Impact of Gastric Bypass Surgery on Gut Hormones and Glucose Homeostasis in Type 2 Diabetes

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Gastric bypass surgery (GBP) for obesity, by constructing an isolated ~30-ml proximal gastric pouch connected to a 75-cm limb of proximal jejunum, bypassing >90% of the stomach, the pylorus, and the duodenum, cures type 2 diabetes in >80% of cases. We review alterations in gastrointestinal peptide release after GBP that affect glucose disposal. We focus on ghrelin and the incretins glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and peptide YY as the most likely candidates for increasing insulin sensitivity after these operations, even before substantial weight loss has occurred. Although we have limited our review to only four gastrointestinal peptides, others may be involved, as are adipocyte-derived molecules such as leptin and adiponectin, and substrate receptor interactions in target tissues including the brain.
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The increasing prevalence of obesity worldwide is accompanied by an explosion in the prevalence of type 2 diabetes (1,2); ~60% of all cases of diabetes are attributable to obesity. In light of this, it has been proposed that obesity has become to diabetes what tobacco is to lung cancer (2).

Surgeons have for some time been able to contribute to the understanding of mechanisms involved in diabetes by studying human tissue (3). Today, surgery is the most effective treatment for obesity and has been proven to improve quality of life, glycemic control, triglyceride levels, and blood pressure with long-term follow-up (4). The surgical procedures in use today can be divided into three different categories: purely restrictive, such as adjustable gastric banding (AGB) (Fig. 1); combined restrictive/malabsorptive, or diversionary procedures, such as gastric bypass (GBP) (Fig. 2); and mainly malabsorptive, exemplified by biliopancreatic diversion (BPD) (Fig. 3) with or without "duodenal switch." These procedures achieve different long-term results with regard to resolving type 2 diabetes, with malabsorptive procedures being most effective and purely restrictive being least effective (4). Many surgeons have observed that patients with type 2 diabetes exhibit improved glycemic control very early after anti-obesity surgery, even before any weight loss has occurred. This seemed to be more pronounced in patients undergoing diversionary rather than purely restrictive operations (5,6), leading to the speculation that the effect is due to alterations in the release of gastrointestinal (GI) peptides that influence glycemic control.

The aim of this article is to explore the phenomenon of improved glycemic control, focusing on GBP, the most commonly performed surgical procedure with the richest literature documenting postoperative resolution of type 2 diabetes. We describe the different anti-obesity procedures, followed by the changes in postoperative GI peptide release, concluding by discussing how these peptides may influence the changes in food intake and glycemic control seen after anti-obesity surgery.

EFFECT OF GASTRIC BYPASS ON GLUCOSE HOMEOSTASIS

That GBP has a long-term positive effect on both the resolution of type 2 diabetes and in preventing new cases with type 2 diabetes is clear (4,6). In a longitudinal study of obese subjects with impaired glucose tolerance followed for 5 years, anti-obesity surgery lowered the rate of progression to type 2 diabetes by >30-fold (7). Today, it is also clear that GBP has an early and very profound positive effect on glucose homeostasis. Several studies have examined the effect of GBP on glucose homeostasis 3–4 weeks after GBP; mean BMI was not significantly changed, but fasting plasma glucose and insulin were significantly reduced. Insulin resistance improved after 4 weeks and continued to improve over the 6 months of follow-up (8,9). Thus, it is now established that GBP significantly improves type 2 diabetes over the short and long term.

DIFFERENT ANTI-OBESITY OPERATIONS

Purely restrictive surgery. Purely restrictive bariatric operations cause weight loss by limiting the capacity of the stomach to accommodate food and constricting the flow of ingested nutrients. Today, two such procedures are performed: vertical banded gastroplasty (VBG) and AGB. VBG entails a partitioning staple line that extends upward from a circular stapled hole in the stomach (to exclude the easily dilatable fundus). A synthetic band is used to reinforce the stoma (Fig. 1*A*), which has a diameter of ~1 cm. The pouch commonly measures 30 ml. Although VBG effectively limits the amount of food that can be consumed at one sitting and causes 30–50% reduction of excess body weight within the first 1–2 years, long-term results from the U.S. are disappointing (10,11). European data are generally more favorable (12). It is possible that differences in eating behavior between patients in the U.S. and

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AGB, adjustable gastric banding; BPD, biliopancreatic diversion; GBP, gastric bypass; GLP-1, glucagon-like peptide 1; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; PYY, peptide YY; VBG, vertical banded gastroplasty.

