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Bariatric Surgery Enhances Splanchnic Vascular Responses in Patients With Type 2 Diabetes

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METABOLISM

Bariatric surgery results in notable weight loss and alleviates hyperglycemia in patients with type 2 diabetes (T2D). We aimed to characterize the vascular effects of a mixed meal and infusion of exogenous glucose-dependent insulinotropic polypeptide (GIP) in the splanchnic region in 10 obese patients with T2D before and after bariatric surgery and in 10 lean control subjects. The experiments were carried out on two separate days. Pancreatic and intestinal blood flow (BF) were measured at baseline, 20 min, and 50 min with ^{15}O-water by using positron emission tomography and MRI. Before surgery, pancreatic and intestinal BF responses to a mixed meal did not differ between obese and lean control subjects. Compared with presurgery, the mixed meal induced a greater increase in plasma glucose, insulin, and GIP concentrations after surgery, which was accompanied by a marked augmentation of pancreatic and intestinal BF responses. GIP infusion decreased pancreatic but increased small intestinal BF similarly in all groups both before and after surgery. Taken together, these results demonstrate that bariatric surgery leads to enhanced splanchnic vascular responses as a likely consequence of rapid glucose appearance and GIP hypersecretion.

Bariatric surgery results in a nearly 30% reduction in body weight and is associated with remission of diabetes (1,2). Although energy restriction and weight loss per se are the major determinants of improved glucose metabolism after surgery (3,4), altered gut microbiota and glucose metabolism (5,6), activation of intestinal nutrient sensing (7), and changes in bile acid composition (8) have been reported as additional contributors.

Blood flow (BF) in the pancreas and small intestine regulates the appearance of glucose, gastrointestinal (GI) hormones, and insulin in the systemic bloodstream after meal ingestion. However, whether the redistribution of BF in the splanchnic region after meal ingestion is changed in obesity and diabetes and in response to altered GI tract anatomy after bariatric surgery is unknown. Supported by previous animal data (9,10), we hypothesized that glucose and glucose-dependent insulinotropic polypeptide (GIP) also contribute to the redistribution of splanchnic BF in the postprandial state in humans. To address this hypothesis, we measured pancreatic and small intestinal BF with ^{15}O-water by using a combined positron emission tomography (PET)/MRI methodology before and after a mixed meal and during GIP infusion in obese patients with type 2 diabetes (T2D) before and after bariatric surgery.

RESEARCH DESIGN AND METHODS

Participants

The study included 10 consecutive obese patients with T2D who were scheduled to undergo Roux-en-Y gastric bypass (RYGB) or vertical sleeve gastrectomy (VSG) (Table 1). In addition, 10 lean control subjects without diabetes were recruited. The inclusion criteria for the control population were BMI of 18–27 kg · m^{-2}, age 18–60 years, fasting plasma glucose <6.1 mmol/L, and normal oral

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Table 1—Subject anthropometric, biochemical, and model-derived data

