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Original Article

Insulin Sensitivity and Secretion in Obese Type 2 Diabetic Women after Various Bariatric Operations

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Key Words
Insulin sensitivity · Beta cell function · Biliopancreatic diversion · Laparoscopic gastric banding · Laparoscopic gastric plication

Abstract
Objective: To compare the effects of biliopancreatic diversion (BPD) and laparoscopic gastric banding (LAGB) on insulin sensitivity and secretion with the effects of laparoscopic gastric plication (P). ***Methods:*** A total of 52 obese women (age 30–66 years) suffering from type 2 diabetes mellitus (T2DM) were prospectively recruited into three study groups: 16 BPD; 16 LAGB, and 20 P. Euglycemic clamps and mixed meal tolerance tests were performed before, at 1 month and at 6 months after bariatric surgery. Beta cell function derived from the meal test parameters was evaluated using mathematical modeling. ***Results:*** Glucose disposal per kilogram of fat free mass (a marker of peripheral insulin sensitivity) increased significantly in all groups, especially after 1 month. Basal insulin secretion decreased significantly after all three types of operations, with the most marked decrease after BPD compared with P and

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LAGB. Total insulin secretion decreased significantly only following the BPD. Beta cell glucose sensitivity did not change significantly post-surgery in any of the study groups. ***Conclusion:*** We documented similar improvement in insulin sensitivity in obese T2DM women after all three study operations during the 6-month postoperative follow-up. Notably, only BPD led to decreased demand on beta cells (decreased integrated insulin secretion), but without increasing the beta cell glucose sensitivity.

Introduction

Bariatric surgery can lead to significant improvement of type 2 diabetes mellitus (T2DM) in morbidly obese patients [1, 2]. A meta-analysis by Buchwald et al. [3] has shown that laparoscopic adjustable gastric banding (LAGB) and biliopancreatic diversion (BPD) induces remission of T2DM in 50% and up to 95% of bariatric T2DM patients, respectively. Weight loss dependent improvement in insulin sensitivity is regarded as the main mechanism for T2DM improvement/remission after LAGB (restrictive bariatric procedure) [1, 2, 4]. However, following BPD (a predominantly malabsorptive procedure) improvement in insulin sensitivity has been demonstrated even within a few days after the operation and, thus, is not only weight loss-dependent [1, 2, 4]. The underlying mechanisms leading to T2DM improvement/remission following more complex bariatric procedures such as the BPD are not fully clarified yet and appear to involve changes not only in insulin resistance but also in insulin and incretin secretion [4, 5]. Novel bariatric procedures such as the laparoscopic gastric plication (P), also referred to as laparoscopic greater curvature plication, total gastric vertical plication, or gastric imbrication [5–8], recently has broadened the arsenal of metabolic surgery interventions for the treatment of obese T2DM patients. This newer procedure eliminates the greater gastric curvature and forms a gastric tube by laparoscopic plication/infolding of the greater gastric curvature through placement of one or two rows of non-absorbable sutures or staples, thus reducing the stomach volume and leading to a restrictive effect without utilizing implantable devices (e.g., gastric band), gastrectomy, or intestinal bypass. Previously, the greater and lesser curvature were used for the creation of an intraluminal fold of the stomach, however the greater curvature was found to be more effective [9]. To date, there are limited data on the effects of this emerging surgical technique in T2DM patients compared to established bariatric procedures. In the present study, we therefore aimed to compare the effects of LAGB, BPD and P on insulin resistance and secretion in obese T2DM women.

Patients and Methods

Study Subjects

For the purposes of this study, we prospectively recruited 52 morbidly obese women (BMI ≥ 35 kg/m^2) with T2DM (age 30–66 years; T2DM duration 1–14 years). Obese T2DM women eligible for bariatric surgery were allocated to the three different bariatric procedures of the study according to consecutive numbers, which were assigned at the beginning of the indication/screening process for study enrollment, providing that there were no contraindications for a particular operation type. In the context of this study, further exclusion criteria included: treatment with either glitazones or DPP-IV inhibitors or GLP1 agonists; evidence or history of clinically significant cardiovascular, pulmonary, endocrine (other than obesity and T2DM), hematological, renal, gastrointestinal, hepatic (other than NAFLD), neurologic, psychiatric, inflammatory, or severe allergic disease; cancer; pregnancy or breastfeeding; weight change more than a 5% of the total body

Table 1. Age, T2DM duration and key weight/anthropometric-related parameters of the obese T2DM women in the three study groups before the bariatric operation (Exam 1), and the effects of BPD, LAGB or P on these parameters at 1 month (Exam 2) and 6 months (Exam 3) after the operation

Parameter	Operation	Exam 1	Exam 2	Exam 3	ANOVA[††]
Age, years	BPD (a) LAGB (b) P (c)	50.6 (47.1; 53.7) 54.8 (51.8; 57.5) 53 (50.1; 55.5)			
DM duration, years	BPD (a) LAGB (b) P (c)	3.48 (2.49; 4.78) 3.18 (2.24; 4.43) 3.35 (2.48; 4.46)			
BMI, kg/m^2	BPD (a) LAGB (b) P (c) a–b, a–c, b–c[+]	44.9 (43.8; 45.9) 42.2 (41.4; 43.0) 42.4 (41.7; 43.2) Exam 1 (a)	41.7 (40.8; 42.7) 40.1 (39.3; 40.8) 39.5 (38.8; 40.2) Exam 2 (b)	37.7 (36.9; 38.5) 38.3 (37.6; 39.0) 37.7 (37.2; 38.4) Exam 3 (c)	operation***, exam***, subject***, operation × exam* a–b, a–c, b–c
FFM, kg	BPD (a) LAGB (b) P (c) a–b, a–c, b–c	60.3 (58.7; 62.2) 58.8 (57.5; 60.3) 58.2 (56.9; 59.6) Exam 1 (a)	55.5 (54.1; 57.0) 56.2 (54.9; 57.6) 56.5 (55.3; 57.7) Exam 2 (b)	55.5 (54.2; 56.9) 54.9 (53.7; 56.1) 55.3 (54.2; 56.5) Exam 3 (c)	exam***, subj*** a–b, a–c, b–c
Waist circumference, cm	BPD (a) LAGB (b) P (c) a–b, a–c, b–c	126 (122; 130) 121 (118; 124) 122 (119; 124) Exam 1 (a)	125 (121; 129) 115 (112; 117) 115 (113; 118) Exam 2 (b)	111 (108; 114) 114 (112; 117) 113 (110; 115) Exam 3 (c)	exam***, subject***, operation × exam** a–b, a–c, b–c

[+]Significant difference for multiple comparisons ($p<0.05$); significant difference for ANOVA factors and between-factor interaction *$p<0.05$, **$p<0.01$, ***$p<0.001$.

