mass). In general, weight loss in response to bariatric surgery (as well as caloric restriction) does not follow a liner time course but is a highly nonlinear function of time, with an initial rapid weight reduction followed by a progressively slower decline in body weight (27).

Reversal of comorbidity (hypertension, diabetes, dyslipidemia) was independent of the degree of weight loss, because it was observed also in the subjects who remained obese (28). A likely explanation for this finding is that it is the lipid malabsorption rather than the weight loss per se that induces the correction of the obesity-related abnormalities. The diversion of biliopancreatic juices drastically reduces fat digestion and absorption. In addition, the reduction of gastric volume may also play a role in the lipid malabsorption, because a reduction in the passage of nutrients, particularly amino acids and lipids, through the stomach causes a decrease in the secretion of gastric lipase, an enzyme that represents one of the initial steps in lipid absorption. Another component is a reduction in the secretion of cholecystokinin, which normally stimulates the secretion of digestive enzymes (lipase, colipase, and proteases) (29). These changes are responsible for a marked decrease in the hydrolysis of triacylglycerols to monoacylglycerols, diacylglycerols, and fatty acids, with consequent reduction of the absorption of free fatty acids. In contrast, carbohydrate and protein malabsorption are limited because these nutrients are also absorbed in the residual ileum because of the presence of proteases on the brush border of enterocytes (20, 30). Incidentally, this is an essential feature that differentiates BPD from the jejunum-ileal bypass, in which ≈35 cm jejunum and 15 cm terminal ileum are preserved. Thus, the difference between the 2 malabsorptive operations depends on the additional 200 cm of ileum, which must play a relevant role in the absorption of proteins, probably through the proteases on the brush border of the enterocytes (31). In fact, although jejunum-ileal bypass frequently produces marked hypoproteinemia, BPD usually preserves plasma albumin mass (21).

The results on insulin resistance confirm and extend our previous reports, in which we showed that the lipid depletion associated with BPD is responsible for the reversal of insulin resistance in both nondiabetic (32) and diabetic patients (33). In the present series, the dependence of insulin sensitivity on fat mass followed a completely distinct function before and after surgery (Figure 3), as if the data were from different groups of people, one group very obese and insulin resistant, the other group moderately obese but metabolically normal. We and others have proposed that intracellular triacylglycerol accumulation in skeletal muscle is causally linked with insulin resistance and that selective depletion of the intramyocellular lipid pool is associated with normalization of cellular insulin action (32–38).

In conclusion, this study shows that the weight loss achieved with BPD is independent of the residual absorbing intestinal surface and that the lipid malabsorption rather than the degree of weight loss is the crucial determinant of the drastic improvement in metabolic and cardiovascular risk factors. Further studies of the pathophysiology of the adaptation of the short bowel, enterohormones, and intestinal villi are necessary to elucidate the mechanism and time course of weight loss in BPD, making it possible to tailor bariatric surgery to preset aims in terms of weight loss, cardiovascular risk reduction, or both.

MEV-M, BS, LG, AS, and MM conducted the experiments and followed the patients; GN and MC performed the surgery; GM and EF were responsible for the study design, data analysis, and interpretation. All authors have had full participation in the overall conduct of the study and agree with the content of the article. None of the authors had a conflict of interest in relation to this study.

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