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ORIGINAL CONTRIBUTIONS

Type 2 Diabetes Remission and Control in Overweight and in Mildly Obese Diabetic Patients at Long-Term Follow-Up After Biliopancreatic Diversion

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Abstract

Background In severely obese patients with type 2 diabetes (T2DM), the metabolic benefits after biliopancreatic diversion (BPD) are due to mechanisms independent of weight loss. Therefore, the anti-diabetic effect of BPD in overweight or mildly obese T2DM patients was investigated.

Methods Ninety T2DM patients with BMI 25–35 underwent BPD and were evaluated 1 and 5 years after the operation (follow-up rate 100 and 83%, respectively).

Results T2DM control (Hb1Ac < 7%) and remission (Hb1Ac < 6 without antidiabetics) was observed in 86.6 and 65% of cases at 1 year and 64.0% and 26.5% at 5 years, respectively. The long-term T2DM remission was predicted by baseline BMI value. Both before BPD and throughout the follow-up period, HOMA values were similar in the metabolically successful and unsuccessful subjects, while C-peptide normalized for FBG value as a marker of beta cell mass and insulin secretion increased progressively only in the former from 1.06 ± 0.64 to 1.44 ± 1.08 mcg/l ml/dl^{-1} * 100 ($p < 0.002$).

Conclusions In T2DM patients with BMI of 25–35, a positive metabolic outcome is less frequent than in their counterparts with morbid obesity. In T2DM overweight patients, in spite of a short-term normalization of FBG and HbA1c levels and a well-sustained increase of insulin sensitivity, a long-term T2DM relapse occurs in the majority of the cases. While the surgically obtained decrease in insulin resistance leads to T2DM control in half of the patients, the increase in insulin secretion is mandatory for T2DM stable remission.

Keywords Bariatric surgery · Type 2 diabetes · Non-morbidly obese patients · Diabetes control · Diabetes remission · Insulin secretion

In severely obese patients, biliopancreatic diversion (BPD) causes the complete long-term disappearance of type 2 diabetes (T2DM) in the vast majority of the preoperatively diabetic individuals [1]. This highly satisfactory metabolic outcome is not only due to the sharp improvement of the insulin sensitivity consequent to the marked surgically induced weight loss. In fact, in the surgical patients, the glucose metabolism normalizes as early as the first phases after BPD, and a physiological insulin sensitivity is maintained in the long term after BMI has stabilized to approximately 30 kg/m^2, even though this is still in the obese range [2–7]. As it is for gastric bypass, the BPD-specific action on glucose metabolism can be identified with a postoperative increase in the food-stimulated incretin GLP-1 production, with consequent improvement in beta cell function [8], stimulation of beta cell proliferation [2], and inhibition of beta cell apoptosis [9]. Moreover, in severely obese patients with T2DM, BPD has shown the ability to restore acute insulin response (AIR) to intravenous glucose load both at short- [10–12] and long-term [10, 13] follow-up, suggesting a restoration toward the normality of the beta cell mass and/or insulin production. The evidence of these beneficial metabolic effects of BPD, which are not simply accounted for by the weight loss, prompted us to investigate

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the antidiabetic effect of BPD on mildly (class 1) obese or overweight patients with T2DM.

In a previous study, the diabetes remission at 1 and 2 years after BPD was investigated in an original cohort of non-morbidly obese and overweight T2DM patients. A marked postoperative reduction of fasting blood glucose (FBG) and $HbA1_C$ concentration was demonstrated, and a slight and progressive increase in the acute insulin response during the first 2 years following the operation raised the hope that an increase of beta cell mass may occur in the long term, with consequent improvement of the metabolic results [14, 15].

In this paper, the clinical results at 5 years of the entire original cohort evaluating mildly obese and overweight T2DM patients who underwent BPD are presented.

