REVIEW

PHYSIOLOGY IN MEDICINE: A SERIES OF ARTICLES LINKING MEDICINE WITH SCIENCE
Physiology in Medicine: Dale J. Benos, PhD, *Editor*; Edward Abraham, MD, *Associate Editor*; Peter D. Wagner, MD, *Associate Editor*

Annals of Internal Medicine: Harold C. Sox, MD, *Series Editor*

Narrative Review: Effect of Bariatric Surgery on Type 2 Diabetes Mellitus

Marion L. Vetter, MD, RD; Serena Cardillo, MD; Michael R. Rickels, MD, MS; and Nayyar Iqbal, MD, MSCE

Bariatric surgery leads to substantial and durable weight reduction. Nearly 30% of patients who undergo bariatric surgery have type 2 diabetes, and for many of them, diabetes resolves after surgery (84% to 98% for bypass procedures and 48% to 68% for restrictive procedures). Glycemic control improves in part because of caloric restriction but also because gut peptide secretion changes. Gut peptides, which mediate the enteroinsular axis, include the incretins glucagon-like peptide-1 and glucose-dependent insulinotropic peptide, as well as ghrelin and peptide YY. Bariatric surgery (particularly bypass procedures) alters secretion of these gut hormones, which results in enhanced insulin secretion and sensitivity. This review discusses the various bariatric procedures and how they alter the enteroinsular axis. Familiarity with these effects can help physicians decide among the different surgical procedures and avoid postoperative hypoglycemia.

Ann Intern Med. 2009;150:94-103. www.annals.org
For author affiliations, see end of text.

Glycemic control in diabetic patients improves markedly within days of bariatric surgery, which suggests that the procedures alter the hormones that control insulin secretion (1). The enteroinsular axis includes the gut hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). These hormones, also known as *incretins*, are secreted by intestinal L and K cells, respectively, in response to nutrients and directly enhance insulin secretion (2). Restrictive, malabsorptive, and combined bariatric surgery procedures affect the enteroinsular axis differently. The various bariatric procedures also affect the secretion of other gut hormones that affect insulin sensitivity, including ghrelin and peptide YY (PYY). Thus, an altered pattern of gut hormone secretion after bariatric surgery may profoundly affect glucose tolerance. We focus on the short-term pathophysiologic changes in the enteroinsular axis and their subsequent effect on insulin secretion and sensitivity after bariatric surgery. Familiarity with these changes can help clinicians decide among the different surgical approaches and formulate treatment regimens that avoid severe postoperative hypoglycemia.

See also:

Print
Key Summary Points. 95
Glossary 95

Web-Only
CME quiz
Conversion of graphics into slides

Methods

We searched English-language publications in PubMed and reference lists from relevant articles published between 1967 and 2008. Our main search terms were *bariatric surgery*, *Roux-en-Y*, *gastric bypass*, *biliopancreatic diversion*, *gastric banding*, *laparoscopic adjustable gastric banding*, *diabetes*, *enteroinsular axis*, *incretins*, *GLP-1*, *GIP*, *ghrelin*, *PYY*, *insulin*, and *postoperative management*. To determine the rates of diabetes resolution, we included studies that enrolled at least 10 diabetic patients (alone or along with nondiabetic patients) and reported diabetes-related outcomes. We retrieved randomized, controlled trials; cohort studies; and case–control studies that reported weight loss, diabetes resolution, and time to restoration of normoglycemia. Because we found few such studies, we also included large case series. We evaluated study quality by using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system (3). We used our judgment to identify high-quality studies that described gut hormone levels after bariatric surgery.

Types of Bariatric Procedures and Effect on Weight Loss and Diabetes

Since its inception in the 1950s, bariatric surgery has become increasingly refined. More recently, it has been touted as a "cure" for diabetes (4). Several procedures are

Key Summary Points

The rapid improvement in glycemic control after bariatric surgery results from caloric restriction and alterations in the gut hormones that control insulin secretion.

The enteroinsular axis includes the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), ghrelin, and peptide YY (PYY) and their subsequent effect on insulin secretion and sensitivity.

Restrictive, malabsorptive, and combined bariatric surgery procedures have different effects on the enteroinsular axis.

Intestinal bypass procedures increase GLP-1 and PYY levels. In contrast, restrictive procedures do not increase incretin or PYY levels.

Familiarity with these changes can help physicians consider the various surgical approaches and develop postoperative treatment regimens for patients.

now available (**Figure 1**). Bariatric procedures were initially classified as restrictive, malabsorptive, or combined, reflecting the purported mechanism of weight loss (1). Restrictive procedures, such as laparoscopic adjustable gastric banding (LAGB) and vertical banded gastroplasty (VBG), greatly reduce the volume of the stomach to decrease food intake and induce early satiety. Malabsorptive procedures, such as biliopancreatic diversion (BPD), shorten the small intestine to decrease nutrient absorption. Combined procedures, such as the Roux-en-Y gastric bypass (RYGB), incorporate both restrictive and malabsorptive elements. Roux-en-Y gastric bypass surgery is the current gold standard treatment for severe obesity. Both BPD and RYGB alter the secretion of orexigenic and anorexigenic gut peptides, which interact with appetitive centers in the arcuate nucleus of the hypothalamus to decrease appetite (5). Because both BPD and RYGB bypass similar segments of the small bowel, we use the term *intestinal bypass procedure* to refer to either.

Weight Loss

Two recent meta-analyses (6, 7) reported weight loss; operative mortality; and obesity-related comorbid conditions, including diabetes, after bariatric surgery. Buchwald and colleagues (7) reported mean excess weight loss (see Glossary) (7–10) of 61% across all procedures in 22 094 patients; weight loss rates associated with each procedure varied (**Table 1**). On average, bariatric surgery reduces body mass index by 10 to 15 kg/m^2 and weight by 30 to 50 kg (11).

Several relatively poor-quality randomized, controlled trials that compared different bariatric surgery procedures (12) showed that weight loss was greater with gastric bypass than with VBG or LAGB. The SOS (Swedish Obese Subjects) study (13), a landmark observational study that followed more than 4000 obese participants, matched those who selected medical management with those undergoing various bariatric procedures, including RYGB, VBG, or LAGB. At 10 years, RYGB was associated with a 25% reduction in total body weight, whereas VBG and LAGB were associated with 16% and 14% weight loss, respectively.

Diabetes Resolution and Improvement

Observational evidence suggests that bariatric surgery is associated with a 60% to 80% rate of diabetes resolution (14). In 1 meta-analysis (7), approximately 15% of the patients were diabetic. In studies reporting complete resolution of diabetes (defined as normoglycemia with no diabetes medications), 1417 of 1846 patients (76.8%) met the criteria for resolution. Among studies reporting resolution or improvement of diabetes, 414 of 485 patients (mean, 86.0%) experienced either outcome. **Table 1** shows rates of diabetes resolution for individual bariatric procedures.