[††]Adjusted for age and BMI.

weight over the preceding 12 weeks, or recent changes in exercise intensity and/or frequency over the preceding 4 weeks before surgery.

In total, 16 subjects underwent BPD; 16 subjects LAGB; and 20 subjects P. For 13 patients included in the P study group, non-comparative, prospective, results without analyses of beta cell function data via mathematical modeling have been previously described by our group in the pilot paper on the effects of gastric plication in T2DM [6].

Age and T2DM duration did not significantly differ between the three study groups (table 1). Antidiabetic treatment was as follows:

- In the BPD group, 2 subjects were on diet only; 11 subjects were treated with metformin only and 3 subjects with a metformin-sulphonylurea combination.
- In the LAGB group, 9 subjects were treated with metformin only, 1 subject with a metformin-sulphonylurea combination, 3 subjects with sulphonylurea only, 1 subject with metformin and insulin, and 1 subject with a metformin-sulphonylurea combination and insulin.
- In the P group, 2 subjects were treated with diet only, 15 subjects with metformin only, 2 subjects with a metformin-sulphonylurea combination, and 1 subject with metformin and insulin.

Study Surgical Procedures

All three types of bariatric procedures of this study were performed laparoscopically and according to established techniques, with standard peri- and postoperative care, as previously described in the literature [6, 7, 10]. Briefly, these three bariatric procedures were performed as follows:

- BPD was performed according to Scopinaro's standard procedure, but with a 90 cm common channel instead of the 50 cm one originally suggested by Scopinaro [10]. Intestinal measurements were taken on the bowel fully stretched, at half-way from the mesenteric and the antimesenteric border. A

relatively larger stomach remnant (up to 400 ml) was also left, aiming to potentially decrease the risk of severe postoperative nutritional deficiencies.
- The LAGB (MiniMizer Extra adjustable gastric band, Bariatric Solutions GmbH, Stein am Rhein, Switzerland) was placed using the standardized pars flaccida technique [7].
- P was performed in standardized fashion, starting the dissection 3–5 cm proximally to the pylorus and stopping approximately 2 cm below the angle of His. Through this dissection, the greater curvature was fully infolded and secured. A 36 F bougie was used for calibration of the stomach tube during the infolding of the stomach in order to maintain a standardized stomach lumen [6].

None of the patients in this study exhibited major intraoperative and/or postoperative complications.

Body Composition

Anthropometric measurements were performed in all patients at three time points (i.e., before the operation and at 1 month and 6 months after the operation), as per protocol. Body weight was measured to the nearest 0.5 kg and height to the nearest 1 cm. BMI was calculated as body weight in kilograms divided by the square of the height in meters. Waist circumference was measured in standing position, at the half of the distance between lower ribs and the iliac crest. Hip circumference was measured as the widest gluteal circumference. Fat free mass (FFM) was measured using a standardized calibrated bioimpedance instrument (TBF-300; Tanita® Corp., Arlington Heights, IL, USA).

Study Protocol Exams

For each study participant a mixed meal tolerance test (MMT) and an euglycemic clamp test were performed in 2 subsequent days before the operation (Exam 1) and at 1 month (Exam 2) and 6 months (Exam 3) after the operation. Oral antidiabetic drugs and long-acting insulin was discontinued 3 days and 24 h before the scheduled study examinations, respectively. In the context of this study, T2DM improvement or resolution at 6 months (Exam 3) was defined according to the European guidelines on metabolic and bariatric surgery [11], although these are recommended based on the 1-year post-operative follow-up.

MMT

A standardized liquid MMT (300 ml; 375 kcal; 1,581 kJ; 30% (28.2 g) protein, 25% (10.5 g) fat, 45% (42 g) carbohydrate) was performed at each of the three study time points, namely at baseline (Exam 1), at 1 month (Exam 2) and at 6 months (Exam 3) after the operation. All patients were tested in the morning after overnight fasting, and venous blood was sampled for measurements of gastric inhibitory polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon at 0, 30, 60, 90, 120, and 180 min after the liquid meal ingestion. These blood samples were collected into chilled ethylene-diamine-tetraacetic acid(EDTA)-containing tubes with aprotinin. Dipeptidyl-peptidase-4 (DPP-IV) inhibitor (Merck Millipore Corp., Billerica, MA, USA) was added immediately after blood sampling. Blood samples were also collected into chilled EDTA-containing tubes without aprotinin for assessment of glucose, insulin and C-peptide levels at –15, –10, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min. All samples were immediately cooled, and plasma was prepared, aliquoted, and stored at –80 °C until assayed. Plasma levels of blood glucose (photometric method with hexokinase), insulin (electro-chemiluminiscence immunoassay; ECLIA), C-peptide (ECLIA), and glycated hemoglobin (HbA1c, immunoturbidimetric method) were measured using the Cobas® 6000 analyzer (Roche Diagnostics, Rotkreuz, Switzerland). Plasma concentrations of GIP, GLP-1, and glucagon were assessed using a multiplex assay (Bio-Plex Pro™ Human Diabetes Assay Panel, BioPlex® 200 System; Bio-Rad Laboratories, Cressier, Switzerland).

Euglycemic Clamp and Insulin Sensitivity Indices

On the next day following each MMT and after overnight fasting, an euglycemic hyperinsulinemic clamp was performed, as previously described [12]. Briefly, after inserting a cannula in a dorsal hand vein for sampling of arterialized venous blood and another one into the antecubital fossa for infusions, subjects rested at least for 30 min in the supine position. Subsequently, the hand with the dorsal hand cannula was placed into a heated blanket in order to get arterialized blood for measuring blood glucose levels, which were maintained at 5 mmol/l via a variable 15% glucose infusion. Insulin was delivered by the primed constant infusion of 240 pmol/min/m^2. Glucose disposal (Mk value), as the 'gold standard' for peripheral insulin sensitivity measurements, was calculated during the last 30-min period of the clamp test, related to fat free mass (in µmol/min/kg).

