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CLINICAL RESEARCH

Bileopancreatic Diversion with Duodenal Switch Lowers Both Early and Late Phases of Glucose, Insulin and Proinsulin Responses After Meal

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Abstract
Background Hyperproinsulinemia is associated with obesity and type 2 diabetes. We explored the after-meal dynamics of proinsulin and insulin and postprandial effects on glucose and lipids in patients treated with bileopancreatic diversion with duodenal switch (BPD-DS) surgery compared with normal-weight controls [body mass index (BMI)±SD, 23.2±2.4 kg/m^2].
Methods Ten previously morbidly obese (BMI±SD, 53.5±3.8 kg/m^2) patients free from diabetes who had undergone BPD-DS (BMI±SD, 29.0±5.2 kg/m^2) 2 years earlier were recruited. A standardised meal (2400 kJ) was ingested, and glucose, proinsulin, insulin, free fatty acids and triglycerides (TGs) were determined during 180 min. Follow-up characteristics yearly on glucose, lipids, creatinine and uric acid over 3 years after BPD-DS are presented.
Results Fasting glucose and insulin were lower, 0.4 mmol/L and 4.6 pmol/L, respectively, in the BPD-DS group despite higher BMI. Fasting proinsulin was similar in both groups. Postprandial area under the curve (AUC) for glucose, proinsulin and insulin did not differ between the two groups (p=0.106–734). Postprandial changes in glucose, proinsulin and insulin were essentially similar but absolute concentrations of proinsulin and insulin were lower in the later phases in the BPD-DS group (p=0.052–0.001). Postprandial AUC for TGs was lower in the BPD-DS group (p=0.005). Postprandial changes in TGs were lowered in the intermediate phase (p=0.07–0.08) and in the late phase (0.002). Follow-up data showed markedly lowered creatinine and uric acid after BPD-DS.
Conclusions BPD-DS surgery induces a large weight loss and lowers, close to normal, postprandial responses of glucose, proinsulin and insulin but with marked lowering of TGs.

Keywords Proinsulin · Insulin · Obesity · Bileopancreatic diversion with duodenal switch

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Introduction

Obesity and type 2 diabetes mellitus (T2DM) are increasing worldwide. Hyperinsulinemia, hyperproinsulinemia and insulin resistance are characteristic features of both obesity [1–3] and T2DM [4]. Hyperproinsulinemia, in addition to insulin resistance, is associated with increased risk of T2DM [4–6] and with coronary heart disease [7, 8].

Bariatric surgery restores fasting glucose concentrations and normalises glucose tolerance in T2DM patients [9, 10]. Both Roux-en-Y gastric bypass (RYGBP) and bileopancreatic diversion with duodenal switch (BPD-DS) are to be considered as potential therapies for T2DM [11, 12]. Previous results on proinsulin and insulin from test meals after weight loss induced by RYGBP and gastric banding, which are restrictive procedures, indicate lowering of fasting and postprandial responses, but gastric banding was less effective than RYGBP in improving proinsulin and

insulin secretion [13–15]. BPD-DS is a more advanced bariatric surgery procedure than RYGBP with restrictive and malabsorptive components combined and with an intact pyloric sphincter and thus a restored emptying of the stomach [16]. The weight loss after BPD-DS surgery is more pronounced than after RYGBP, and weight loss is initially rapid and is ongoing for longer time than for RYGBP, often 15–18 months after surgery before it is stabilised. We hypothesised that BPD-DS has the potential of normalising postprandial insulin and proinsulin responses. Previous reports regarding proinsulin and insulin responses after a test meal in patients treated with BPD-DS surgery are scant.

Furthermore, fasting glucose and serum lipid concentrations are normalised permanently after BPD-DS in obese T2DM patients [17]. Also long-term data after RYGBP indicate improvements in glucose and lipids [9, 10, 18, 19], lowering of alanine aminotransferase (ALT) and elevation of circulating magnesium [20, 21].

The aim of the present study was to investigate fasting and postprandial proinsulin and insulin responses, as well as glucose, FFAs and triglycerides after BPD-DS surgery in weight-stable, previously morbidly obese patients in comparison with a contrast group of normal-weight (NW)-controls. A second aim was to investigate long-term data regarding glucometabolic status, lipids, ALT, serum concentrations of creatinine, uric acid and electrolytes including magnesium over 3 years after BPD-DS surgery.

Patients and Methods

Participants

Ten morbidly obese patients who had undergone BPD-DS surgery (five men, five women), all Caucasians, free from established diabetes and not on pharmacological treatment for diabetes, were recruited from the Outpatient Clinic of Obesity Care, Uppsala University Hospital, Uppsala, Sweden.

These patients were recruited for a standardised test meal study separated from clinical standard follow-ups. The test meal composition used and procedures performed has previous been described [15].Test meal data from the BPD-DS group was compared with data obtained from normal-weight controls (six men, six women) [15]. The BPD-DS surgery-treated patients were considered weight-stable with an average body mass index (BMI) of 29.0±5.2 kg/m^2 (mean±SD). They had undergone surgery 26 months (median, 18–44 months range) before the test meal study. The mean pre-surgery BMI was 53.5±3.8 kg/m^2. Age and gender distribution were similar in both groups, but the contrast group of NW-controls weighted 20% less than the BPD-DS group, BMI 23.2±2.4 kg/m^2. Basal characteristics of the participants are presented in Table 1.