Conclusions about bariatric surgery and diabetes resolution come with an important qualifier: The studies had serious methodological weaknesses. Few are randomized, controlled trials; most surgical outcome studies are uncontrolled case series with considerable missing data (6, 10). In 1 meta-analysis (6), one quarter of the studies did not report enrolling consecutive patients and fewer than 50% reported how many enrolled patients provided follow-up data. **Table 2** (4, 14–22) includes selected studies that met the minimum GRADE criteria quality standards and reported follow-up rates of at least 80% (3). Paired comparisons of surgical procedures typically favored RYGB or BPD over the restrictive procedures (23).

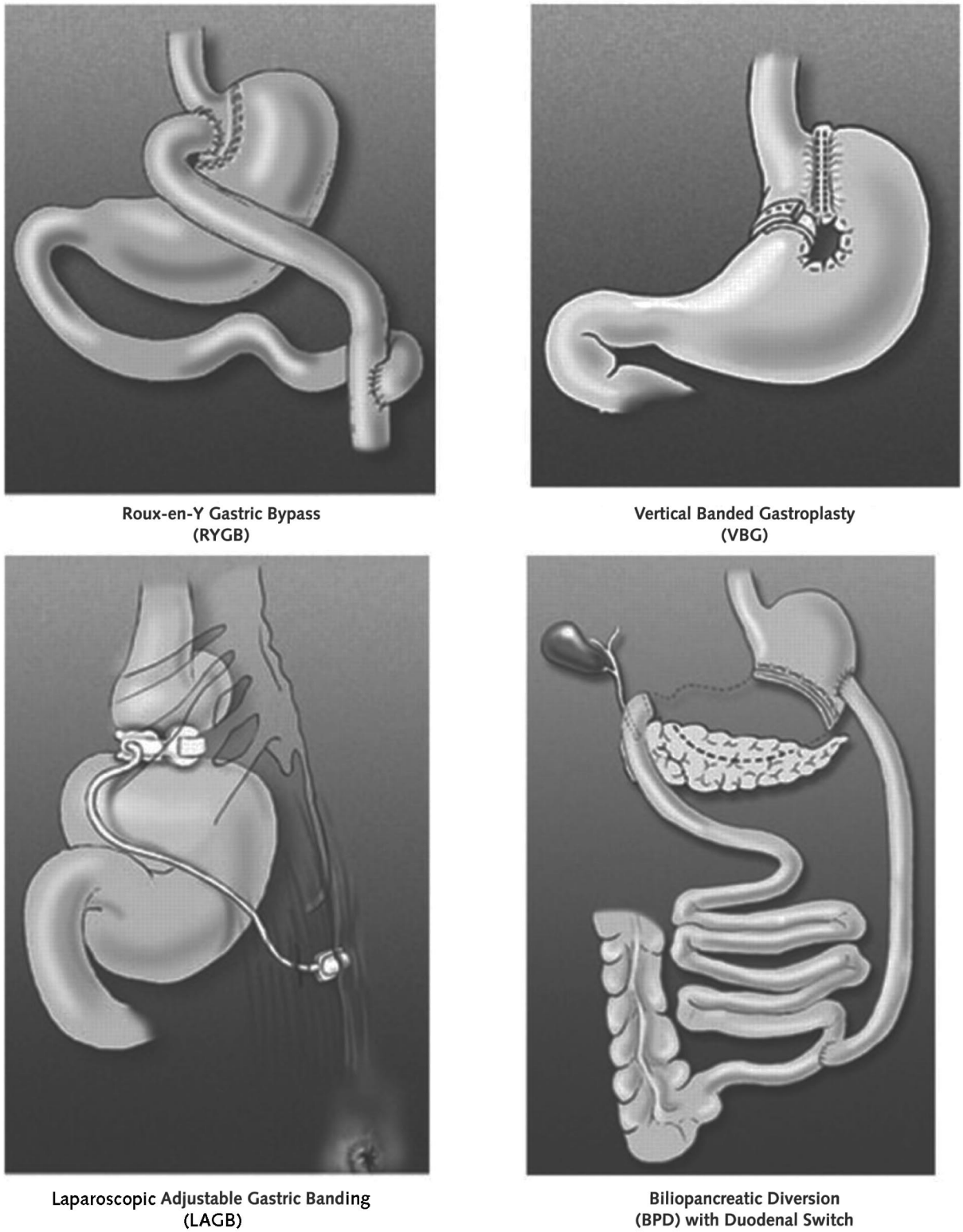
Predictors of Diabetes Resolution

Identifying preoperative predictors of diabetes resolution is critical for determining which diabetic patients will obtain the greatest benefit from surgery. In earlier studies of RYGB, longer duration of diabetes (>10 years), poor preoperative glycemic control, and preoperative insulin use reduced the probability of diabetes resolution (18, 19); however, these studies did not adjust for the effects of known confounding factors. More recently, Torquati and colleagues (24) adjusted for body mass index, sex, and preoperative hemoglobin A_{1c} level and found that preoperative treatment with oral antidiabetic agents (as opposed to insulin) and smaller preoperative waist circumference pre-

Glossary

Excess weight loss: The surgical literature typically expresses weight loss as percentage of excess weight lost, defining excess weight as (total preoperative weight minus ideal weight) and percentage of excess weight lost as (weight lost/excess weight) × 100 (7). Some studies reported percentage change in total weight and percentage change in body mass index (7–10).

Figure 1. **Surgical procedures.**



dicted diabetes resolution (18). Shorter duration of diabetes was a weaker, statistically nonsignificant predictor, which supports earlier studies of RYGB (18).

The same factors predict diabetes resolution after gastric banding. Dixon and colleagues (25) reported that diabetes for less than 3 years predicted diabetes resolution, after they controlled for age and excess weight loss. Less deterioration in β-cell function at the time of surgery may maximize the effect of the surgery-altered secretion of gut peptides that enhance β-cell insulin secretion.

The Enteroinsular Axis

Bayliss and Starling first described the connection between the gut and the pancreas in 1902, when they demonstrated that intestinal mucosa extracts contained a factor, which they called *secretin*, that acted through the bloodstream to stimulate exocrine secretion by the pancreas (26). Sixty-five years later, Perley and Kipnis (27) demonstrated that ingested nutrients stimulated greater insulin release than intravenously administered glucose. In 1979, Creutzfeldt (28) defined "incretins" as gastrointestinal hormones that stimulate insulin release after enteral nutrition. This connection between the gut and pancreatic islet cells is called the *enteroinsular axis*, a term first used by Unger and Eisentraut (29).

