Influence of diabetes surgery on gut hormones and incretins

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Abstract

The dramatic rise in the prevalence of obesity and type 2 diabetes mellitus (T2DM) has become a major global public health issue. There is increasing evidence that metabolic surgery is more effective than diet and exercise for diabetes remission and weight loss. Moreover, the rapid time course and disproportional degree of T2DM improvement after metabolic procedures compared with equivalent weight loss with conservative treatment, suggest surgery-specific, weight-independent effects on glucose homeostasis. Gut hormones has been proposed as one of the potential mechanisms for the weight-independent diabetes remission and long-term weight loss after these procedures. In this review we discuss the available current metabolic procedures and we review the current human data on changes in gut hormones after each metabolic procedure.

Key words: Bile acid. Metabolic surgery. Enteroinsular axis.

Introduction

Type 2 diabetes mellitus (T2DM) is a heterogeneous disorder and, while its causes have yet to be fully explained, obesity is considered as the primary risk factor.¹ The term “diabesity” has been used to show the strong relationship between the two conditions.² It has been estimated that the risk of developing T2DM is increased 93-fold in women and 42-fold in men who are severely obese compared to those with a normal weight.³,⁴ A healthy diet and exercise remain the cornerstones of T2DM treatment; bariatric surgery is undoubtedly more effective in the remission and improvement of T2DM compared to lifestyle modifications and pharmacotherapy.⁵ Due to the dramatic effects of these operations on the resolution of T2DM and metabolic syndrome, these procedures are now considered as “metabolic” operations, particularly as many of their metabolic actions occur before any noticeable weight loss.⁶,⁷

Thus far there is only one randomised controlled trial that has investigated bariatric surgery as a treatment of T2DM compared to conservative non surgical treatment. It compared adjustable gastric banding (AGB) to conventional medical T2DM therapy with a focus on weight loss by diet and exercise. After 2 years, remission of T2DM was significantly higher in those who received surgery (73% vs 13%).⁵ The Swedish Obese Subjects study, a large cohort prospective study has clearly shown the impressive effects of surgery on the prevention and sustained remission of T2DM (72% at 2 years and 36% at 10 years of patients with T2DM preoperatively remained free of the disorder) when compared with well-matched controls treated medically.⁸ A meta analysis that preceded the consensus meeting from the
American Diabetes Association where complete remission of diabetes was defined as a fasting glucose < 5.6 mmol/L and a HbA1c < 6% after 1 year of treatment,6 reported that 78.1% of T2DM patients had complete “remission”, and the condition was improved or resolved in 86.6% of cases.10

The effectiveness and the speed at which T2DM goes into remission differ between the various procedures.6 The rapid resolution of T2DM cannot entirely be explained by weight loss alone and some procedures like RYGB, biliopancreatic diversion (BPD) and sleeve gastrectomy (SG) improve glycaemia within days, long before any significant weight loss occurs.6,11,12

Indeed, there is increasing evidence that alterations in circulating gut hormone concentrations by surgery play a key role in improved glucose homeostasis. As the gastrointestinal tract is the largest endocrine organ in the body, many of these hormones are contributing to the regulation of glucose homeostasis, working through the so-called entero-insular axis.13

In this article we will summarise the current evidence on the changes after metabolic procedures in fasting and postprandial circulating levels of the gut hormones. The focus will be on those hormones implicated in glucose and energy homeostasis such as Glucagon like Peptide-1 (GLP-1), Peptide YY (PYY), glucose-dependent insulinotropic polypeptide (GIP) and ghrelin.

**Metabolic surgery techniques**

During the RYGB the stomach is divided into the upper stomach pouch, which is 15- to 30 mL in volume and the lower, gastric remnant. The stomach pouch is then anastomosed to the jejunum, through a gastrojejunal anastomosis in a so called Roux-en-Y fashion. The continuity of the bowel is restored via a jejuno-jejunal anastomosis, between the excluded biliary limb and the alimentary limb, performed at 75-100 cm distally from the gastrojejunostomy.14,15

SG is a relatively new procedure increasing in popularity. It originated as part of the duodenal switch operation and later has been used as a first stage procedure for the very obese and high risk patients. In SG the stomach is transected vertically creating a gastric tube and leaving a 150 to 200 mL pouch. The remaining stomach is excised.15