Exclusion criteria for participants were liver disease, high alcohol consumption (>21 units per week, 1 unit=8 g alcohol) and use of hypoglycaemic agents or lipid-lowering medication at baseline or follow-ups. All BPD-DS patients were given the same kind of dietary advice after surgery and were recommended to take a daily oral supplement containing vitamins and minerals (Vitamineral®) which is not containing magnesium. Data from clinical investigations before BPD-DS (baseline) and at follow-up visits at 1, 2 and 3 years (1st, 2nd and 3rd follow-up, respectively) after BPD-DS surgery are shown in Table 3.

The study was approved by the regional ethics review board at Uppsala University. All patients gave written informed consent.

BPD-DS Surgery Procedure

The greater curvature of the stomach is resected leaving a gastric tube along the lesser curvature. The pylorus region is left intact. The duodenum is divided 3 cm distal to the pylorus. The small bowel is divided into two segments, a proximal and a distal segment, by dividing it 250 cm proximal to the ileo-caecal valve. The proximal segment is closed at the oral end, and its function will be to transport bile and pancreatic juices from the duodenum; it is therefore called the bilio-pancreatic limb. The oral end of the distal 250-cm segment is anastomosed to the remaining duodenal bulb, i.e., 3 cm below the pylorus. All ingested food will pass through this segment of the ileum, called the alimentary limb, until emptied into the colon. The distal end of the bilio-pancreatic limb is connected to the alimentary limb, 100 cm proximal to the ileo-caecal valve. This 1-m-long segment of the small bowel is thus the only segment of the small bowel where ingested food, bile and pancreatic juices are mixed [16].

After a BPD-DS, the ingested food will pass through the gastric tube with an intact pylorus and the few remaining centimetres of the proximal duodenum before transported through the 250-cm-long alimentary limb, in which proteins and carbohydrates are absorbed. The digestion of alimentary fat by juices from the upper gastrointestinal tract occurs in the most distal segment of ileum. The majority of ingested fat and a proportion of the ingested proteins are thus incompletely absorbed as they are rapidly transferred to the colon.

Test Meal

The meal was composed to fit with the amount of food possible to eat due to the reduced gastric volume after bariatric surgery. Total energy content was 2,400 kJ

Table 1 Clinical characteristics in the fasting state of the meal test for morbidly obese patients, median 26 months (range, 18–44), after BPD-DS surgery and for normal-weight controls

	BPD-DS patients	Controls	*P* for difference
Gender (women/men)	5/5	6/6	–
Age (years)	39.1 (6.5)	41.1 (7.5)	0.501
BMI (kg/m^2)	29.0 (5.2)	23.2 (2.4)	0.002
Weight (kg)	87.6 (22.5)	70.9 (12.5)	0.039
Height (cm)	173.0 (12.1)	174.2 (9.6)	0.778
f-P-glucose (mmol/l)	4.2 (0.3)	4.8 (0.6)	0.007
HbA_{1c} (%)	3.9 (0.5)	4.2 (0.2)	0.800
f-P-proinsulin (pmol/l)	2.6 (1.0)	5.9 (7.4)	0.179
f-P-insulin (pmol/l)	15.2 (4.7)	19.8 (13.2)	0.005
f-P-FFA (mmol/l)	0.53 (0.22)	0.78 (0.32)	0.054
f-P-TG (mmol/l)	0.78 (0.30)	0.91 (0.65)	0.560

Data given are arithmetic means (±SD)

f fasting, *P* plasma, *FFA* free fatty acid, *TG* triglycerides, *BPD-DS* bileopancreatic diversion with duodenal switch

The standardised test meal was separated in time from ordinary follow-ups

(570 kcal), consisting of: carbohydrates 68.2 g, fat 22.3 g, proteins 24.6 g and fibre 6.4 g, as previously described in detail [15].

Test Procedures

After an overnight fast for 17 h, the standardised test meal was ingested at 1 PM at the outpatient clinic for obesity care, allowing supervision of the food intake which was finished within 15 min. Blood samples were collected, centrifuged and freshly frozen immediately before the test meal and thereafter at 30, 60, 90, 120 and 180 min after ingestion. Data were collected in pre-printed Case Report Forms.

All patients in the BPD-DS group underwent routine investigations before and at 1st, 2nd and 3rd annual follow-ups with 1-year intervals after surgery. Routine results presented were collected from patient's medical records.

Body Mass Index

Weight (in kilogrammes) and height (in metres) were measured on standardised calibrated scales and BMI (kilogrammes per squaremetre) was calculated.

Laboratory Analyses

Plasma proinsulin and insulin concentrations were determined using the Proinsulin ELISA and the Insulin ELISA immunoassays (Mercodia AB, Uppsala, Sweden) on a Bio-Rad Coda automated EIA analyzer (Bio-Rad Laboratories, CA, USA). FFAs were determined using the Wako NEFA C-test kit (Wako Chemicals GmbH, Neuss, Germany). At the department of Clinical Chemistry at the University Hospital, Uppsala, basal routine tests for concentrations of plasma glucose, glycosylated haemoglobin (HbA_{1c}), ALT, creatinine, albumin, uric acid, magnesium, calcium, sodium, potassium, total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides were analysed using routine methods.