	Control subjects (n = 10)	Obese subjects (n = 10)				
		Presurgery	Postsurgery	P value*	P value†	P value‡
Anthropometric						
Sex, n						
Male	2	2				
Female	8	8				
Age (years)	50 (46–52)	47 (46–59)	48 (47–59)	0.569	—	—
Weight (kg)	61.5 (59.3–66.5)	121 (95.3–130)	103 (81–111)	<0.001	<0.001	<0.001
BMI ($kg \cdot m^{-2}$)	23.2 (21.8–24.1)	38.9 (37.4–44.8)	34.4 (30.1–39.3)	<0.001	<0.001	<0.001
Body fat (%)	26.0 (23.8–29.9)	49.9 (47.3–51.8)	46.8 (40.0–5.03)	0.005	0.030	0.009
Diabetes, n (%)	0 (0)	10 (100)	2 (20)	—	—	—
Biochemical						
Fasting glucose (mmol/L)	5.0 (4.7–5.2)	7.1 (6.4–7.4)	5.4 (5.1–6.2)	<0.001	0.096	<0.001
2-h glucose (mmol/L)	6.1 (5.3–6.9)	11.7 (10.0–13.8)	6.8 (6.1–9.4)	<0.001	0.377	<0.001
GHb (%)	5.2 (5.1–5.4)	5.9 (5.6–6.1)	5.5 (5.3–5.6)	0.001	0.302	0.009
GHb ($mmol \cdot mol^{-1}$)	33.2 (32.3–35.2)	40.5 (37.8–42.8)	36.5 (34.0–37.8)	<0.001	0.251	0.013
Fasting insulin ($mU \cdot L^{-1}$)	3.0 (2.0–6.0)	23.5 (15.5–28.5)	11.0 (8.0–13.5)	<0.001	0.007	0.002
Fasting GIP (pmol/L)	10.7 (8.8–12.2)	8.4 (6.1–12.8)	7.9 (6.5–9.1)	0.687	0.688	1.00
Fasting GLP-1 (pmol/L)	3.6 (3.2–7.0)	3.8 (3.0–6.2)	6.0 (3.6–6.9)	0.696	0.903	0.826
Insulin sensitivity indices						
HOMA-IR (fraction)	0.7 (0.4–1.5)	6.9 (4.2–8.5)	2.6 (2.1–3.6)	<0.001	0.006	0.001
2-h OGIS ($mL \cdot min^{-1} \cdot m^{-2}$)	451 (429–481)	306 (272–358)	365 (337–382)	<0.001	0.004	0.067
β-Cell function parameters						
Glucose sensitivity ($pmol/L \cdot min^{-1} \cdot m^{-2} \cdot mmol/L^{-1}$)	75.9 (63.1–91.8)	49.4 (36.2–59.4)	69.5 (59.0–89.6)	0.241	0.999	0.048
Potentiation factor ratio (dimensionless)	1.4 (1.2–2.2)	1.1 (1.0–1.1)	1.1 (1.0–1.3)	0.062	0.112	0.821

Data are median (IQR) unless otherwise indicated. GHb, glycated hemoglobin; HOMA-IR, HOMA of insulin resistance; OGIS, oral glucose insulin sensitivity index. *P value for obese patients presurgery vs. control subjects; †P value for obese patients postsurgery vs. control subjects; ‡P value for obese patients post- vs. presurgery.

glucose tolerance test. The Ethics Committee of the Hospital District of Southwest Finland (Turku, Finland) (NCT01880827) approved the study, and all subjects gave written consent before enrollment.

PET Study Design

The study flowchart and PET experimentation are shown in Supplementary Fig. 1*A–C*. Imaging was performed after an overnight fast with a combined PET/MRI scanner (Philips Ingenuity; Philips Healthcare, Cleveland, OH) (11). After a whole-body T_2-weighted MRI, baseline ^{15}O-water PET image acquisition of the abdomen was done. During the experiments, plasma levels of glucose, insulin, C-peptide, GIP, and glucagon-like peptide 1 (GLP-1) were measured at time points 0, 15, 30, 45, 60, and 90 min. Experiments were performed before a very-low-calorie diet in patients undergoing bariatric surgery.

Mixed-Meal Testing

Subjects ingested a 250-kcal liquid meal (Nutridrink; Nutricia Advanced Medical Nutrition, Amsterdam, the Netherlands) in 10 min that consisted of 40 g carbohydrates, 6 g fat, and 9 g protein. A ^{15}O-water PET scan was repeated at 20 and 50-min postingestion to quantitate splanchnic BF responses during the gastric and intestinal phases of absorption, respectively. Mixed-meal testing was repeated 69 (55–97) days after surgery.

GIP Infusion

A constant infusion of GIP_{1-42} (Bachem Holding AG, Bubendorf, Switzerland) at the rate of 4.0 $pmol \cdot kg^{-1} \cdot min^{-1}$ was initiated. After 15 min, the rate was halved to 2.0 $pmol \cdot kg^{-1} \cdot min^{-1}$ with the intention to reproduce GIP excursion seen after the ingestion of a mixed meal (12). The ^{15}O-water PET scan was repeated at 20- and 50-min postinfusion. GIP infusion was repeated 80 (47–92) days after surgery.