BPD includes a partial gastrectomy, leaving a 400 mL gastric pouch. The small bowel is divided 250 cm proximally to the ileocecal valve and the alimentary limb is connected to the gastric pouch to create a Roux-en-Y gastroenterostomy. An anastomosis is performed between the excluded biliopancreatic limb and the alimentary limb at 50 cm proximally to the ileocecal valve.17 In the biliopancreatic diversion with duodenal switch (BPD-DS) a vertical sleeve gastrectomy is constructed and the division of the duodenum is performed immediately beyond the pylorus. The alimentary limb is connected to the duodenum while the biliopancreatic limb is anastomosed to the ileum 75 cm proximally to the ileocecal valve.18

Adjustable gastric banding (AGB) involves the insertion of an adjustable plastic and silicone ring around the proximal aspect of the stomach, immediately below the gastroesophageal junction creating a small proximal pouch.19

Novel operations are geared toward the treatment of T2DM and not necessarily to induce weight loss per se. Among the most prominent of these operations are the duodenal-jejunal bypass and the ileal interposition. First described by Rubino,20 the duodenal-jejunal bypass (DJB) is a stomach-sparing bypass of a short portion of proximal intestine, a gastric bypass without the stomach stapling. DJB has been shown to improve T2DM in both lean and obese animal models and it is currently being investigated in early human trials.

The ileal interposition (II), previously called "transposition" involves the removal of a small segment of the ileum with its vascular and nervous supply and its insertion into the proximal small intestine. Overall, early studies of humans undergoing ileal interposition have shown promising results, and the procedure is now combined with SG when weight loss is also desirable [sleeve gastrectomy with ileal interposition (SG-ileal interposition)].21

**Gut hormones implicated in glucose homeostasis**

**Enteroinsular axis**

The enteroinsular axis as a concept was introduced by Unger and Eisentraut in 1969 and describes the connection between the gut and the pancreatic islets.22 Creutzfeldt suggested that this axis encompasses nutrient, neural and hormonal signals from the gut to the islet cells.23 The main gut hormones involved in the enteroinsular axis are GLP-1 and GIP which are also called “incretins”, whilst ghrelin and PYY seems to play a less prominent role in glucose homeostasis. The incretin effect, defined by Creutzfeld, describes “the phenomenon of oral glucose eliciting a greater insulin response than intravenous glucose, even when the same amount of glucose is infused or an equivalent rise in glycaemia is caused by the parenteral route”.22 GLP-1 and GIP, which are the dominant peptides responsible for nutrient-stimulated insulin secretion account for 50% to 60% of nutrient-stimulated insulin release.13,24

**GLP-1**

GLP-1 synthesized by the L-cells located mainly in the ileum at the distal gastrointestinal tract. A major physiologic role of GLP-1 is stimulation of insulin release in response to nutrient ingestion. Moreover, GLP-1 exerts its glucose-lowering effects through inhibition of gastric emptying, which delays digestion and blunts postprandial glycaemia, restoration of
insulin sensitivity and inhibition of glucagon secretion. Additionally, GLP-1 acts on the central nervous system to induce satiety and decrease food intake.24,26

**GIP**  
GIP is an incretin which is secreted from K cells in the duodenum in response to absorbable carbohydrates and lipids. GIP is degraded rapidly in the plasma by the enzyme dipeptidyl peptidase 4 (DPP4) to GIP,3-42 which is biologically inactive. The main physiologic role of GIP, which is a less potent insulin secretagogue than GLP-1, is the stimulation of pancreatic β-cells to increase the glucose-dependent insulin secretion.24,26 Moreover, GIP causes a postprandial rise of glucagon and promotes lipoprotein lipase activity. Its secretion is associated with the induction of β-cell proliferation and the enhanced resistance to apoptosis.27

**Other gut peptides associated with the enteroinsular axis**

**Ghrelin**  
Ghrelin is a peptide mainly produced from the X/A-like cells of the stomach and to a lesser degree from the small intestine and acts on the hypothalamus to regulate appetite. Ghrelin is a known orexigenic hormone, it stimulates appetite and food intake. Furthermore, ghrelin impairs insulin sensitivity and also inhibits insulin secretion. Circulating ghrelin concentrations increase with fasting and decrease following nutrient ingestion. Moreover, ghrelin levels increase with diet-induced weight loss.25,28

**PYY**  
PYY is a peptide released into the circulation by intestinal endocrine L-cells of the distal gut following food ingestion along with GLP-1. PYY is released postprandially in proportion to the calories ingested and has an inhibitory effect on gastrointestinal mobility. It increases satiety, reduces food intake and delays gastric emptying.25,29,30 In addition to regulating appetite and body weight, PYY exerts glucoregulatory properties especially in rodents.29 Thus, elevated levels of PYY after bariatric surgery could contribute to the improved glucose homeostasis.