Statistics

All analyses were defined a priori. Results are given as arithmetic mean with their standard deviation and SEM in figures. Areas under the curve (AUC) for glucose, proinsulin, insulin, FFAs and TGs were calculated using the trapezoidal method for group comparisons. Test meal data are given as absolute concentrations (Table 2) and as changes (delta-values) in concentrations (Fig. 1a–e). Student's *t* test was used for group comparisons. The changes between different time-points were analysed using paired *t* test. Statistical analyses were performed using changes from basal concentrations because absolute differences in basal concentrations of variables (glucose, proinsulin, insulin, FFA and TG) were expected between groups.

ANOVA was used for trend tests over 3 years of follow-up of BPD-DS patients. Paired *t* test was used for comparisons between the 1st, 2nd and 3rd follow-up. All tests were two-tailed and a p value<0.05 was considered significant. Statistical software JMP 3.2 for PC (SAS Corporation, Cary, TX, USA) was used.

Table 2 Postprandial test meal data for obese patients, median 26 months (range, 18–44), after BPD-DS surgery and for normal-weight controls

	Time-points					
	0min	30min	60min	90min	120min	180min
BPD-DS group						
P-glucose (mmol/l)	4.2 (0.3)	6.2 (0.9)	6.7 (0.9)	6.0 (1.3)	5.0 (1.2)	4.2 (0.5)
P-proinsulin (pmol/l)	2.6 (1.0)	11.9 (6.2)	18.0 (6.0)	20.1 (10.2)	15.7 (7.9)	8.6 (4.7)
P-insulin (pmol/l)	15.2 (4.7)	177 (136)	136 (136)	85.6 (74.3)	39.8 (15.7)	26.2 (12.1)
P-FFA (mmol/l)	0.53 (0.22)	0.45 (0.20)	0.14 (0.06)	0.08 (0.02)	0.08 (0.04)	0.23 (0.10)
P-TG (mmol/l)	0.78 (0.3)	0.76 (0.29)	0.73 (0.28)	0.69 (0.28)	0.70 (0.30)	0.69 (0.28)
NW control group						
P-glucose (mmol/l)	4.8 (0.6)	7.3 (1.0)	7.4 (1.3)	6.5 (1.0)	5.8 (0.7)	5.3 (0.7)
P-proinsulin (pmol/l)	5.9 (7.4)	17.1 (10.8)	27.8 (14.6)	29.7 (11.8)	26.3 (8.9)	19.9 (10.8)
P-insulin (pmol/l)	19.8 (13.2)	190 (91.2)	196 (97.2)	147 (67.8)	88.8 (37.8)	52.2 (38.4)
P-FFA (mmol/l)	0.78 (0.32)	0.69 (0.27)	0.38 (0.23)	0.26 (0.11)	0.29 (0.19)	0.29 (0.14)
P-TG (mmol/l)	0.91 (0.65)	0.95 (0.89)	1.03 (0.97)	1.07 (1.02)	1.07 (0.96)	1.08 (0.81)

Data given are arithmetic means (±SD)

P plasma, *FFA* free fatty acids, *TG* triglycerides, *BPD-DS* bileopancreatic diversion with duodenal switch, *NW* normal weight

Results

Test Meal Results

Fasting Data

Clinical characteristics in morbidly obese patients after BPD-DS surgery and NW-controls before the test meal in the basal state are presented in Table 1. The mean BMI was 5.8 kg/m^2 higher in the BPD-DS group compared with NW-controls. Fasting plasma glucose concentrations and HbA_{1c} values were within the normal reference ranges in all participants. Fasting plasma glucose concentration was 0.4 mmol/l lower in the BPD-DS group compared with the NW-controls. Fasting proinsulin did not differ between the BPD-DS group and NW-controls, whereas insulin concentrations were 4.6 pmol/l lower and fasting FFAs tended to be lower in the BPD-DS group. TGs did not differ between groups.

Postprandial Data

Absolute concentrations during the test meal are presented in Table 2. Changes in glucose, proinsulin, insulin, FFA and TG from the basal state are shown in Fig. 1a–e and are presented below.

Glucose

The AUC (mean±SD) for glucose (millimole*minutes) did not differ between the BPD-DS group (230±150) and NW-controls (250±130), (p=0.734).

Data for changes in glucose are presented in Fig. 1a. The glucose concentrations changed equally during the early phase (0–60 min) in both groups. During the intermediate (60–120 min) and the late (120–180 min) phases after ingestion, the reductions in glucose concentrations were also similar.

Absolute concentrations of glucose was lower in the BPD-DS group in the early phase (p=0.02–0.007) as well at 180 minutes (p<0.001) as compared with NW-controls, c.f. Table 2.

Proinsulin

The AUC (mean±SD) for proinsulin (picomol*minutes) was numerically lower in the BPD-DS group (2,000±850) compared with NW-controls (3,000±1,600) but the difference was statistically not significant (p=0.106).

