Specific Effects of Biliopancreatic Diversion on the Major Components of Metabolic Syndrome

A long-term follow-up study

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OBJECTIVE — Gastric bypass and biliopancreatic diversion (BPD) are known to have a beneficial effect on glucose metabolism superior to that of the other bariatric operations. Thanks to its excellent weight loss results and to its specific actions, BPD has proven able to guarantee permanent normalization of serum glucose, triglygeride, and cholesterol levels in the vast majority, if not the totality, of operated patients. However, clinical studies on the duration of these effects in large patient populations are still lacking.

RESEARCH DESIGN AND METHODS — The files of 312 BPD obese patients with type 2 diabetes operated on from June 1984 to January 1993 were examined. Pre- and postoperative serum glucose, triglyceride, and cholesterol levels, along with arterial pressure measurements, were considered.

RESULTS — After BPD, fasting serum glucose concentration fell within normal values in all but two of the operated subjects and remained in the physiological range in all but six up until 10 years. Serum triglyceride and total cholesterol steadily normalized in all subjects with abnormally high preoperative values, and arterial hypertension disappeared in the vast majority of the preoperatively hypertensive patients.

CONCLUSIONS — BPD proved able to reverse all the major components of the metabolic syndrome in nearly all the operated subjects, with results being strictly maintained over a 10-year follow-up period. This outcome, which far exceeds those following similar weight loss at short or long term obtained by any other means, confirms the existence of specific actions of BPD on the major components of metabolic syndrome.

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Obesity is a serious health problem associated with important morbidity and mortality (1,2), much of which is secondary to conditions either determined or exacerbated by the obesity itself. These conditions, which include type 2 diabetes, arterial hypertension, and hyperlipidemia (3–7), are major causes of cardiovascular disease, as well as retinopathy, neuropathy, and renal disease. The prevalence of type 2 diabetes among severely obese patients is high, and despite medical treatment, type 2 diabetes is a leading cause of an overall increased mortality in obesity.

Previous reports have shown that diabetic obese patients become euglycemic following surgery for severe obesity (8–10). Roux-en-Y gastric bypass and biliopancreatic diversion (BPD) are the most effective surgical procedures for the treatment of type 2 diabetes in obese patients, both being followed by normalization of plasma glucose and insulin concentrations in the vast majority of the operated individuals (8,11–14). Plasma insulin and glucose concentration often fall back into a normal range after resumption of food intake and long before a significant weight loss occurs, thus suggesting that the control of diabetes might be a specific effect of the operation that contributes with the weight loss to the amelioration of the metabolic status (9,15,16). Although the marked immediate and sustained improvement of insulin action after BPD is well documented (15–18), long-term studies in large cohorts of diabetic obese patients undergoing BPD are still lacking. This article represents our attempt to provide such long-term follow-up data.

RESEARCH DESIGN AND METHODS

Biliopancreatic diversion consists of a distal gastrectomy with long Roux-en-Y recontruction, where the enteroenterostomy is placed 50 cm proximal to the ileocecal valve (Fig. 1). Both the volume of the gastric remnant and the length of the so-called alimentary limb, which are partly responsible for the level of weight stabilization, are adapted to patients' individual characteristics (ad hoc stomach ad hoc alimentary limb BPD, in use since September 1992). The mechanism of action of BPD essentially consists of limiting fat and starch, and thus energy, absorption while preserving the intestinal absorption of protein and noncaloric essential aliments. A constant maximum energy absorption capacity exists after BPD, which guarantees both weight loss and indefinite weight maintenance (12).