PET Image Processing

PET data were corrected for decay and photon attenuation. Regional time-activity curves were obtained from pancreas, duodenum, and jejunum by using Carimas 2.9 software, which was downloaded from the Turku PET Centre website (www.turkupetcentre.fi). Input function was obtained from the abdominal aorta (13).

Calculations

BF rates were calculated by using the one-tissue compartment model (14) and equate to clearance rate k_2 multiplied by the physiological partition coefficient (p_{phys} = 0.880 and 0.975 $mL \cdot g^{-1}$ for pancreas and intestine, respectively). Thereafter, the values were normalized for organ volume as follows: Pancreatic volume was measured manually from MRIs, whereas conventional values of 57.30 and 556.62 mL were used for duodenum and jejunum, respectively

(15). Insulin secretion rate (ISR) was derived from the C-peptide deconvolution (16). Insulin sensitivity is expressed as HOMA for insulin resistance and 2-h oral glucose sensitivity index (17). β-Cell glucose sensitivity and the potentiation factor ratio were calculated as previously described (18,19). Incremental areas under the curve (iAUCs) were calculated by the trapezoidal rule.

Biochemical Analysis

Glucose, insulin, and C-peptide concentrations were measured as previously described (5). Plasma total GIP and active GLP-1 concentrations were measured with an ELISA kit (EMD Millipore, Billerica, MA).

Statistics

Results are expressed as median (interquartile range [IQR]). Changes over time and between groups were tested with repeated-measures analyses using linear mixed models, and Tukey-Kramer method was used to adjust the *P* values of pairwise comparisons. The normality of the residuals was checked for justification of the analyses, and transformations were used for variables that were not normally distributed. Differences between surgery groups were tested by using Student *t* test or Wilcoxon rank sum test. Spearman correlation coefficient was calculated to explore the correlations between variables. $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SAS 9.4 for Windows software (SAS Institute, Cary, NC).

RESULTS

Glucose, Insulin Secretion, and Incretins During Mixed-Meal Testing

Before surgery, patients and control subjects had similar incremental (i.e., above baseline) glucose excursion, whereas after surgery, glucose response was considerably higher and occurred earlier (Fig. 1*A*). The insulin response was suppressed during the first 15 min in patients before surgery, whereas after surgery, incremental insulin response was increased nearly 2.5-fold compared with presurgery ($P < 0.001$) (Fig. 1*B*). Plasma level of GIP increased in all groups (Fig. 1*C*), whereas no change in plasma GLP-1 was observed in patients before surgery and in control subjects (Fig. 1*D*). However, postsurgery mixed-meal ingestion provoked a robust increase in plasma GLP-1 level.

Pancreatic BF During Mixed-Meal Testing

The fasting pancreatic BF rate was similar in patients and control subjects. Meal ingestion increased pancreatic BF (Fig. 2*A*) in both groups at 20 min; at 50-min postingestion, the pancreatic BF returned to baseline. At postsurgery, the basal pancreatic BF rate was similar to presurgery values ($P = 0.983$). However, mixed-meal ingestion resulted in a marked (1.48-fold) increase in pancreatic BF in patients after surgery. In control subjects and patients before surgery but not after surgery, the incremental pancreatic BF was associated with incremental glucose response (Fig. 2*B*), GIP, and GLP-1 (Supplementary Table 1). In contrast, pancreatic BF during the mixed-meal test was not directly associated with ISR.

Small Intestinal BF During Mixed-Meal Testing

Fasting BF rate in the duodenum and jejunum were similar between patients before surgery and control subjects. Mixed-meal ingestion did not change duodenal BF (Fig. 2*C*) in either group, whereas jejunal BF (Fig. 2*D*) increased similarly at 20-min postingestion and remained elevated during the 50-min PET experimentation. Bariatric surgery did not affect basal BF in the duodenum ($P = 0.983$) or jejunum ($P = 1.00$). At postsurgery, duodenal BF did not change in response to mixed-meal ingestion. In contrast, postsurgery mixed-meal ingestion resulted in a 2.15-fold increase in jejunal BF rate.