Material and Methods

This study was carried out in overweight and in non-morbidly obese patients with T2DM undergoing BPD for T2DM treatment between September 2007 and February 2011 at the Department of Surgery of the University of Genova. All patients had been diabetic for almost 3 years, and all were on antidiabetic treatment. The sample included individuals who participated in a pilot study investigating the effect of BPD on overweight and mildly obese patients with T2DM [14, 15]. Other T2DM patients represented an investigational sample for the evaluation of the entero-hormonal changes after BPD [5]. The studies were approved by the local ethical committee, and all patients gave their informed consent. In total, 90 T2DM individuals undergoing BPD were considered, 42 of them with baseline BMI values ranging from 25 to 30 kg/m^2, and 48 with a baseline BMI ranging from 30 to 35 kg/m^2. The demographic, anthropometric, and clinical data obtained before the operation are illustrated in Table 1. The standard type of BPD was performed in all patients [7]. For the purpose of this investigation, only the preoperative data and those recorded on the occasion of the regular follow-up visit at the first and at the fifth postoperative year were considered. Body weight (BW) was determined to the nearest 0.1 kg, and stature, to the nearest 0.5 cm. Fasting blood glucose (FBG, mg/dl) and glycated hemoglobin ($HbA1_C$, %) concentrations were measured with a routine analyzer, while insulin and C-peptide blood concentration were measured by a commercial enzymatic method (Randox, Crumlin, UK) and sandwich immunoradiometric assay (Immunotech, Prague, Czech Republic). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated [16]. The C-peptide data are reported both as absolute serum levels and normalized by FBG values [17]. The overall follow-up rate was 100% at 1 year and 84% at 5 years. After the operation, the diabetes was considered in remission when $HbA1_C$ was equal to or lower than 6% and FBG lower than 125 mg/dl without the use of any antidiabetic drugs [18]. Furthermore, when HbA1C was equal to or lower to 7% with or without specific medication, T2DM was regarded as in control.

Longitudinal changes were assessed with the Wilcoxon rank test, cross-sectional differences with the Mann-Whitney *U* test for unpaired data, and categorical data, with the McNemar chi-square method. A logistic regression model was employed to evaluate the relationship between metabolic outcome (diabetes remission at 5 years after BPD) as the dependent variable and the preoperative data (demographics, baseline BMI, FBG and HbA1C value, diabetes duration, and preoperative use of insulin) as independent variables. Calculations were carried out with Statview 2.3 (Carey, NC).

Results

The demographic, anthropometric, and clinical data of the patients of this study, both prior to BPD and at post-BPD follow-up, are reported in Table 1. The preoperative T2DM duration ranged from 3 and 33 years, and 50% of the patients were treated with insulin; 48 individuals were obese (BMI > 30 kg/m^2), while 42 subjects categorized as overweight. BPD was uneventful in all cases, and no major nutritional complications were observed throughout all the follow-up period. At 1 year following the operation, the BW and BMI values fell significantly and then remained substantially unchanged at the fifth year with the excess weight loss (%EWL) being stabilized at approximately 25% both in the short and at long term following the operation.

At 1-year post-BPD, a sharp reduction in FBG and $HbA1_c$ values was observed, with a slight increase for both values (statistically significant for $HbA1_C$) in the long term.

At 1 year post-BDP, the HOMA values and the C-peptide level absolute values decreased significantly without any noteworthy further change in the long term, while a slight and progressive increase in C-peptide levels normalized for FBG was observed both at 1 and 5 years after BPD (Table 1).

T2DM control was observed in 87 and 64% of patients at the first and fifth postoperative year, respectively, and the T2DM postoperative remission occurred in 51 and 27% of the patients at the first and fifth year after the operation, respectively. Thus, the rate of favorable outcome (T2DM control or remission) was significantly lower at 5 years than at 1 year post-BDP (Table 1; Figs. 1 and 2).

In the multiple regression model, the T2DM remission at 5 years following BPD (as the dependent variable) was predicted ($r^2 = 0.385$) by the baseline BMI values, while this metabolic outcome was fully independent of age, gender, T2DM duration, insulin use, and preoperative FBG and Hb1Ac as independent variables.