Data for changes in proinsulin are shown in Fig. 1b. In the early phase, proinsulin concentrations changed equally in both groups but increased to a higher peak in the NW-controls. In the intermediate and late phases, plasma proinsulin decreased similar in both groups in a parallel manner.

Absolute concentrations were lower in the intermediate and late phases in the BPD-DS group (p=0.06–0.006), c.f. Table 2.

Insulin

The AUC (mean±SD) for insulin (picomol*minutes) did not statistically differ between the BPD-DS group (12,000±9,700) and NW-controls (18,000±8,300), (p=0.151).

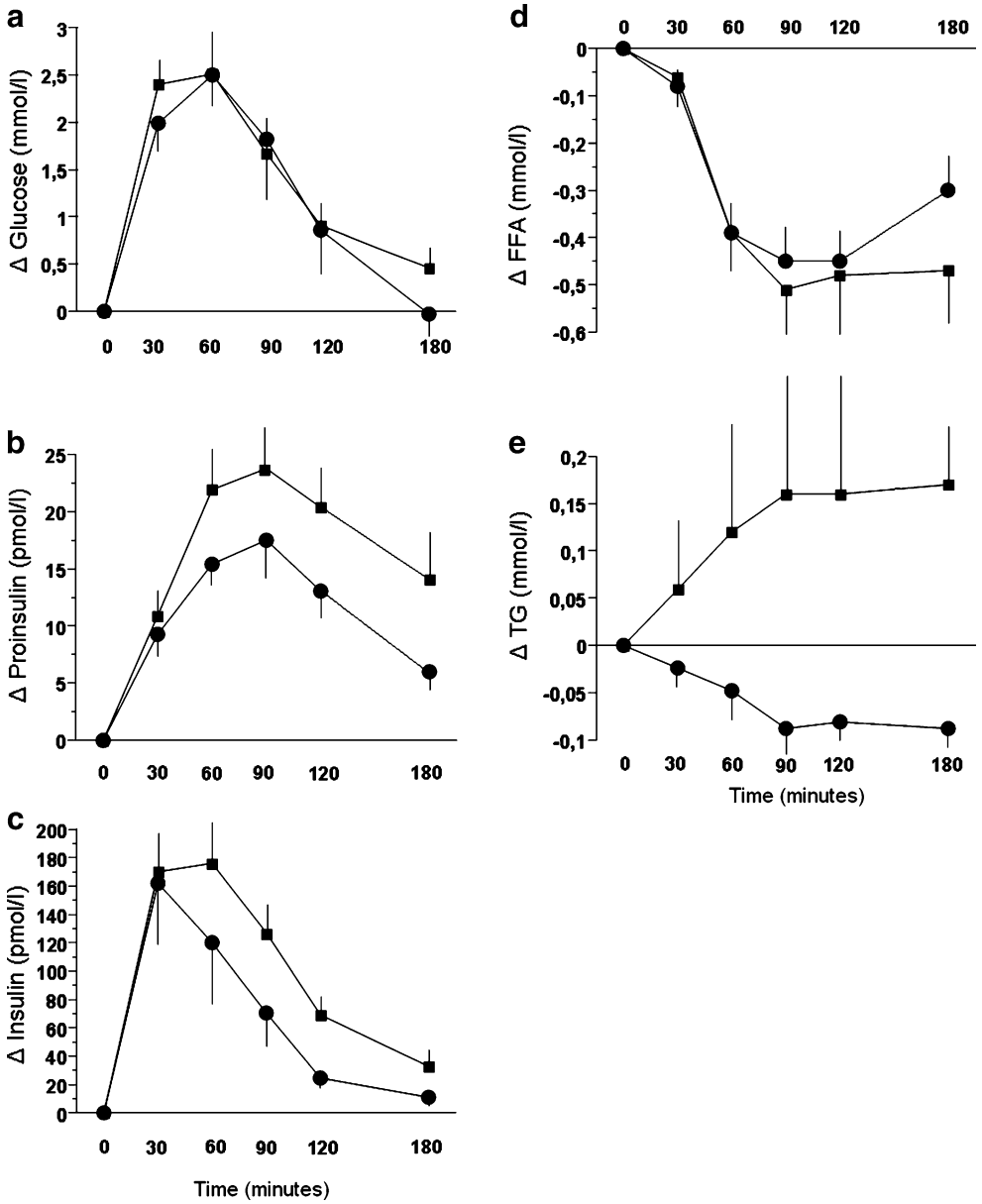

Fig. 1 **a**–**e** The postprandial changes in glucose (**a**), proinsulin (**b**), insulin (**c**), free fatty acid (FFA; **d**) and triglyceride (TG; **e**) concentrations are shown for 180 min after the ingestion of the standardised test meal (mean±SEM). *Filled circle*, morbidly obese subjects treated with bileopancreatic diversion with duodenal switch (BPD-DS) surgery; *filled square*, NW-controls. *Glucose*: In both groups, similar increase in glucose concentrations were observed in the early phase (30–60 min) and with a similar decrease in intermediate phase (60–120 min) and the late phase (120–180 min; p=0.976–0.136). *Proinsulin*: In early phase, proinsulin concentrations were equally increased in both groups but to a higher peak in the NW-controls. In the intermediate and late phase, concentrations of plasma proinsulin were lowered in a parallel manner in both groups with lower absolute values in the BPD-DS group (p=0.606–0.097). *Insulin*: The postprandial changes were similar in both groups, but in the NW-controls, increased to a higher peak in the early phase. In the intermediate and late phases, insulin response was declining in a similar pattern but separated from each other and significantly lower in BPD-DS group at 120 min (p=0.0079). *Free Fatty Acids*: During the test meal, FFA were suppressed in a similar manner in both groups. No differences were observed regarding postprandial changes (p= 0.969–0.209). *Triglycerides*: Regarding postprandial changes in the BPD-DS group compared with NW-control subjects, a trend for lower TG concentrations were observed in the intermediate phase (p=0.07–0.08), and they were significantly lowered in the late phase at 180 min (p=0.002)

Data for changes in insulin are presented in Fig. 1c. Both groups had similar increments of insulin in the early phase, but there was a higher peak in NW-weight controls. In the intermediate and the late phases, insulin response was declining in a similar pattern in both groups and was significantly lower at 120 min (p=0.0079) in the BPD-DS group. Absolute concentrations were lower in the BPD-DS group during intermediate and late phases (p=0.052–0.001), c.f. Table 2.

Free Fatty Acids

The AUC (mean±SD) for FFA (millimole*minutes) did not differ between the BPD-DS group (57±29) and NW-controls (63±54; $p=0.764$). Data for changes are presented in Fig 1d.

No significant differences were observed regarding postprandial changes in circulating FFAs concentrations between the two groups.

