

Restoration of Acute Insulin Response in T2DM Subjects 1 Month After Biliopancreatic Diversion

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Objective: Biliopancreatic diversion (BPD) restores normal glucose tolerance in a few weeks in morbid obese subjects with type 2 diabetes, improving insulin sensitivity. However, there is less known about the effects of BPD on insulin secretion. We tested the early effects of BPD on insulin secretion in obese subjects with and without type 2 diabetes.

Methods and Procedures: Twenty-one consecutive morbid obese subjects, 9 with type 2 diabetes (T2DM) and 12 with normal fasting glucose (NFG) were evaluated, just before and 1 month after BPD, by measuring body weight (BW), glucose, adipocytokines, homeostasis model assessment of insulin resistance (HOMA-IR), acute insulin response (AIR) to e.v. glucose and the insulinogenic index adjusted for insulin resistance ($[\Delta I5/\Delta G5]/HOMA-IR$).

Results: Preoperatively, those with T2DM differed from those with NFG in showing higher levels of fasting glucose, reduced AIR (57.9 ± 29.5 vs. 644.9 ± 143.1 pmol/l, $P < 0.01$) and reduced adjusted insulinogenic index (1.0 ± 0.5 vs. 17.6 ± 3.9 1/mmol², $P < 0.001$). One month following BPD, in both groups BW was reduced (by ~11%), but all subjects were still severely obese; HOMA-IR and leptin decreased significantly, while high-molecular weight (HMW) adiponectin and adjusted insulinogenic index increased. In the T2DM group, fasting glucose returned to non-diabetic values. AIR did not change in the NFG group, while in the T2DM group it showed a significant increase (from 58.0 ± 29.5 to 273.8 ± 47.2 pmol/l, $P < 0.01$). In the T2DM group, the AIR percentage variation from baseline was significantly related to changes in fasting glucose ($r = 0.70$, $P = 0.02$), suggesting an important relationship exists between impaired AIR and hyperglycaemia.

Discussion: BPD is able to restore AIR in T2DM even just 1 month after surgery. AIR restoration is associated with normalization of fasting glucose concentrations.

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INTRODUCTION

Type 2 diabetes mellitus (DM2) is a complex disease resulting from a dual defect: the association of insulin resistance with failure of insulin secretion (1). The observation of increased prevalence of DM2 in overweight and obese people (2), together with the demonstrated possibility of DM2 prevention in subjects with impaired glucose tolerance by means of dieting and exercise (3–5), support the theory that excessive fat deposition plays a key element in the development of DM2. Reduction of body weight (BW) is a pivotal tool in the anti-diabetic armamentarium. Unfortunately durable BW reduction is almost an unrealistic target in clinical practice. For this reason, bariatric surgery is becoming a relatively common therapeutic strategy for patients with morbid obesity, complicated by DM2. Several prospective studies have

shown that bariatric surgery is often associated with recovery from DM2 and with its prevention (6). Glucose concentrations normalize in ~50% of obese patients with DM2 after the restrictive procedure, with results substantially dependent on weight loss. The recovery rate following gastric bypass and biliopancreatic diversion (BPD), conversely, is respectively 80 and 95% (6,7). BPD often normalizes blood glucose before a substantial weight loss (8), suggesting that other mechanisms beyond weight reduction might play a role.

Several observations suggest there is the possibility of improved beta-cell function acting as a mechanism by which bariatric surgery normalizes glucose metabolism. It has been shown that lack of early insulin secretion or acute insulin response (AIR), elicited by e.v. glucose, is the most striking defect of beta-cell dysfunction in DM2 (9) and

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that this alteration does not revert following weight loss (10). Recently it has been reported that BPD increases AIR between 3 and 12 months after the operation (11), leaving it unclear as to the relative role of BPD itself and progressive weight loss on beta-cell function. Moreover, there has been shown to be increased beta-cell sensitivity on administration of the oral glucose test as early as 1 week after the operation (12).

