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A Rodent Model of Partial Intestinal Diversion: A Novel Metabolic Operation

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Abstract

Background—Metabolic surgery is safe and the most effective therapy for obesity and its comorbidities. New procedures may allow for better tailoring of metabolic surgery to the individual patient.

Objective—To evaluate the impact, comparative effectiveness, and mechanisms of the partial intestinal diversion (PID), vertical sleeve gastrectomy (VSG), and the combination of PID and VSG on body weight and glucose regulation.

Setting—University research facility, United States.

Methods—Three cohorts of high-fat diet-induced obese male rats were randomized to distal partial intestinal diversion (DPID), proximal partial intestinal diversion (PPID), vertical sleeve gastrectomy (VSG), VSG and DPID (VSG/DPID), or sham operation (Sham). Animals were followed for 11 (cohort 1) or 10 (cohorts 2 and 3) weeks. Outcomes included body weight and composition, food intake, glucose metabolism, lipids, bile acids, and energy balance. Statistical comparisons were performed using Tukey's multiple comparison test applied to ANOVA.

Results—DPID and not PPID resulted in significant weight and body fat reductions relative to Sham. Improved glucose tolerance was seen in all surgical groups though this reached statistical significance for only DPID and VSG when compared with Sham. Improvements in baseline glucose and insulin, corresponding insulin resistance, and plasma lipids were noted in DPID compared to Sham. Though the magnitude of weight and body composition changes and metabolic benefit tended to be larger for VSG relative to DPID, it only reached statistical significance for lipids. VSG and VSG/DPID resulted in similar outcomes. Markedly reduced food intake occurred after VSG and more modestly after DPID. Stool caloric content was higher in DPID relative to all groups.

Conclusions—DPID is an effective metabolic operation resulting in notable weight and fat loss and metabolic improvement relative to sham-operated rodents. Interestingly, combining VSG with DPID added little additional benefit to the effects of VSG.

Graphical Abstract

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Distal partial intestinal bypass is an effective metabolic operation resulting in weight loss and improvement in glucose tolerance. Analyses performed by Tukey's multiple comparison test applied to values obtained from one-way analysis of variance (ANOVA). Circle denotes the enteroenterostomy. Black arrows indicate the usual path of chyme while white arrows represent to newly created path followed by the fraction of chyme bypassing a loop of small intestine. S; stomach; C, cecum; LoT, ligament of Treitz; ICV, ileocecal valve. DPID, distal partial intestinal diversion; VSG, vertical sleeve gastrectomy; VSG/DPID, vertical sleeve gastrectomy and distal partial intestinal diversion; AUC, Area under curve; *, denotes statistical significance relative to Sham. \$ indicates statistical significance relative to DPID. ****, $p < 0.0001$; ***, $p < 0.001$; \$\$, $p < 0.01$.

Keywords

Metabolic surgery; bariatric surgery; weight loss surgery; animal study; partial intestinal diversion; PID; vertical sleeve gastrectomy; VSG; weight loss; body composition; glucose metabolism; lipid metabolism; bile acids; energy balance

Introduction

The prevalence of obesity continues to rise in the US and worldwide.^{1,2} Metabolic surgery is the most effective for severe obesity and related comorbidities and several randomized clinical trials have proven its safety and long-lasting benefits.^{3,4} Vertical sleeve gastrectomy (VSG) and Roux-en-Y gastric bypass (RYGB) account for most of the metabolic procedures performed in the US.⁵ While these operations have endured the test of time, as the rates of obesity and associated comorbidities continue to grow, novel metabolic surgical therapies may allow for better tailoring of these procedures to specific patient groups.

The partial intestinal diversion (PID) is one of such newer procedures. This operation has also been referred to as partial jejunal diversion and side-to-side jejunoileal anastomosis.^{6,7} The procedure is performed by creating a single side-to-side enteroenterostomy partially excluding a loop of small intestine from the flow of chyme (Figure 1). Given the relative technical ease and potentially low complications associated with constructing a single

enteroenterostomy, if effective, the PID could expand the surgical choices available for the treatment of obesity and related comorbidities. Notably, animal data exploring the comparative effectiveness of this operation and its variations relative to established metabolic procedures are lacking. Moreover, the mechanisms whereby PID may cause weight loss and metabolic improvements are not known.

In this study, we compared two versions of PID, a distal (DPID) and a more proximal one (PPID), to VSG and sham-operated (Sham) rodents. We also explored the potentially additive benefit, or lack thereof, of DPID and VSG by combining these two procedures into one operation (VSG/DPID). Moreover, we evaluated the underlying mechanisms of the DPID as a metabolic operation by examining the components of energy balance resulting from each of these procedures. Herein we report on the differences, among these metabolic operations, on body weight and composition, metabolic outcomes including glucose and lipid metabolism and bile acids, and the components affecting energy balance.

Materials and Methods

Animals and Design

Male Long-Evans rats were housed in individual cages maintained at 25°C, 50–60% humidity, and a 12:12-h light-dark cycle. High-fat diet (HFD) was used pre- and post-operatively. Three separate cohorts were used. Cohort #1 explored the comparative effectiveness of two versions of the PID, a proximal (PPID) and a distal one (DPID). Cohort #2 studied the addition of the DPID to the VSG while cohort #3 was used to further explore details of glucose tolerance in DPID. In cohort 1, 40 animals were randomized to either DPID (n=10), PPID (n=10), VSG (n=10), or Sham (n=10). One animal in the Sham group died. In cohort 2, 49 animals were randomly assigned to either DPID (n=12), VSG (n=12), VSG/DPID (n=15), or Sham (n=10). Two animals in the DPID group were euthanized due to excessive weight loss secondary to anastomotic narrowing and obstruction. Two animals in the VSG group were euthanized secondary to contained gastric leaks and abscesses. One animal in the VSG/PID group fell below 90% of preoperative lean body mass and was also euthanized according to our protocol with no abnormalities noted at necropsy. In cohort 3, 36 animals were randomized to DPID (n=12), VSG (n=12), or Sham (n=12). One animal in the PID group died and no cause was identified at necropsy. One animal in the VSG group was euthanized secondary to rapid shallow breathing and lack of righting reflex and another due to gastric leak and abscess. To conduct an intravenous glucose tolerance test (IVGTT), the remaining animals in this cohort underwent internal jugular vein (IJV) and carotid cannulation 5 weeks after metabolic surgery which resulted in additional losses (PID=2; VSG=5; Sham=2). Data collected from animals suffering these complications were excluded from analyses. All procedures were approved by the Institutional Animal Care and Use Committee.