The study was carried out on the charts of the 1,540 obese subjects who underwent BPD at the Department of Surgery of the University of Genoa School of Medicine from June 1984 (ad hoc stomach BPD, 12) to January 1993. Among these individuals, 312 patients diagnosed as type 2 diabetes either before or during their preoperative evaluation were used for this study. There were 120 males and 192 females, aging from 18 to 65 years (mean 43 years). Body weight (in kilograms) and BMI (weight [in kilograms] divided by the square of height [in

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Abbreviations: BPD, biliopancreatic diversion.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

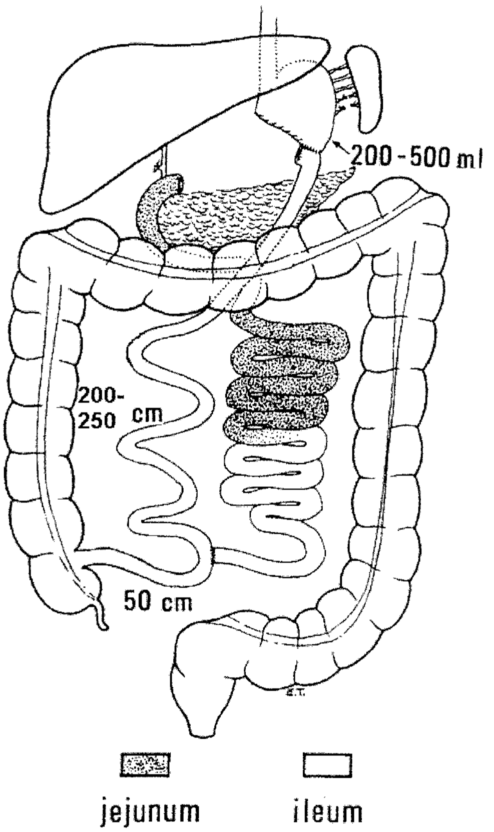

Figure 1—*Schematic representation of ad hoc stomach ad hoc alimentary limb BPD. Alimentary limb, from gastroenterostomy to enteroenterostomy; biliopancreatic limb, from duodenum to enteroenterostomy; common limb, from enteroenterostomy to ileocecal valve.*

meters]) data are reported in Table 1. These patients underwent the ad hoc stomach type of BPD, where the gastric volume, which is the main determinant of the initial weight loss, is adapted to the preoperative excess weight and to other individual characteristics such as sex, age, eating habits, social-economical status, and expected degree of compliance (12). Patients were evaluated before the operation and after 1, 2, and 3 years with the occasion of the routine follow-up visits. The majority of the patients came to an additional visit at the 5th year. The 10-year data were obtained by requesting a further follow-up visit or blood exams.

At each evaluation visit, after a clinical and anthropometric evaluation, blood samples were obtained for determination of glucose, triglyceride, and total cholesterol serum concentrations. Blood pressure was measured twice with the patient lying down, and the values were averaged.

Patients were considered to have type 2 diabetes when fasting serum glucose concentration was higher than 125 mg/dl. The upper normal value for serum triglyceride and total cholesterol were considered 150 mg/dl and 200 mg/dl, respectively. The diagnosis of arterial hypertension required a lying blood pressure of at least 140 mmHg systolic and/or at least 90 mmHg diastolic (measured preoperatively using a wide-cuff sphygmomanometer), and the hypertension was considered resolved when both systolic and diastolic pressure, without medication, were steadily below 140 and 90 mmHg, respectively. The subjects taking regular medication for high blood pressure were considered as having arterial hypertension regardless of the values recorded at the visit (19). Over the 10 years of the study, 42 subjects were lost to follow-up and 33 died. At the 5- and 10-year controls, serum glucose value was available in 91 and 80% of cases, respectively, and serum triglyceride and cholesterol concentrations in 89 and 79%, while arterial pressure was obtained in 60 and 50% of the patients, respectively.

Data are expressed as means ± SDs. The differences between continuous data were analyzed with the Student's *t* test for paired comparisons, and the differences between proportions and categorical variables were evaluated with the Fisher's exact test.