The aim of this investigation was to directly evaluate the early effects of BPD on insulin secretion measuring the AIR to glucose in both diabetic and non-diabetic severely obese subjects before and 1 month after BPD, when subjects still remain severely obese.

METHODS AND PROCEDURES

The study was carried out in 21 consecutive severely obese subjects (9 male) undergoing BPD: 9 with type 2 diabetes (T2DM) and 12 with normal fasting glucose (NFG). All consecutive patients who agreed to participate in the investigations were enrolled. All patients were free of neoplastic, immunologic, endocrine disease or severe diabetic complications, and gave their informed consent to the study before the operation. The diagnosis of diabetes was established according to the criteria of the American Diabetes Association (13). The duration of diabetes ranged from 2 to 6 years and four subjects were treated with oral hypoglycemic agents. Hypoglycemic drugs were discontinued 7 days before the study.

Surgery

BPD consists of a distal gastrectomy with a very long Roux-en-Y reconstruction at 50 cm from the ileocecal valve (14). Because of the new anatomical condition created by the operation, subjects develop a permanent and selective maldigestion and then malabsorption of energy-rich substrates, in prevalence fat, due to the displacement of digestive juices with respect to the food transit in the small gut.

Subjects evaluations

Subjects were evaluated the day before and 1 month following BPD, on the occasion of the first follow-up visit. During the first month following BPD, the overall food consumption, assessed by an accurate alimentary interview, was in all cases nearly half of the preoperative one. BW and height were measured in the morning to the nearest 0.1 kg and 0.5 cm, respectively. Blood was drawn after a 12-h overnight fast to test for glucose, insulin, leptin, adiponectin and for high-molecular weight (HMW) isoforms adiponectin determination and intravenous glucose tolerance test (IVGTT).

Intravenous glucose tolerance test

Between 8:30 and 9:30 AM after a 12-h overnight fast, blood samples were collected just 10 min before the e.v. infusion of 35 g glucose (35% wt/vol, over 2 min), and 2, 3, 5, 10, 20, and 30 min after the end of infusion. The first phase of insulin or AIR was calculated as the difference of the mean insulin concentration at 2, 3, 5, and 10 min minus the mean insulin concentration at -10 and 0 min of the test. The difference between the baseline value and the value at 5 min after glucose infusion was considered as the incremental serum insulin (ΔI_5) and glucose (ΔG_5) response. An expression of beta-cell function is the insulinogenic index, expressed as the ratio of incremental insulin to glucose responses. Because insulin sensitivity is an essential modulator of insulin response, we used an adjusted insulinogenic index obtained dividing ($[\Delta I_5/\Delta G_5]/\text{HOMA-IR}$) (15). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as reported (16).

Assays

After separation, serum samples were stored at -20°C until analysis. Glucose and insulin concentrations were measured by commercial enzymatic method (Randox) and sandwich immunoradiometric assay (Immunotech SA), respectively. Serum adiponectin and leptin were measured in basal conditions by commercial radioimmunoassay (DRG Instruments). Adiponectin isoforms were evaluated as previously reported (17).

Statistical analysis

Data are reported as mean \pm s.e. Two-sided $P < 0.05$ was considered significant. The Mann-Whitney U -test was used for a non-parametric evaluation of differences between groups and Wilcoxon's signed-rank test was used to compare data from the same subject before and after BPD. Predictors of AIR changes were tested using the Spearman correlation. Multiple linear regression was then used to fit models to predict AIR changes after BPD.