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The homeostatic model assessment (HOMA) method was also applied to assess insulin resistance (HOMA-IR) based on the fasting glucose and insulin levels according to the following formula: HOMA-IR = (fasting glucose (mmol/l) × fasting insulin (mIU/l)) / 22.5, as previously described [13]. This index reflects more the hepatic insulin sensitivity rather than the whole body/peripheral one.

Beta Cell Function and Hepatic Insulin Extraction

Beta cell function was assessed by mathematical modeling, as previously described [14]. Briefly, insulin secretion is described as the sum of two components, i.e., $S_g(t)$ and $S_d(t)$. The first term, Sg(t), is that originating from a dose-response function (f(G)); the dose response is modulated by a function of time (P(t)) that averages one during the MMT and increases with time, thus determining the late insulin secretion enhancement. The term P(t) modulating the dose response is denoted as the potentiation factor.

The second term, Sd(t), describes the early response. This is proportional to the time derivative of glucose concentration when it is positive and is otherwise zero. Thus, this component is significant as long as the glucose concentration is increasing, i.e., in the early phase of the MMT. The proportionality constant of the early secretion component (Kd) is termed rate sensitivity.

As such, the primary results obtained from this modeling analysis are: the dose response (f(G)), the potentiation factor (P(t)), and the rate sensitivity (scalar parameter).

Because f(G) and P(t) are functions (of glucose concentration and time, respectively), other scalar parameters are derived from them. Hence, two parameters characterizing the dose response are calculated: the slope of the dose response, denoted as glucose sensitivity, and insulin secretion at a fixed glucose level, which is representative of the basal glucose value (e.g., 5 mmol/l in subjects with normal glucose tolerance). The potentiation factor excursions are typically quantified using the ratio between the value at 2 h and the basal value (potentiation ratio). In addition to these parameters, the modeling analysis provides basal insulin secretion and total insulin secretion (the integral of insulin secretion during the whole MMT). Insulin secretion is calculated from C-peptide deconvolution using the method by Van Cauter et al. [15] and is expressed in pmol/min/m^2 of estimated body surface area.

Finally, hepatic insulin extraction was computed in the basal state as the molar ratio of C-peptide to insulin levels.

Statistical Analysis

The relationships between individual metric variables and factors were evaluated by ANOVA models followed by least significant difference multiple comparisons. The first model, used for the evaluation of anthropometric, basal state and euglycemic hyperinsulinemic clamp-derived parameters, consisted of subject factor (separating inter-individual variability from remaining factors), between-subject factor operation, within-subject factor exam and operation × exam interaction. The second model, used for the evaluation of the MMT time curves, consisted of subject factor, between-subject factor operation, within-subject factors exam and time, and all interactions between these factors. The original raw data were transformed by a power transformation to attain symmetric data distribution and constant variance. The homogeneity of data was checked using residual analysis, as previously reported [16, 17]. The results are presented as mean (lower limit of CI; upper limit of CI) unless stated otherwise. Statistical significance was set at $p < 0.05$. Both ANOVA models were adjusted to constant initial BMI, age and initial values of the dependent variable. These variables were divided into two groups (≤median, >median) and the corresponding dichotomous variables were added into the model.

Results

Effects on Weight Loss-Related Parameters

Table 1 presents the outcomes relating to selected weight loss-related parameters in the three study groups. BMI was the highest in the BPD group, followed by the LAGB and the P group (operation: $F = 6$; $p < 0.001$). BMI decreased in a similar way in the P and LAGB groups and more markedly in the BPD group, both between Exam 1 and 2 and from Exam 2 to 3. Furthermore, waist circumference and FFM decreased in a similar way in the LAGB and P groups and more markedly in the BPD group (table 1).

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Table 2. Effects of BPD, LAGB, and P on key blood glucose- and insulin-related parameters at 1 month (Exam 2) and 6 months (Exam 3) after the operation (Exam 1: baseline levels before the bariatric operation)