Table 1 Type 2 diabetic (T2DM) patients with BMI between 25 and 35 kg/m^2. Anthropometric, biochemical, and clinical data (mean ± sd) prior to and at 1 and 5 years following biliopancreatic diversion (BPD). *FBG* fasting blood glucose, *HbA1c* blood glycated hemoglobin level. T2DM was considered in remission when $HbA1_C$ was less than 6% at free diet and without antidiabetic therapy and controlled when $HbA1_C$ was less than 7%

	Prior to BPD	At 1 year after BPD	At 5 years after BPD
Cases (no.)	90	90	75
Age (years and range)	54.0 (35–69)		
Gender (M/F)	63/28		
T2DM duration (years and range)	13.5 (± 7.2)		
Insulin therapy (#)	45	15	8
Oral antidiabetics	46	2	11
Obese patients (BMI > 30 kg/m^2)	51	3	1
Body weight (kg)	86.3 ± 12.7	71.1 ± 11.9*	71.8 ± 10.9*
BMI (kg/m^2)	30.6 ± 3.3	24.6 ± 3.8*	25.1 ± 4.5*
% Excess weight loss		24.8 ± 11.9	23.3 ± 12.0
FBG (mg/dl)	233 ± 64	133 ± 44*	140 ± 43*
HbA1c (%)	9.4 ± 1.4	6.1 ± 1.1*	6.7 ± 1.1*, **
HOMA-IR	9.30 ± 10.76	2.85 ± 3.18*	3.03 ± 1.23*
C-peptide (mcg/l)	2.4 ± 1.3	1.7 ± 0.9 *	1.76 ± 1.1*
C-peptide/FBG (mcg/l* ml/dl^{-1}*dl)	1.04 ± 0.62	1.47 ± 0.93 *	1.41 ± 1.08
T2DM remission (no. and %)		46 (51.1)	20 (26.6) **
T2DM control (no. and %)		78 (86.6)	48 (64.0) **

**$p < 0.001$ vs. 1 year after BPD

*$p < 0.001$ vs. prior to BPD

In Table 2, the clinical results obtained in the preoperatively obese (BMI 30–35 kg/m^2) and overweight (BMI 25–30 kg/m^2) T2DM patients are reported. T2DM control after the operation occurred in a substantially similar proportion in the preoperatively obese and overweight patients both at short- (90 vs. 86%) and at long-term (70 vs. 52%) follow-up (Table 2; Fig. 1). In contrast, in the preoperative obese patients, the T2DM remission after BPD was observed in a greater number of patients than in their overweight counterparts at both 1 and 5 years (60 vs. 40% $p < 0.05$ and 44 vs. 8%, $p < 0.01$, respectively) after the operation (Table 2; Fig. 2). Throughout the follow-up period, within the preoperatively obese T2DM subjects, the proportion of patients having experienced a T2DM control after BPD decreased (from 90% at 1 year to 70% at 5 years, $p < 0.02$), with no significant further change in the T2DM remission rate (60% at 1 year and 44% at 5 years). In contrast, a progressive decrease ($p < 0.001$) both in T2DM control and remission rate was observed in the preoperatively overweight T2DM patients, with T2DM control having been observed in 86% of the patients at 1 year and in 52% at 5 years after BPD ($p < 0.002$), and T2DM remission in 40% of the patients at 1 year and in 8% at 5 years after BDP (Table 2; Fig. 2).

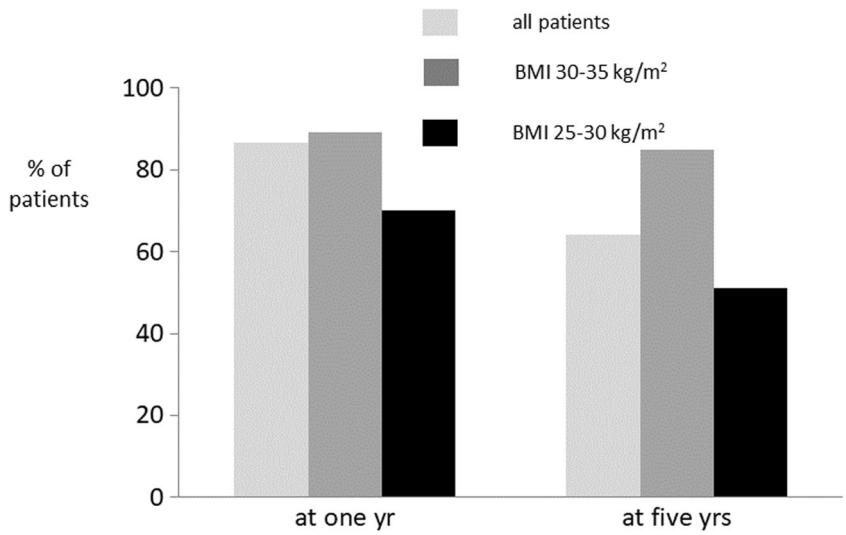

Fig. 1 Type 2 diabetes control (glycated hemoglobin lower than 7%) at 1 and 5 years after biliopancreatic diversion. The results obtained in all cases, in the obese (BMI 30–35 kg/m2) and in the overweight (BMI 25–30 kg/m2) patients