RESULTS — Mean values of body weight and BMI preoperatively and at the different follow-up times are shown in Table 1. At 1 year following the operation, a marked reduction of mean body weight was observed with concomitant sharp decrease of mean BMI. Throughout all the follow-up period, the mean body weight and BMI values remained essentially unchanged at the levels reached at 1 year after BPD. One year following BPD, mean serum glucose fell to within the normal range and remained unchanged thereafter until the 10th postoperative year (Table 1). In all but two patients fasting serum glucose concentration normalized at the 1st postoperative year and remained below the cutoff value of 110 mg/dl in all cases. A fasting serum glucose above 125 mg/dl was observed in one additional patient at 3 years and in three patients at 5 years after the operation; since these conditions were maintained, fasting serum glucose levels in the diabetic range were observed in six cases at 10 years following

Table 1—*Diabetic obese patients: anthropometric and biochemical data prior to BPD and throughout the follow-up period*

	Prior to BPD	At 1 year	At 2 years	At 3 years	At 5 years	At 10 years
n	312	305	300	290	272	243
Body weight (kg)	135.4 ± 25.6	88.9 ± 20.9	84.3 ± 16.5	88.2 ± 18.3	85.8 ± 18.3	86.6 ± 18.5
BMI (kg/m^2)	50.1 ± 9.0	32.8 ± 7.4	31.1 ± 6.5	32.1 ± 7.0	31.6 ± 6.4	32.0 ± 6.7
GL (mg/dl)	178 ± 61	84 ± 15	85 ± 18	84 ± 14	86 ± 18	89 ± 24
TG (mg/dl)	220 ± 155	120 ± 55	124 ± 107	96 ± 61	83 ± 36	82 ± 35
CHOL (mg/dl)	222 ± 75	136 ± 34	133 ± 33	126 ± 32	126 ± 31	113 ± 29

Data are means ± SD. All postoperative versus preoperative values: $P < 0.01$. No significant differences between postoperative data. CHOL, total serum cholesterol concentration; GL, fasting serum glucose concentration; TG, serum triglyceride concentration.

Table 2—*Diabetic obese patients undergoing BPD*

	Hyperglycemia	Hypertriglyceridemia	Hypercholesterolemia	Arterial hypertension
Prior to BPD	312/312 (100)	119/311 (38)	197/312 (63)	268/312 (86)
At 1 year	2/305 (0.7)	24/305 (8)	1/305 (0.3)	152/305 (50)
At 2 years	2/300 (0.7)	20/300 (7)	0/300 (0)	129/300 (43)
At 3 years	3/290 (1)	5/288 (2)	0/290 (0)	128/290 (44)
At 5 years	6/247 (2)	2/245 (1)	0/242 (0)	59/163 (36)
At 10 years	6/195 (3)	2/193 (1)	0/192 (0)	31/121 (26)

Data are prevalence/total subjects (%). All postoperative versus preoperative values: $P < 0.01$. No significant difference between postoperative data.

BPD. None of the previously diabetic BPD patients, not even those with incomplete recovery or mild relapse, ever had any medication in the 10-year follow-up.

Before BPD, the serum triglyceride and total cholesterol were above normal values in nearly one-third and two-thirds of the patients, respectively (Table 2). A marked and highly significant reduction of the mean value of serum triglyceride and total cholesterol concentration was seen by the 1st postoperative year, with only one subject showing a serum cholesterol value slightly above normal. The percentage of hypertriglyceridemic patients showed a progressive decrease, reaching 1% at 5 and 10 years. In all subjects the serum total cholesterol level was in the normal range at the 2nd year and at all subsequent follow-up times, all subjects being with no medication and on totally free diet (Table 1 and 2).

Hypertension was present in 86% of the diabetic obese patients before BPD. A significant reduction of the frequency of hypertension following the operation was observed (Table 2). At 1 year after the operation 50% of the operated patients showed a normal arterial pressure. The percentage of normal values rose to 64% at 5 years and to 74% at 10 years.

Among the subjects of this study there were six deaths (1.9%) within 30 days from the operation, three from pulmonary embolism, two from anastomotic leakage, and one from cardiac arrest. There were 27 late deaths (10.2% of the 264 survivors): four patients died from malnutrition, four from alcoholic cirrhosis, four from fatal cardiovascular event, four from malignancy, five from accidents, and six from unknown causes. The overall mortality of the surveyed group (total minus lost to follow-up: 270 subjects) was 12.2%.