Parameter	Operation	Exam 1	Exam 2	Exam 3	ANOVA[††]
Fasting blood glucose, mmol/l	BPD (a) LAGB (b) P (c) a-b, a-c, b-c	8.07 (7.51; 8.70) 8.81 (8.23; 9.46) 8.33 (7.83; 8.89) Exam 1 (a)	6.56 (6.17; 6.99) 7.06 (6.67; 7.49) 7.23 (6.85; 7.66) Exam 2 (b)	6.26 (5.86; 6.69) 6.92 (6.55; 7.34) 6.84 (6.47; 7.24) Exam 3 (c)	operation*, exam***, subject** a–b, a–c, b–c
Blood glucose at 120th min, mmol/l	BPD (a) LAGB (b) P (c) a-b, a-c	9.63 (8.72; 10.69) 9.74 (8.93; 10.67) 9.71 (8.93; 10.59) Exam 1 (a)	6.53 (5.99; 7.13) 8.05 (7.43; 8.75) 7.61 (7.06; 8.23) Exam 2 (b)	7.18 (6.55; 7.91) 7.59 (7.02; 8.23) 7.79 (7.21; 8.46) Exam 3 (c)	exam***, subject** a–b, a–c
Glycated hemoglobin, mmol/mol	BPD (a) LAGB (b) P (c) a-b, a-c, b-c	46.9 (45.9; 48.1) 48.5 (47.5; 49.5) 47.6 (46.7; 48.6) Exam 1 (a)	42.4 (41.7; 43.1) 45.5 (44.7; 46.4) 45.6 (44.8; 46.4) Exam 2 (b)	42.4 (41.6; 43.2) 45.0 (44.3; 45.8) 45.4 (44.6; 46.2) Exam 3 (c)	operation***, exam***, subject***, operation × exam* a–b, a–c, b–c
HOMA-IR	BPD (a) LAGB (b) P (c) 	9.19 (7.59; 11.23) 9.62 (8.12; 11.47) 9.07 (7.72; 10.72) Exam 1 (a)	3.89 (3.23; 4.69) 4.68 (4.01; 5.47) 5.12 (4.37; 6.03) Exam 2 (b)	3.56 (2.98; 4.25) 4.66 (3.99; 5.44) 4.84 (4.17; 5.63) Exam 3 (c)	exam***, subject*** a–b, a–c, b–c
Mkper FFM, mmol/min/kg	BPD (a) LAGB (b) P (c) a-c, b-c	15.6 (12.4; 19.1) 17.4 (14.6; 20.4) 20.2 (17.5; 23.2) exam 1 (a)	28.5 (24.2; 33.3) 26.1 (22.5; 30.0) 27.2 (23.9; 30.6) exam 2 (b)	32.6 (28.2; 37.5) 28.5 (24.9; 32.4) 29.0 (25.7; 32.6) exam 3 (c)	exam***, subject** a–b, a–c
Basal insulin secretion, pmol/min/m^2	BPD (a) LAGB (b) P (c) a-b, a-c, b-c	177.5 (162.6; 194.1) 185.4 (171.5; 200.4) 162.5 (150.9; 175.1) Exam 1 (a)	146.7 (133.7; 161) 142 (131.5; 153.3) 151.8 (140.6; 164) Exam 2 (b)	127.4 (116.1; 139.7) 139.6 (129.3; 150.7) 142.9 (132.4; 154.3) Exam 3 (c)	exam***, subject*** a–b, a–c, b–c
Total insulin secretion, nmol/m^2	BPD (a) LAGB (b) P (c) a-b, a-c	61.3 (55.9; 67.1) 60.5 (55.8; 65.6) 59.6 (55.1; 64.4) Exam 1 (a)	35.8 (32.0; 39.9) 54.3 (49.9; 58.9) 67.2 (62.1; 72.7) Exam 2 (b)	38.9 (34.8; 43.2) 53.2 (48.9; 57.8) 60.5 (55.8; 65.5) Exam 3 (c)	operation***, exam***, subject***, operation × exam*** a–b, a–c
Potentiation factor ratio	BPD (a) LAGB (b) P (c) a-b, a-c	1.28 (1.16; 1.42) 1.30 (1.19; 1.43) 1.32 (1.21; 1.44) Exam 1 (a)	1.10 (0.99; 1.19) 1.29 (1.19; 1.42) 1.36 (1.25; 1.48) Exam 2 (b)	1.13 (1.03; 1.24) 1.24 (1.15; 1.36) 1.25 (1.15; 1.37) Exam 3 (c)	operation* a–b, a–c
Rate sensitivity, pmol/m^2/mmol/l	BPD (a) LAGB (b) P (c) 	1,348 (943; 1,856) 1,203 (873; 1,606) 1,337 (1006; 1,733) Exam 1 (a)	932 (576; 1,406) 1,284 (937; 1,706) 891 (651; 1,184) Exam 2 (b)	1,228 (827; 1,740) 1,084 (799; 1,428) 1,110 (801; 1,487) Exam 3 (c)	

Table 2 continued on next page

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Table 2. Continued

Parameter	Operation	Exam 1	Exam 2	Exam 3	ANOVA[††]
Glucose sensitivity, pmol/m^2/mmol/l	BPD (a) LAGB (b) P (c)	68.9 (51.8; 89.7) 61.0 (47.2; 77.5) 58.6 (45.6; 73.9) Exam 1 (a)	54.8 (40.4; 72.5) 92.2 (73.4; 114.3) 74.5 (59.1; 92.6) Exam 2 (b)	64.4 (48.2; 84.2) 88.6 (70.4; 110.2) 82.3 (65.2; 102.4) Exam 3 (c)	
Hepatic insulin extraction, %	BPD LAGB P a-b, a-c	59.6 (55.8; 63.2) 60.6 (57.4; 63.7) 61.3 (58.2; 64.4) Exam 1 (a)	78.2 (75.4; 80.9) 63.9 (60.8; 66.8) 64.5 (61.5; 67.4) Exam 2 (b)	77.3 (74.3; 80.2) 64.1 (61.0; 66.9) 64.2 (61.1; 67.2) Exam 3 (c)	operation***, exam***, subject**, operation × exam*** a–b, a–c

[†]Significant difference for multiple comparisons ($p<0.05$); significant difference for ANOVA factors and between-factor interaction *$p<0.05$, **$p<0.01$, ***$p<0.001$.

[††]Adjusted for age and BMI.

Effects on T2DM Improvement

At the 6-month time point, in the BPD group T2DM was resolved in 9/16 subjects (60%), whilst in 6/16 (40%) it was significantly improved. Accordingly, in the LAGB group, T2DM was resolved in 3/16 (19%) of the subjects and improved in 10/16 (63%). Finally, in the P group, T2DM was resolved in 4/20 (20%) patients and improved in 12/20 (60%). The mean HbA1c decreased significantly in all study groups, whilst the drop between the study time points was most prominent in the BPD group (table 2).

Effects on Insulin Sensitivity and Beta Cell Function

Table 2 presents the key outcomes with respect to insulin sensitivity and beta cell function for our study cohort. Insulin sensitivity improved after all three types of operations. Indeed, HOMA-IR decreased similarly after all three operations, whilst glucose disposal (Mk per FFM) increased significantly and similarly in all study groups, especially after 1 month.

The total secretory demand on beta cells was reduced markedly only after the BPD, while the basal insulin secretion decreased significantly after all three operations, with the most marked decrease in the BPD group. However, the total insulin secretion decreased significantly only in the BPD group in Exam 2 versus 1 and in Exam 3 versus 1, whereas it did not change significantly following the operation in the LAGB and P group (table 2).

In addition, the potentiation factor ratio tended to decrease after BPD, whereas it did not change significantly after the operation in the LAGB or the P group.

Moreover, neither the beta cell glucose sensitivity nor the rate sensitivity exhibited significant changes after any of the three study operations.

Finally, the hepatic insulin extraction increased significantly in the BPD group in Exam 2 versus 1 and in Exam 3 versus 1, whereas it did not change significantly following the operation in the LAGB or the P group.

Effects on MMT Glucose/Insulin Parameters and Selected Gastrointestinal Hormones

Blood glucose levels during the MMT decreased between Exam 1 and 2 in all three study groups (fig. 1i). Moreover, insulin levels also decreased after all three types of operations in this study; this effect was more pronounced in the BPD group (fig. 1ii). The insulin curve following the BPD in Exam 2 and 3 was more flat than in Exam 1 (fig. 1ii).