Absolute concentrations of FFA were lower at each postprandial time point ($p=0.05$–0.001) except at 180 min in the BPD-DS group compared with the NW-controls, c.f. Table 2.

Triglycerides

The AUC (mean±SD) for TGs (millimole*minutes) was markedly lower in the BPD-DS group (−11±4), compared with NW-control subjects (8±15; $p=0.005$).

Data for changes are presented in Fig. 1e. Lowered TG concentrations were observed in the BPD-DS group in the late phase ($p=0.002$) and a trend in the intermediate phase ($p=0.07$–0.08).

Absolute concentrations of TGs decreased with time during the test meal in the BPD-DS group whereas TGs increased in NW-controls, c.f. Table 2.

Gender Comparisons

Fasting as well as postprandial changes in glucose, proinsulin, insulin, FFA and TG did not differ between men and women (Fig. 1).

Clinical Characteristics During 3 Years of Follow-up Study

Baseline Data

Clinical characteristics for patients before they underwent BPD-DS surgery and at follow-ups over 3 years after surgery are shown in Table 3. No patient was identified with diabetes before surgery or at follow-ups. None of the patients in this study had any clinical complications during the surgical procedure or during the follow-up period.

Data from 1st, 2nd and 3rd follow-ups, 1, 2 and 3 years after BPD-DS surgery

Over 3 years of follow-up, there were significant trends in lowering of BMI, f-P-glucose, HbA_{1c}, P-ALT, P-creatinine, P-uric acid, f-P-total cholesterol, f-P-LDL cholesterol, f-P-LDL/HDL cholesterol, f-P-triglycerides and increasing trends of P-magnesium, c.f. Table 3. There were no significant changes in P-albumin, P-calcium, P-sodium, P-potassium and f-P-HDL cholesterol.

BMI was reduced by 43%, from 53.5 kg/m^2 to 30.7 kg/m^2 at 1st follow-up and further 28.4 kg/m^2 at 2nd and to 30.2 at 3rd follow-up ($p<0.001$, respectively). The slight changes of 7% between 1st and 2nd follow-up and of 6% between 2nd and 3rd follow-up as borderline significant ($p=0.046$–0.050).

Fasting glucose concentrations were lowered by 16%, from 5.5 to 4.6 μkatal/L at 1st follow-up ($p<0.001$). There were no statistical significant changes between later follow-ups.

HbA1c concentrations were lowered by 22%, from 4.9 to 3.8% at 1st follow-up ($p<0.001$, Fig. 2a). There were no statistical significant changes between later follow-ups.

ALT was markedly lowered by 46%, from 0.79 to 0.43 μkatal/L at 1st follow-up ($p=0.017$, Fig. 2b). There were no statistically significant changes between later follow-ups.

Creatinine was lowered by 20%, from 85.6 to 68.8 mmol7L at 1st follow-up and continued to lower to 58.9 mmol/L at 2nd follow-up ($p<0.001$, respectively, Fig. 2c). The decrease of 14%, between 1st and 2nd follow-up, was significant ($p=0.043$). There were no statistical significant changes between 2nd and 3rd follow-up.

Uric acid was lowered by 35%, from 411 to 266 μmol/L at 1st follow-up and continued to lower to 233 μmol/L at 2nd follow-up and to 209 μmol/L at 3rd follow-up ($p<0.001$, respectively, Fig. 2d). There were no statistical significant changes between later follow-ups.