The Incretins: GLP-1 and GIP

By potentiating glucose-dependent insulin secretion, GLP-1 and GIP account for 50% to 60% of nutrient-stimulated insulin release (2). In animal models of diabetes, GLP-1 also increases β-cell mass through regulation of proliferation, neogenesis, and apoptosis (30).

Glucagon-like peptide-1 is a potent insulin secretatogue that is secreted by the L cells of the distal ileum in response to ingested nutrients and is inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV) (31). By activating adenylate cyclase, GLP-1 acts on pancreatic islets to augment glucose-dependent insulin secretion. The subsequent increase in insulin levels within islets inhibits glucagon secretion, possibly through direct activation of GLP-1 receptors on α cells (31). Glucagon-like peptide-1 also slows gastric emptying, which delays digestion and blunts postprandial glycemia (32), and acts on the central nervous system to induce satiety and decrease food intake (33, 34). Finally, GLP-1 increases glycogenesis in hepatocytes and skeletal muscle and increases lipogenesis in adipocytes, which may improve insulin sensitivity (35).

Glucose-dependent insulinotropic peptide is secreted by the K cells of the proximal gut in response to carbohydrate and lipid-rich meals (36). It acts on pancreatic β cells to increase insulin secretion through the same mechanisms as GLP-1, although it is less potent (30), and also stimulates lipoprotein lipase activity (36). Glucose-dependent insulinotropic peptide does not affect gastric emptying or satiety (36).

Table 1. **Results of Different Types of Bariatric Surgery***

Result	Malabsorptive (BPD)	Restrictive (LAGB, VBG)	Combined (RYGB)
Excess weight loss, %	72	48–68	62
Resolution of comorbid conditions, %			
Type 2 diabetes	98	48–72	84
Hypertension	81	28–73	75
Dyslipidemia improved	100	71–81	94
Operative mortality rate, %	1.10	0.1	0.5

BPD = biliopancreatic diversion; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass; VBG = vertical banded gastroplasty.
* Mean values from a meta-analysis of 22 094 patients. Data from reference 7.

Nonincretin Gut Peptides

Peptide YY (PYY)

Like GLP-1, PYY is secreted by the L cells of the distal intestine. Peptide YY is present in 2 molecular forms: PYY_{1-36} and PYY_{3-36}, a cleavage product (37). Peptide YY increases satiety and delays gastric emptying through neuropeptide Y-receptor subtypes in the central and peripheral nervous system (37). Intravenous PYY_{3-36} increases satiety and decreases food intake in humans (37).

Ghrelin

Ghrelin is secreted principally by the gastric fundus and proximal small intestine and acts on the hypothalamus to regulate appetite (38). Both ghrelin and its receptor are expressed in pancreatic islet cells, where ghrelin inhibits insulin secretion by a paracrine mechanism (39). Systemic ghrelin levels increase before a meal and decrease afterward. Ghrelin stimulates appetite and food intake and suppresses energy expenditure and fat catabolism (38–40), perhaps by conveying signals to the brain about the status of energy stores. Serum ghrelin levels are inversely proportional to body weight. Weight loss by any means increases ghrelin levels, which suggests that ghrelin affects the long-term regulation of body weight (40).

Defects in the Enteroinsular Axis in Obesity and Diabetes

Diabetes blunts the incretin effect through incompletely understood mechanisms (41). Two defects are decreased insulin secretion in response to GIP (10% to 20% of the normal response [41]) and decreased secretion of GLP-1. Potential explanations for the decreased GIP insulinotropic activity include defective expression of GIP receptors (42) and downregulation of GIP receptors on β cells (43). Studies of GIP levels in diabetic patients have been inconsistent, with some reporting normal GIP levels and others reporting elevated fasting and postprandial levels (44, 45). The mechanism of decreased secretion of GLP-1 is not known (42). Levels of GLP-1 decrease in obesity and decrease further in diabetes (2), but the target tissues respond normally when GLP-1 levels are restored by giving it intravenously (46).

Table 2. **Efficacy for Resolution of Diabetes**

Study, Year (Reference)	Type	GRADE Quality Rating*	Procedure	Patients With Type 2 Diabetes Mellitus, *n*	Patients Who Recovered, *n*	Follow-up, *y*	Resolution, %
Malabsorptive							
Scopinaro et al, 2005 (15)	Case series	Very low†	BPD	312	303	1	97
						10	97
Marceau et al, 1998 (16)	Case series	Very low‡	BPD	377	347	15	92
Combined							
Pories et al, 1995 (4)	Case series	Very low§	RYGB	146 with type 2 diabetes mellitus	121	14	83
				152 with impaired glucose tolerance	150		99
MacDonald et al, 1997 (17)	Retrospective cohort	Low‖	RYGB	154	NA	9	NA (percentage of patients requiring diabetic medications decreased from 31.8 to 8.6)
Schauer et al, 2003 (18)	Case series	Very low¶	RYGB	177	137	2	78
Sugerman et al, 2003 (19)	Case series	Very low**	RYGB	127	106	2	83
Restrictive							
Pontiroli et al, 2002 (20)	Case–control	Moderate††	LAGB	17	17	4	45
Sjöström et al, 2004 (21)	Prospective observational	High‡‡	VBG	82	59	2	72
			LAGB	30	NA	10	36
Ponce et al, 2004 (22)	Case series	Very low§§	LAGB	53	35	1	66
Dixon et al, 2008 (14)	Randomized, controlled trial	High‖ ‖	LAGB	30	22	2	73

BPD = biliopancreatic diversion; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; LAGB = laparoscopic adjustable gastric banding; NA = not available; RYGB = Roux-en-Y gastric bypass; VBG = vertical banded gastroplasty.
* We used the GRADE criteria outlined in the Cochrane Handbook (3) to qualitatively assess study quality: high = randomized trials or double-upgraded observational studies; moderate = downgraded randomized trials or upgraded observational studies; low = double-downgraded randomized trials or observational studies; very low = triple-downgraded randomized trials, downgraded observational studies, or case series/case reports.
† Long-term follow-up of 91% at 5 years and 80% at 10 years; large number of patients.
‡ Follow-up of 80%; large number of patients followed for many years.
§ Large case series over 14 years. Follow-up rate at 1 year reported at 100%. Reported rates of resolution for patients with "adequate follow-up," but the proportion of patients who were followed at the various points is not specified.
‖ Nonoperative control–matched control group compared with group that underwent gastric bypass surgery; information on the proportion of patients who followed up was not reported.
¶ Reported follow-up rate of 80%; large number of patients.
** Follow-up rate of 50% reported at 5 years and 37% at 10 to 12 years.
†† Matched control group of obese diabetic patients who declined surgery; follow-up rate of 100%.
‡‡ Largest long-term, ongoing prospective evaluation of surgery, which included a nonsurgical control group of 2037 followed for more than 10 years.
§§ Follow-up rate of 98% at 1 year and 62% at 2 years. Only 3 of 53 diabetic patients completed follow-up at 36 months.
‖ ‖ Matched control group had medical therapy with intensive lifestyle modification program.