RYGB Versus VSG

Although both postsurgical groups responded to the mixed-meal ingestion with increased glucose and insulin (Supplementary Fig. 2*A* and *B*), incremental GIP tended to be higher in the VSG group than in the RYGB group, and incremental GLP-1 tended to be higher in the RYGB group than in the VSG group (Supplementary Fig. 2*C* and *D*). Pancreatic BF response was similar in the two surgical groups (Supplementary Fig. 3*A* and *B*). Consistent with the surgical manipulation, duodenal BF response was markedly increased in the VSG group but not in the RYGB group (Supplementary Fig. 3*C* and *D*), whereas jejunal BF response did not differ between the two surgical groups (Supplementary Fig. 3*E* and *F*).

Metabolic and Vascular Effects of GIP Infusion

During the experiment, supraphysiological GIP concentrations were achieved in all the groups and accompanied by elevated serum insulin levels (Fig. 3*A* and *B*). Plasma GLP-1 levels were unchanged in all groups. A stable hypoglycemic response was seen only in patients before surgery (Fig. 3*C*). Pancreatic BF decreased ~20%, and jejunal BF increased ~100–130% (both $P < 0.001$) in all groups (Fig. 3*D*–*F*). In contrast, no change in duodenal BF ($P = 0.126$) was observed during GIP infusion.

DISCUSSION

The current study explored the redistribution of BF in the splanchnic region in obese patients with T2D before and after bariatric surgery during a mixed-meal test and GIP infusion. We found that after surgical manipulation of the GI tract, mixed-meal ingestion is followed by a preponed appearance of glucose and GIP into the bloodstream and, consequently, enhanced pancreatic and jejunal BF responses.

After mixed-meal ingestion, small intestinal BF responses were identical in patients before surgery and in lean control subjects, suggesting that the vascular regulatory orchestra of the gut remains intact after the onset of obesity and the diabetic state. After bariatric surgery, small intestinal BF responses were markedly upregulated after mixed-meal ingestion as a result of rapid delivery of nutrients to the gut and concomitant stimulation by chyme, GIP (9), and GLP-1 (20). Differences in intestinal BF response between VSG- and RYGB-treated patients suggest that perfusion closely approximates meal transit kinetics and GI tract anatomy in the postbariatric setting.

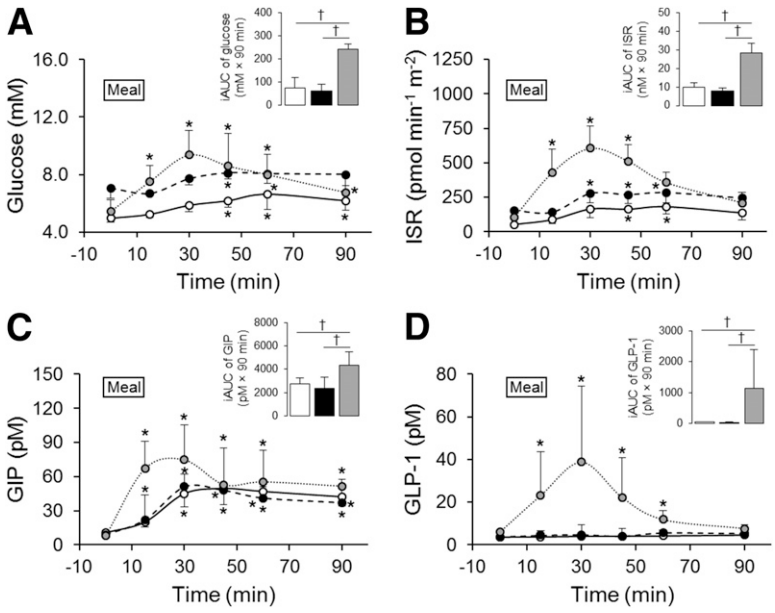

Figure 1—Plasma glucose (*A*), insulin secretion (*B*), GIP (*C*) and GLP-1 (*D*) responses during mixed-meal testing in lean control subjects (○ and white bars) and obese patients before (● and black bars) and early after (◔ and gray bars) bariatric surgery. The responses differed ($P < 0.001$ for time × group interaction in the linear mixed model for all measured variables) between the groups. Insets denote iAUCs for plasma over the time course of the 90-min mixed-meal test. Data are median (IQR). *$P < 0.05$ vs. baseline in the linear mixed model with Tukey-Kramer correction for individual group; †$P < 0.05$ between groups in the linear mixed model.

