ELSEVIER

Surgery for Obesity and Related Diseases 18 (2022) 1392–1398

SURGERY FOR OBESITY AND RELATED DISEASES

Original article

Impact of biliopancreatic diversion with duodenal switch on glucose homeostasis and gut hormones and their correlations with appetite

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Received 4 April 2022; accepted 21 August 2022

Abstract

Background: Biliopancreatic diversion with duodenal switch (BPD/DS) results in lifelong changes in gastrointestinal physiology with unclear associations with appetite perception.
Objective: To explore mixed meal–induced changes in glucose homeostasis and gut hormones and their correlations with appetite perception.
Setting: University hospital.
Methods: Of 28 patients studied preoperatively (age: 38.4 ± 11.3 years; body mass index [BMI]: 56.5 ± 5.1 kg/m^2; 14 women), 19 (68%) returned for postoperative follow-up. Plasma was sampled for 180 minutes during a 260-kcal standardized mixed meal. Concentrations of leptin, glucose, insulin, triglycerides, active acyl-ghrelin, motilin, total glucose-dependent insulinotropic polypeptide (GIP), active glucagon-like peptide 1 (GLP-1), and total peptide YY (PYY) were measured. Subjective appetite sensations were scored.
Results: BPD/DS resulted in 66.1% ± 23.3% excess BMI loss. Leptin was halved. Glucose and insulin levels were reduced, blunting a preoperative peak at 30 minutes, giving a lower homeostasis model assessment for insulin resistance (HOMA-IR; 13.9 versus 4.8). In contrast, reduced ghrelin and motilin concentrations were accompanied by pronounced peaks 20–30 minutes prior to meal responses. GIP was reduced, whereas GLP-1 and PYY responses were markedly increased, with an early postprandial peak ($P < .05$, for all). HOMA-IR correlated with insulin ($r = .72$) and GIP ($r = .57$). Postoperatively, satiety correlated with GLP-1 ($r = .56$), whereas the gastric motility index correlated with the desire to eat ($r = .60$), percentage excess BMI loss ($r = –.55$), and percentage total weight loss ($r = –.49$). Delta insulin, GLP-1, and leptin correlated positively with percentage total weight loss ($r = .51$, $r = .48$, and $r = .58$, respectively).
Conclusions: BPD/DS reduces leptin, HOMA-IR, and GIP while markedly increasing GLP-1 and PYY. This study marks the magnitude change in GLP-1 with additional effects of PYY as important factors for weight loss. (Surg Obes Relat Dis 2022;18:1392–1398.)

Keywords: Gut peptides; HOMA-IR; Leptin; Biliopancreatic diversion with duodenal switch

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https://doi.org/10.1016/j.soard.2022.08.010

Bariatric surgery remains the most effective treatment for patients with obesity and its co-morbidities. Surgical alterations of the gut anatomy result in restriction of food intake and malabsorption as well as changes in meal responses of gut hormones [1] and bowel microbiota composition [2]. Collectively, these parallel, if not outright contribute to, significant weight loss [3].

Changes in gut hormone levels differ depending on surgical procedure. In sleeve gastrectomy (SG), the fundal resection reduces ghrelin secretion, consistent with lowering appetite [4]. The rapid passage into the small bowel following Roux-en-Y gastric bypass (RYGB) [5,6] increases glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) levels, along with enhanced satiety [7,8]. Combination of SG and a long-limb Roux-en-Y-like construction in biliopancreatic diversion with duodenal switch (BPD/DS) augments the weight loss effect [9]. BPD/DS is considered the most effective bariatric procedure and is often used in patients with a body mass index (BMI) $\geq$50 kg/m^2 [10,11]. It is usually associated with a higher remission rate of type 2 diabetes (T2D), although the mechanism is not fully understood. This add-on effect, characterized by reduced insulin resistance, seems to be driven by, or occurs concomitantly with, changes in circulating gut hormone concentrations [1,12]. Studies in animal models demonstrate a reduction of glucose-dependent insulinotropic polypeptide (GIP), a lipogenic hormone promoting nutrient storage [13], leading to significant improvement and remission of T2D and obesity [14,15]. This is also supported by our previously reported higher average GIP in nonresponding patients after RYGB [16].