Magnesium did not significantly increase from 0.79 mmol/L at 1st follow-up ($p=0.692$) but did significantly so to 0.89 mmol/L at 2nd follow-up ($p=0.025$, Fig. 2e).The increase of 11%, between 1st and 2nd follow-ups, was significant ($p=0.019$). There were no statistical significant changes between 2nd and 3rd follow-up.

Total cholesterol was lowered by 32%, from 5.0 to 3.38 mmol/L at 1st follow-up ($p<0.001$). LDL cholesterol was decreased by 38%, from 3.18 to 1.96 mmol/L at 1st follow-up ($p<0.001$). LDL/HDL cholesterol ratio was decreased by 39%, from 3.03 to 1.85 at 1st follow-up ($p<0.001$). Triglycerides were lowered by 31%, from 1.74 to 0.92 mmol/L at 1st follow-up ($p<0.001$). There were no statistical significant changes in total-, LDL-, LDL/HDL-cholesterol or TGs between later follow-ups.

Discussion

Test Meal

Postprandial glucose, proinsulin, insulin and FFAs responses were similar in BPD-DS treated patients compared with a contrast group of NW-controls after a standardised meal, whereas TGs were markedly lower in the PBD-DS patients. Postprandial AUC for glucose did not differ between the BPD-DS group and NW-controls. Postprandial changes of

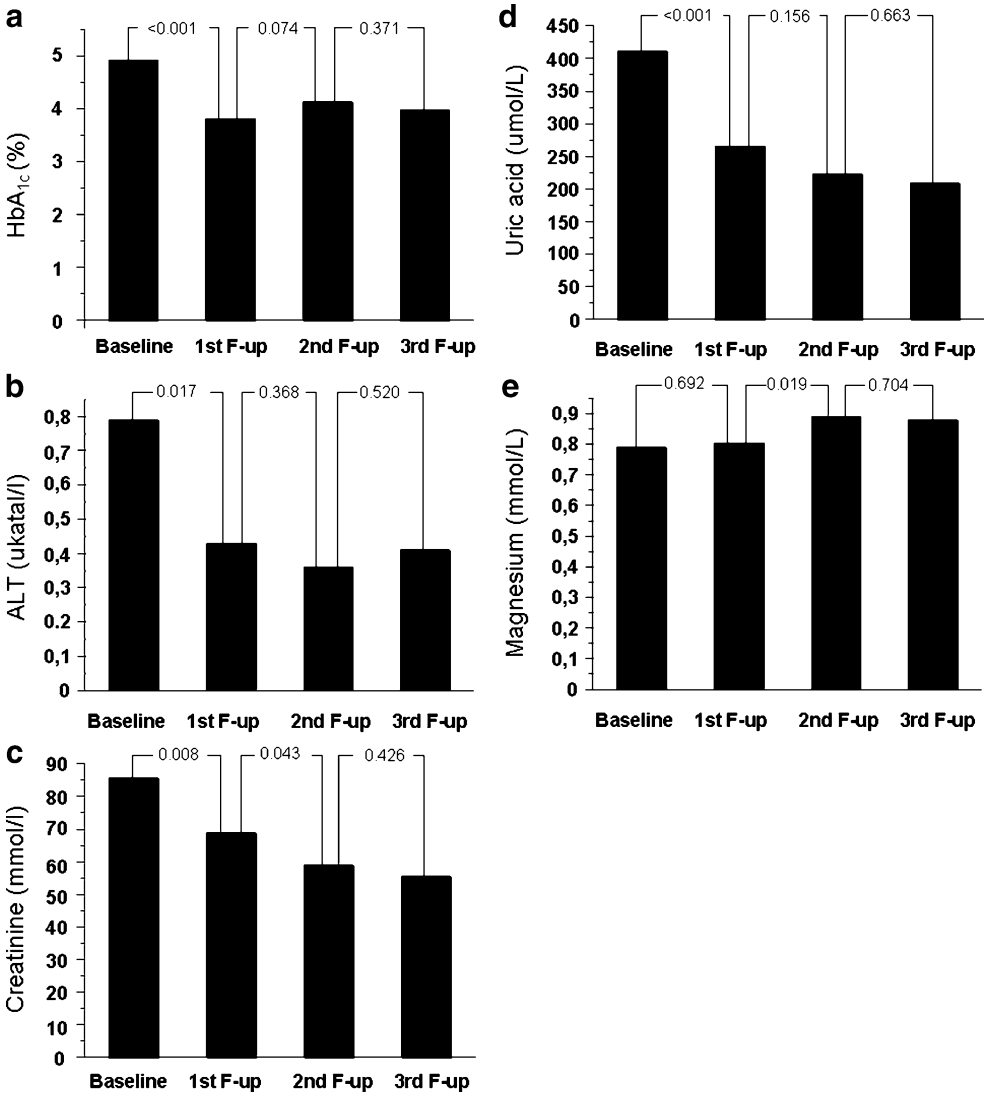

Fig. 2 a–e The changes in HbA1c (**a**) and concentrations of alanine aminotransferase, *ALT* (**b**), creatinine (**c**), uric acid (**d**) and magnesium (**e**) are shown at baseline, at first follow-up (1 year), at second follow-up (2 years) and at third follow-up (3 years) after bileopancreatic diversion with duodenal switch. Mean values are shown. Statistical significance is presented as *p* values. *F-up* denotes follow-up

proinsulin and insulin were essentially similar in the BPD-DS group compared with NW-controls, but proinsulin was lower in the BPD-DS group as expressed as absolute values in the later phases. Previously, proinsulin has not been analysed in meal tolerance or glucose tolerance studies after BPD-DS surgery. The present study analysed glucose, proinsulin and insulin after a standardised test meal where effort was made to compose a test meal representing an "every day lunch" for bariatric surgery-treated patients.