Basal and postprandial levels of PYY and ghrelin are lower in obese people than in lean people (47, 48) and may be even lower in diabetic people (49).

Proposed Mechanisms for Improved Glycemic Control After Bariatric Surgery

Effects of Decreased Caloric Intake on Fasting Glycemia

Decreased caloric intake profoundly affects glucose metabolism (50, 51), and all patients have minimal caloric intake immediately after bariatric surgery. If caloric restriction alone accounted for lower blood glucose, the rate of diabetes remission would be the same in all types of bariatric surgery. However, complete diabetes resolution occurs within days of intestinal bypass procedures (4) but takes months to occur after LAGB (14). In studies that compared VBG with RYGB in patients with similar postoperative caloric intake, glucose levels decreased further and faster after bypass (52).

Additional Antidiabetic Effects of Gastrointestinal Bypass Surgery

Gastrointestinal rearrangement seems to confer additional antidiabetic effects independent of weight loss and caloric restriction. Rubino and colleagues (53) performed duodenal–jejunal bypass (DJB) in Goto-Kakizaki rats, a nonobese animal model for type 2 diabetes. This procedure leaves the stomach intact but bypasses the proximal intestine by the same amount as RYGB. Rats that underwent DJB had less fasting and postprandial hyperglycemia than

sham-operated control rats within 1 week of surgery. Glycemic control did not improve in a second control group of Goto-Kakizaki rats that had undergone significant weight loss by caloric restriction.

Two hypotheses compete to explain improvement in glucose metabolism in patients undergoing gastric bypass procedures. The hindgut hypothesis, also called the "lower intestinal hypothesis" by Cummings and colleagues (54) because it more accurately reflects gut physiology, suggests that rapid delivery of nutrients to the distal bowel improves glucose metabolism by enhancing secretion of GLP-1 and other anorexigenic gut peptides (55). This theory is supported by experiments in which transit time through the gut in rodents is increased by anastomosing a segment of the ileum to the proximal bowel while leaving the stomach intact (54). This intestinal rearrangement speeds the delivery of nutrients to the distal intestine, which causes exaggerated GLP-1 and PYY levels and improves glucose tolerance and insulin secretion without affecting body weight and food intake.

Rubino (56) proposed an alternative hypothesis: the foregut exclusion theory (or "the upper intestinal hypothesis" [54]), in which causing food to bypass the duodenum and proximal jejunum prevents the secretion of an as-yet unidentified "putative signal" that promotes insulin resistance and type 2 diabetes. In an effort to distinguish between foregut exclusion and lower intestinal mechanisms, Rubino and colleagues (57) performed either stomach-sparing DJB or gastrojejunostomy in Goto-Kakizaki rats. (Gastrojejunostomy bypasses the same amount of intestine as DJB but leaves nutrient flow in the proximal intestine intact.) Rats that underwent DJB had improved glucose tolerance, whereas rats that underwent gastrojejunostomy did not improve. When the procedures were surgically reversed, diabetes returned when DJB was converted to gastrojejunostomy and resolved when gastrojejunostomy was converted to DJB. These findings suggest that bypass of the proximal gut prevents the secretion of an "anti-incretin" factor (or "decretin") that may be implicated in the pathogenesis of diabetes. Cohen and colleagues (58) recently described 2 overweight diabetic patients who underwent a DJB-like procedure in which the stomach volume remained intact but a short segment of the proximal gut was bypassed. Although their weight did not change, diabetes resolved in both patients.

These experiments show that both hypotheses have strong support and suggest that multiple mechanisms contribute to the remission of diabetes after intestinal bypass. The rapid delivery of nutrients to the distal intestine enhances GLP-1 and PYY secretion, whereas duodenal exclusion may exert other antidiabetic effects.

The Effect of Bariatric Surgery on Gut Peptide Secretion

Normal Patterns of Gut Peptide Secretion

The gut mucosa secretes the incretins GLP-1 and GIP, as well as PYY, in response to direct contact with unabsorbed nutrients (59). In addition, vagally mediated parasympathetic neural mechanisms modulate gut peptide secretion. Ghrelin levels normally increase before and decrease after a meal, perhaps because of a nutrient-mediated, direct inhibitory effect and possible neurohormonal regulation (38).

Glucagon-like Peptide-1

Many studies show that GLP-1 levels increase after gastric bypass and BPD (57, 60, 61). To rule out weight loss as the cause of increased incretin levels, Laferrère and colleagues (61) compared incretin levels in diabetic patients 1 month after gastric bypass with those in matched control participants who had equivalent weight loss by dieting. Incretin levels and the response to incretins increased after gastric bypass but not after dieting, which suggests that gastric bypass rather than weight reduction mediated the improved incretin effect. Glucagon-like peptide-1 levels remain elevated 1 year after gastric bypass (62) and up to 20 years after jejeunoileal bypass (63). **Table 3** (64) shows the responses of gut peptides to different bariatric surgery procedures.

Restrictive procedures do not alter GLP-1 levels (65–67), in part because gastric restrictive procedures do not alter gastric emptying (11, 68). Korner and colleagues (69) showed that postprandial GLP-1 levels increased 3-fold after gastric bypass but not after gastric banding.

Table 3. **Overview of Gut Peptide Response to Different Bariatric Surgical Procedures***

Hormone	Cell Type (Location)	Effect on Insulin Secretion	Changes Induced, by Type of Surgery		
			BPD	RYGB	LAGB
Ghrelin	X/A cells (stomach)	Decrease	Increase	Increase/decrease	Increase/no change
Glucose-dependent insulinotropic peptide	K cells (duodenum)	Increase	Decrease	Decrease	No change
Glucagon-like peptide-1	L cells (distal ileum)	Increase	Increase	Increase	No change
Peptide YY	L cells (distal ileum)	Decrease	Increase	Increase	No change

BPD = biliopancreatic diversion; LAGB = laparoscopic adjustable gastric banding; RYGB = Roux-en-Y gastric bypass.
* Adapted from reference 64, with permission of Elsevier.