Table 2 Postoperative type 2 diabetes (T2DM) control and remission after biliopancreatic diversion (BPD) in mildly obese (OB) and overweight (OW) patients. T2DM was considered in remission when glycated hemoglobin ($HbA1_C$) was less than 6% at free diet without antidiabetic therapy and controlled when $HbA1_C$ was less than 7%

	Postoperative T2DM control		Postoperative T2DM remission	
	At 1 year	At 5 years	at 1 year	At 5 years
OB (BMI 30–35 kg/m^2, %)	43/5 (90)	28/12 (70)*	29/19 (60)	17/22 (44)
OW (BMI 25–30 kg/m^2, %)	36/6 (86)	17/16 (52)*	17/25 (40)	3/33 (8)**
p	ns	ns	$p < 0{,}05$	$p < 0.01$

*$p < 0.002$ vs. 1 year

**$p < 0.001$ vs. 1 year

Regardless of T2DM remission, control, persistence, or recurrence at 5 years following BPD, the mean HOMA values sharply decreased at 1 year and remained substantially unchanged throughout the entire follow-up period, without any difference between groups (Table 3). In those achieving long-term remission, an increase in the mean values of serum C-peptide normalized for FBG was observed at 1 year following BPD, with a further significant increase at 5 years. In contrast, in the groups of patients not achieving T2DM remission at 5 years following BPD, the C-peptide normalized for FBG serum values did not change after the operation and remained at low levels throughout the entire follow-up period, without a difference between T2DM controlled and uncontrolled patients (Table 3). Finally, in the individuals achieving T2DM remission, the C-peptide normalized for FBG serum mean values were higher than in the patients with postoperatively controlled and uncontrolled T2DM, both at 1 year ($p < 0.05$) and at 5 years ($p < 0002$) after BPD.

Discussion

Primarily, the findings of this study confirm, in a large and well-followed cohort, that the highly satisfactory long-term metabolic outcome observed following BPD in severe obese T2DM patients is not replicated in mildly obese or overweight T2DM patients. In this cohort that includes T2DM patients with mild obesity or simply overweight, the long-term T2DM remission after bariatric surgery appears to be unrelated to the preoperative T2DM duration, while T2DM duration becomes a powerful predictor of long-term metabolic outcome when only or predominantly T2DM patients with severe obesity are considered [19, 20]. In obese T2DM patients with high preoperative BMIs, nearly all of the patients with a recent onset of T2DM showed a long-term stable normalization of FBG following BPD, while in their counterparts with a T2DM duration greater than 10 years, T2DM recurred in one-quarter of the patients [21]. The association of the long-term T2DM resolution to the duration of T2DM disappears and that to the baseline BMI becomes evident when T2DM subjects with a preoperative low degree of obesity are considered [22].

In the T2DM patients with mild obesity at 1 year after BPD, the postoperative T2DM control and remission rate is substantially similar to that observed after other types of bariatric operations in subjects with the same degree of obesity [23–26]. However, at 5 years after BPD, our study shows a reduction in the postoperative T2DM control and remission rate, the long-term T2DM relapse occurring in nearly half of