The rapid and prominent glucose peak inducing prominent early phase insulin and proinsulin responses during a test meal after RYGBP, where ingested food is rapidly emptied to the foregut, is not seen after BPD-DS where the passage of food through the stomach and the intact pyloric sphincter into the remaining part of the duodenum enables a gastric delay and by this, avoiding the rapid increase in glucose absorption and insulin and proinsulin responses in the early postprandial phase. If a rapid increase in glucose, insulin and proinsulin is observed or not after a BPD ad modum Scopinaro, where a duodenal switch (DS) is not performed is not possible to address in the present study as we lack such data.

The low fasting glucose and HbA1c in the follow-up part discussed below and insulin responses during test meal implies improved hepatic insulin sensitivity. This is possibly induced or caused by hormonal changes related to the nutrient diversion from the duodenum and jejunum which might prevent secretion of signals that promote insulin resistance (anti-incretin factors) and/or caused by direct delivery of relatively undigested nutrients in the distal ileum and triggered incretin response [22, 23]. Almost immediate resolution of diabetes occurs after both RYGBP and BPD-DS, before any significant weight loss [23, 24]. Furthermore, a recent study using IVGTT, OGGT and euglycemic insulin clamp in obese T2DM patients before and after BPD without DS showed restored first phase–phase insulin secretion, normalised B cell glucose sensitivity and normalised peripheral insulin sensitivity already after 1 month [25].

Table 3 Clinical characteristics for patients before BPD-DS surgery and at follow-ups 1, 2 and 3 years after surgery

	0	1year	2year	3year	*P* for trend
Gender (women/men)	5/5	5/5	5/5	5/5	–
Age (years)	37.5	–	–	–	–
BMI (kg/m^2)	53.5 (3.8)	30.7 (4.6)	28.4 (3.8)	30.2 (5.0)	<0.001
Weight (kg)	161.3 (26.7)	92.9 (21.4)	86.0 (19.4)	91.9 (25.8)	<0.001
Height (cm)	173.0 (10.1)	173.4 (10.7)	173.3 (10.6)	173.4 (10.7)	0.999
f-P-glucose (mmol/l)	5.5 (0.9)	4.6 (0.58)	4.5 (0.35)	4.6 (0.22)	<0.001
HbA_{1c} %	4.9 (0.39)	3.8 (0.28)	4.1 (0.45)	4.0 (0.29)	<0.001
P-ALT(μkatal/l)	0.79 (0.39)	0.43 (0.18)	0.36 (0.16)	0.41 (0.13)	0.001
P-creatinine (mmol/l)	85.6 (9.7)	68.8 (10.7)	58.9 (9.6)	55.4 (8.8)	<0.001
P-albumin (mmol/l)	40.4 (2.3)	38.9 (4.5)	39.8 (3.9)	39.3 (3.2)	0.322
P-uric acid (μmol/l)	411 (82)	266 (52)	233 (70)	209 (64)	<0.001
P-magnesium (mmol/l)	0.79 (0.10)	0.80 (0.07)	0.89 (0.07)	0.88 (0.06)	0.017
P-calcium (mmol/l)	2.30 (0.05)	2.26 (0.09)	2.18 (0.12)	2.20 (0.10)	0.058
P-sodium (mmol/l)	141 (3.5)	136 (4.9)	139 (0.6)	140 (2.1)	0.231
P-potassium (mmol/l)	3.8 (0.25)	3.4 (0.09)	3.6 (0.29)	3.7 (0.44)	0.106
f-P-total cholesterol (mmol/l)	5.0 (0.45)	3.38 (0.28)	3.38 (0.47)	3.20 (0.43)	<0.001
f-P-LDL-C (mmol/l)	3.18 (0.41)	1.96 (0.30)	1.99 (0.35)	1.93 (0.35)	<0.001
f-P-HDL-C (mmol/l)	1.07 (0.14)	1.10 (0.20)	1.13 (0.22)	0.98 (0.16)	0.316
f-P-LDL/HDL-C ratio	3.03 (0.61)	1.85 (0.58)	1.83 (0.58)	1.99 (0.56)	<0.001
f-P-TG (mmol/l)	1.74 (0.63)	0.92 (0.19)	0.93 (0.48)	0.90 (0.31)	<0.001

Data given are arithmetic means (±SD)

ALT alanine aminotransferase, *LDC-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *TG* triglycerides, *f* fasting, *P* plasma

The changes in FFA after BPD-DS were similar to our earlier observation after RYGBP-surgery except the post-prandial lowering of TGs after BPD-DS. The majority of dietary TGs are digested in duodenum by pancreatic lipase and by secreted bile salts from the gallbladder, stimulated by cholecystokinin induced by food intake. Fatty acids are absorbed by epithelial cells, and bile salts are re-absorbed in the ileum and pass back to the liver via the enterohepatic circulation. Short- and medium-chain fatty acids pass through the enterocyte to the hepatic portal blood whereas long-chain fatty acids are resynthesised into TGs before transfer to the lymphatic system as chylomicrons regulated by apolipoprotein B48 [26].