The aim of this study was to investigate intraparticipant changes in glucose homeostasis and gastrointestinal hormone plasma levels following BPD/DS with special focus on correlations with appetite control.

Methods

Participants (n = 28; age 38.4 ± 11.3 [mean ± standard deviation] years; 14 women) with a BMI of 56.5 ± 5.1 kg/m^2 were recruited between 2016 and 2020. All patients underwent a classical 2-anastomotic BPD/DS, resulting in a narrow gastric sleeve, a 150-cm Roux limb, and a 100-cm common limb. The remaining small bowel constituted the biliopancreatic limb. Eight patients were operated on with an open technique and 19 with a laparoscopic technique. Patients were examined by detailed blood testing and wireless motility capsule (WMC) before surgery and at a study-specific visit during the second postoperative year.

Ethics

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments. The study was approved by the Regional Ethics Board in Uppsala (2012/142). Written informed consent was obtained from all individual participants included in the study.

Examination procedure

Participants arrived fasted in the morning, without taking their morning medication, and received a standardized 260 kcal mixed meal (75% carbohydrates, 3% fiber, 21% protein, and 3% fat) according to the manufacturer's instructions. Blood samples (6 mL K_2-EDTA) were drawn at 0, 10, 20, 30, 60, 90, 120, and 180 minutes after peroral intake of the meal and WMC and were immediately put on ice. A protease inhibitor cocktail including DPP-4 inhibitor KR-62436 was added, tubes were centrifuged (2500 RCF, 10 minutes, 4°C), and plasma was aliquoted and frozen at –70°C until assayed, as detailed previously [16]. Data on bowel motility and transit times were assessed by the WMC [17].

Laboratory analyses

Glucose and triglycerides were analyzed at an accredited clinical chemistry laboratory. Plasma concentrations of leptin, insulin, active acyl-ghrelin (hereinafter ghrelin), total GIP, active GLP-1, and total PYY were assayed by multiplex ELISA using electrochemiluminescence detection (U-Plex Metabolic Group 1, Meso Scale Diagnostics, Rockville, MD, USA). Motilin was assayed by human motilin ELISA kit (Cat. No. NBP2-66719, Novus Biologicals, Littleton, CO, USA) and 450 nm absorbance read by TECAN Spark Microplate Reader (Tecan Group, Männedorf, Switzerland).

Appetite control and motility index

In our previous study [17], subjective appetite sensations, that is, hunger, satiety, prospective food consumption, and desire to eat, were measured before and at 0, 60, 120, and 180 minutes after food intake by 100-mm visual analog scales (VAS) according to Blundell et al. [18]. Motility index (MI) values, calculated as MI = ln(sum of amplitudes × number of contractions + 1), were analyzed for separate 30-minute intervals just before and after WMC passage through the pylorus as well as the ileocecal valve. MI demonstrates both chronotropic and ionotropic assessments of gastrointestinal motility.

Statistics

Data are presented as the mean ± standard deviation unless specified otherwise. Normally distributed data were compared by Student *t* test, whereas a paired-samples Wilcoxon signed-rank test was used for the remaining variables. Nonparametric correlations used Spearman's rho method. A

P value <.05 was considered significant. Percentage excess BMI loss (%EBMIL) was defined as ([baseline BMI – BMI after surgery]/[baseline BMI – 25]) × 100. Percentage total body weight loss (%TWL) was calculated by kilograms lost divided by the starting weight × 100. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR), the equation of which is (insulin [μIU/L] × glucose [mmol/L]/22.5). Area under the curve ($AUC^{0–180min}$) was calculated for all hormones as total area under the curve from concentration zero. Because this surgery could alter numbers of enteroendocrine cells, meal responses of the hormones were normalized as mean concentrations at 30 minutes divided by the mean at 0 minutes (hereinafter referred to as *fold changes*). SPSS Statistical Software version 26 (IBM, Armonk, NY, USA) was used for statistics.