Diet

Animals were placed on 40% high-fat 4.54 kcal/g butter diet (Research Diets, New Brunswick, NJ) on arrival and for 8 weeks thereafter. Three days before operation food was removed and the animals provided with Osmolite 1 Cal (Abbott Laboratories, Columbus,

OH). One day before operation, Osmolite was removed. Osmolite was given back on POD0 after operation. On POD3, HFD was re-introduced and used throughout the duration of the study. On POD4, Osmolite was removed.

Surgeries

A component of some metabolic operations such as the RYGB, full bypass in the Roux-en-Y manner of a portion of the small intestine is thought to contribute to the weight loss and metabolic benefits incurred by these procedures. Whether a standalone partial small intestinal bypass can achieve similar results is not known. A partial bypass such as that accomplished through the PID is technically simpler and has the potential added benefit of preventing some of the complications associated with the Roux-en-Y configuration such as internal herniation given that no breaks in the mesentery need to be created. The animal model of the PID herein described allows for further exploration of the mechanisms whereby this surgery may result in weight loss and metabolic improvements.

Table 1 details each operation. Surgeries were performed under isoflurane and following standard sterile technique. Several factors were considered in choosing the location of the anastomosis in our PID model. Given the well-described physiologic distinctions between the duodenum and jejunum, cohort 1 was designed to study the differential surgical effect which may result from proximal (PPID) and distal (DPID) versions of the operation while keeping the length of the partially bypassed loop constant. The entire duodenum and a small portion of proximal jejunum were then partially bypassed in PPID while 40 cm of jejunum were bypassed in the same fashion for DPID. Though more distal locations for the proximal enterotomy could have been chosen for DPID, we elected ours to be at 15 cm from the ligament of Treitz (LoT) because we thought this would afford enough mobility away from the fixed jejunum while minimizing the measurement errors which may result from moving further distally from this anatomic landmark. Anastomoses were created via interrupted suturing and intraoperatively assessed by milking chyme through and observing no leaks. VSG was performed as previously described, resecting approximately 80% of the stomach along the greater curvature with an application of the ETS-FLEX 35-mm staple gun (Ethicon Endo-Surgery, Cincinnati, OH).⁸ VSG/DPID was created by combining VSG with DPID. Five weeks after bariatric surgery, animals in cohort 3 underwent cannulation of their right IJV and left carotid artery with microcatheters (Fisher Scientific International Inc., Pittsburgh, PA) through bilateral neck incisions. Catheters were tunneled and brought out through a separate posterior neck incision. Catheters were locked with heparin solution and flushed periodically to ensure patency.

Postoperative Care

Rats were given meloxicam 0.5 mg/kg of body weight once daily and buprenorphine hydrochloride 0.03 mg/kg twice daily for 3 days, and 10 ml of warm saline twice daily on POD0 and once on POD1. Food intake and body weight were monitored at baseline, daily for 1 week postoperatively, and weekly thereafter. Nuclear magnetic resonance was used to assess lean and fat mass (Echo MRI: Echo Medical Systems, Houston, TX) preoperatively and before sacrifice.

Glucose Tolerance Tests

Five weeks after metabolic surgery, rats in cohorts 1 and 2 underwent an intraperitoneal glucose tolerance test (IPGTT) by injecting 2g/kg 25% dextrose (Phoenix Pharmaceutical, St. Joseph, MO) intraperitoneally after a 5-hr fast. Blood glucose levels were measured at baseline, 15, 30, 45, 60 and 120-min using Accu-chek glucometers and test strips (Roche, Indianapolis, IN). Insulin levels at baseline were also sampled for animals in cohort 2. Baseline glucose and insulin values were used to calculate the homeostatic model assessment for insulin resistance (HOMA-IR). All blood samples were obtained from the tip of the tail vein of moving rats.

Seven weeks after metabolic surgery, animals in cohort 3 underwent an intravenous glucose tolerance test (IVGTT) as described elsewhere,⁹ by injecting 1g/kg of 25% dextrose (Phoenix Pharmaceutical, St. Joseph, MO) into the cannulated IJV after a 5-hr fast. Blood samples for insulin and glucose levels were then obtained from the cannulated carotid artery at 10 minutes prior to dextrose injection and 1, 2, 12, 16, 20, 30, 45, and 60 minutes following injection.

Tissue Collection and Assays

To assess digestible energy content, fecal matter excreted over 72 hrs by animals in cohort 2 was collected and submitted for bomb calorimetry performed by the University of Michigan Animal Phenotyping Core and with methods described elsewhere.¹⁰ Animals were sacrificed at the end of week 10 (cohorts 2 and 3) and or 11 (cohort 1) after an overnight fast. Several factors were considered in selecting 10–11 weeks as our follow-up period. First, others have estimated that an interval of 10–11 weeks of life in adult rats correlates to 5.9–6.5 human years and as such, represents a reasonable term of postoperative follow-up.¹¹ It would therefore be expected that less permanent surgical effects would fade by the end of this follow-up term. Second, several of the metabolic outcomes of interest including glucose and lipid homeostasis, improve in the early postoperative period and therefore are captured within the chosen follow-up interval.¹² Third, the follow-up period herein selected parallels the published animal literature in the field which allows for comparability of our data with historical results.^{12–14} Finally, the focus of the present work is not on identifying long-term outcomes or complications. Rodent investigations cannot substitute for studies following human patients for such work. Rather, the work here is focused on mechanistic aspects of how this procedure might exert its effects and thereby combine with other procedures. One hour before sacrifice, gavage with 2 ml of 0.5% Hostaperm Blue dye (Clariant, Charlotte, NC) and 5% gum acacia/gum Arabic powder (Fisher Scientific International Inc., Pittsburgh, PA) in distilled water was performed. Dye was observed in the partially bypassed loop and distal small intestine. At this time, the length of the loop was measured. Whole blood for cohort 2 was collected via a cardiac puncture and cold-centrifuged to obtain plasma which was stored at –80 °C.