For C-peptide, the changes in Exam 2 and 3 differed according to operation (Operation × Exam: $F = 40.5$, $p < 0.001$) (fig. 1iii). C-peptide levels decreased between Exam 1 and 2, and

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between Exam 1 and 3 in the LAGB and BPD group and between Exam 2 and 3 in the P group. Furthermore, in the BPD group, the C-peptide curve in Exam 2 and Exam 3 was more flat than in Exam 1 (fig. 1iii).

GIP levels decreased in Exam 2 and remained lower in Exam 3 in the BPD group (fig. 2i). Conversely, GIP levels increased in the P group, whereas they did not change significantly in the LAGB group (fig. 2i).

GLP-1 levels increased from Exam 1 to Exam 2 and then remained unchanged in the BPD group (fig. 2ii). Moreover, in the LAGB group GLP-1 levels did not change significantly from Exam 1 to Exam 2, but increased between Exam 2 and 3; whereas in the P group they did not change significantly from Exam 1 to Exam 2 and decreased between Exam 2 and 3 (fig. 2ii).

Finally, glucagon levels did not change significantly after the operation in any of the three study groups (fig. 2iii).

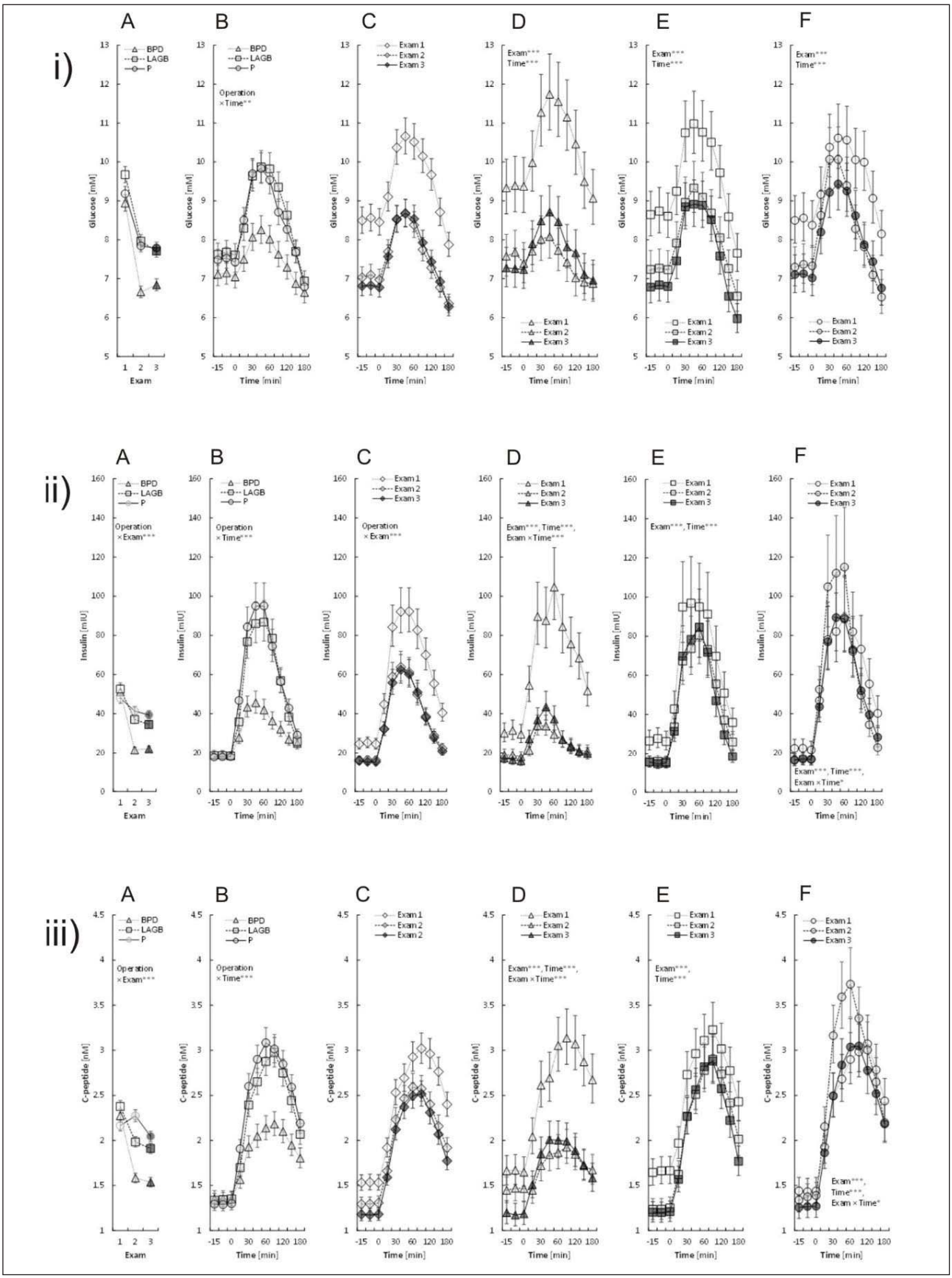
Discussion

To our knowledge, this is the first study in obese T2DM patients reporting the effects of the emerging bariatric technique P on insulin resistance and secretion in comparison to established bariatric procedures such as the LAGB and BPD. Our study results indicate that insulin sensitivity improves similarly after all these bariatric operations. However, only the BPD resulted in significantly decreased total insulin secretion during the 6-month follow-up period, and it was also more effective compared with the LAGB and the P in improving T2DM within this timeframe.

Our study results are in accord with recent meta-analysis data on predictors of T2DM remission after bariatric surgery in obese subjects [18]. Indeed, T2DM resolution was noted in 89% of the patients after BPD, while lower rates were noted following Roux en Y gastric bypass (RYGB), LAGB, and sleeve gastrectomy (SG). Of note, in this meta-analysis the only significant predictor of HbA1c reduction was waist circumference. Interestingly, T2DM remission was independent of the initial BMI of the patients when the groups with BMI < 35 kg/m^2 and BMI ≥ 35 kg/m^2 were compared [18].