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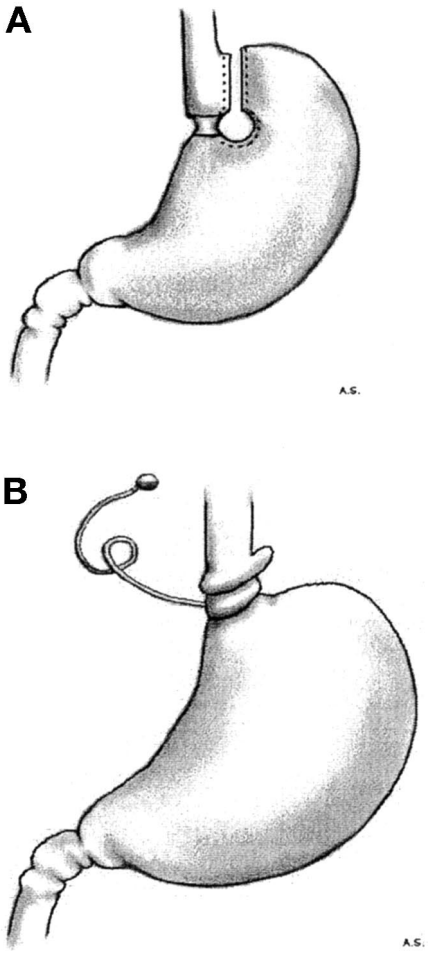

FIG. 1. *A*: Vertical banded gastroplasty. *B*: Adjustable gastric banding.

Europe, as well as the severity of obesity, explain why VBG works less well in U.S. patients. Our own unpublished data in a subsequent series of 254 patients with laparoscopic VBG show a reduction in BMI from 41.3 to 32.5 kg/m^2 after 7 years. Some patients accommodate to gastric restriction by eating frequent small meals and calorie-dense foods, such as milkshakes (13), developing what we termed the "soft calorie syndrome" (14). Snacking seems more prevalent in the U.S., while traditional family meals appear to be more common in Europe. VBG has fallen out of favor in the U.S. (13), whereas laparoscopic AGB is the dominant purely restrictive bariatric procedure, mainly because of its relative ease (Fig. 1*B*). ABG involves placement of an inflatable silicone band around the upper stomach to partition it into a small ~30-ml proximal pouch and a large distal remnant, connected through a narrow adjustable constriction (15). Weight loss after gastric banding is similar to that of VBG (4). Similar to VBG, some patients develop the "soft calorie syndrome" after AGB; however, this seems to be less prevalent in Europe and Australia than in the U.S. (16).

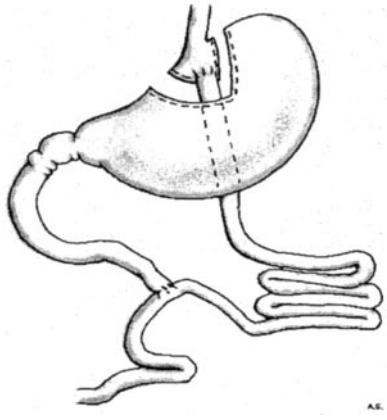

FIG. 2. Gastric bypass.

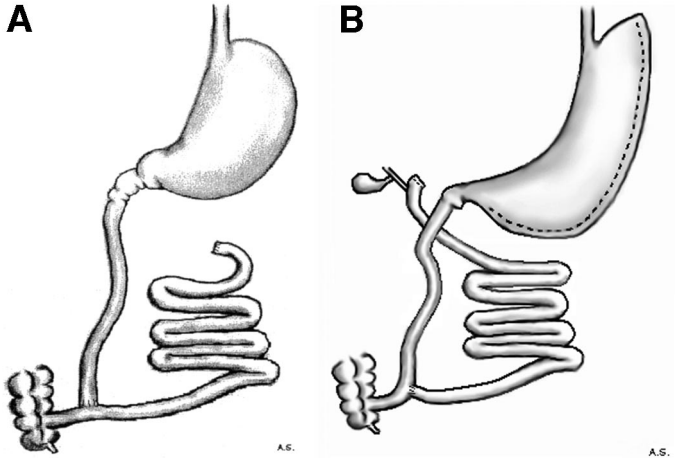

FIG. 3. *A*: Jejunoileal bypass end-to-side (40 cm to 10 cm). *B*: BPD with pylorus sparing duodenal switch with 100-cm common channel.