Plasma was submitted to the University of Michigan Diabetes Research Center Chemistry Laboratory for triglycerides and total cholesterol levels by a GPO-PAP method run on a Randox RX Series Daytona chemistry analyzer. Total bile acid data were obtained by colorimetric analysis with the Total Bile Acids Assay Kit (BQ Kits, San Diego, CA). Rat

Glucose Assay (Crystal Chem, Elk Grove Village, IL) and Ultra Sensitive Rat Insulin Enzyme-linked Immunosorbent Assay (ELISA) Kit (Crystal Chem, Elk Grove Village, IL) kits were used to measure glucose and insulin levels on samples obtained at week 5.

Energy Balance and Statistical Analysis

We calculated the amount of kcal consumed in food, kcal gained or lost in fat, and kcal lost in feces over the study period. Values were then used to estimate energy expenditure which is given as kcal per gram of body weight spent during the entire study period. GraphPad Prism statistical software 7.0c (La Jolla, CA) was used to analyze data. Results are expressed as means $\pm$ SE, and one-way and two-way independent repeated-measures analysis of variance (ANOVA) were applied where appropriate. Tukey's multiple comparison test was performed to further analyze significant interactions. *P* value <0.05 was considered to be statistically significant.

Results

Figure 2a–h contrasts body weight and composition, food intake, and glucose tolerance between DPID, PPID, VSG, and Sham in cohort 1. Relative to Sham, DPID and VSG resulted in statistically significant lower body weight. Differences in body weight were due to lower fat mass in DPID and VSG relative to Sham but also PPID. Cumulative food intake was lower in VSG relative to Sham. Intraperitoneal glucose tolerance (IPGT) was significantly improved in DPID and VSG compared to Sham. Though not quite reaching statistical significance ($p=0.056$), PPID also showed improvement in IPGT compared with Sham. The length of the partially bypassed loop was confirmed to be around the intended 40 cm and not to differ between DPID and PPID (Figure 2i).

Cohort 2 compares DPID, VSG, VSG/DPID, and Sham. Body weight was lower for all surgical groups compared with Sham, primarily due to the loss of fat mass. Body weight and fat mass tended to be lower for VSG and VSG/DPID compared with DPID though only reaching statistical significance between DPID and VSG/DPID for fat mass (Figure 3a–d). All surgical groups, particularly VSG and VSG/DPID, had lower cumulative food intake relative to Sham. Cumulative food intake was also reduced in VSG and VSG/DPID compared with DPID (Figure 3e–f). Plasma cholesterol and triglycerides were lower for DPID, VSG, and VSG/DPID compared to Sham. Additionally, VSG resulted in lower plasma cholesterol relative to DPID and VSG/DPID animals had lower plasma triglycerides compared to rodents in the DPID group (Figure 4g–h). Higher levels of total plasma bile acids were appreciated for all surgical groups relative to Sham though achieving statistical significance for VSG/DPID only (Figure 4f). Improved glucose metabolism was observed in DPID, VSG, and VSG/DPID relative to Sham (Figure 4a–e). These benefits are reflected by lower glucose AUC following IPGTT but also by improvements in fasting glucose and insulin levels and corresponding insulin resistance by HOMA-IR. Insulin levels and HOMA-IR values were also lower for VSG/DPID relative to DPID.

To further assess insulin homeostasis, an IVGTT was conducted on a third cohort including DPID, VSG, and Sham groups. To compensate for insulin resistance, the sham surgery animals had higher insulin secretion that did not completely normalize glucose levels

compared with both DPID and VSG (Figure 5a–d). The fact that peak insulin levels at 1–2min after the glucose load were not different between the three groups suggests that neither VSG nor DPID impacted pancreatic β -cell response to glucose.

Energy balance was assessed for cohort 2. Animals in the DPID group produced more feces than rodents in the VSG and VSG/DPID groups. Moreover, caloric content per gram of stool was higher in DPID relative to Sham and VSG. VSG/DPID animals showed higher stool caloric content compared to rodents in the VSG group only. When combined, these data show that DPID resulted in significantly more kcal lost in the stool relative to VSG, VSG/DPID, and Sham (Figure 6a–b,e). The per gram caloric content of the diet and cumulative food intake were used to calculate caloric intake over the entire study period (Figure 6c). Similarly, kcal gained and lost in fat mass were also calculated (Figure 6c). These parameters were used to estimate energy expenditure by subtracting kcal gained or lost in fat and kcal lost in stool from kcal consumed revealing no differences between groups regarding the amount of energy spent per gram of body weight.

Discussion

PID resulted in notable improvements in glucose metabolism across multiple cohorts and these benefits were derived, at least partially, from enhanced insulin sensitivity (Figures 2g–h, 4a–e, and 5a–d). Moreover, improvements in glucose metabolism in PPID occurred independently from weight change (Figure 2a–c,g–h). The distal (DPID) version of this operation resulted in lower body weight secondary to fat mass loss relative to the proximal (PPID) variation and Sham (Figure 2a–c). Furthermore, location of the partially bypassed intestinal loop rather than its length, which was similar for DPID and PPID, accounted for the differences in body weight and composition between DPID and PPID (Figure 2i). Addition of the DPID to VSG (VSG/DPID) did not result in additional benefit compared to the standard VSG (Figure 3 and 4). Lastly, while marked reduction in caloric intake was seen after VSG and VSG/DPID relative to DPID and Sham, DPID resulted in more calories lost in feces relative to all other groups and just modest intake reduction (Figure 6). Our data support further exploration of the PID as a metabolic operation in animal models as well as clinical studies.