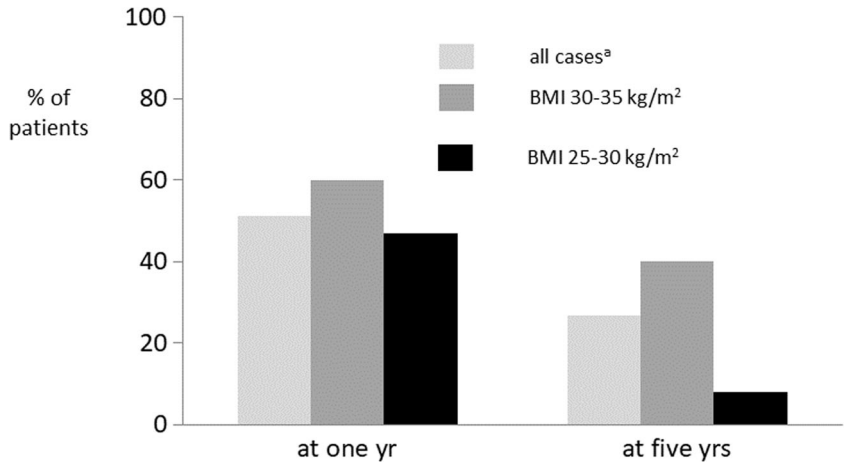

Fig. 2 Type 2 diabetes remission (glycated hemoglobin lower than 6% at free diet and without antidiabetic therapy) at 1 and 5 years after biliopancreatic diversion. The results obtained in all cases, in the mildly obese (BMI 30–35 kg/m^2) and in the overweight (BMI 25–30 kg/m^2) patients

Table 3 Type 2 diabetic (T2DM) patients with BMI between 25 and 35 kg/m^2 following biliopancreatic diversion (BPD). Insulin resistance (HOMA-IR) and insulin secretion (C-peptide/fasting blood glucose) parameters in patients with postoperative long-term T2DM remission (HbA1C ≤ 6% without therapy), T2DM control (HbA1C ≤ 7%), and uncontrolled T2DM (Hba1C)

		Prior to BPD	At 1 year after BPD	At 5 years after BPD
T2DM remission (20 cases)	HOMA-IR	12.73 ± 17.64	2.46 ± 3.56 ‡	2.35 ± 0.85 ‡
	C-peptide/FBG (mcg/l*ml/dl¯1*100)	1.21 ± 0.78	1.71 ± 0.76 *	2.11 ± 1.34*§
T2DM control (28 cases)	HOMA-IR	7.80 ± 4.77	2.64 ± 2.18 ‡	2.95 ± 2.3 ‡
	C-peptide/FBG (mcg/l*ml/dl^{-1}*100)	1.11 ± 0.60	1.41 ± 1.06	1.27 ± 1.92
Uncontrolled T2DM (27 cases)	HOMA-IR	9.45 ± 9.86	3.65 ± 4.11 ‡	3.76 ± 1.96 ‡
	C-peptide/FBG (mcg/l*ml/dl^{-1}*100)	0.84 ± 0.4	1.32 ± 0.95	1.08 ± 0.61

‡$p < 0.001$ vs. prior to BPD

*$p < 0.05$ vs. prior to BPD; §$p < 0.02$ vs. 1 year after BPD

the patients. This finding suggests that this longer-term finding could also happen after other types of bariatric operations acting with similar specific metabolic effects.

In contrast, in the overweight T2DM patients, the long-term post-BPD metabolic results are disappointing: in fact, in this study, at the 5-year follow-up, T2DM control and remission were observed in fewer patients than in the first year, thus indicating a substantial tendency toward T2DM postoperative relapse in the majority of the cases, supporting the results observed at the third year after Roux-en-Y gastric bypass [26].

In the STAMPEDE cohort, which evaluates the long-term results of Roux-en-Y gastric bypass in T2DM patients with a baseline BMI ranging from 27 to 43 kg/m^2, the diabetes remission rate was lower than that observed after RYGBP in other clinical populations of T2DM patients with morbid obesity [27, 28], and the successful metabolic outcome rate tended to decrease in the long term [19, 29]. This likely reflects the unsatisfactory results obtained in the T2DM patients with low preoperative BMI values.