CONCLUSIONS — Following bariatric surgery, a decrease in glycemic levels, a reduced need of antidiabetic medication, and an overall improvement of the metabolic conditions have been widely reported (8–14,20,21). After gastric restriction procedures, the weight loss is accompanied by a normalization of the serum glucose concentration in 40–50% of cases (20–23), while gastric bypass surgery provides a long-term glycemic control in >80% of the type 2 diabetic obese subjects (8,11,13,14). The proposed mechanisms that may explain the efficacy of bariatric surgery in the resolution of diabetes are the weight loss, the decreased energy intake, and the reduced intra-abdominal fat mass (24). Furthermore, changes in gut hormone secretion due to foregut bypass are thought to elicit a reduction of insulin levels and an improvement in insulin sensitivity (9,25–27). This could account specifically for the far better results achieved following gastric bypass surgery compared with pure restrictive procedures. Following BPD, besides the above-mentioned specific action, an additional mechanism may lead to the normalization of serum glucose concentration. Due to the rearrangement of the gastrointestinal tract, in the post-BPD subjects a profound limitation of fat absorption occurs (28), which greatly contributes to the long-term maintenance of fully satisfactory weight loss results. According to Randle et al. (29,30), the increased free fatty acid oxidation that occurs in obese patients inhibits glucose oxidation, thus causing insulin resistance. Therefore, a reduced fat absorption should result in enhanced insulin sensitivity. Moreover, recent investigations showed that lipid deprivation selectively reduces intramyocellular lipid stores, therefore inducing an improvement of insulin action by acting on the insulin-mediated whole-body glucose disposal, on the intracellular insulin signaling, and on the circulating leptin levels (16,18,31,32). Finally, the reduced β-cell fat toxicity (33,34) certainly also plays a role in the improvement of glucose metabolism. It can then be postulated that the strongly reduced fat absorption might effectively contribute with other mechanisms to normalization of the metabolic status, thus explaining the complete resolution of type 2 diabetes in obese patients following BPD.

In addition to serum glucose level normalization, this study highlights other beneficial effects of BPD on some components of the metabolic syndrome.

Gastric restrictive procedures or gastric bypass surgery induce an overall improvement of serum lipid profiles entailing a marked fall of serum triglyceride level with a relatively small decrease in serum total cholesterol. These effects most likely derive merely from weight loss and decreased dietary cholesterol intake (35–37). As far as serum triglyceride level is concerned, the same applies to BPD, the improvement being greater and longer lasting because of the better weight loss results. By contrast, in the diabetic obese patients undergoing BPD in this study, the serum cholesterol level normalized in all cases and remained below the 200-mg/dl threshold at very long term. Therefore, since the simple reduction of cholesterol intestinal absorption alone cannot yield such an outcome, a specific action of BPD on cholesterol metabolism also has to be postulated. In fact, the enterohepatic bile salt circulation is partly interrupted after BPD, with the consequent loss of bile salts causing enhancement of hepatic bile acid synthesis at the expense of the cholesterol pool (38,39). Furthermore, a sharp reduction of endogenous cholesterol is likely to occur, along with other lipid absorption. The reduced availability of free cholesterol ultimately stimulates the synthesis of LDL receptors, thus resulting in an increased removal of LDL from the bloodstream (40,41). The normalization of serum total cholesterol at long term following BPD is accompanied by a rise of HDL cholesterol (12); unfortunately, since the initial findings of this study date back >15 years, the preoperative HDL data are not available for the majority of subjects.