Peptide YY

The L cells of the distal ileum secrete both PYY and GLP-1, and PYY levels also increase after procedures that expedite nutrient delivery to the distal ileum (67, 69–73). le Roux and colleagues (70) reported that postprandial PYY and GLP-1 levels increased as early as 2 days after RYGB. Morínigo and colleagues (71) reported similar findings 6 weeks after RYGB. The large, early postprandial increase in PYY levels after gastric bypass may account for the immediate decrease in appetite after surgery (72, 73).

Few investigators have measured PYY levels after restrictive procedures. Korner and colleagues (74) reported blunted total and postprandial PYY_{3-36} levels in patients who had gastric banding compared with those who underwent gastric bypass and had similar weight loss. We found no studies that reported PYY levels within the first few weeks after surgery.

Glucose-Dependent Insulinotropic Peptide

The response of GIP to bariatric surgery has not been studied as extensively as GLP-1 or PYY, and studies have yielded inconsistent results. Laferrère and colleagues (75) reported a 1.6-fold increase in postprandial GIP levels 1 month after RYGB, although increased levels were not sustained 6 to 12 months later (62). In contrast, Clements and colleagues (60) reported blunted GIP levels as early as 2 weeks after RYGB. Blunted GIP levels have been consistently reported several months after RYGB, an anticipated consequence of bypassing the K cells in the proximal gut (62, 69, 76). Patriti and colleagues (77) offer an alternative explanation, suggesting that upregulation of GIP receptors on β cells after gastric bypass may account for the lower levels after surgery.

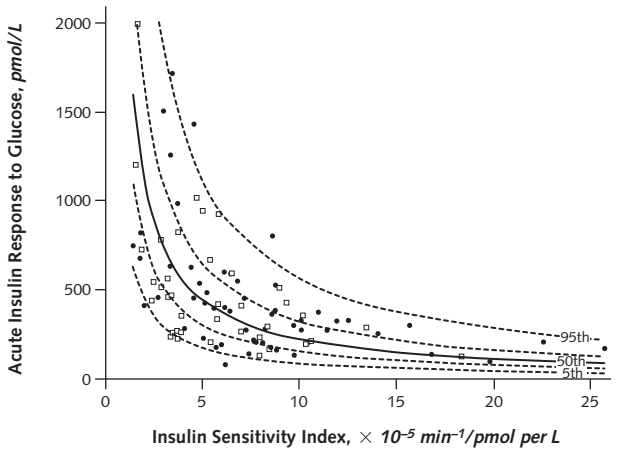
Few studies have evaluated the effect of restrictive procedures on GIP levels. Shak and colleagues (65) reported that GIP levels were unchanged 6 and 12 months after LAGB, and Korner and colleagues (69) reported that GIP levels were unchanged 23 months after LAGB.

Ghrelin

The effects of gastric bypass on ghrelin levels are inconsistent (78–82). Although several early studies reported decreased ghrelin levels after gastric bypass (78, 79), others have reported no change (80) or increased levels (81). Cummings and Shannon (40) suggest that subtle variations in surgical technique may account for these disparate effects. If the surgeon leaves a small amount of intact ghrelin-producing tissue, ghrelin levels can be normal.

The vagus nerve also affects ghrelin levels. Ghrelin levels are higher after procedures that leave the fundus and the vagal nerve intact, such as adjustable gastric banding or BPD, than after gastric bypass (78, 79, 82, 83).

Figure 2. **Hyperbolic relationship between insulin sensitivity and insulin secretion quantified as the acute insulin response to glucose in a healthy population.**



The relationship is best described by a hyperbolic function, so that any change in insulin sensitivity is balanced by a reciprocal and proportionate change in insulin secretion. Glucose tolerance is determined by the interaction of insulin secretion and sensitivity, so that patients with normal glucose tolerance are at about the 50th percentile and those below it exhibit increasing impairment to diabetic glucose tolerance. Reproduced from reference 84, with permission of the American Diabetes Association.

Short-Term Effect of Surgery on Insulin Secretion and Sensitivity

Bariatric surgery affects both insulin secretion and sensitivity, which in turn affect glucose tolerance, according to the hyperbolic relationship shown in **Figure 2** (84). Caloric restriction alone substantially improves insulin sensitivity, and weight loss improves it still further (51). The altered secretion of incretins may account for additional improvements in insulin secretion and sensitivity. Laferrère and colleagues (75) reported that RYGB simultaneously increased incretin levels and the incretin effect on insulin secretion (by comparing the insulin response to oral and isoglycemic intravenous glucose loads) in patients with type 2 diabetes. The incretin effect was similar to that of matched control participants without diabetes, which suggests that RYGB normalized the incretin response and insulin secretion.

Summary

Levels of GLP-1, PYY, and ghrelin decrease in obese patients and decrease even further in diabetic patients by mechanisms that are unknown. In contrast, GIP levels may be normal to increased in diabetic patients.

Bariatric procedures that expedite nutrient delivery to the distal ileum, such as BPD and RYGB, increase GLP-1 and PYY levels. In contrast, restrictive procedures do not increase levels of incretins or PYY. Ghrelin levels after surgery are determined by the remaining amount of residual ghrelin-producing tissue and by whether vagal innervation

is intact (40). Augmented levels of GLP-1 probably account for the antidiabetic effect of procedures that bypass the small bowel (33, 40). In addition, altered secretion of anorexigenic peptides, such as GLP-1 and PYY, may mediate the reduction in appetite and sustained weight loss that occurs more often after intestinal bypass procedures.

A Rational Approach to Diabetes Management After Bariatric Surgery

Diabetes Management in the Immediate Postoperative Period

Caloric intake is minimal after any bariatric procedure, and patients are at high risk for hypoglycemia if their preoperative regimens are not appropriately adjusted. Treatment with oral antidiabetic medications is typically stopped immediately before surgery. Insulin requirements often dramatically and rapidly decrease after surgery (85), and patients may require only long-acting basal insulin in the immediate postoperative period, with rapid-acting insulin for correction of hyperglycemia as necessary. Once patients resume eating, rapid-acting insulin is preferable to regular insulin for prandial coverage because it can be administered immediately after meals and its short action reduces the risk for dose-stacking and subsequent hypoglycemia (85). Sulfonylureas and meglitinides should be avoided until patients begin eating regularly (85). After surgery, patients often cannot tolerate medications that cause gastrointestinal side effects; such agents include metformin, α-glucosidase inhibitors, or GLP-1 analogues or DPP-IV inhibitors. Thiazolidinediones are safe in the absence of any contraindications.

Emerging Concerns With GLP-1 Analogues and DPP-IV Inhibitors

Gastric bypass nearly normalizes incretin levels. Patients who take drugs that augment GLP-1 and GIP levels, whether by inhibiting their degradation by DPP-IV (DPP-IV inhibitors) or stimulating β-cell GLP receptors (GLP-1 agonists), may experience hypoglycemia from endogenous hyperinsulinemia. Hyperinsulinemic hypoglycemia mediated by GLP-1 has occurred after gastric bypass (86, 87), and the safety of GLP-1 analogues or DPP-IV inhibitors in patients who have gastric bypass needs careful study.