PID Results in Notable Improvement in Glucose Metabolism

Significant improvements in glucose homeostasis ensued after diet-induced obese animals were treated with PID resulting in lower fasting glucose and insulin levels. Enhanced insulin sensitivity and improvements in insulin resistance were confirmed on glucose tolerance tests (Figures 2g–h, 4a–e, and 5a–d). Others have reported improved glucose metabolism following PID in animal models and clinical studies involving patients.^{6,7,15,16} It is clear that in the case of PPID, we observed a significant (and comparable to VSG) improvement in glucose tolerance despite a non-significant reduction in body fat. VSG and DPID improve glucose tolerance and cause profound reductions in body fat. Hence, a reasonable interpretation is that in the case of PPID, the glucose improvement is likely to be independent of body fat loss. However, we cannot rule out a shift in body fat distribution including loss of visceral fat that may contribute to the improved glucose tolerance

particularly for DPID. Importantly, while previous work from our group and others makes a case for metabolic surgery resulting in weight loss-independent improvements in glycemic control,^{14,17} the current studies were not designed to make that determination. Interestingly, our data show that improved glucose metabolism was observed regardless of location of the partially bypassed intestinal loop as similar results were appreciated with the distal and proximal versions of this procedure (Figure 2g–h). Enhanced glucose homeostasis is seen after duodenal-jejunal bypass (DJB), a metabolic operation in which a similar portion of the small intestine as in PPID is instead fully bypassed.^{18–21} Mechanisms that have been identified as potentially contributing to improvements in glycemia include higher bile acids levels, alterations to the intestinal microbiome, and improved beta cell function.^{18,19,21} Our data suggest that β -cell function, per se, is not driving differences in glucose levels. Given the conceptual anatomic similarities between PPID and DJB, it is plausible that analogous mechanisms result in enhanced glucose metabolism for both operations. Ultimately, DJB and both versions of PID share a common feature whether complete or partial, the bypass of a portion of the small intestine. These and other potential mechanisms linked to better glycemic control after PID should be further investigated.

A great deal of debate has occurred as to the most important reason for the potent effects of RYGB. One school of thought has focused on the contribution of introducing relatively undigested chyme further down the small intestine. This is often termed the “hindgut” hypothesis. A second school of thought has focused on bypassing the duodenum, termed the “foregut” hypothesis. While a number of procedures and device approaches that serve to functionally bypass the duodenum result in improvements in glucose regulation,^{3,20,22,23} the current data add to notion that such a duodenal bypass is not required to improved glucose regulation. Both VSG and PID are clearly effective at improving glucose regulation without any bypass of the duodenum.^{3,16} Consequently, we favor the hypothesis that gut adaptation produced when components of the GI tract are defunctionalized underlie the systemic changes that result in improved glucose handling.²⁴ Such a hypothesis has the advantage of being able to account for both “foregut” and “hindgut” focused procedures.

DPID Induces Lower Body Weight and Fat Mass Relative to Sham and It is Superior to PPID

Location of the partially bypassed intestinal loop better determined body weight and fat mass loss. Superior weight and fat mass loss were appreciated with DPID compared with PPID and Sham (Figure 2a–c). Differences in body weight and composition between DPID and PPID were less impacted by loop length which was similar for both groups (Figure 2i). The impact of PID on body weight has been described by a handful of reports.^{6,7,15,16} One study of 10 patients with mean preoperative body mass index (BMI) of 41.1 kg/m² reported 14.6% of total body weight loss (%TBWL) at 12 months.⁶ Others studied this operation in patients with mean BMI of 31.2 and 34.1 kg/m² and described a %TBWL at 12 months of 11.4 and 10.5 correspondingly.^{15,16} Body weight and fat mass loss relative to Sham has also been reported in animals.^{7,15} Though notable improvements in glucose metabolism are observed after DJB, body weight and composition outcomes relative to Sham are not altered by this procedure.^{19,25,26} These data support our findings that a duodenal component to the PID may render this operation less effective for weight loss. Reasons for this may include

differences in absorptive capacity and types of macronutrient absorbed between the duodenum and jejunum and or less effective partial bypass accomplished with the duodenal-jejunal anastomosis.²⁷ Given that most macronutrient absorption occurs in the jejunum and that fecal caloric loss was an important phenotype noted after DPID (Figure 6e), partially bypassing the duodenum may not result in optimal weight loss. Additionally, the relatively fixed duodenum and associated angulation, greater diameter, and shorter transit time may result in less effective rerouting of nutrients away from the partially bypassed loop, consequently making PPID a poorer variation for weight loss.

DPID vs. VSG vs. VSG/DPID

All three operations resulted in significant body weight and fat mass loss and metabolic benefit relative to Sham. Reaching statistical significance for fat mass loss, insulin resistance as measured by HOMA-IR, and plasma triglycerides between DPID and VSG/DPID and plasma cholesterol and triglycerides between DPID and VSG, weight and metabolic outcomes tended to be better for VSG and VSG/DPID relative to DPID (Figures 3 and 4). On the other hand, no statistically significant differences in weight loss and metabolic improvement were appreciated between VSG and VSG/DPID. (Figures 3 and 4). These data oppose the addition of the PID to the VSG as doing so may expose patients to the potential risks of the PID portion of the operation without conferring additional apparent benefit. Moreover, these findings argue for overlapping mechanisms between VSG and DPID. One of such mechanisms could involve bile acids as total fasted plasma bile acids were elevated relative to Sham for all surgeries (Figure 4f). Several reports have documented increase in bile acids following metabolic surgery.^(12,28) This interesting finding has prompted a variety of investigations exploring the means whereby bile acids may influence weight loss and metabolic benefit following metabolic surgery identifying FXR and TGR5 as potential mediators.^(29,30)