Results

Patient characteristics are given in Table 1. Blood samples from 27 of 28 patients were collected preoperatively. Of these, 19 (68%) returned for a postoperative follow-up test, having had %EBMIL of 66.1% ± 23.3%, corresponding to a %TWL of 36.6% ± 12.1% over a period averaging 1.8 ± .7 years. Furthermore, at the postoperative visit, no patient was on antidiabetic drugs nor under pharmacological treatment for dyslipidemia.

Leptin

As shown in Fig. 1 and Supplementary Table 1, leptin concentrations were more than halved after surgery, and AUC was reduced by 62% (*P* = .003) (Supplementary Table 2). Leptin correlated negatively with weight loss (*r* = –.781; *P* > .001) for both %EBMIL and %TWL.

Glucose, insulin, and triglycerides

After BPD/DS, fasting glucose and insulin levels were lower (Fig. 1). The preoperative glucose excursion at 30 minutes dropped from almost 8 mmol/L to just above 6 mmol/L, and after surgery, glucose was lower at all the following time points (*P* < .05, for all). In parallel, baseline insulin levels were reduced from 1524 to 554 pg/mL (*P* = .001), and in line with glucose, the early insulin peak after oral intake was reduced, thus demonstrating lower insulin values from 20 minutes and throughout the study period. The AUC values for glucose and insulin were reduced by 26% and 73%, respectively. Postoperative HOMA-IR averaged lower (13.9 ± 11.4 versus 4.8 ± 2.8; *P* < .05) and correlated positively with the AUC for insulin (*r* = .723; *P* < .001) and GIP (*r* = .568; *P* = .011). Corresponding baseline to 30-minute fold responses for insulin before versus after surgery were 3.3- and 3.7-fold, suggesting slightly higher meal-induced insulin secretion relative to baseline. Triglycerides averaged lower at all time points, resulting in a 48% reduction of the AUC.

Gut hormones

Postoperative ghrelin concentrations (Fig. 1) were lower at 0, 10, and 60 minutes into the meal (*P* < .05), and a trend (*P* = .064) toward a 28% reduction of the AUC was seen. A 44% reduction of the motilin AUC was seen, with differences in concentrations at 90 minutes (*P* < .05). Furthermore, an altered release pattern, with a sharp rise at 20–30 minutes, was noted for both ghrelin and motilin. This time interval is presumably the transition from fasting rise into a meal response, which is a trough, as in lean participants. Postoperative GIP levels were significantly lower between 30 and 180 minutes, resulting in a 42% reduction of the AUC. Baseline to 30-minute fold responses before versus

Table 1
Characteristics of biliopancreatic diversion with duodenal switch patients

Characteristic	Preoperative (n = 28)	Postoperative (n = 19)	*P* value
Biometric measures			
Age (y)	35.5 ± 11.2	37.3 ± 10.9	<.001
Sex, M/F (% female)	14/14 (50%)	11/8 (42%)	—
BMI (kg/m^2)	56.6 ± 5.1	36.1 ± 8.1	<.001
Obesity-related diseases,* n (%)			
Type 2 diabetes	10 (36%)	0 (0%)	.031
Hypertension	12 (43%)	3 (16%)	.250
Dyslipidemia	3 (11%)	0 (0%)	.999
Osteoarthritis	7 (25%)	4 (21%)	.999
Years until second visit	—	1.8 ± .7	—
%EBMIL	—	66.1 ± 23.3	—
%TWL	—	36.6 ± 12.1	—
HOMA-IR	13.9 ± 11.4	4.8 ± 2.8	.005

BMI = body mass index; %EBMIL = percentage excess BMI loss; %TWL = percentage total weight loss; HOMA-IR = homeostatic model assessment for insulin resistance.

Data are presented as the mean ± standard deviation.

* Obesity-related diseases are defined by continuous use of disease-specific medication.