A striking percent increase of patients with normal arterial pressure was observed after BPD, reaching 50% at 1 year. The percentage of normal values rose to 64% at 5 years and 74% at 10 years, despite aging and the absence of any further weight change. This phenomenon was also observed in the whole population of hypertensive patients undergoing BPD controlled up to the 10th year (42). At short term, these findings are essentially similar to those observed in hypertensive obese and diabetic obese patients undergoing gastric restrictive procedures or gastric bypass (8,13,14,43–46). However, in the Swedish Obese Subjects study no difference in the frequency of hypertension between the operated patients and obese controls at long term was observed (45,46), due to long-term increase in hypertension prevalence irrespective of weight changes. In the BPD subjects of this study exactly the opposite was found, the good outcomes being increased throughout the 10-year follow-up period, despite aging and no change in body weight. This suggests a specific action of BPD also on hypertension. In fact, the highly satisfactory effects on arterial hypertension can be accounted for on one hand by the excellent weight loss and long-term weight maintenance occurring following BPD and on the other hand by the complete and sustained disappearance of insulin resistance (17) with its key role in the metabolic syndrome (47–49). This is further supported by the greater effects on blood pressure observed in the Swedish Obese Subjects study in the small subset (68 vs. 1,089 pure gastric restrictive procedures) of patients submitted to gastric bypass, which, besides yielding much better weight loss results, also has a specific beneficial action on insulin sensitivity (45,46).

Besides insulin resistance, dyslipidemia, and hypertension, central obesity, defined by excessive waist circumference (>40 in or 100 cm in men and >35 in or 87.5 cm in women), is a major component of the metabolic syndrome. The mean waist value 1 year following BPD was reduced from 138 to 105 cm at 1 year in men, and from 131 to 99 cm in women, the patients with abnormal values being decreased from 100 to 75%. These figures remained substantially unchanged throughout the 10-year follow-up. The reason why these data were not considered in the present study is the lack of meaning of waist circumference value in severely obese patients. In fact, the visceral fat, which represents central obesity, is the actual risk factor in metabolic syndrome, while waist value measures also the peripheral subcutaneous fat. When body mass increases, the subcutaneous component of waist circumference increases much more than the visceral component, so that in severe obesity, which is the case of the present study population, waist value measures much more subcutaneous than visceral fat, thus losing its meaning. However, the abnormal waist values in metabolically normalized subjects after BPD is a further demonstration of the specific effects of the operation.

The operative mortality in this study was higher than that observed in the general BPD series (12) and closely resembles that observed in a population of diabetic obese patients undergoing gastric bypass surgery (11). The overall mortality in a 10-year follow-up period was also comparable to that reported following gastric bypass surgery in the above study. This mortality rate was similar to that observed over 10 years in general populations of both U.S. and Italian subjects in the same age range (50,51), and much lower than that reported in cohorts of diabetic patients (52).

Regretfully, a group of nonoperated diabetic obese patients for matched comparisons was not available in this study. However, it is possible to compare our data with those of MacDonald et al. (11), who provide a control group of diabetic obese patients who did not undergo surgery because of either personal choice or insurance company's refusal to pay for the operation. During a nearly 7-year follow-up period, the mortality rate in these nonoperated patients was 28%, which is sharply higher than that observed after BPD in the present investigation. Moreover, there was a marked difference in the percentage of cardiovascular death, which was responsible for 12 deaths among the 78 control subjects compared with the 4 deaths out of 264 subjects in this study.

In conclusion, this study demonstrates that BPD is very effective in normalizing serum glucose level in diabetic obese patients. The achievement of a good glycemic control is reflected in the reduction of the overall mortality rate compared with that of diabetic and diabetic obese patients, as well as in the very low frequency of death from cardiovascular events, thus implying a true clinical recovery. In terms of percentage of diabetic obese subjects becoming euglycemic following the operation, BPD has proven to achieve better results than not only the restrictive operations but also the gastric bypass procedures. It can be postulated that the striking results obtained with BPD might be due to the foregut hormonal changes (a specific mechanisms shared with the gastric bypass procedures), and to the lipid deprivation, acting on insulin activity concurrently with the nonspecific mechanisms of bariatric surgery. Moreover, BPD is extremely effective in reversing dyslipidemia, a condition which very often accompanies type 2 diabetes and represents a major component of the metabolic syndrome. Finally, arterial hypertension was also cured in the majority of cases by BPD, thus completing the reversal of the major components of metabolic syndrome. Prospective studies are needed to assess the possible use of BPD for the treatment of severe type 2 diabetes and hypercholesterolemia in mildly obese or simply overweight patients.

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