We confirmed previous preclinical evidence that glucose is a significant regulator of pancreatic BF in vivo after mixed-meal ingestion (10). Despite delayed glucose elevation in patients before surgery compared with lean control subjects, pancreatic BF increased similarly in both groups at 20-min postingestion, suggesting operational neural (cephalic) factors (21). Postsurgically, an ~50% increase in pancreatic BF was observed after mixed-meal ingestion.

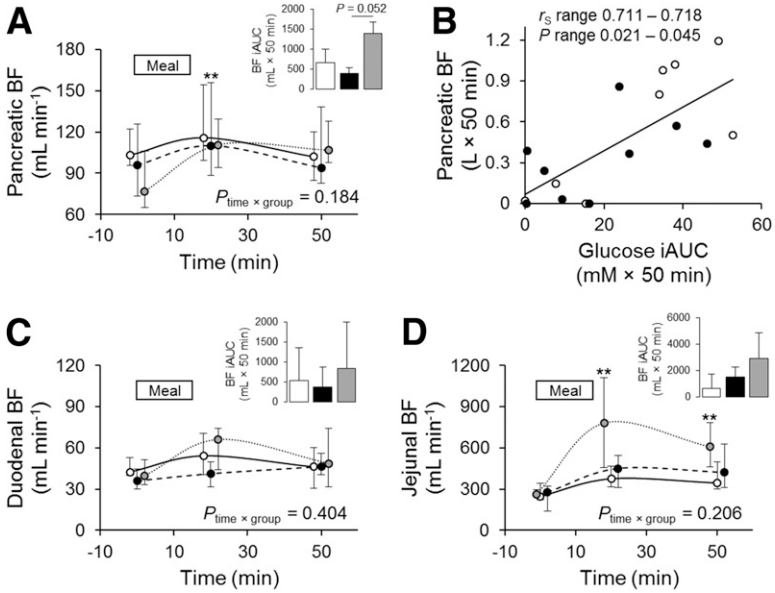

Figure 2—Total pancreatic (*A* and *B*), duodenal (*C*), and jejunal (*D*) BF responses after mixed-meal ingestion in lean control subjects (○ and white bars) and obese patients before (● and black bars) and after (◔ and gray bars) bariatric surgery. In lean control subjects and patients before surgery, incremental glucose was a significant determinant of the magnitude of total pancreatic BF response. Data are median (IQR) and Spearman correlation coefficient r_s (*P* value) for both groups. Insets denote iAUCs for the respective BF measurement over the time course of 50 min (i.e., when the last ^{15}O-water PET scan was acquired). **$P < 0.001$ vs. baseline in the linear mixed model with Tukey-Kramer correction for pooled data.