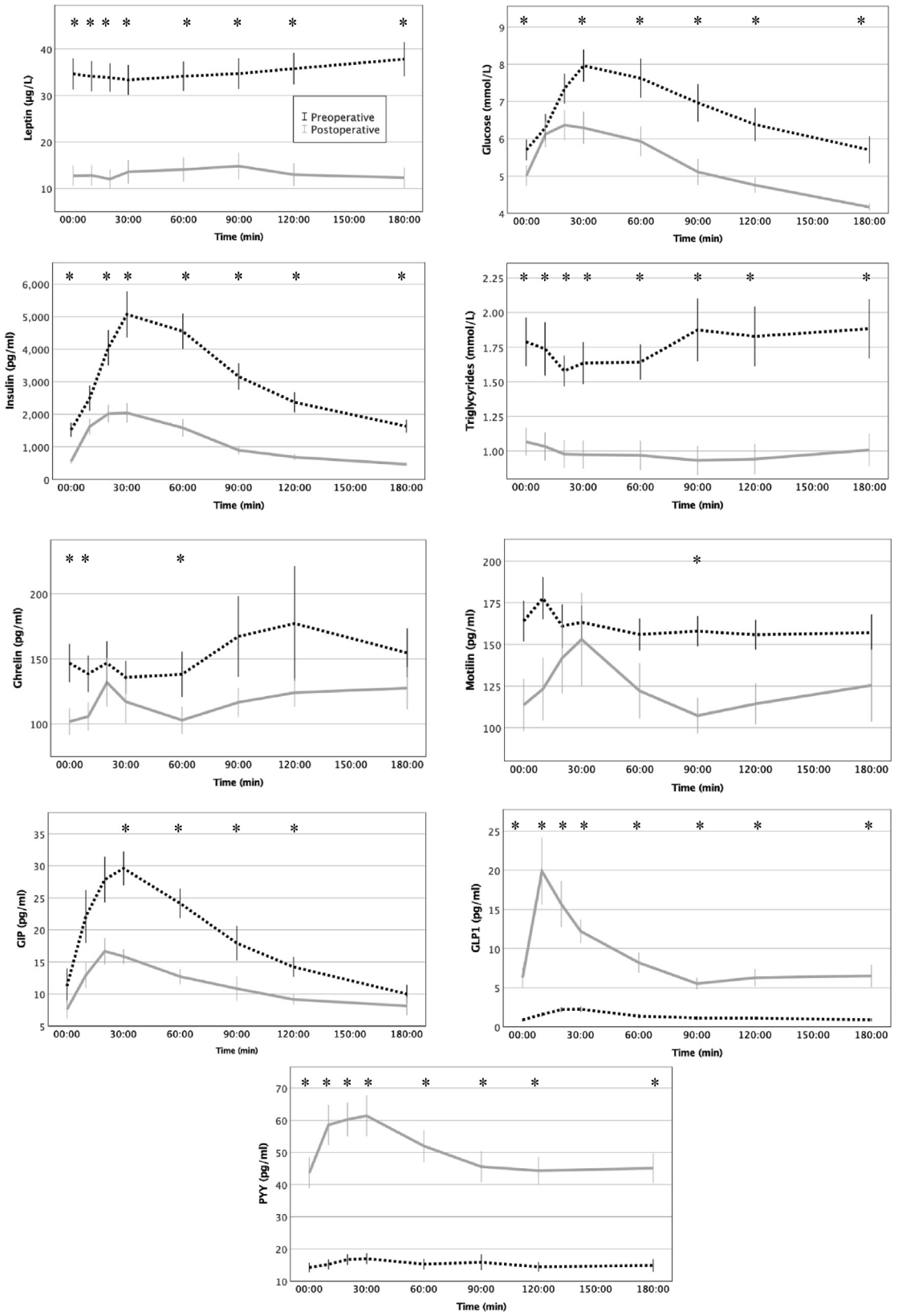

Fig. 1. Gastrointestinal hormones in biliopancreatic diversion with duodenal switch patients before (n = 27, ▪▪▪▪) and after (n = 19, ——) surgery. Data are mean ± standard error of the mean. *$P < .05$ between pre- and postoperative values.

after surgery were 2.6- versus 2.5-fold. Hence surgery did not alter the fold GIP response relative baseline.

In contrast, a rapid meal-induced increase of GLP-1 was seen after surgery, creating a large early peak at 10–30 minutes after meal ingestion. The AUC for GLP-1 was 6.2 times larger after surgery. Baseline to 30-minute fold responses were 2.4- versus 2.3-fold. As with GIP, surgery did not alter the fold GLP-1 response relative baseline.