RESULTS

Effects of BPD on weight loss and adipocytokines

Baseline age, anthropometric findings, serum leptin and adiponectin concentrations and serum HMW (percentage) adiponectin were similar in T2DM obese subjects and in the NFG group (Table 1). One month following BPD, a slight ($\sim 11\%$) reduction of mean BW and BMI values was observed in both T2DM and NFG obese patients, without differences between the two groups. A sharp reduction of serum leptin concentration was observed in both groups. In the NFG group, postoperative

Table 1 Anthropometric characteristics and adipocytokines

	Type 2 diabetes			NFG		
	Pre-BPD	Post-BPD	BPD effect*	Pre-BPD	Post-BPD	BPD effect*
M/F	3/6			5/7		
Age (years)	42.1 \pm 2.1			36.1 \pm 2.5		
Weight (kg)	134.8 \pm 8.5	119.9 \pm 7.9	+	130.4 \pm 4.6	114.9 \pm 3.5	+
BMI (kg/m ²)	48.7 \pm 3.2	41.7 \pm 3.0	+	48.4 \pm 2.0	42.6 \pm 1.3	+
Leptin (ng/ml)	35.1 \pm 24.2	16.1 \pm 9.2	+	36.3 \pm 5.9	20.1 \pm 3.8***	+
Adiponectin ($\mu\text{g/ml}$)	7.1 \pm 1.5	9.9 \pm 2.2		8.8 \pm 0.6	10.3 \pm 0.9	
HMW (%)	36.2 \pm 5.1	46.3 \pm 6.1	+	40.4 \pm 3.2	49.0 \pm 2.5	+

Data are means \pm ES.

HMW (%), percentage of high molecular weight adiponectin; NFG, normal fasting glucose.

*The plus sign indicates $P \leq 0.05$ for the difference between pre- and post-BPD. ** $P \leq 0.05$ vs. type 2 diabetes subjects; *** $P \leq 0.01$ vs. type 2 diabetes subjects.

Table 2 Fasting glucose, insulin resistance and insulin secretion parameters

	Type 2 diabetes			NFG		
	Pre-BPD	Post-BPD	BPD effect*	Pre-BPD	Post-BPD	BPD effect*
Fasting glucose (mmol/l)	10.81 ± 3.32	5.24 ± 0.21	+	5.13 ± 0.05**	4.73 ± 0.10	
Fasting insulin (pmol/l)	137.5 ± 87.5	68.7 ± 14.1	+	115.2 ± 15.9	79.3 ± 11.8	+
AIR (pmol/l)	57.9 ± 29.5	273.8 ± 47.1	+	644.9 ± 143.1***	632.5 ± 84.8**	
Adjusted-ins. index	1.0 ± 0.5	76.6 ± 26.0	+	17.6 ± 3.9**	116.1 ± 17.5	+
HOMA-IR	8.7 ± 2.3	2.4 ± 0.6	+	3.8 ± 0.6	2.4 ± 0.4	+

Data are means ± ES.

Adjusted-ins. index, adjusted insulinogenic index; AIR, acute insulin response.

*The plus sign indicates $P \leq 0.05$ for the difference between pre- and post-BPD. ** $P \leq 0.05$ vs. type 2 diabetes subjects; *** $P \leq 0.01$ vs. type 2 diabetes subjects.

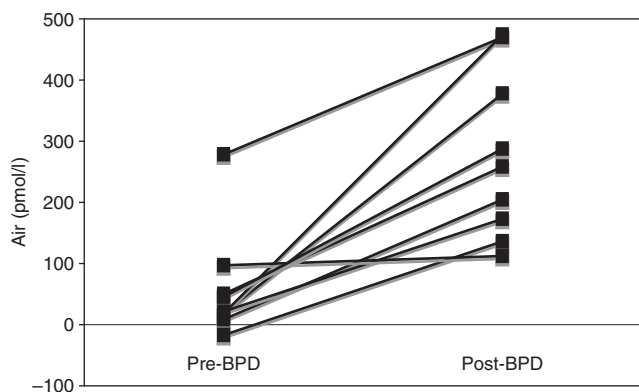


Figure 1 Acute insulin response (AIR) in type 2 diabetic subjects pre- and 1 month post-biliopancreatic diversion (BPD).

leptin concentrations were greater than in the T2DM patients. No changes in total serum adiponectin concentration were found, while after 1 month the adiponectin HMW increased significantly both in T2DM and in NFG subjects.