Many reports have documented the improvements in lipid profile that occur following metabolic surgery. Such beneficial impact on lipid metabolism parallels the positive changes observed with glucose homeostasis.^{3,31} Others have concentrated on the effects of lipid metabolism which may result from the partial ileal bypass.³¹ In a well-designed randomized clinical trial with a mean follow-up of 9.7 years, this study noted statistically significant reductions in total cholesterol and low-density lipoprotein cholesterol while statistically significant higher levels of triglycerides and very-low-density lipoprotein cholesterol were appreciated in the surgical group. Moreover, their data suggested a survival benefit for patients with an ejection fraction < 50% and a reduction in the combined end points of death due to coronary artery disease and nonfatal myocardial infarction for the surgical group. Our study shows significant lower levels in plasma of total cholesterol and triglycerides in VSG, DPID, and VSG/DPID compared with Sham (Figure 4g–h). Triglycerides and cholesterol are also lower in VSG compared to the DPID (Figure 4g–h). This finding closely parallels insulin resistance for each of the groups given by HOMA-IR (Figure 4e) and support the observation that improvements in glucose and lipid metabolism usually go hand in hand after metabolic surgery. Contrasting results for plasma triglyceride values between the partial ileal bypass and DPID may relate to anatomical and likely physiological differences between both models. The partial ileal bypass totally bypasses most of the ileum and creates

a long blind-ending loop which is not in contact with chyme. Instead, our model of DPID, partially diverts chyme away from a segment of jejunum. This jejunal segment is still in contact with some chyme and there is no long blind-ending loop. While DPID was associated with increased Kcal lost in the stool compared to the other models (Figure 6e), this variable in isolation may not account for improvements in lipid metabolism. Kilocalories lost in stool is just but a variable within the larger picture of energy balance which may be better represented by Kcal gained/lost in body fat (Figure 6d). The latter closely matches improvements in lipid and glucose metabolism and HOMA-IR (Figure 4e,g–h).

While other studies comparing PID with VSG are lacking, one clinical study compared 32 patients with baseline mean BMI of 45.7 kg/m² undergoing VSG plus a version of PID to a retrospectively matched cohort of 32 patients with preoperative mean BMI of 46.9 kg/m² undergoing just the VSG.³² Although no conclusions can be made regarding diabetes resolution or improvement given the small overall number of patients with diabetes examined in this study the authors did report superior percent excess body weight loss at 12 months in the VSG plus PID group (77.3% vs. 61.4%; p=0.006). Additional studies in animal models and patients that compare PID and its variations to established metabolic operations are needed to conclude on the comparative effectiveness of this novel procedure.

DPID Causes Increased Fecal Energy Losses

While VSG results in marked reductions in caloric intake accompanied by non-statistically significant enhanced intestinal nutrient absorption, DPID causes notable fecal caloric losses not compensated by greater food intake (Figure 6c,e). In fact, reduction in food intake relative to Sham, albeit less pronounced than that observed for VSG, is also seen with DPID (Figure 6c). Food intake reductions after VSG has been extensively documented in animal and clinical studies.^{33,34} Moreover and supported by our data (Figure 6c,f), a significant portion of the weight loss appreciated after this operation may be explained by reduction in food intake rather than changes in energy expenditure.³⁵ Our data show that increased fecal caloric loss is an important effect of DPID. Importantly, animals do not compensate for that loss of calories by increasing their food intake resulting in the overall loss of fat mass. Such data are consistent with the hypothesis that both VSG³⁶ and DPID lower the defended setpoint for body weight. Understanding the mechanisms underlying this new body weight and composition homeostasis ensuing after these procedures is a crucial goal for future research.

Additional investigation could focus on further defining the optimal variation of this model and identifying additional mechanisms whereby this procedure may exert its effects. In this regard, attempts at better defining the optimal length of the partially bypassed loop should be made. In generating our model, one concern involved the length of the partially bypassed loop in order to detect a potential surgical effect while minimizing the occurrence of physiologic short bowel syndrome. In human adults, this may ensue when small intestinal length is less 100–150 cm or 17–25% of total small bowel length.^{37,38} Therefore, while we selected 40 cm as the length of the partially bypassed loop leaving an ample 60% of fully

functional small intestine, this length may not provide the optimal balance between surgical benefit and risk.

An important consideration whenever apprising a new metabolic procedure encompasses its risk-benefit profile. For reference, the historical jejunoileal bypass resulted in severe side-effects including hepatic complications up to cirrhosis and liver failure and extensive metabolic problems such as renal oxalosis, fat soluble vitamin deficiencies, gallstones, enteritis, arthritis, encephalopathy, and dermatitis just to list a few.³⁹ While we acknowledge the potential for complications from any metabolic surgical intervention, there are clear reasons to believe that DPID will not produce some of the most problematic side-effects observed with jejunoileal bypass. The jejunoileal bypass completely excludes about 90% of the small bowel and creates a very long blind-ending loop. On the other hand, the DPID model used in our study partially diverts chyme from approximately 40% of the proximal small intestine, namely the jejunum. This jejunal segment is still in contact with some chyme and there is no long blind-ending loop. Moreover, studies in RYGB have noted a reasonable incidence of complications related to the bypass portion of the operation as long as less than 70% of small intestine, defined as the sum of biliopancreatic and alimentary limbs, is bypassed.⁴⁰ Thus, we believe that the negative complication profile associated with the jejunoileal bypass should not be transposed to the DPID model used in our study. However, no rodent study can adequately address all the possible side-effects that can develop over years and further work will be necessary to adequately assess the complication profile associated with DPID. Lastly, while at least one mechanism inducing weight loss after DPID entails an increased loss of calories in the feces not adequately compensated by increased food intake, exploration of other mechanisms already associated with bariatric surgery and its derived weight and metabolic benefits including intestinal hormone signaling and morphological adaptation, bile acids, and the microbiome should be undertaken.