Gastric restriction combined with maldigestion. Gastric bypass divides the stomach into a small proximal pouch measuring ~30 ml and a separate large distal defunctionalized remnant. The upper pouch is joined to the jejunum through a narrow gastro-jejunal anastomosis (Fig. 2). The proximal divided jejunum is reattached to the jejunum 75–150 cm below the gastro-jejunal anastomosis, creating a Roux-en-Y limb. Thus, storage capacity of the stomach is reduced to ~5% of its normal volume, and ingested food bypasses ~95% of the stomach, the entire duodenum, and a small portion (15–20 cm) of the proximal jejunum. Initially, the operation relies on gastric restriction much like gastroplasty (6–18 months). Subsequently, when the pouch and stoma have stretched, other mechanisms take effect to maintain the loss, accounting for the superior weight loss maintenance compared with purely restrictive operations.

The appetitive mechanisms of the diversionary component of GBP are achieved through the absence of a pyloric "meter" or "brake," allowing rapid transit via the gastrojejunostomy, and maldigestion caused by the absence of acid and pepsin and the grinding-mixing forces of the stomach. Thus, undigested food rapidly shunted into the small bowel can cause nimiety via mechanoreceptors and possibly satiety via chemoreceptors (17) or neurohumoral mechanisms. These changes in GI peptides after GBP will be discussed in detail further on.

Malabsorptive procedures. Malabsorptive procedures reconstruct the small intestine to reduce the area of mucosa available for nutrient absorption. The first such procedure was the jejunoileal bypass (Fig. 3*A*), which is rarely performed today but is interesting owing to well-described altered GI peptide release.

A second malabsorptive procedure is BPD, with or without a pylorus-sparing duodenal switch (Fig. 3*B*). Malabsorption occurs as pancreatic and biliary secretions are

diverted to the distal small intestine ~50 cm from the ileocecal valve, thus diverting digestive juices from contact with food. Thus, absorption is limited to the distal ileum where the two are combined in a common channel. This arrangement promotes selective malabsorption of fat (18). Weight loss is effective with BPD, but compared to GBP, it causes more complications, such as protein malnutrition, diarrhea, and deficiencies of various vitamins (19). It is interesting to note that BPD has a much higher success rate in Italy than in the U.S., again suggesting that perhaps the diets consumed in the different countries may affect the success of different surgical procedures for obesity.

GI PEPTIDES

After food intake, plasma concentrations of several GI peptides either fall or rise. Our discussion focuses on ghrelin, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide 1 (GLP-1), and peptide YY (PYY).

Ghrelin. Ghrelin was discovered as the endogenous ligand for the orphan G protein–coupled growth hormone secretagogue receptor (GHS-R) and was demonstrated to specifically stimulate growth hormone release from rat pituitary cells in vitro as well as in vivo (20,21). The growth hormone secretagogue receptor appears in two distinct forms: the ghrelin receptor (GRLN) (formerly known as GHS-R 1a) has orexigenic and motility-stimulating properties, whereas GHS-R 1b is thought to be inactive or to have opposite effects (22). In situ hybridization indicates that ghrelin is produced and released from enteroendocrine X/A-like cells in the gastric mucosa (23) and to circulate in human blood at a considerable concentration (20). Ghrelin-containing neural cells are localized in the arcuate nucleus of the hypothalamus, a well-known center for appetite regulation, suggesting involvement of ghrelin in the regulation of feeding behavior (24,25).