Conclusion

Short-term improvements in glycemic control in diabetic patients undergoing bariatric surgery are probably mediated by several mechanisms, including caloric restriction and changes in the secretion of the gut hormones that constitute the enteroinsular axis. Restrictive procedures and intestinal bypass procedures improve glycemia by different mechanisms. Caloric restriction and increased satiety account for the antidiabetic effects of restrictive procedures, whereas intestinal bypass offers additional mechanisms: Bypass of the upper gut excludes the duodenum and proximal jejunum, which reduces the secretion of ghrelin and GIP, and bypass of the distal small intestine expedites delivery of nutrients to the distal ileum, which enhances secretion of GLP-1 and PYY.

Collectively, caloric restriction and alterations in the enteroinsular axis probably affect both insulin secretion and sensitivity. Physicians must anticipate the rapid improvements in insulin action after bariatric surgery and adjust diabetic regimens accordingly to avoid hypoglycemia. In addition to identifying the antidiabetic mechanisms of bariatric surgery, future research should focus on making postoperative medical management safer, particularly if the patient takes GLP-1 analogues or DPP-IV inhibitors.

From the Hospital of the University of Pennsylvania and Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania.

Note: Dr. Iqbal is currently an adjunct faculty member at the University of Pennsylvania and is employed at Bristol-Myers Squibb, Lawrenceville, New Jersey.

Acknowledgment: The authors thank Thomas A. Wadden, PhD, for his critical review of the manuscript and James P. Guevara, MD, MPH, for his expertise in qualitative assessment.

Potential Financial Conflicts of Interest: *Employment:* N. Iqbal (Bristol-Myers Squibb).

Requests for Single Reprints: Marion L. Vetter, MD, RD, Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Hospital of the University of Pennsylvania, One Maloney Building, 3400 Spruce Street, Philadelphia, PA 19104; e-mail, marion.vetter@uphs.upenn.edu.

Current author addresses are available at www.annals.org.

References

1. **Rubino F.** Bariatric surgery: effects on glucose homeostasis. Curr Opin Clin Nutr Metab Care. 2006;9:497-507. [PMID: 16778583]
2. **Fetner R, McGinty J, Russell C, Pi-Sunyer FX, Laferrère B.** Incretins, diabetes, and bariatric surgery: a review. Surg Obes Relat Dis. 2005;1:589-97; discussion 597-8. [PMID: 16925299]
3. **Higgins JP, Green S, eds.** Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.0 [updated February 2008]. The Cochrane Collaboration; 2008. Accessed at www.cochrane-handbook.org on 2 September 2008.
4. **Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al.** Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222:339-50; discussion 350-2. [PMID: 7677463]
5. **Murphy KG, Bloom SR.** Gut hormones and the regulation of energy homeostasis. Nature. 2006;444:854-9. [PMID: 17167473]
6. **Maggard MA, Shugarman LR, Suttorp M, Maglione M, Sugerman HJ, Sugarman HJ, et al.** Meta-analysis: surgical treatment of obesity. Ann Intern Med. 2005;142:547-59. [PMID: 15809466]
7. **Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al.** Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;292:1724-37. [PMID: 15479938]
8. **Schneider BE, Mun EC.** Surgical management of morbid obesity. Diabetes Care. 2005;28:475-80. [PMID: 15677820]
9. **Ferchak CV, Meneghini LF.** Obesity, bariatric surgery and type 2 diabetes—a