Our data have limitations. Animals were followed for 10–11 weeks and no conclusions can therefore be made regarding outcomes at later time points. However, improvements in metabolic outcomes including glucose tolerance and lipid profiles occur early and independently of weight loss in rodent models and the length of this experiment is equivalent to most published animal studies.^{12,14} Appraisal of the potential impact PID may have on patients made from data derived from animal investigations should always be made with caution. Nevertheless, the available studies exploring this surgical model in a small number of patients points to similar findings. Although comparable to most animal experiments in metabolic surgery, small group size could potentially result in type II error. While enhanced insulin sensitivity is a significant mechanism whereby PID improves glucose metabolism, insulin secretion and beta cell function were not directly assessed in this study. The mechanisms whereby fecal energy loss remains uncompensated through alterations in intestinal nutrient absorption and caloric intake remain unknown. This study did not investigate other processes such as gut hormones, intestinal histology, microbiome changes, and bile acid composition and signaling all of which have been implicated as potential mechanisms in metabolic surgery. These data do not capture procedural complications other than those already listed in the Materials and Methods section. Another potential side effect associated with this procedure include “blind” loop syndrome. Also referred to as stasis syndrome or stagnant loop syndrome, this condition results in small

intestinal bacterial overgrowth presenting with symptoms including flatulence, bloating, chronic watery diarrhea, abdominal discomfort, and even weight loss in severe cases. Moreover, metabolic surgery is associated with changes to the intestinal microbiome which are the current target of much scientific effort and small intestinal bacterial overgrowth, if present, could alter this relationship. Further studies should help identify whether small intestinal bacterial overgrowth is a complication of PID.

Conclusions

PID is an effective operation to combat obesity and related metabolic comorbidities. Improvements in glucose metabolism due to enhanced insulin sensitivity occurred independently from location (i.e. distal vs. proximal) of the partially bypassed intestinal loop. Location of PID may be more important than its length for inducing body weight and fat mass loss as these were observed with the distal DPID only. The addition of the DPID to VSG did not result in further weight loss or metabolic benefit compared to VSG suggesting overlapping mechanisms between VSG and DPID. Weight loss after DPID is associated with increased loss of calories in the feces that is not adequately compensated by increased food intake. These findings support further studies of this novel metabolic operation and its underlying mechanisms in animal models and patients.

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References

1. Ogden CL, Carroll MD, Fryar CD, et al. Prevalence of Obesity Among Adults and Youth: United States, 2011–2014. NCHS Data Brief. 2015;1–8.
2. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384:766–781. [PubMed: 24880830]
3. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric Surgery versus Intensive Medical Therapy for Diabetes - 5-Year Outcomes. N Engl J Med 2017;376:641–651. [PubMed: 28199805]
4. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. Lancet. 2015;386:964–973. [PubMed: 26369473]
5. Ponce J, Nguyen NT, Hutter M, et al. Estimate of Bariatric Surgery Numbers, 2011–2015 Available from: <http://asmbs.org/resources/estimate-of-bariatric-surgery-numbers>. 2016 Accessed June 27, 2017.
6. Machytka E, Buzga M, Zonca P, et al. Partial jejunal diversion using an incisionless magnetic anastomosis system: 1-year interim results in patients with obesity and diabetes. Gastrointest Endosc 2017;86:904–912. [PubMed: 28716404]

7. Melissas J, Peirasmakis D, Lamprou V, et al. Is a Simple Food-Diverting Operation the Solution for Type 2 Diabetes Treatment? Experimental Study in a Non-Obese Rat Model. *Obes Surg* 2016;26:1010–1015. [PubMed: 26323659]
8. Stefater MA, Perez-Tilve D, Chambers AP, et al. Sleeve gastrectomy induces loss of weight and fat mass in obese rats, but does not affect leptin sensitivity. *Gastroenterology*. 2010;138:2426–2436, 2436.e1–3. [PubMed: 20226189]
9. Morton GJ, Matsen ME, Bracy DP, et al. FGF19 action in the brain induces insulin-independent glucose lowering. *J Clin Invest* 2013;123:4799–4808. [PubMed: 24084738]
10. Asai M, Ramachandrapa S, Joachim M, et al. Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity. *Science*. 2013;341:275–278. [PubMed: 23869016]
11. Andreollo NA, Santos EF dos, Araujo MR, et al. Rat's age versus human's age: what is the relationship? *Arq Bras Cir Dig* 2012;25:49–51. [PubMed: 22569979]
12. Cummings BP, Bettaieb A, Graham JL, et al. Vertical sleeve gastrectomy improves glucose and lipid metabolism and delays diabetes onset in UCD-T2DM rats. *Endocrinology*. 2012;153:3620–3632. [PubMed: 22719048]
13. Alvarez R, Lewis AG, Toure MH, et al. A comparison of rodent models of vertical sleeve gastrectomy. *Surg Obes Relat Dis* Epub ahead of print July 2, 2018. DOI: 10.1016/j.soard.2018.06.022.
14. Chambers AP, Jessen L, Ryan KK, et al. Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. *Gastroenterology*. 2011;141:950–958. [PubMed: 21699789]
15. Fried M, Dolezalova K, Chambers AP, et al. A novel approach to glycemic control in type 2 diabetes mellitus, partial jejunal diversion: pre-clinical to clinical pathway. *BMJ Open Diabetes Res Care*. 2017;5:e000431.
16. Melissas J, ErenTaskin H, Peirasmakis D, et al. A Simple Food-Diverting Operation for Type 2 Diabetes Treatment. Preliminary Results in Humans with BMI 28–32 kg/m2. *Obes Surg* 2017;27:22–29. [PubMed: 27581799]
17. Kadera BE, Portenier DD, Yurcisin BM, et al. Evidence for a metabolic mechanism in the improvement of type 2 diabetes after sleeve gastrectomy in a rodent model. *Surg Obes Relat Dis* 2013;9:447–452. [PubMed: 23462596]
18. Yang P-J, Yang W-S, Nien H-C, et al. Duodenojejunal Bypass Leads to Altered Gut Microbiota and Strengthened Epithelial Barriers in Rats. *Obes Surg* 2016;26:1576–1583. [PubMed: 26615407]
19. Wu D, Yan Z-B, Cheng Y-G, et al. Deactivation of the NLRP3 inflammasome in infiltrating macrophages by duodenal-jejunal bypass surgery mediates improvement of beta cell function in type 2 diabetes. *Metab Clin Exp* 2018;81:1–12. [PubMed: 29129820]
20. Petry TZ, Fabbri E, Otoch JP, et al. Effect of Duodenal-jejunal Bypass Surgery on Glycemic Control in Type 2 Diabetes: A Randomized Controlled Trial. *Obesity (Silver Spring)*. 2015;23:1973–1979. [PubMed: 26414562]
21. Weng SG, Zhang B, Wang X, et al. Effects of Duodenal-jejunal Exclusion and New Bilio-Pancreatic Diversion on Blood Glucose in Rats with Type 2 Diabetes Mellitus. *Obes Surg* 2017;27:2067–2072. [PubMed: 28233263]
22. Bolckmans R, Himpens J. Long-term (>10 Yrs) Outcome of the Laparoscopic Biliopancreatic Diversion With Duodenal Switch. *Ann Surg* 2016;264:1029–1037. [PubMed: 26764870]
23. Schouten R, Rijs CS, Bouvy ND, et al. A multicenter, randomized efficacy study of the EndoBarrier Gastrointestinal Liner for presurgical weight loss prior to bariatric surgery. *Ann Surg* 2010;251:236–243. [PubMed: 19858703]
24. Seeley RJ, Chambers AP, Sandoval DA. The role of gut adaptation in the potent effects of multiple bariatric surgeries on obesity and diabetes. *Cell Metab* 2015;21:369–378. [PubMed: 25662404]
25. Li M, Li H, Zhou Z, et al. Duodenal-jejunal Bypass Surgery Ameliorates Glucose Homeostasis and Reduces Endoplasmic Reticulum Stress in the Liver Tissue in a Diabetic Rat Model. *Obes Surg* 2016;26:1002–1009. [PubMed: 26205216]