Peripheral administration of ghrelin causes weight gain by reducing fat utilization and stimulating food intake in rats (21). Serum ghrelin concentrations are increased by fasting and reduced by refeeding in rats and humans (26). They rise sharply before and fall within 1 h of a meal (27). Several studies on rats and humans confirm that ghrelin initiates food intake (28,29). Circulating ghrelin levels are increased up to threefold in states of negative energy balance, such as anorexia nervosa, starvation, and cachexia, and also after weight loss in obesity (30) and are conversely decreased in conditions such as obesity, hyperglycemia, and feeding (31,32), suggesting that ghrelin plays a central role in short- and long-term energy homeostasis (33).

Additional data indicate that ghrelin also plays a role in the regulation of GI motility and acid secretion. Thus intravenous administration of ghrelin stimulates gastric motility and acid secretion in rats, and the effects are abolished by pretreatment with atropine or bilateral cervical vagotomy (34,35). Several studies also show a significant acceleration of gastric emptying in rodents (36,37), although the results are equivocal (38). Because gastric emptying rates and hunger usually are correlated in humans (39), one might expect that ghrelin increases gastric emptying in humans, but intravenous ghrelin did not show such effect in normal human volunteers (29). In patients suffering from gastroparesis, however, intravenous ghrelin accelerated gastric emptying (40–42). We recently found that intravenous ghrelin increased gastric emptying correlated with sensations of hunger in normal-weight humans (42a) (Fig. 4).

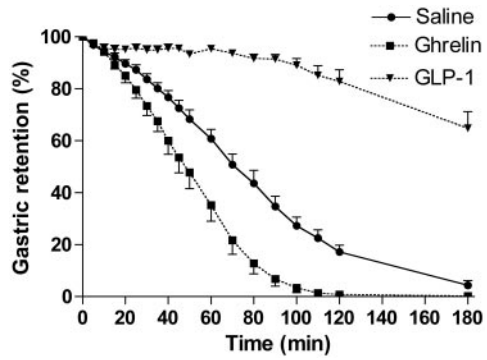

FIG. 4. The effect of ghrelin and GLP-1 on gastric emptying in two sets of normal-weight humans (42a,59). Data shown as mean ± SEM.

Ghrelin has been suggested to be a counterregulatory hormone that blocks insulin secretion (32). As mentioned earlier, ghrelin stimulates growth hormone (20), but also cortisol (43) and adrenaline (44), three of the classic counterregulatory hormones. Results are less convincing for the fourth, glucagon. Ghrelin enhances glucagon secretion in vitro, while results in vivo are equivocal (45). In the liver, ghrelin blocks gluconeogenesis and glycogen synthesis mediated by insulin, and, in adipocytes, ghrelin blocks the release of the insulin-sensitizing peptide adiponectin (46,47). In addition, exogenous ghrelin administration decreases circulating insulin concentrations in both rodents and humans (48,49). Ghrelin is also produced by islet α-cells and may affect β-cells through a paracrine action (50).

Ghrelin levels are lower in obese subjects than in normal-weight subjects. A 3,000-kcal meal suppressed ghrelin less in obese subjects than did a 1,000-kcal meal in lean subjects (51).

The effect of GBP on plasma concentrations of ghrelin is controversial. Dietary weight loss increases plasma levels of ghrelin (52), so one would expect plasma ghrelin to increase after GBP, but results are inconsistent. Some studies have demonstrated increased plasma levels and some no change, but the majority have shown a decrease (53). The reasons for these discrepancies are not clear. Surgical procedures differ in the amount of conserved fundus, with its higher density of ghrelin-producing cells included in the upper stomach pouch. Furthermore, vagal nerve fibers are cut during the procedure, interfering with the release of ghrelin mediated by vagal stimulation (54).

Study design may also influence the results. For example, in a recent publication, 15 lean (13 women) and 12 obese (9 women) subjects were compared with 6 women who underwent either GBP or AGB with a follow-up of 6–36 months; no significant difference was found in plasma ghrelin in the obese compared with the post-GBP patients (55), although known sex differences in plasma ghrelin concentrations may have confounded the results.