As previously mentioned, in the severely obese T2DM patients undergoing BPD, a complete restoration of the acute insulin response (AIR) to the glucose load was observed very soon after the operation and a strong response is maintained at long-term follow-up [10–13]. The full and steady AIR restoration may be considered a specific effect of the operation, which likely reflects an adequate recovery of the beta cell secretion capacity. The permanent improvement in insulin secretion, along with the consequent stable disappearance of the glucotoxicity, substantially accounts for the highly satisfactory metabolic postoperative outcome maintained at long-term follow-up after BPD. A previous study demonstrated that a full recovery of the AIR to intravenous glucose loads was sustained at long-term follow-up only in T2DM patients with baseline severe obesity, while in the T2DM individuals who were overweight or with class 1 obesity, the AIR remains reduced or absent throughout the entire 5-year follow-up period. In these patients, the rearranging of the entero-hormonal pattern due to the operation and the disappearance of a glucotoxic environment subsequent to the improvement of insulin sensitivity cannot restore an AIR compromised by the diabetic status; this corresponds to a lower rate of postoperative T2DM remission rate in non-morbidly obese patients [13].

This study fully confirms the pivotal role of the recovery of insulin secretion capacity for T2DM remission after bariatric surgery. The post-BDP metabolically successful and unsuccessful patients in this cohort have essentially the same insulin resistance throughout the entire postoperative follow-up period, as indicated by very similar HOMA values. In contrast, a progressive increase in the C-peptide-to glucose ratio as index of insulin secretion [17, 30] was observed only in the subjects who experienced long-term T2DM remission. Therefore, it can be suggested that the improvement of insulin resistance leads to long-term T2DM control in more than half of the patients, while, for a true T2DM remission maintained at long term, a recovery in beta cell mass and a restoration of insulin secretion is mandatory. After BPD, this became a reality in only a small minority of the overweight and in less than half of the mildly obese T2DM patients.

In obese patients, the beta cell mass increased by nearly 50% due to an increase in beta cell number without any increase of beta cell apoptosis, and the beta cell mass size is positively correlated to the degree of obesity [31, 32]. While beta cell mass is well preserved with advancing age in healthy individuals, beta cell apoptosis increases progressively throughout the years in T2DM patients. This is most likely one of the main characteristics of the disease itself and is partly due to the environment toxicity subsequent to the glucose imbalance and fat accumulation around islets [33–37]. After BPD, in T2DM severely obese

patients, the metabolic conditions improve early after the operation, with normalization of insulin resistance and the AIR stable recovery is most likely due to an expanded beta cell mass starting to once again secrete enough insulin for peripheral needs. It can be hypothesized that a metabolic environment maintained in a physiological range by a normal FBG, an optimal insulin resistance, and an efficient insulin secretion can prevent the progressive loss of beta cell function that characterizes the diabetic status [13].

In contrast, in the overweight T2DM patients with a defective beta cell mass due to the diabetic conditions by itself [38, 39], the postoperative beta cell toxicity discontinuance does not allow for a resumption of an insulin secretion sufficient to cause and/or maintain a long-term T2DM remission, and the transient decrease in FBG observed at 1 year is exclusively due to a surgically and/or weight-mediated decrease in insulin resistance. Throughout the follow-up period, the stable improvement in insulin sensitivity makes T2DM control easier; however, the stable T2DM post-BPD remission is an unusual event, and the progressive diabetes-dependent loss of beta cell function causes the T2DM relapse observed in the vast majority of the cases.

In the T2DM patients with mild obesity, the T2DM remission rate was greater than in their overweight counterparts. This suggests that among T2DM patients with a BMI value between 30 and 35 kg/m^2, most individuals may have had an increased beta cell mass before the operation and thus, they may have had the same metabolic advantages from the operation as the severely obese T2DM patient, with similar mechanism.

In conclusion, this study demonstrates that in the T2DM patients with overweight or class 1 obesity, the post-BPD metabolic control or T2DM remission rate is markedly lower than that observed in their counterparts with severe obesity. In the T2DM individuals with a baseline BMI ranging from 30 to 35 kg/m^2, the positive postoperative metabolic outcome, though less frequently observed than in the severely obese patients, is substantially maintained in the long term. In contrast, in the TDM overweight patients, in spite of a short-term normalization of FBG and HbA1c levels and a well-sustained increase of insulin sensitivity, a long-term T2DM relapse occurs in the majority of the cases. While the surgically obtained decrease in insulin resistance led to steady control of T2DM in nearly half of the patients, the increase in insulin secretion is mandatory for stable T2DM remission after BPD.

Compliance with Ethical Standards

The studies were approved by the local ethical committee, and all patients gave their informed consent.

Conflict of interest The authors declare that they have no conflict of interest.

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