26. Kindel TL, Martins PJF, Yoder SM, et al. Bypassing the duodenum does not improve insulin resistance associated with diet-induced obesity in rodents. *Obesity (Silver Spring)*. 2011;19:380–387. [PubMed: 21030948]
27. Gropper SS, Smith JL. *Advanced nutrition and human metabolism*. 6th Ed Belmont, OH: Cengage Learning; 2012.
28. Myronovych A, Kirby M, Ryan KK, et al. Vertical sleeve gastrectomy reduces hepatic steatosis while increasing serum bile acids in a weight-loss-independent manner. *Obesity (Silver Spring)*. 2014;22:390–400. [PubMed: 23804416]
29. Ryan KK, Tremaroli V, Clemmensen C, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. *Nature*. 2014;509:183–188. [PubMed: 24670636]
30. McGavigan AK, Garibay D, Henseler ZM, et al. TGR5 contributes to glucoregulatory improvements after vertical sleeve gastrectomy in mice. *Gut* 2017;66:226–234. [PubMed: 26511794]
31. Buchwald H, Varco RL, Matts JP, et al. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). *N Engl J Med* 1990;323:946–955. [PubMed: 2205799]
32. Melissas J, Peppe A, Askoxilakis J, et al. Sleeve gastrectomy plus side-to-side jejunoileal anastomosis for the treatment of morbid obesity and metabolic diseases: a promising operation. *Obes Surg* 2012;22:1104–1109. [PubMed: 22527590]
33. Verger EO, Aron-Wisnewsky J, Dao MC, et al. Micronutrient and Protein Deficiencies After Gastric Bypass and Sleeve Gastrectomy: a 1-year Follow-up. *Obes Surg* 2016;26:785–796. [PubMed: 26205215]
34. Schneck A-S, Iannelli A, Patouraux S, et al. Effects of sleeve gastrectomy in high fat diet-induced obese mice: respective role of reduced caloric intake, white adipose tissue inflammation and changes in adipose tissue and ectopic fat depots. *Surg Endosc* 2014;28:592–602. [PubMed: 24196540]
35. Bielohuby M, Stemmer K, Berger J, et al. Carbohydrate content of post-operative diet influences the effect of vertical sleeve gastrectomy on body weight reduction in obese rats. *Obes Surg* 2012;22:140–151. [PubMed: 21971629]
36. Stefater MA, Wilson-Perez HE, Chambers AP, et al. All bariatric surgeries are not created equal: insights from mechanistic comparisons. *Endocr Rev* 2012;33:595–622. [PubMed: 22550271]
37. Messing B, Crenn P, Beau P, et al. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. *Gastroenterology*. 1999;117:1043–1050. [PubMed: 10535866]
38. Parrish CR, DiBaise JK. Managing the Adult Patient With Short Bowel Syndrome. *Gastroenterol Hepatol (N Y)*. 2017;13:600–608. [PubMed: 29230136]
39. Singh D, Laya A-S, Clarkston W-K, et al. Jejunioileal bypass: a surgery of the past and a review of its complications. *World J Gastroenterol* 2009;15:2277–2279. [PubMed: 19437570]
40. Caruana JA, Monte SV, Jacobs DM, et al. Distal small bowel bypass for weight regain after gastric bypass: safety and efficacy threshold occurs at <70% bypass. *Surg Obes Relat Dis* 2015;11:1248–1255. [PubMed: 26499355]

Highlights

- Distal PID results in weight loss
- Distal or proximal PID result in improved glucose metabolism
- PID results in improved insulin sensitivity
- Distal PID and VSG may share overlapping mechanisms of action
- Distal PID results in increased loss of calories in feces

Figure 1. Partial Intestinal Diversion (PID). DPID (Distal) and PPID (Proximal) are graphically represented in a and b respectively. Circle denotes the enteroenterostomy. Black arrows indicate the usual path of chyme while white arrows represent to newly created path followed by the fraction of chyme bypassing a loop of small intestine. S; stomach; C, cecum; LoT, ligament of Treitz; ICV, ileocecal valve.