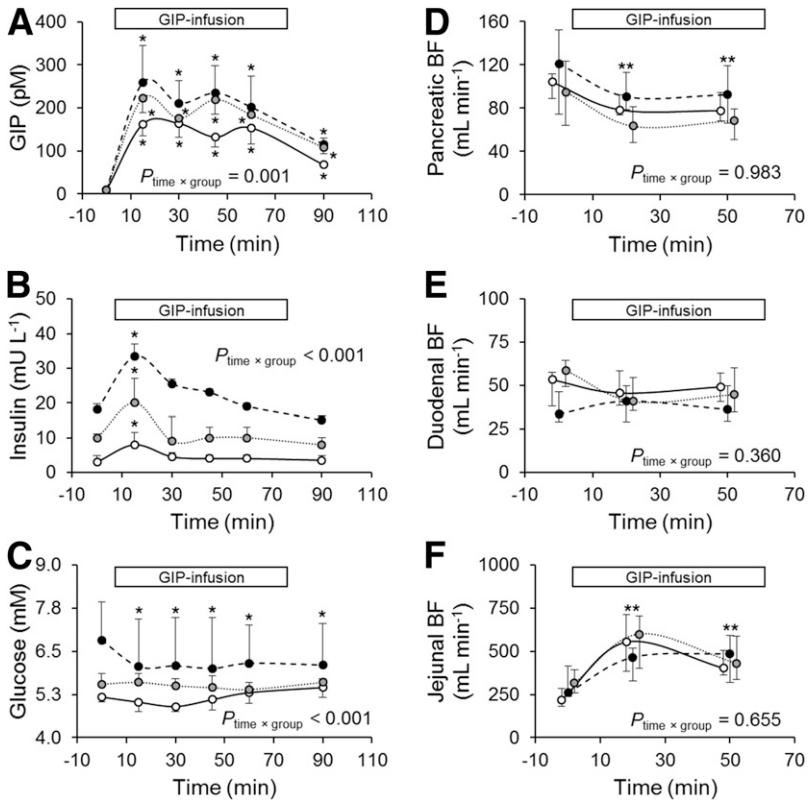

Figure 3—The effects of prime continuous GIP infusion (concentration in venous plasma) (*A*) on insulin glucose concentration (*B*); glucose concentration (*C*); and pancreatic (*D*), duodenal (*E*), and jejunal (*F*) BF in lean control subjects (○) and obese patients before (●) and after (◐) bariatric surgery procedure. Data are median (IQR). *$P < 0.05$ vs. baseline in the linear mixed model with Tukey-Kramer correction for individual group; **$P < 0.001$ vs. baseline in the linear mixed model with Tukey-Kramer correction for pooled data.

Of note, although a prominent leftward shift of the plasma glucose time course was observed in patients after surgery, glucose was not directly associated with the total pancreatic BF increment postsurgically. These data suggest that additional factors, such as intestinal glucoreceptors and jejunal nutrient sensing (6), are the main regulators of pancreatic BF postsurgically. In contrast to glucose and intestinal transit per se, incretins seem to play a lesser role in the regulation of pancreatic BF in the postprandial state.

Several studies have shown that after the onset of diabetes, the insulinotropic activity of GIP is reduced (22,23). We hypothesized that this so-called GIP resistance is present in the vascular smooth muscle cells of patients with T2D. In contrast to subcutaneous adipose tissue (24), we found that during GIP infusion, splanchnic vascular responses were similar in all groups. Because serum insulin levels increased in all groups during the experiment, the data support the observations by Meier et al. (25) that a specific defect in the GIP receptor and postreceptor signaling in vascular smooth muscle cells and β-cells is improbable.

To our knowledge, this study is the first to use PET/MRI methodology to investigate splanchnic BF kinetics during mixed-meal testing in patients undergoing bariatric surgery. However, a few limitations need to be recognized. First, in the infusion study, GIP levels were higher in patients than in control subjects. In lacking a dose-response curve, the GIP effect on splanchnic vasculature possibly was lower in control subjects. However, because supraphysiological concentrations of GIP were achieved in all groups, GIP receptor saturation presumably was maximal in all groups. Second, the control group was not matched for obesity. The recruitment of lean individuals was done with the intention to clarify the redistribution of splanchnic BF in health. Third, because the study group had a relatively low HbA_{1c}, the results may not be directly generalized to patients with long-standing or poorly controlled diabetes. Finally, although the current design allowed for the comparison of the two commonly applied bariatric procedures, we appreciate that the power is still a limiting factor and possibly interferes with data interpretation.

In summary, early after bariatric surgery, mixed-meal ingestion leads to augmented BF to the pancreas and small intestine but not to the duodenum. Although much of this increase may be caused by rapid nutrient exposure to the small intestine, the contribution of GIP cannot be discarded, especially in patients who undergo VSG. Furthermore, the splanchnic vascular effects of GIP are preserved in patients with hyperglycemia. We conclude that the

splanchnic vascular redistribution is a potential regulator of glucose homeostasis during the postprandial state.

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Author Contributions. H.H. and J.K. contributed to the study design, acquired and researched data, and wrote the manuscript. S.K. was responsible for the surgical procedures, contributed to the study design and discussion, and edited the manuscript. J.T. contributed to the image reconstruction development and analysis and offered technical support. S.H. was responsible for the statistical analyses and edited the manuscript. A.M. researched data, contributed to the discussion, and edited the manuscript. A.L., N.W., L.G., and P.N. contributed to the study design and discussion and edited the manuscript. All authors approved the final version of the manuscript. P.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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