**GLP-1 levels after metabolic surgery**

**GLP-1 levels after RYGB**  
In the vast majority of the studies, fasting GLP-1 levels do not change significantly postoperatively and only a few studies have reported increased levels postoperatively.21,44 Postprandial GLP-1 levels are increased after RYGB and have a higher peak at 15 to 30 minutes after meal ingestion compared to preoperative responses.21,36,43 The postprandial GLP-1 levels gradually increase during the first two years after the operation.21,44 These changes in postprandial GLP-1 levels are independent of weight loss and the caloric reduction during the early postoperative period.21,37

**GLP-1 levels after BPD**  
Fasting GLP-1 levels are increased from the first postoperative week.44-46 Similar to RYGB, postprandial GLP-1 levels are increased after BPD from the first postoperative week and these changes are independent of weight loss.47,48

**GLP-1 levels after AGB**  
The vast majority of AGB studies did not find any significant change of fasting GLP-1 levels at the postoperative follow-up.33,49-52 Furthermore, three studies that measured the postprandial GLP-1 levels after meal did not find any significant difference compared to preoperatively up to 12 months postoperatively.33,49,52

**GLP-1 levels after SG**  
Fasting GLP-1 levels preoperatively and 3 months postoperative are similar after SG.40,53 Postprandial AUC and peak levels of GLP-1 at 30 minutes after the ingestion of a meal do increase as early as the first postoperative week.40,53

**GLP-1 levels after experimental procedures**  
The only human study that reports GLP-1 levels after DJB reports found increased postprandial levels of GLP-1 at 1 month postoperatively when at 6 months there was no significant change compared to preoperatively.54 Similarly to the results after DJB, a study by DePaula et al. which investigated the changes in GLP-1 levels after SG with ileal interposition found that postprandial levels of GLP-1 were significantly increased after the procedure.55

**GIP levels after metabolic surgery**

**GIP after RYGB**  
The findings on fasting GIP levels after RYGB are inconclusive. The majority of the studies reported no changes in fasting GIP,31,35,36 but some showed decreased levels of GIP,41,46 especially in T2DM patients.31 Regarding postprandial GIP levels after
RYGB, many studies report no significant changes in postprandial AUC levels, but there is a cross-sectional study which found decreased postprandial GIP levels compared to controls. Lafferere reported that postoperative postprandial GIP levels had an increased peak at 30 minutes after meals, however Hansen did not confirm this finding.

**GIP levels after BPD**

Active fasting GIP levels decreased immediately after the BPD. In addition, GIP postprandial levels after BPD are decreased from the first postoperative week after the biliopancreatic diversion and this change is independent of the weight loss.

**GIP levels after AGB**

Usinger et al. and Shak studied fasting GIP levels in 8 and 24 patients after AGB respectively. Both of them did not find any significant changes postoperatively. Postprandial GIP levels did not change after AGB.

**GIP levels after experimental procedures**

In the only study that has been performed to investigate GIP levels after DJB, the investigators didn’t find any postprandial changes in GIP levels. On the other hand, studies after SG with ileal interposition showed a significant increase in postprandial GIP levels postoperatively in patients with T2DM.

**Ghrelin**

**Ghrelin levels after RYGB**

Several studies have assessed the impact of metabolic surgery on circulating ghrelin profiles, measuring either total (acyl- and desacyl-ghrelin) or acyl-ghrelin in the fasting and/or meal-stimulated state. The majority of the studies on fasting ghrelin levels have shown either no significant change or decreased levels, especially in the early postoperative period. However, a significant number of long-term follow-up studies have reported increased fasting ghrelin levels. It is noteworthy that in many studies which reported decreased ghrelin levels immediately postoperatively, there was a trend for increased levels in longer follow-up.