It should be noted that the primary objective of the present study was to compare the effects of P (a bariatric operation that can be categorized between purely restrictive and malabsorptive bariatric procedures) with an established restrictive procedure (i.e., LAGB) and a predominantly malabsorptive procedure (i.e., BPD). Verdi et al. [19] have recently reported a study comparing the effects of P to those of laparoscopic SG, a bariatric operation that can be also categorized between the purely restrictive and the malabsorptive bariatric procedures. This study documented greater weight loss following SG; however, the study cohort included obese subjects without diabetes, and additional metabolic effects were not followed up [19].

Moreover, in another recent study Robert et al. [20] reported that short diabetes duration (≤4 years), good preoperative glycemic control, BMI ≤ 50 kg/m^2, and absence of insulin therapy constitute predictive factors of T2DM remission at 1 year after bariatric surgery. Additionally, in this study there was no significant difference for T2DM remission at 1 year with regard to the surgical procedure, i.e., LAGB, RYGB, or SG [20]. Contrary, the data from our cohorts indicate a higher T2DM remission rate in patients treated with BPD, followed by those receiving LAGB and P [21]. Importantly, a UK population-based cohort study with more than 500 diabetic patients treated by bariatric surgery documented the highest T2DM remission rate after RYGB, followed by SG, and LAGB [22] – results which are similar to the findings of our study. Interestingly, the potent BPD effect on hyperglycemia has also been shown in patients with moderate obesity or overweight [10]. Indeed, Scopinaro et al. [10]



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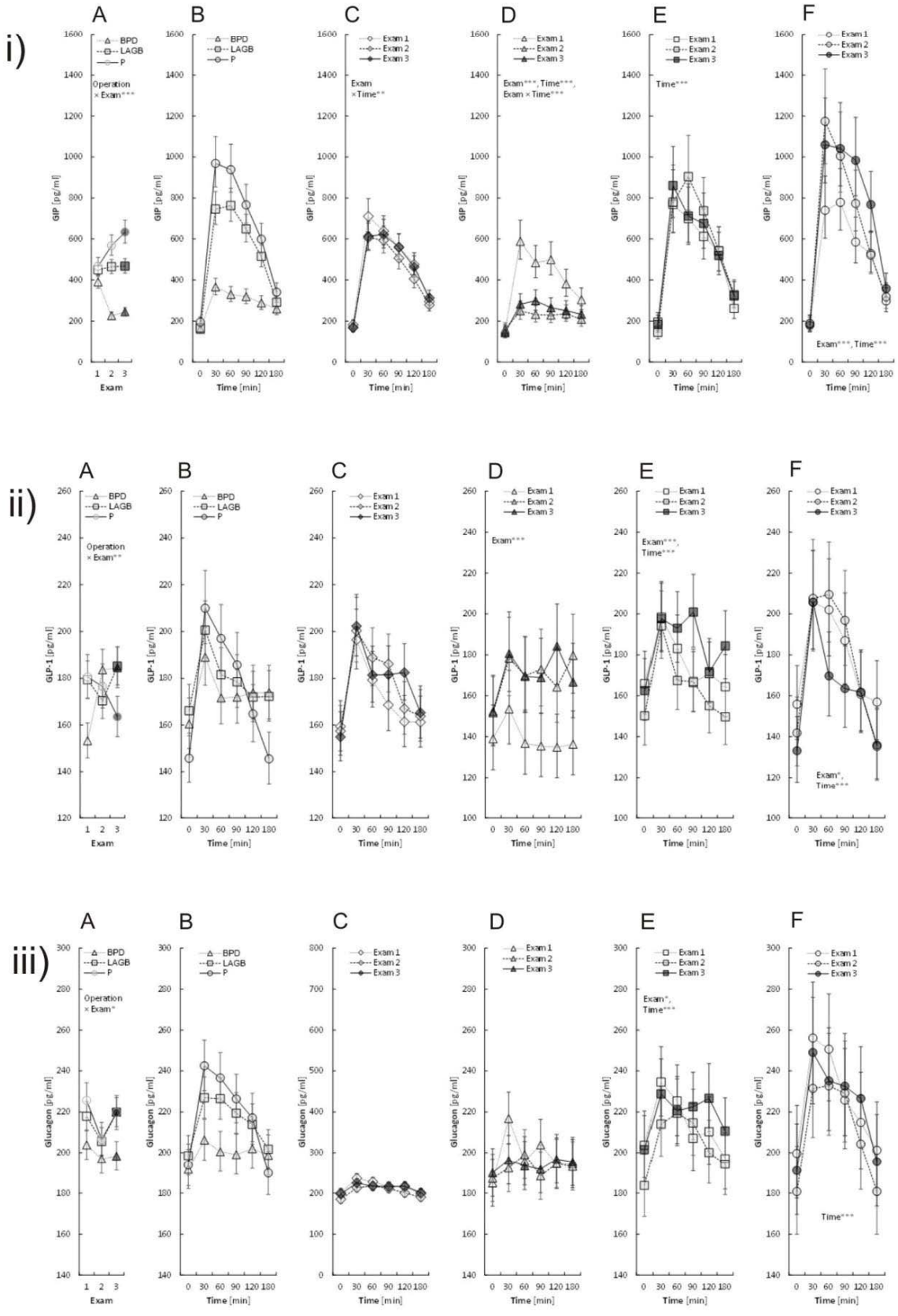
have reported that BPD improves or resolves T2DM in subjects with BMI ranging from 25 to 35 kg/m^2 without causing excessive weight loss, potentially due to improved insulin sensitivity and beta cell function. Of note, in this study there was a markedly different response between morbidly obese patients and patients with lower BMI, potentially due to a different beta cell defect, whilst T2DM resolution correlated positively with BMI [10].

Limitations of our study were as follows: The number of patients is the rather low number of patients although the examinations of patients were very detailed. Only selected methods of bariatric surgery, i.e., the procedures usually performed in our bariatric center, were evaluated, and some usually applied methods such as sleeve gastrectomy and RYGB were not included .