systematic review. Diabetes Metab Res Rev. 2004;20:438-45. [PMID: 15386803]
10. **Shah M, Simha V, Garg A.** Review: long-term impact of bariatric surgery on body weight, comorbidities, and nutritional status. J Clin Endocrinol Metab. 2006;91:4223-31. [PMID: 16954156]
11. **Bult MJ, van Dalen T, Muller AF.** Surgical treatment of obesity. Eur J Endocrinol. 2008;158:135-45. [PMID: 18230819]
12. **Colquitt J, Clegg A, Loveman E, Royle P, Sidhu MK.** Surgery for morbid obesity. Cochrane Database Syst Rev. 2005:CD003641. [PMID: 16235331]
13. **Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, et al. Swedish Obese Subjects Study.** Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357:741-52. [PMID: 17715408]
14. **Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, et al.** Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. JAMA. 2008;299:316-23. [PMID: 18212316]
15. **Scopinaro N, Marinari GM, Camerini GB, Papadia FS, Adami GF.** Specific effects of biliopancreatic diversion on the major components of metabolic syndrome: a long-term follow-up study. Diabetes Care. 2005;28:2406-11. [PMID: 16186271]
16. **Marceau P, Hould FS, Simard S, Lebel S, Bourque RA, Potvin M, et al.** Biliopancreatic diversion with duodenal switch. World J Surg. 1998;22:947-54. [PMID: 9717420]
17. **MacDonald KG Jr, Long SD, Swanson MS, Brown BM, Morris P, Dohm GL, et al.** The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. J Gastrointest Surg. 1997;1:213-20; discussion 220. [PMID: 9834350]
18. **Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G, et al.** Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann Surg. 2003;238:467-84; discussion 84-5. [PMID: 14530719]
19. **Sugerman HJ, Wolfe LG, Sica DA, Clore JN.** Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. Ann Surg. 2003; 237:751-6; discussion 757-8. [PMID: 12796570]
20. **Pontiroli AE, Pizzocri P, Librenti MC, Vedani P, Marchi M, Cucchi E, et al.** Laparoscopic adjustable gastric banding for the treatment of morbid (grade 3) obesity and its metabolic complications: a three-year study. J Clin Endocrinol Metab. 2002;87:3555-61. [PMID: 12161474]
21. **Sjöström L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, et al. Swedish Obese Subjects Study Scientific Group.** Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med. 2004; 351:2683-93. [PMID: 15616203]
22. **Ponce J, Haynes B, Paynter S, Fromm R, Lindsey B, Shafer A, et al.** Effect of Lap-Band-induced weight loss on type 2 diabetes mellitus and hypertension. Obes Surg. 2004;14:1335-42. [PMID: 15603648]
23. **Levy P, Fried M, Santini F, Finer N.** The comparative effects of bariatric surgery on weight and type 2 diabetes. Obes Surg. 2007;17:1248-56. [PMID: 18074502]
24. **Torquati A, Lutfi R, Abumrad N, Richards WO.** Is Roux-en-Y gastric bypass surgery the most effective treatment for type 2 diabetes mellitus in morbidly obese patients? J Gastrointest Surg. 2005;9:1112-6; discussion 1117-8. [PMID: 16269382]
25. **Dixon JB, Dixon AF, O'Brien PE.** Improvements in insulin sensitivity and β-cell function (HOMA) with weight loss in the severely obese. Homeostatic model assessment. Diabet Med. 2003;20:127-34. [PMID: 12581264]
26. **Creutzfeldt W.** The [pre-] history of the incretin concept. Regul Pept. 2005; 128:87-91. [PMID: 15780427]
27. **Perley MJ, Kipnis DM.** Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic sujbjects. J Clin Invest. 1967;46:1954-62. [PMID: 6074000]
28. **Creutzfeldt W.** The incretin concept today. Diabetologia. 1979;16:75-85. [PMID: 32119]
29. **Unger RH, Eisentraut AM.** Entero-insular axis. Arch Intern Med. 1969;123: 261-6. [PMID: 4885674]
30. **Hansotia T, Drucker DJ.** GIP and GLP-1 as incretin hormones: lessons from single and double incretin receptor knockout mice. Regul Pept. 2005;128: 125-34. [PMID: 15780432]
31. **Holst JJ.** The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87: 1409-39. [PMID: 17928588]
32. **Flint A, Raben A, Ersbøll AK, Holst JJ, Astrup A.** The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. Int J Obes Relat Metab Disord. 2001;25:781-92. [PMID: 11439290]
33. **Gutzwiller JP, Göke B, Drewe J, Hildebrand P, Ketterer S, Handschin D, et al.** Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut. 1999;44:81-6. [PMID: 9862830]
34. **Toft-Nielsen MB, Madsbad S, Holst JJ.** Continuous subcutaneous infusion of glucagon-like peptide 1 lowers plasma glucose and reduces appetite in type 2 diabetic patients. Diabetes Care. 1999;22:1137-43. [PMID: 10388979]
35. **Luque MA, González N, Márquez L, Acitores A, Redondo A, Morales M, et al.** Glucagon-like peptide-1 (GLP-1) and glucose metabolism in human myocytes. J Endocrinol. 2002;173:465-73. [PMID: 12065236]
36. **Meier JJ, Nauck MA, Schmidt WE, Gallwitz B.** Gastric inhibitory polypeptide: the neglected incretin revisited. Regul Pept. 2002;107:1-13. [PMID: 12137960]
37. **Ballantyne GH.** Peptide $YY_{(1-36)}$ and peptide $YY_{(3-36)}$: Part I. Distribution, release and actions. Obes Surg. 2006;16:651-8. [PMID: 16687037]
38. **Cummings DE, Overduin J.** Gastrointestinal regulation of food intake. J Clin Invest. 2007;117:13-23. [PMID: 17200702]
39. **Kageyama H, Funahashi H, Hirayama M, Takenoya F, Kita T, Kato S, et al.** Morphological analysis of ghrelin and its receptor distribution in the rat pancreas. Regul Pept. 2005;126:67-71. [PMID: 15620416]
40. **Cummings DE, Shannon MH.** Ghrelin and gastric bypass: is there a hormonal contribution to surgical weight loss? J Clin Endocrinol Metab. 2003;88: 2999-3002. [PMID: 12843132]
41. **Vollmer K, Holst JJ, Baller B, Ellrichmann M, Nauck MA, Schmidt WE, et al.** Predictors of incretin concentrations in subjects with normal, impaired, and diabetic glucose tolerance. Diabetes. 2008;57:678-87. [PMID: 18057091]
42. **Holst JJ, Gromada J, Nauck MA.** The pathogenesis of NIDDM involves a defective expression of the GIP receptor. Diabetologia. 1997;40:984-6. [PMID: 9267997]
43. **Tseng CC, Boylan MO, Jarboe LA, Usdin TB, Wolfe MM.** Chronic desensitization of the glucose-dependent insulinotropic polypeptide receptor in diabetic rats. Am J Physiol. 1996;270:E661-6. [PMID: 8928774]
44. **Crockett SE, Mazzaferri EL, Cataland S.** Gastric inhibitory polypeptide (GIP) in maturity-onset diabetes mellitus. Diabetes. 1976;25:931-5. [PMID: 976601]
45. **Ross SA, Brown JC, Dupré J.** Hypersecretion of gastric inhibitory polypeptide following oral glucose in diabetes mellitus. Diabetes. 1977;26:525-9. [PMID: 324834]
46. **Nauck MA, Kleine N, Orskov C, Holst JJ, Willms B, Creutzfeldt W.** Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. Diabetologia. 1993;36:741-4. [PMID: 8405741]
47. **Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, et al.** Inhibition of food intake in obese subjects by peptide YY3-36. N Engl J Med. 2003;349:941-8. [PMID: 12954742]
48. **Tschöp M, Weyer C, Tataranni PA, Devanarayan V, Ravussin E, Heiman ML.** Circulating ghrelin levels are decreased in human obesity. Diabetes. 2001; 50:707-9. [PMID: 11289032]
49. **Pöykkö SM, Kellokoski E, Hörkkö S, Kauma H, Kesäniemi YA, Ukkola O.** Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. Diabetes. 2003;52:2546-53. [PMID: 14514639]
50. **Grey N, Kipnis DM.** Effect of diet composition on the hyperinsulinemia of obesity. N Engl J Med. 1971;285:827-31. [PMID: 5570845]
51. **Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M.** Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1993;77:1287-93. [PMID: 8077323]
52. **Gumbs AA, Modlin IM, Ballantyne GH.** Changes in insulin resistance following bariatric surgery: role of caloric restriction and weight loss. Obes Surg. 2005;15:462-73. [PMID: 15946423]
53. **Rubino F, Gagner M, Gentileschi P, Kini S, Fukuyama S, Feng J, et al.** The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg. 2004;240:236-42. [PMID: 15273546]
54. **Cummings DE, Overduin J, Foster-Schubert KE, Carlson MJ.** Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery [Editorial]. Surg Obes Relat Dis. 2007;3:109-15. [PMID: 17386391]
55. **Patriti A, Aisa MC, Annetti C, Sidoni A, Galli F, Ferri I, et al.** How the hindgut can cure type 2 diabetes. Ileal transposition improves glucose metabolism and beta-cell function in Goto-kakizaki rats through an enhanced Proglucagon