The findings on postprandial ghrelin levels after RYGB are also inconclusive, as there are groups which showed no changes, increases and decreases following surgery. The majority of the studies have shown decreased or no significant change in postprandial ghrelin levels in the early postoperative period (first six weeks). The differences in the methodologies between the different studies are probably one of the main reasons behind the discrepant findings. Blood samples for hormone assays were collected and processed in diverse ways (i.e., tubes chilled or not; with or without protease or DPP-4 inhibitors; acidified or not; diverse commercial assays; different durations of centrifugation). Moreover, there were differences in the experimental meals, (including their carbohydrate and lipid content), follow-up and also blood sampling points. Furthermore, the technical variations between the same surgical procedures may be partially responsible for the published differences as the variable damage of the vagus nerve and the difference in gastric fundus management may affect ghrelin levels. Glucose homeostasis may also play a role in gut hormone responses after the same bariatric procedure. Hyperinsulinaemia and insulin resistance per se are associated with ghrelin suppression in obese individuals.

**Ghrelin levels after BPD and BPD-DS**

Similar to RYGB, the findings regarding ghrelin levels after BPD are inconclusive; some groups have reported increases, others no change and one reported decreases. After a growth hormone-releasing hormone/arginine test post-BPD ghrelin levels are increased 18 months postoperatively compared to baseline. Moreover, the 24 hour production of ghrelin has been found to be increased after BPD. Regarding BPD-DS, Kotidis reported that total fasting ghrelin was decreased 18 months postoperatively.

**Ghrelin levels after AGB**

Fasting ghrelin levels are increased in the majority of the studies after AGB; however there is also a significant number of studies which report no significant differences in fasting ghrelin levels compared to preoperatively. Two studies have measured prospectively ghrelin postprandial levels and did not find significant changes up to twelve months postoperatively.

**Ghrelin levels after SG**

All the studies that have measured fasting ghrelin levels, with a follow-up of up to 5 years after SG have found decreased levels. The only study that reported on postprandial ghrelin levels was a randomised controlled trial which found decreased levels at 1 week and 3 months compared to preoperatively, but also RYGB.

**Ghrelin levels after experimental procedures**

Fasting and postprandial ghrelin levels are significantly decreased after the SG with ileal interposition.
**PYY levels after metabolic surgery**

**PYY levels after RYGB**

Fasting PYY levels after RYGB have been studied extensively after gastric bypass with prospective follow-up up to 2 years. Similarly to GLP-1, in the vast majority of cases baseline PYY levels remained unchanged after RYGB. Postprandial PYY AUC and PYY peak levels are increased after RYGB from the second postoperative day and these changes appear to be independent of weight loss. Moreover, PYY postprandial levels are increased progressively after RYGB.

**PYY levels after BPD and BPD-DS**

García-Fuentes demonstrated in a group of 38 patients that total fasting PYY levels are increased after BPD. However, a recent study on fasting and postprandial PYY levels after BPD-DS reported that they are increased compared to preoperatively. The rapid gastric emptying in combination with the anatomical changes has been proposed as the main reasons.

**PYY levels after AGB**

All studies which have measured PYY levels after AGB have found no change in postoperative fasting PYY levels. Furthermore, prospective studies that have measured PYY AUC and PYY peak levels after AGB did not report any change postoperatively.

**PYY levels after SG**

The results regarding fasting PYY fasting levels after LSG are inconclusive. Karamanakos studied fasting PYY levels at 1, 3, 6 and 12 months postoperatively and found that total fasting PYY levels increased postoperatively from the first month. Peterli however reported that fasting total PYY levels decrease at 1 week and 3 months after the operation when Valderas did not find any significant change 2 months postoperatively. Postprandial PYY levels increased from the early postoperative period with a significant peak of PYY levels at 30 minutes after meal ingestion.

**PYY levels after experimental procedures**

Postprandial PYY levels in humans after SG-ileal interposition were elevated 16 months postoperatively.

**Possible mechanisms for the changes in gut hormone levels after metabolic procedures**

Significant differences between the hormonal profiles of bariatric procedures have been shown in this study. A number of possible physiological mechanisms have been proposed for these differences.