Glucose-dependent insulinotropic polypeptide. GIP is synthesized and released by the K-cells of the duodenum and proximal jejunum in response to glucose and fat ingestion. Defects in GIP pathways are considered to underlie type 2 diabetes, where the incretin effect of GIP is attenuated secondary to decreased expression of GIP receptors (56). GIP has not been studied extensively after GBP surgery. One would expect that GIP levels decrease after GBP, since the duodenum is no longer in continuity and the jejunum is not protected by the pylorus. Indeed, GBP was found to decrease GIP levels (57); however, in

another study, GBP resulted in reduced plasma GIP concentrations in type 2 diabetes but not in nondiabetic obese patients (8).

GLP-1. GLP-1 and PYY are produced and secreted from endocrine L-cells in the mucosa of the ileum and colon. Both peptides are released in equimolar amounts after a meal (58). GLP-1 is a major contributor to the ileal brake mechanism of the upper GI tract, thereby modulating gastric emptying and acid secretion (59). It also exerts dual actions in glucose homeostasis through its concurrent insulinotropic and glucagonostatic actions (60). Because GLP-1 slows gastric emptying of both liquids and solids (Fig. 4) (59,61), the metabolic requirements for insulin after food intake are reduced or at least delayed (62). Accumulating evidence indicates that GLP-1 exerts its effects on GI functions through the vagus nerve in both animals and humans (63).

Postprandial GLP-1 release can have two different mechanisms of action, affecting food intake and satiety. Intracerebroventricular injection of GLP-1 in rats inhibited food and water intake (64,65) and induced *c-fos* expression in the paraventricular nucleus of the hypothalamus (64). Intracerebroventricular administration of the GLP-1 receptor antagonist exendin(9-39) amide also results in increased food intake in satiated, but not in fasted, rats (64). With continuous intracerebroventricular treatment, exendin(9-39) amide rats increase not only their food intake, but also body weight (66).

In humans, intravenous administration invariably induces decreased food intake with ratings of reduced hunger and increased fullness in normal-weight, diabetic, and obese subjects (67–69). In some of these studies, gastric emptying was inhibited. A second mechanism by which GLP-1 can inhibit satiety is therefore by decreasing the rate of gastric emptying and thus increasing gastric distention.

PYY. The truncated form of PYY, PYY (3-36), is released from the GI tract after a meal and induces satiety (70). The effect of PYY (3-36) has been suggested to have a longer duration of action than other GI satiety peptides. Animal studies show that PYY (3-36) exerts its effect as a Y_2 receptor agonist, thereby suppressing neuropeptide Y–induced hunger in the arcuate nucleus of the hypothalamus. In analogy to GLP-1, postprandial plasma PYY concentrations have recently been shown to be lower in obese than lean subjects (71), which supports the proposal that PYY (3-36) is a mediator of satiety. As pointed out above, however, this property does not seem to be specific, but rather a common feature of obesity (compare with GLP-1), due to weak signaling of the gut inhibitory mechanisms on food intake.

PYY (3-36) has also been shown to decrease food intake in rodents (70); however, there is an ongoing debate, since other researchers have been unable to reproduce these results. In analogy with other GI peptides involved in regulating food intake, PYY also inhibits fasting small bowel motility (72) and gastric emptying (73). In rodents, PYY (3-36) does not influence glucose metabolism in the fasted state but increases glucose disposal during the hyperinsulinemic clamp. This effect is most likely mediated by changes in glucose uptake in muscle and adipose tissue and not by effects on insulin release (74).

Obese subjects have attenuated release of GLP-1 and PYY (55,75). The products from the L-cells have been studied early on with regard to changes after anti-obesity surgery. In patients undergoing jejunoileal bypass, plasma concentrations of GLP-1 were attenuated before surgery compared with normal-weight control subjects, but were significantly elevated 9 months after surgery (75) and were found to be very elevated 20 years after surgery (76). After GBP, there have been conflicting data regarding GLP-1. Again, some of this confusion is related to study protocol. Some studies found fasting plasma GLP-1 to be unchanged after surgery, whereas postprandial concentrations were elevated in several studies (8,9,55). In analogy to GLP-1, plasma PYY concentrations are elevated after GBP (9,55).

MECHANISMS OF ACTION OF GBP ON GLUCOSE HOMEOSTASIS

Which mechanisms can explain the rapid reversal of type 2 diabetes after GBP? Patients do not eat much in the immediate postoperative period and caloric restriction is known to improve type 2 diabetes (77). When patients start consuming regular food, they still remain in negative energy balance, which in itself improves glucose tolerance.