As changes in FFA were equal in both groups, the difference in TGs may unlikely be explained by endogenous TGs, e.g., mobilisation of FFA from the adipose tissue to the liver.

The uptake of exogenous TG from the intestine could be lowered due to fat malabsorption after BPS-DS surgery as nutrients are delivered more directly into the ileum and are rapidly transferred to the colon. BPD-DS patients more frequently develop diarrhoea and flatulence compared with RYGBP patients [27]. Similarly, jejuno-ileal bypass patients develop steatorrhoea [28] and BPD without DS surgery induces markedly limited fat absorption [29]. In BPD-DS, fat malabsorption may be explained by several factors: A small absorptive area in the common channel, a shorter and possibly faster food passage in the alimentary limb of approximately 1.5 m and a reduced uptake in the 1 m common channel because of passage time difference between the long and short limbs and a longer passage in the bileopancreatic limb of approximately 4.5 m for pancreatic enzymes and bile salt. Furthermore, the discrepancy in timing of emptying the gallbladder promoted by cholecystokinin underscore possibly reduced uptake of TGs in the common channel. The limited fat absorption and lipid depletion of peripheral target cells results in consequent return to glucose utilisation as the energy source and thus increase insulin sensitivity [30]. Furthermore, the improved liver insulin sensitivity, as indicated in the present study by low fasting insulin and HbA1c, may play a role in long-term suppressing of VLDL and TG synthesis. The lowered postprandial TGs after BPD-DS may be an additive effect of both improved hepatic insulin sensitivity and fat malabsorption. Further studies may measure chylomicrons using ultracentrifugation or apolipoprotein B48 for analyse of reduction of uptake.

Follow-up

Follow-up data over 3 years showed long-term improvements in glucose, ALT and lipids indicating lowered insulin resistance. Free fatty acids (FFA) are increased in insulin resistant states and may contribute to increased hepatic glucose output possibly by accumulation of triglycerides and FFA metabolites in the liver and muscle [31]. Obesity, insulin resistance and dyslipidemia are the major factors associated with non-alcoholic fatty liver disease (NAFLD) [32, 33], and ALT is a marker of non-alcoholic fatty liver

disease (NAFLD) and liver fat content which also reflects the glucometabolic status [34].

Uric acid is associated with obesity and insulin resistance [35], oxidative stress, endothelial damage, CVD and mortality [36, 37]. Obesity has been implicated as a cause of both uric acid overproduction and poor renal clearance [38]. Weight loss changes uric acid metabolism by increasing renal clearance [39]. The observed long-term improvement and markedly lowered uric acid over 3 years after BPD-DS in the present study are more pronounced than earlier data report after BPD without DS [40].

The plasma creatinine concentrations decreased markedly during the 3-year follow-up period after BPD-DS, suggesting a loss of muscular mass, possible more prominent than previously reported 1 year after RYGBP-surgery [41]. Already 6 month after RYGBP-surgery a body composition study showed that one fifth of weight loss was due to possible muscle mass loss [42]. BPD-DS induce greater weight loss than RYGBP with possible larger impact on muscular mass loss and thus more prominent reduction of creatinine. Measurements of body composition after BPD-DS is warranted as well as more precise analyses of renal function as this may have clinical implications. Renal function is usually estimated by serum creatinine measurements in clinical praxis and early signs of renal function abnormalities may go undetected after BPS-DS. The increased serum magnesium concentrations after BPD-DS are congruent with our previous report on magnesium status after RYGBP-surgery, reflecting the association of reduced obesity and lowered plasma glucose with increased circulating magnesium concentrations.

Possible Limitations

Age and gender distribution were similar in both BPD-DS patients and NW-controls but the BPD-DS group weighted 20% more than the contrast group of NW-controls. The possible influence of weight on glucose metabolism that is known to deteriorate with higher weight would have driven results towards the null-hypothesis, thus possibly underestimating differences rather than overestimate them if a BMI-matched control group would have been chosen. However, longer follow-up time in the standardised meal test would have been desirable to observe late changes post-load in FFA and TGs. The diet regime after BPD-DS surgery is characterised by a limited caloric intake, but with a high content of nutrients, however, no dietary registration was carried out in the present study.

In summary, BPD-DS which is a combined restrictive and malabsorptive procedure cause a large weight loss and close to normalise postprandial glucose, proinsulin and insulin responses but with lowering of TG concentrations. Possible mechanisms of malabsorption of triglycerides need further studies including bowel specific uptake and transition time measurements. A prominent lowering of creatinine was observed. Body composition and renal function studies are warranted after BPD-DS.

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