Overall, compiling data indicate that bariatric surgery results in better glycemic control in obese T2DM patients compared to medical treatment [23, 24]. Importantly, different postoperative effects/outcomes following different types of bariatric procedures appear to be related to distinct mechanisms contributing to improved insulin sensitivity and/or secretion [1, 4, 25]. As such, the LAGB effect is considered mostly weight loss-dependent [1, 4, 25], whilst P may exert effects that are not only related to food restriction and weight loss but are also mediated through distinct incretin/hormonal effects [5, 6]. Potential mechanisms that have been suggested for incretin/hormonal changes following P include i) devascularization of the greater curvature and therefore decreased blood supply to some of the active cells in the stomach (lowering their secretion); ii) effects on the mechanical constriction of the plicated/infolded stomach tissue; iii) interference in the majority of the vagal nerve fibers alongside the greater curvature of the stomach; and iv) potentially quicker gastric evacuation time. These mechanisms are relatively similar to those considered to mediate the effects of SG [1, 5, 6]. On the other hand, proposed mechanisms for the metabolic outcomes of BPD include i) malabsorption and ii) limited contact of pancreatic enzymes with ingested food in

Fig. 1. Blood glucose, insulin and C-peptide levels during the MMT in the BPD, LAGB and P study groups at the three study time points (before the operation (Exam 1) and at 1 month (Exam 2) and 6 months (Exam 3) after the operation). **i)** Blood glucose levels during the MMT. Symbols: BPD – triangles; LAGB – squares; P – circles, Exam 1 – white symbols; Exam 2 – light grey symbols; Exam 3 –dark grey symbols. *A, B, C – all three study groups*: operation: F = 71.3, p < 0.001; exam: F = 323.7, p < 0.001; time: F = 61.5, p < 0.001; operation × exam: F = 10.5, p < 0.001; operation × time: F = 2, p = 0.005; exam × time: F = 0.8, p = 0.73; operation × exam × time: F = 0.9, p = 0.591; subject: F = 28.4, p < 0.001. *D – BPD study group*: exam: F = 182.9, p < 0.001; time: F = 8.7, p < 0.001; exam × time: F = 0.9, p = 0.617; subject: F = 26.6, p < 0.001. *E – LAGB study group*: exam: F = 105.6, p < 0.001; time: F = 32.4, p < 0.001; exam × time: F = 0.3, p = 1; subject: F = 51.6, p < 0.001. *F – P study group*: exam: F = 51.3, p < 0.001; time: F = 25.3, p < 0.001; exam × time: F = 1, p = 0.502; subject: F = 50.3, p < 0.001. **ii)** Insulin levels during the MMT. Symbols: BPD – triangles; LAGB – squares; P – circles, Exam 1 – white symbols; Exam 2 – light grey symbols; Exam 3 – dark grey symbols. *A, B, C – all three study groups*: operation: F = 86.5, p < 0.001; exam: F = 194.5, p < 0.001; time: F = 216.3, p < 0.001; operation × exam: F = 35.1, p < 0.001; operation × time: F = 7.8, p < 0.001; exam × time: F = 1.1, p = 0.327; operation × exam × time: F = 2.1, p < 0.001; subject: F = 33.3, p < 0.001. *D – BPD study group*: exam: F = 354.7, p < 0.001; time: F = 43.1, p < 0.001; exam × time: F = 3.2, p < 0.001; subject: F = 98.6, p < 0.001. *E – LAGB study group*: exam: F = 43.3, p < 0.001; time: F = 101.4, p < 0.001; exam × time: F = 1.1, p = 0.363; subject: F = 14.8, p < 0.001. *F – P study group*: exam: F = 8.1, p < 0.001; time: F = 102.2, p < 0.001; exam × time: F = 1.9, p = 0.011; subject: F = 30.3, p < 0.001. **iii)** C-peptide levels during the MMT. Symbols: BPD – triangles; LAGB – squares; P – circles, Exam 1 – white symbols; Exam 2 – light grey symbols; Exam 3 – dark grey symbols. *A, B, C – all three study groups*: operation: F = 78.7, p < 0.001; exam: F = 136.1, p < 0.001; time: F = 231.1, p < 0.001; operation × exam: F = 40.5, p < 0.001; operation × time: F = 6.7, p < 0.001; exam × time: F = 1, p = 0.51; operation × exam × time: F = 2, p < 0.001; subject: F = 36.8, p < 0.001. *D – BPD study group*: exam: F = 168.5, p < 0.001; time: F = 35.6, p < 0.001; exam × time: F = 2.6, p < 0.001; subject: F = 60.6, p < 0.001. *E – LAGB study group*: exam: F = 56, p < 0.001; time: F = 112.8, p < 0.001; exam × time: F = 0.9, p = 0.631; subject: F = 37.9, p < 0.001. *F – P study group*: exam: F = 11.5, p < 0.001; time: F = 114.5, p < 0.001; exam × time: F = 1.7, p = 0.037; subject: F = 26.8, p < 0.001.



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the distal ileum but also iii) contact of undigested food with the ileal mucosa leading to a potentiated incretin effect and iv) acceleration and intensification of the enterohepatic circulation of bile acids [4, 25].

In our study, insulin sensitivity, measured by HOMA-IR, as well as by euglycemic clamp tests, improved in a similar way after all three study operations. Other studies have reported greater improvement of HOMA-IR and QUICKI following BPD compared with LAGB [26]. Similarly, Tsoli et al. [27] have shown greater improvement in insulin sensitivity after BPD compared to SG. Such different results may be attributed to the heterogeneous patient cohorts studied, while it should be also noted that HOMA-IR is a surrogate marker primarily of hepatic insulin resistance, whereas glucose disposal during the euglycemic clamp measures insulin sensitivity mainly in skeletal muscles.