Compared with the rather flat curve before surgery, PPY demonstrated a tripled fasting plasma concentration, followed by a rapid and augmented postprandial concentration in operated patients. A threefold increase in the AUC was seen after surgery ($P < .001$). Baseline to 30-minute fold responses before versus after surgery were 1.2- and 1.4-fold, suggesting slightly higher meal-induced PYY secretion.

Correlations with appetite control and motility index

Except for patients' higher scoring of hunger and desire to eat at 180 minutes postoperatively ($P < .05$), no other differences in appetite control were found [17]. A negative correlation was found between the AUC for motilin and hunger ($r = –.482$; $P = .011$) as well as desire to eat ($r = –.478$; $P = .012$) before surgery, but this was lost postoperatively. The AUC values for GLP-1 and ghrelin preoperative correlated significantly with %TWL ($r = .552$, $P = .018$ and $r = .482$, $P = .043$, respectively). In contrast, postoperative satiety before the test meal correlated positively with the AUC for GLP-1 ($r = .562$; $P = .012$) and the GLP-1 peak concentration ($r = 639$; $P = .003$). Postoperatively, there was a positive correlation between stomach MI and desire to eat before the test meal ($r = .602$; $P = .011$) and a negative correlation with weight loss (%EBMIL: $r = –.550$, $P = .018$; %TWL: $r = –.486$; $P = .041$). Delta AUC values for GLP-1, leptin, and insulin correlated positively with %TWL ($r = .505$, $P = .033$; $r = .486$, $P = .011$; and $r = .581$, $P = .041$, respectively).

Discussion

Metabolic control after BPD-DS surgery was superior to preoperative conditions, primarily by reducing fasting glucose and insulin levels, as reflected by the much-improved HOMA-IR. Ameliorating insulin resistance with complete diabetes remission and lowering the high triglyceride level, in which the latter is believed to be an early share for development of insulin resistance [19], are considered part of the remission state of the metabolic syndrome.

The prevalence of T2D is increasing in parallel with the obesity pandemic, with up to 40% prevalence among individuals with morbid obesity [20,21]. Improved glucose metabolism and remission of T2D are the most important outcomes of bariatric surgery, where our results in BPD/DS are commensurate with those of other studies [1,22]. This metabolic improvement is believed to be due mainly to the incretin effect of GLP-1, which amplifies insulin secretion when glucose rises following oral ingestion. The defective response of GIP in patients with obesity and T2D [23,24] supports our observation of higher preoperative GIP levels. In line with the enteroendocrine concept, we could demonstrate a reduced postprandial release of GIP postoperatively because the ingested nutrients no longer come in contact with GIP-containing K cells in the mixing segment of the proximal small bowel. Reduced GIP in fasting and postprandial states has been shown after BPD/DS [25]. While after RYGB, results have been less consistent, showing increased, unchanged, and decreased GIP levels [26–28]. We therefore propose that the present reduced meal response of GIP is more important than earlier recognized in achieving sustainable weight loss.

The role of white adipose tissue in regulating energy balance has been illustrated previously [29]. Leptin is mainly secreted from adipose tissue but also from the stomach [30,31], and its concentration is regulated by a feedback mechanism of the sympathetic system. Leptin targets parts of the brain (e.g., hypothalamic arcuate nucleus, ventromedial nucleus, and nucleus of the solitary tract) that control energy balance, inhibiting food intake and affecting energy expenditure. However, adipose tissue in patients with obesity overproduces inflammatory markers and leptin, explaining why *leptin resistance* is common [32] where appetite is not suppressed despite the elevated leptin levels. This process is reversed by weight loss, thus correcting both leptin and insulin resistance. The marked reduction in leptin also seems to correlate with the weight loss achieved postoperatively. Resolution of leptin resistance is probably one of the factors that helps maintain weight loss after surgery.