Effects of BPD on insulin resistance, insulin secretion and fasting glucose

Before BPD, the T2DM group had significantly higher fasting glucose concentrations compared with the NFG group (Table 2), despite there being no significant difference in insulin values and HOMA-IR, suggesting that the degree of insulin resistance was similar in the two groups of obese subjects. On the contrary, AIR was very low or absent in all subjects with T2DM in comparison with those with NFG, as well as the insulinogenic index adjusted for insulin resistance. In all T2DM subjects, 1 month after BPD, fasting plasma glucose was <6.1 mmol/l and only slightly higher than the glucose values for NFG subjects (5.13 ± 0.05 vs. 4.73 ± 0.10 mmol/l, $P = 0.05$). Post BPD fasting insulin concentrations and HOMA-IR were reduced in T2DM and NFG groups compared to pre-surgery values, whereas insulinogenic index adjusted for insulin resistance was increased in both groups. When comparing the post-BPD values of fasting insulin, HOMA-IR and insulinogenic index between T2DM and NFG groups, there were not found any significant differences. One month after BPD in diabetic subjects AIR

showed a significant increase, while in the NFG group BPD did not affect AIR. All diabetic subjects increased their AIR after BPD (Figure 1).

In T2DM subjects the AIR percentage variation from baseline was significantly related to the change in fasting glucose ($r = 0.7$, $P = 0.02$) and to the percentage variation in BMI ($r = 0.68$, $P = 0.023$).

In subjects with diabetes a multivariate model was considered, using as the dependent variable changes in AIR and as independent variables the percent variation of BMI, HMW adiponectin, leptin, HOMA-IR and fasting glucose changes. The only independent variable that significantly predicted post-BPD AIR changes was fasting glucose variations, explaining 56% of AIR changes.

DISCUSSION

The two main findings of this study are that BPD reduces insulin resistance in both NFG and T2DM morbid obese subjects; furthermore in T2DM, together with the normalization of fasting glucose, BPD restores AIR. These effects are present within a few weeks after surgery, when in all subjects BW still remains in the obese range, suggesting that the effects are at least in part independent of weight loss.

The effects of BPD on insulin sensitivity and glucose tolerance have been widely documented (8,18,19). In agreement with previous studies (12,20), in obese subjects a marked reduction of insulin resistance and a normalization of fasting blood glucose concentrations in diabetic subjects were observed soon after BPD. Several mechanisms might play a role in the increase in insulin sensitivity after bariatric surgery: weight loss and negative energy balance with reduction of fat mass, action of intestinal hormones (21) and, in the case of BPD, selective fat malabsorption (22,23).

Reduction of body fat and insulin resistance are important mechanisms responsible for improvement of glucose metabolism. In addition, beta-cell function and insulin secretion seem to be modified by bariatric surgery. We studied the effects of BPD on insulin secretion, focusing on AIR. The absence of AIR to glucose has been recognized as a specific and irreversible marker of beta-cell dysfunction in T2DM. Polyzogopoulou *et al.* (11) reported a restoration of AIR in T2DM 3 and 12 months after BPD, leaving unsolved the

relative role of bariatric surgery itself and weight loss, respectively, on beta-cell function. In the present study we have shown that AIR was already restored 1 month after BPD when the weight loss was only ~11%, suggesting that the improvement of AIR induced by BPD is rapid and not completely dependent on weight loss.

[Q13] Restoration of AIR after BPD could be due to changes of gastrointestinal (GI) hormones, BW, adipokines, gluco- and lipotoxicity.