Furthermore, in agreement with results from previously published studies [28], total insulin secretion in our study decreased significantly only in the BPD group. However, it cannot be excluded that the decreased insulin levels after BPD may be also attributed to the increased hepatic insulin clearance. Notably, we did not observe an increase in beta cell glucose sensitivity in the 6-month period after any of the three study operations. Interestingly, insufficient increase of beta cell glucose sensitivity has also been reported in non-obese diabetic patients 1 year after BPD, even in subjects with T2DM remission [29]. Moreover, Mari et al. [14] have also reported nonsignificant changes in beta cell glucose sensitivity in 11 morbidly obese T2DM patients after BPD. Nevertheless, BPD appears to result in T2DM resolution in a greater proportion of subjects when compared with LAGB and P. A possible explanation for these observations could be that the beta cell glucose sensitivity is basically secretion normalized to glucose levels; thus, insulin secretion is decreased after the BPD, and glucose levels decrease as well, but in proportion to the decrease in insulin secretion. Accord-

Fig. 2. GIP, GLP-1 and glucagon levels during the MMT in the BPD, LAGB and P study groups at the three study time points (before the operation (Exam 1) and at 1-month (Exam 2) and 6-months (Exam 3) after the operation). **i)** GIP levels during the MMT. Symbols: BPD – triangles; LAGB – squares; P – circles, Exam 1 – white symbols; Exam 2 – light grey symbols; Exam 3 – dark grey symbols. *A, B, C – all three study groups*: operation: $F = 135.4$, $p < 0.001$; exam: $F = 3.9$, $p = 0.022$; time: $F = 178.5$, $p < 0.001$; operation × exam: $F = 10.3$, $p < 0.001$; operation × time: $F = 0.4$, $p = 0.944$; exam × time: $F = 2$, $p = 0.007$; operation × exam × time: $F = 11.5$, $p < 0.001$; subject: $F = 23.5$, $p < 0.001$. *D – BPD study group*: exam: $F = 53.3$, $p < 0.001$; time: $F = 29.1$, $p < 0.001$; exam × time: $F = 3.6$, $p < 0.001$; subject: $F = 12.5$, $p < 0.001$. *E – LAGB study group*: exam: $F = 0.6$, $p = 0.547$; time: $F = 77.6$, $p < 0.001$; exam × time: $F = 0.9$, $p = 0.551$; subject: $F = 8.6$, $p < 0.001$. *F – P study group*: exam: $F = 10.4$, $p < 0.001$; time: $F = 108.7$, $p < 0.001$; exam × time: $F = 1.5$, $p = 0.135$; subject: $F = 20.1$, $p < 0.001$. **ii)** GLP-1 levels during the MMT. Symbols: BPD – triangles; LAGB – squares; P – circles, Exam 1 – white symbols; Exam 2 – light grey symbols; Exam 3 – dark grey symbols. *A, B, C – all three study groups*: operation: $F = 0.9$, $p = 0.39$; exam: $F = 1.8$, $p = 0.161$; time: $F = 14.4$, $p < 0.001$; operation × exam: $F = 2.7$, $p = 0.003$; operation × time: $F = 0.7$, $p = 0.734$; exam × time: $F = 0.5$, $p = 0.957$; operation × exam × time: $F = 12.7$, $p < 0.001$; subject: $F = 9.2$, $p < 0.001$. *D – BPD study group*: exam: $F = 19.4$, $p < 0.001$; time: $F = 1.6$, $p = 0.167$; exam × time: $F = 0.6$, $p = 0.823$; subject: $F = 9.5$, $p < 0.001$. *E – LAGB study group*: exam: $F = 8.2$, $p < 0.001$; time: $F = 6.7$, $p < 0.001$; exam × time: $F = 0.9$, $p = 0.576$; subject: $F = 15.2$, $p < 0.001$. *F – P study group*: exam: $F = 3.6$, $p = 0.031$; time: $F = 15.3$, $p < 0.001$; exam × time: $F = 0.8$, $p = 0.619$; subject: $F = 24.1$, $p < 0.001$. **iii)** Glucagon levels during the MMT. Symbols: BPD – triangles; LAGB – squares; P – circles, Exam 1 – white symbols; Exam 2 – light grey symbols; Exam 3– dark grey symbols. *A, B, C – all three study groups*: operation: $F = 11.8$, $p < 0.001$; exam: $F = 7.3$, $p < 0.001$; time: $F = 12.9$, $p < 0.001$; operation × exam: $F = 2.2$, $p = 0.015$; operation × time: $F = 0.6$, $p = 0.858$; exam × time: $F = 0.3$, $p = 0.998$; operation × exam × time: $F = 12$, $p < 0.001$; Subject: $F = 1$, $p = 0.435$. *D – BPD study group*: exam: $F = 1.2$, $p = 0.316$; time: $F = 1.4$, $p = 0.245$; exam × time: $F = 0.8$, $p = 0.605$; subject: $F = 18.7$, $p < 0.001$. *E – LAGB study group*: exam: $F = 3.6$, $p = 0.031$; time: $F = 4.5$, $p < 0.001$; exam × time: $F = 0.6$, $p = 0.828$; subject: $F = 14.3$, $p < 0.001$. *F – P study group*: exam: $F = 2$, $p = 0.138$; time: $F = 9$, $p < 0.001$; exam × time: $F = 0.2$, $p = 0.993$; subject: $F = 6.1$, $p < 0.001$.

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ingly, beta cell glucose sensitivity, reflecting the ratio between insulin secretion and glucose levels, does not change significantly. However, more research is required to elucidate the regulation of glucose sensitivity in T2DM patients following complex bariatric procedures, such as the BPD.

Notably, beta cell dysfunction may also persist after RYGB, even in patients with T2DM remission [30]. This impairment can be rescued by oral glucose stimulation, suggesting that RYGB leads to an important gastrointestinal effect [30]. Similar results have been shown after gastric banding, indicating that beta cell function does not fully recover even in cases of clinical T2DM resolution [31]. Finally, in our study we documented a decrease in the secretion of GIP and an increase in the secretion of GLP-1 after BPD, being consistent with results from previous studies. Indeed, Tsoli et al. [27] reported significantly increased GLP-1 and peptide YY responses during oral glucose tolerance test after both BPD and SG.

In conclusion, we have found similar improvement in insulin sensitivity in obese T2DM women after all three types of bariatric operations during a 6-month postoperative follow-up period. Of note, only BPD led to a significant decrease in the demand of beta cells (decreased integrated insulin secretion during the MMT), but without increasing significantly the beta cell glucose sensitivity. Long-term follow-up is scheduled for this study cohort in order to prospectively explore the long-term outcomes of LAGB, P, and BPD at a 1-, 2-, and 4-year post-operative follow-up.

Ethical Approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards [32].

Informed consent was obtained from all individual participants included in the study.

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Disclosure Statement

The authors declare no conflicts of interest.

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