Ghrelin is mainly produced in X/A-like endocrine cells in the mucosa of the stomach. The present reduction in fasting levels is associated with resection of the major part of the stomach, whereas the rapid surge at 20 minutes may be explained by the motility changes in the gastric sleeve (i.e., faster propagation of food through the pylorus). The more pronounced ghrelin decline at 60 minutes postoperatively augments the effect of surgery with less hunger and increased early satiety. Our trend toward a reduced AUC for ghrelin is in line with other studies done on RYGB [33]. Motilin is secreted by the M-cells in the upper small intestine [34,35] and shares similarity with ghrelin in both amino acid sequences and functional characteristics such as controlling appetite and gastrointestinal motility. This may explain the similar pattern of a 20- to 30-minute postprandial peak the 2 hormones share. Both the higher motilin levels in individuals with obesity and the reduction after RYGB, as demonstrated by Deloose et al. [36], are in line with this study.

The L-cell products GLP-1 and PYY are known to increase after RYGB, and the present increase in these hormones is mainly due to food reaching the distal bowel much faster than before the operation [17]. Gut hormones

(i.e., ghrelin, GLP-1, GIP, and PYY) were markedly changed. The altered AUC values for GLP-1, GIP, and PYY combined with the trivial differences in fold responses from baselines to peaks before versus after surgery could be explained by reduced GIP- and increased GLP-1- and PYY-secreting cells with preserved metabolic and electrophysiologic properties. There is evidence of faster gastric emptying after SG [37], but this was not the case in our participants by WMC testing [17]. Unchanged gastric emptying time after BPD/DS could be due to an enhanced relaxatory effect of increased GLP-1 [38], this counteracting the sleeve effect by slowing gastric emptying [39]. Moreover, reducing the length of the small bowel that is exposed to nutrients in the postoperative state will result in anatomic changes, such as bowel hypertrophy and cellular adaptation [40]. This might amplify the presented elevation of gut hormones at 2 years. With the increase of GLP-1, one would expect nausea as a complication of this type of bariatric surgery. However, employing gastric sleeve surgery would possibly operate as a therapeutic add-on by reducing the capability of the stomach to dilate in response to high levels of GLP-1, thereby counteracting nausea.

Interestingly, the observed MI correlations with weight loss and leptin suggest that gastric motility is an important factor for determining the long-term result in BPD/DS. This is an important finding that needs further clarification, for example, by studying weight loss responders versus non-responders. Additionally, because %TWL correlated with change in AUC for GLP-1, leptin, insulin, and preoperative GLP-1, concentrations of these hormones could be of value in explaining weight regain or poor weight loss after bariatric surgery.

VAS scoring showed only slight differences, with higher scores for hunger and desire to eat at the very end of the study period after surgery. We hypothesize that this finding could be explained in part by the earlier demonstrated faster small bowel transit time after surgery [17]. The otherwise similar VAS ratings to the preoperative state, despite the different changes in gut peptides in this study, verify that patients can still experience hunger like before surgery [33], even with lower ghrelin levels.

Strengths and limitations

The detailed and frequent blood sampling, resulting in high resolution of hormonal changes, is a major strength of this study. However, the use of only 2 time points, one before and one after surgery, is a limitation. Furthermore, the fact that blood sampling did not include 40 and 50 minutes, where the trough in the ghrelin meal response typically occurs, is another methodologic limitation. The presence of bowel motility data in the same cohort of patients is an added strength of this study. Although only 19 patients returned for their second test, this was sufficient to identify changes in gut hormones. Another strength is that all patients were operated on at the same unit and had identical procedures (e.g., the same small bowel lengths) and that all hormonal analyses were done in the same sequence in the same laboratory.

Conclusions

Biliopancreatic diversion with duodenal switch improved glucose homeostasis by reduced insulin resistance and leptin, thus resulting in T2D remission. The mechanism by which bariatric surgery triggers T2D remission apparently involves, and may even require, both increased GLP-1 and PYY and decreased GIP. We believe that the demonstrated changes in gut hormones, correlating with changes in satiety and weight loss, will aid patients in maintaining their body weight after surgery.

Acknowledgments

All authors gratefully acknowledge funding from ALF-medel, Uppsala University hospital (2017-2022). Per M. Hellström and Dominic-Luc Webb gratefully acknowledge funding from Vetenskapsrådet (2017-02243). Dominic-Luc Webb gratefully acknowledges support from Selander's Foundation (2020 and 2021), the O.E. och Edla Johansson's Science Foundation (2017 and 2018) and Uppsala University Foundation, Section of Medicine and Pharmacy (2022).

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2022.08.010.

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