Other more interesting mechanisms may be related to the alterations in GI peptide release after GBP, working singly or in conjunction. The relative importance of bypass of the foregut versus a more rapid stimulation of the hindgut remains to be determined.

Gastric bypass excludes the foregut and its ghrelin-producing cells from digestive continuity, which may be the cause of the decreased plasma ghrelin concentrations. As mentioned earlier, ghrelin has several effects on glucose metabolism, including suppression of insulin in humans (49). Thus, at least in pharmacological doses, ghrelin disrupts insulin secretion and action. If, as postulated, ghrelin acts as an anti-incretin in the fasted state, then suppression of plasma ghrelin after GBP could enhance glucose disposal and improve glucose metabolism in type 2 diabetes.

Recently, ghrelin has been found to vary with nutrient status and also as a learned response. This suggested that ghrelin might act as a cephalic phase hormone, further emphasizing the role of ghrelin in glucose homeostasis (78). As mentioned earlier, vagotomy disrupts ghrelin release. In addition, ghrelin slows gut transit (79), resulting in more even uptake of nutrients from the gut, which may decrease fluctuations in plasma glucose levels. Recently, a 23–amino acid peptide encoded by the ghrelin gene was discovered, named obestatin, which has been suggested to have opposite effects to ghrelin in terms of food intake and GI motility (80). It is not known whether this peptide is influenced by GBP.

In a recent study, gastrojejunal bypass was performed in Goto-Kakizaki rats, a nonobese model of type 2 diabetes. This procedure leaves the stomach untouched; the duodenum is separated from the stomach and the bowel continuity is interrupted 8 cm from the ligament of Treitz. The distal of the two limbs was directly connected to the stomach, and the proximal limb carrying the biliopancreatic juice was reconnected down the alimentary limb at a distance of 12 cm from the gastrojejunal anastomosis—similar proportions as in the BPD–duodenal switch in people (81). The operated rats had significant improvements in glucose tolerance and fasting glucose compared with sham-operated controls, despite similar weight gains at all time points to 9 months after surgery. The results of surgery were compared with oral rosiglitazone and with energy restriction and in both instances were found to be superior. Thus, bypass of the foregut similar to GBP in an animal model can ameliorate type 2 diabetes independent

of weight loss. The mechanism behind this is unclear, but alterations in gut hormone levels might be responsible (81). Decreased GIP concentrations have been shown after bypass of foregut in patients with type 2 diabetes (8).

GBP results in accelerated delivery of nutrients to the hindgut, which results in decreased gastric emptying and GI transit, dubbed the "ileal brake." GLP-1 and PYY have been suggested as mediators of the "ileal brake." Both GLP-1 and PYY release are augmented after GBP and have been shown independently to decrease food intake in humans (67,71). Hunger was decreased and satiety increased 6 weeks after BPD with concomitant increases in plasma GLP-1 and PYY (82). Thus, increased postprandial plasma GLP-1 and PYY after GBP may decrease food intake and lower plasma glucose, whereas GLP-1 increases insulin and decreases glucagon secretion. GLP-1 also has trophic effects on the pancreas via anti-apoptotic and proliferative effects on β-cells (83). These trophic effects have recently been linked to nesidioblastosis (84). Just as decreased ghrelin concentrations may decrease intestinal transit, so may increased GLP-1 and PYY.

To summarize, GBP markedly ameliorates type 2 diabetes. This review proposes that alterations in GI peptide release may at least partly mediate this effect. Decreased plasma concentrations of ghrelin, as a result of bypassing the foregut, and increased concentrations of GLP-1, as a result of a more rapid stimulation of the hindgut, are the most prominent candidates for this effect. Ghrelin may have anti-incretin effects, counteracting GLP-1. Together, these actions may explain both the early and late effects of GBP on type 2 diabetes. Although this review has limited itself to a few GI peptides, several others are also altered after GBP, as are adipokines such as leptin and adiponectin. All these changes affect trafficking of free fatty acids and glucose, which may also contribute to the pronounced positive effects of GBP on type 2 diabetes.

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