Figure 2.

Body Weight and Composition, Food Intake, Glucose Metabolism, and Loop Length for Cohort 1. Percentage weight change over time (a). Percentage weight change at week 11 (b). Percentage fat mass change at week 11 (c). Percentage lean mass change at week 11 (d). Mean weekly food intake (e). Cumulative food intake (f). Glucose levels at baseline and at different time points after injection of intraperitoneal dextrose 2g/kg (g). Area under the curve (AUC) for glucose levels over time obtained shown in g (h). Loop length at sacrifice (i). Loop length was analyzed via t-test. All other analyses performed by Tukey's multiple comparison test applied to values obtained from one-way analysis of variance (ANOVA). PID, partial intestinal diversion; VSG, vertical sleeve gastrectomy; *, denotes statistical significance relative to Sham. \$ indicates statistical significance relative to PPID. ****/\$ \$ \$ \$, $p < 0.0001$; **/\$ \$ \$, $p < 0.001$; **/\$ \$, $p < 0.01$; */\$, $p < 0.05$.

Figure 3.

Body Weight and Composition and Food Intake for Cohort 2. Percentage weight change over time (a). Percentage weight change at week 10 (b). Percentage fat mass change at week 10 (c). Percentage lean mass change at week 10 (d). Mean weekly food intake (e). Cumulative food intake (f). All analyses performed by Tukey's multiple comparison test applied to values obtained from one-way analysis of variance (ANOVA). DPID, partial intestinal diversion; VSG, vertical sleeve gastrectomy; VSG/DPID, vertical sleeve gastrectomy and partial intestinal diversion; *, denotes statistical significance relative to Sham. \$ indicates statistical significance relative to DPID. ****/\$ \$ \$ \$, $p < 0.0001$; **/\$ \$ \$, $p < 0.001$; **/\$ \$, $p < 0.01$; */\$, $p < 0.05$.

Figure 4.

Glucose and Lipid Metabolism and Bile Acids for Cohort 2. Glucose levels at baseline and at different time points after injection of intraperitoneal dextrose 2g/kg (a). Area under the curve (AUC) for glucose levels over time obtained shown in g (b). Baseline glucose (c) and insulin (d) and corresponding Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values (e). Total fasted bile acids (f). Fasting plasma total cholesterol (g) and triglycerides (h). All analyses performed by Tukey's multiple comparison test applied to values obtained from one-way analysis of variance (ANOVA). DPID, partial intestinal diversion; VSG, vertical sleeve gastrectomy; VSG/DPID, vertical sleeve gastrectomy and partial intestinal diversion; *, denotes statistical significance relative to Sham. \$ indicates statistical significance relative to DPID. ****/\$\$/\$\$, $p < 0.0001$; **/\$\$\$, $p < 0.001$; **/\$\$, $p < 0.01$; */\$, $p < 0.05$.

Figure 5.

Glucose Metabolism for Cohort 3. Glucose levels at baseline and at different time points after injection of 25% dextrose 1g/kg over 15 seconds into jugular vein (a) with corresponding area under the curve (AUC) (b). Insulin levels at baseline and at different time points after corresponding to glucose levels in a (c) and AUC (d). All analyses performed by Tukey's multiple comparison test applied to values obtained from one-way analysis of variance (ANOVA). DPID, partial intestinal diversion; VSG, vertical sleeve gastrectomy; *, denotes statistical significance relative to Sham. ****, $p < 0.0001$; ***, $p < 0.001$; **, $p < 0.01$; *, $p < 0.05$.

Figure 6.

Energy Balance for Cohort 2. Stool collected over 72 hrs. (a) and its per gram caloric content by bomb calorimetry (b). Calculated kcal content of cumulative food intake (c), body fat lost or gained over the study (d), stool excreted (e), and energy expenditure per gram of body weight (f). All analyses performed by Tukey's multiple comparison test applied to values obtained from one-way analysis of variance (ANOVA). DPID, partial intestinal diversion; VSG, vertical sleeve gastrectomy; VSG/DPID, vertical sleeve gastrectomy and partial intestinal diversion; *, denotes statistical significance relative to Sham. \$ indicates statistical significance relative to DPID. Statistical significance relative to VSG/DPID is given by &. ****/\$ \$ \$ \$/ & & & &, $p < 0.0001$; **/\$ \$ \$ \$/ & & &, $p < 0.001$; **/\$ \$ \$/ & &, $p < 0.01$; */\$ / &, $p < 0.05$.

Table 1**Long-Evans Intestinal Length and Operations**

	Intestinal Measurements			Total Intestinal Length
	Jejunum and Ileum	Small Bowel	Colon	
Duodenum 8–10 cm	90–100 cm	98–110cm	16–20 cm	114–130 cm
Operations				
DPID	Proximal enterotomy at 15 cm distal from LOT anastomosed to enterotomy 40 cm distal from proximal enterotomy creating a 40 cm loop			
PPID	Proximal enterotomy just distal to pylorus anastomosed to distal enterotomy 31 cm from LOT creating a 40 cm loop			
VSG	Stapled VSG			
VSG/DPID	Stapled VSG plus 40 cm PID loop with proximal enterotomy at 15 cm distal from LOT anastomosed to enterotomy 40 cm distal from proximal enterotomy			
Sham [*]	Dissection of the greater curvature and gentle compression of stomach as well as longitudinal duodenal enterotomy closed transversely with interrupted sutures and longitudinal enterotomy at 55 cm from LOT closed transversely with interrupted sutures			
Sham ^{\$}	Dissection of the greater curvature and gentle compression of stomach as well as longitudinal enterotomies closed transversely with interrupted sutures at 15 and 55 cm from LOT			

DPID, distal partial intestinal diversion; PPID, proximal partial intestinal diversion; VSG, vertical sleeve gastrectomy; LOT, ligament of Treitz

^{*} sham model used in cohort 1

^{\$} sham model used in cohorts 2 and 3.