gene expression and L-cell number. Surgery. 2007;142:74-85. [PMID: 17630003]
56. **Rubino F.** Is type 2 diabetes an operable intestinal disease? A provocative yet reasonable hypothesis. Diabetes Care. 2008;31 Suppl 2:S290-6. [PMID: 18227499]
57. **Rubino F, Forgione A, Cummings DE, Vix M, Gnuli D, Mingrone G, et al.** The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244:741-9. [PMID: 17060767]
58. **Cohen RV, Schiavon CA, Pinheiro JS, Correa JL, Rubino F.** Duodenal-jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22-34 kg/m2: a report of 2 cases. Surg Obes Relat Dis. 2007;3:195-7. [PMID: 17386401]
59. **Deacon CF.** What do we know about the secretion and degradation of incretin hormones? Regul Pept. 2005;128:117-24. [PMID: 15780431]
60. **Clements RH, Gonzalez QH, Long CI, Wittert G, Laws HL.** Hormonal changes after Roux-en Y gastric bypass for morbid obesity and the control of type-II diabetes mellitus. Am Surg. 2004;70:1-4; discussion 4-5. [PMID: 14964537]
61. **Laferrère B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, et al.** Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab. 2008;93:2479-85. [PMID: 18430778]
62. **Laferrère B, Tran H, Egger JR, Yap K, Bawa B, Teixeira J, et al.** The increase in GLP-1 levels and incretin effect after Roux-en-Y gastric bypass surgery (RYGBP) persists up to 1 year in patients with type 2 diabetes mellitus (T2DM) [Abstract]. Obesity 2007;15:7
63. **Näslund E, Grybäck P, Backman L, Jacobsson H, Holst JJ, Theodorsson E, et al.** Distal small bowel hormones: correlation with fasting antroduodenal motility and gastric emptying. Dig Dis Sci. 1998;43:945-52. [PMID: 9590405]
64. **Folli F, Pontiroli AE, Schwesinger WH.** Metabolic aspects of bariatric surgery. Med Clin North Am. 2007;91:393-414, x. [PMID: 17509385]
65. **Shak JR, Roper J, Perez-Perez GI, Tseng CH, Francois F, Gamagaris Z, et al.** The effect of laparoscopic gastric banding surgery on plasma levels of appetite-control, insulinotropic, and digestive hormones. Obes Surg. 2008;18: 1089-96. [PMID: 18408980]
66. **le Roux CW, Aylwin SJ, Batterham RL, Borg CM, Coyle F, Prasad V, et al.** Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg. 2006;243:108-14. [PMID: 16371744]
67. **Rodieux F, Giusti V, D'Alessio DA, Suter M, Tappy L.** Effects of gastric bypass and gastric banding on glucose kinetics and gut hormone release. Obesity (Silver Spring). 2008;16:298-305. [PMID: 18239636]
68. **Horowitz M, Collins PJ, Chatterton BE, Harding PE, Watts JM, Shearman DJ.** Gastric emptying after gastroplasty for morbid obesity. Br J Surg. 1984; 71:435-7. [PMID: 6722479]
69. **Korner J, Bessler M, Inabnet W, Taveras C, Holst JJ.** Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis. 2007;3:597-601. [PMID: 17936091]
70. **le Roux CW, Welbourn R, Werling M, Osborne A, Kokkinos A, Laurenius A, et al.** Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. Ann Surg. 2007;246:780-5. [PMID: 17968169]
71. **Morínigo R, Moizé V, Musri M, Lacy AM, Navarro S, Marín JL, et al.** Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab. 2006;91:1735-40. [PMID: 16478824]
72. **Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, et al.** Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. J Clin Endocrinol Metab. 2005;90:359-65. [PMID: 15483088]
73. **Morínigo R, Vidal J, Lacy AM, Delgado S, Casamitjana R, Gomis R.** Circulating peptide YY, weight loss, and glucose homeostasis after gastric bypass surgery in morbidly obese subjects. Ann Surg. 2008;247:270-5. [PMID: 18216532]
74. **Korner J, Inabnet W, Conwell IM, Taveras C, Daud A, Olivero-Rivera L, et al.** Differential effects of gastric bypass and banding on circulating gut hormone and leptin levels. Obesity (Silver Spring). 2006;14:1553-61. [PMID: 17030966]
75. **Laferrère B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, et al.** Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care. 2007;30: 1709-16. [PMID: 17416796]
76. **Whitson BA, Leslie DB, Kellogg TA, Maddaus MA, Buchwald H, Billington CJ, et al.** Entero-endocrine changes after gastric bypass in diabetic and non-diabetic patients: a preliminary study. J Surg Res. 2007;141:31-9. [PMID: 17574036]
77. **Patriti A, Facchiano E, Sanna A, Gullà N, Donini A.** The enteroinsular axis and the recovery from type 2 diabetes after bariatric surgery. Obes Surg. 2004; 14:840-8. [PMID: 15318993]
78. **Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, et al.** Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. N Engl J Med. 2002;346:1623-30. [PMID: 12023994]
79. **Geloneze B, Tambascia MA, Pilla VF, Geloneze SR, Repetto EM, Pareja JC.** Ghrelin: a gut-brain hormone: effect of gastric bypass surgery. Obes Surg. 2003;13:17-22. [PMID: 12630608]
80. **Faraj M, Havel PJ, Phélis S, Blank D, Sniderman AD, Cianflone K.** Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab. 2003;88:1594-602. [PMID: 12679444]
81. **Holdstock C, Engström BE, Ohrvall M, Lind L, Sundbom M, Karlsson FA.** Ghrelin and adipose tissue regulatory peptides: effect of gastric bypass surgery in obese humans. J Clin Endocrinol Metab. 2003;88:3177-83. [PMID: 12843162]
82. **Frühbeck G, Diez-Caballero A, Gil MJ, Montero I, Gómez-Ambrosi J, Salvador J, et al.** The decrease in plasma ghrelin concentrations following bariatric surgery depends on the functional integrity of the fundus. Obes Surg. 2004; 14:606-12. [PMID: 15186626]
83. **Nijhuis J, van Dielen FM, Buurman WA, Greve JW.** Ghrelin, leptin and insulin levels after restrictive surgery: a 2-year follow-up study. Obes Surg. 2004; 14:783-7. [PMID: 15318982]
84. **Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, et al.** Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes. 1993;42:1663-72. [PMID: 8405710]
85. **Dunn JP, Jagasia SM.** Case study: management of type 2 diabetes after bariatric surgery. Clin Diabetes 2007;25:112-4.
86. **Patti ME, McMahon G, Mun EC, Bitton A, Holst JJ, Goldsmith J, et al.** Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia. 2005;48:2236-40. [PMID: 16195867]
87. **Goldfine AB, Mun EC, Devine E, Bernier R, Baz-Hecht M, Jones DB, et al.** Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. J Clin Endocrinol Metab. 2007;92:4678-85. [PMID: 17895322]

Current Author Addresses: Drs. Vetter, Cardillo, Rickels, and Iqbal: Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Hospital of the University of Pennsylvania, One Maloney Building, 3400 Spruce Street, Philadelphia, PA 19104.