**Anatomical differences between the procedures**

Long term changes in ghrelin levels after BPD and RYGB remain inconclusive as discussed above, but it appears that both operations result in decreased or unchanged levels in the early postoperative period, following which concentrations increased progressively. BPD-DS and SG are associated with decreased ghrelin levels. The fact that in both these operations the fundus of the stomach, which is the main location of ghrelin producing cells does not have contact with food, lead to speculation that its presence could play a significant role on circulating ghrelin levels. Further-

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**Table I**

The profile of the gut hormones’ changes after RYGB, BPD-DS, SG, AGB

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↔: No significant change in the majority of studies; ↑: Significant increased in the majority of studies; ↓: Significant decreased in the majority of the studies; –: No studies for this parameter; GLP-1: Glucagon Like Peptide-1; PYY: Peptide YY; GIP: gastric inhibitory polypeptide/glucose -dependent insulinotropic polypeptide; RYG: Roux-en-Y Gastric Bypass; BPD: Biliopancreatic Diversion; SG: Sleeve Gastrectomy; AGB: Adjustable Gastric Banding; BPD-DS: Biliopancreatic Diversion with Duodenal Switch; AUC: Area Under the Curve.
more, in two recent randomised controlled trials, ghrelin levels were significantly lower after SG compared to RYGB and this could also be partially explained by the anatomical differences in the stomach postoperatively. On the other hand, ghrelin levels remain unchanged or increased after AGB due to the body’s response to a diet-like induced weight loss.

Consistent with the lower intestinal hypothesis, the majority of the metabolic operations such as BPD, BPD-DS, SG, DJB and SG with ileal interposition known for rapid postoperative glycaemic control, create gastrointestinal shortcuts for food to access the distal bowel. After BPD and BPD-DS, which conduct food directly from the stomach to the distal jejunum and ileum, postprandial GLP-1 and PYY excursions are unquestionably increased. Despite that RYGB and DJB bypass less jejunum, increased GLP-1 and PYY levels occur progressively. Consistent with elevated postprandial GLP-1 secretion, post-RYGB patients display an increased incretin effect. GLP-1 and PYY postprandial levels, as a segment of the L-cell-rich ileum is transplanted into the upper intestine near the duodenum-jejenum boundary, thereby increasing its exposure to ingested nutrients. As predicted, this operation greatly enhances postprandial GLP-1 and PYY secretion with no gastric restriction or malabsorption and results in improved glycaemic control.

The different limb length after the intestinal bypass procedures seems to play a role on GIP postprandial levels. In procedures with very long limbs, such as BPD, the GIP levels are decreased. In RYGB and DJB, with shorter limbs, postprandial GIP levels remain unchanged, when after SG with ileal interposition rapid gastric emptying and the quick contact of undigested food with the K-cells leads to increased postprandial GIP levels.

Changes in gastric emptying

The rapid gastric emptying that occurs after some of the procedures could lead to early contact of the food with the ileum creating an enhanced gut hormones response from the L-cells (PYY and GLP-1). Gastric emptying is accelerated after RYGB from the third postoperative day and accompanied by shortened intestinal time in morbidly obese patients. This was accompanied by an increased postprandial GLP-1 response. SG and BPD-DS are also associated with increased gastric emptying although one study suggested no change postoperatively. Further support to the rapid gastric emptying is provided from the presence of dumping symptoms after SG.

Differences in bile acids secretion

A recent study has shown that ghrelin levels in obese patients are negatively correlated with bile acids levels when PYY and GLP-1 postprandial levels are positively correlated with specific types of bile acids. Moreover, increased bile acid secretion after RYGB has been associated with GLP-1 peak levels. More studies in bile acids changes after metabolic procedures and their associations with changes in gut hormones levels postoperatively are necessary in order to understand the role of bile acids in gut hormone secretion and glucose and energy homeostasis.

Gut hypertrophy and differences in DPP-4 activity

Following BPD, significant gut hypertrophy has been reported in both humans and rats. This could explain the increased GLP-1 and PYY fasting levels after BPD and BPD-DS, as well as the increased postprandial levels. On the other hand, the activity of the enzyme DPP-4 which degrades the GLP-1, GIP and PYY is reduced after RYGB, but does not change after BPD. The association between DPP-4 activity and the differences in the fasting and postprandial levels of GLP-1, GIP and PYY after RYGB compared to BPD still needs further exploration.

Conclusion

Each metabolic procedure has a unique gut hormone profile. These differences in gut hormones secretion may partially explain the different rate and effectiveness as regards the glycaemic control and the weight loss of these procedures. Future work with more standardized protocols is needed to finally confirm the differences in hormonal profile after various metabolic procedures. Using what we have learnt about gut hormones from metabolic surgery will allow us to refine our surgical procedures and may help those patients that are not eligible or able to have metabolic surgery.

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