[Q14] Glucagon-like peptide-1 and gastrointestinal peptide (GIP) are important regulators of beta-cell function and insulin secretion and changes in their secretion patterns have been described following gastric bypass and BPD (24,25). It has been proposed that alterations in GIP secretion might be involved in the metabolic effect of gastric bypass (24,26). AIR is only minimally affected, if any, by gastric bypass suggesting that GIPs do not play a critical role in AIR rescue. However, since glucagon-like peptide-1 has a stimulatory effect on glucose induced insulin secretion, the role of GIP on AIR improvement following bariatric surgery cannot be excluded.

Although AIR is an abnormality at least in part inherited (27,28), many environmental and metabolic conditions might affect early insulin secretion. In subjects with glucose intolerance, weight gain leads to a relative impairment in AIR (29). In T2DM obese patients weight reduction obtained by dieting is unable to restore AIR (10), while contrasting data are reported after gastric bypass (10,30). In the present study we initially found a correlation between BW change and AIR improvement, which failed to persist after multivariate analysis, suggesting a non primary role for weight reduction in rescue of AIR.

It is well known also that moderate hyperglycemia seems to reduce first-phase insulin secretion even in non-diabetic subjects (31), but in type 2 diabetes questions arise about the reversibility of the altered AIR also after normalization of plasma glucose with insulin treatment (32,33). In previous studies in obese diabetic subjects weight loss was not associated with a normalization of fasting plasma glucose (10). The importance of these results for restoration of AIR, even if clear, is not completely understood. In fact high glucose concentrations affect AIR and conversely AIR is important for glucose regulation (34). To our knowledge BPD is the only measure able to induce an early improvement of AIR, but not only by the normalization of glucose concentrations. The significant correlation between changes in glucose concentrations and improvement in AIR that we observed confirms the important bi-directional connections between glucotoxicity and acute insulin secretion.

[Q15] A relationship between adipocyte-derived factors and beta-cell function has been suggested. In fact both leptin and adiponectin receptors are localized in the pancreatic beta cell. *In vitro* leptin suppresses insulin secretion from human islets (35) while in islets from insulin resistant mice adiponectin shows a dual effect: at lower glucose concentrations it inhibits, but at higher glucose concentrations it increases insulin secretion (36). After BPD we observed a significant reduction of leptin, but we did not find any relation between

acute insulin secretion and leptin changes, as well as between adiponectin and insulin secretion. A possible explanation could be the small changes in adiponectin after BPD with a prevalent increase of HMW form. The effect of these isoforms on insulin secretion is still unknown.

BPD causes a selective malabsorption of lipid substrate. There has been reported an increase of Glut4 expression in the muscles of obese subjects after BPD (37). This result and its effect on insulin resistance have been associated with the intramyocellular fat depletion induced by BPD. Recently in a murine model it has been demonstrated that diabetes induced by a chronic high fat diet is characterized by an attenuation of the expression of Glut2 expression in pancreatic beta cell (38). Glut2 is essential for glucose-stimulated insulin secretion; therefore it could be supposed a similar mechanism exists in humans as the molecular base of beta-cell lipotoxicity. According to this view, we can hypothesize that a reduction of lipotoxicity induced by BPD is a possible mechanism for the increment of insulin secretion in obese subjects after BPD.

In obese non-diabetic subjects an improvement of beta-cell function has been reported after a 15 and 25% weight reduction (39). In accordance with this observation, we found after a lower weight loss an increase of insulin response to glucose, expressed as insulinogenic index corrected for insulin resistance, both in diabetic and non-diabetic obese subjects. Interestingly, this parameter was not different after BPD in the two groups. This observation can justify the reported high rate of normalization in the long term, of blood glucose in the diabetic obese after BPD (19).

In conclusion, in obese subjects with type 2 diabetes we observed a reduction of fasting blood glucose and a restoration of AIR 1 month after BPD, when the subjects are still severely obese. Selective fat malabsorption, obtained by BPD, with the consequent reduction of gluco and lipotoxicity might be the mechanism responsible for the normalization of fasting blood glucose and restoration of AIR.

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DISCLOSURE

The authors declared no conflict of interest.

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