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Review

The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones

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ABSTRACT

Bariatric surgery for obesity has proved to be an extremely effective method of promoting long-term weight reduction with additional beneficial metabolic effects, such as improved glucose tolerance and remission of type 2 diabetes. A range of bariatric procedures are in common use, including gastric banding, sleeve gastrectomy and the Roux-en-Y gastric bypass. Although the mechanisms underlying the efficacy of bariatric surgery are unclear, gastrointestinal and pancreatic peptides are thought to play an important role. The aim of this review is to summarise the effects of different bariatric surgery procedures upon gastrointestinal and pancreatic peptides, including ghrelin, gastrin, cholecystokinin (CCK), glucose-dependent insulinotropic hormone (GIP), glucagon-like peptide 1 (GLP-1), peptide YY (PYY), oxyntomodulin, insulin, glucagon and somatostatin.

Contents

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1. Introduction

Obesity, defined as a body mass index over 30 kg/m^2, is considered one of the greatest public health challenges of our time [1]. Obesity is associated with multiple metabolic comorbidities, including type 2 diabetes. Bariatric surgery, which aims to promote weight loss by either reducing stomach size or bypassing a portion of intestine, is associated with effective long-term weight loss and beneficial metabolic sequelae [2]. The mechanisms which underlie these consequences of bariatric surgery remain unclear, but they are likely to include effects upon peptide hormones, particularly gut-derived peptides [3]. The aim of this review is to describe the different bariatric procedures available and their known effects upon peptide hormones.

2. Bariatric surgery procedures

A wide range of surgical procedures have been used to promote weight loss since bariatric surgery was initially developed in the 1950 s. In general, bariatric procedures act by reducing the size or capacity of the stomach, by bypassing a portion of the intestine or by a mixture of these two approaches. The most commonly used procedures at present are gastric banding, sleeve gastrectomy and the Roux-en-Y gastric bypass (Fig. 1).

2.1. Gastric banding

Gastric banding was first introduced in the 1970 s and involves the placement of a silicone ring around the stomach to create a small upper gastric pouch at the bottom of the oesophagus. This procedure is safe, well tolerated and efficacious with a low risk of serious complications such as malabsorption. The band needs to be adjusted intermittently to optimise weight loss and to minimise complications.

2.2. Sleeve gastrectomy

The sleeve gastrectomy involves creating a long, thin gastric pouch or sleeve by stapling the stomach longitudinally. This reduces the volume of the stomach but leaves the pylorus intact. The sleeve gastrectomy was initially performed as a precursor to a larger procedure but has been increasingly used alone due to its efficacy. Sleeve gastrectomy is now one of the most commonly performed bariatric surgery procedures.

2.3. Roux-en-Y gastric bypass

The Roux-en-Y gastric bypass (RYGB) is the most commonly performed bypass procedure. It involves the creation of a small gastric pouch which is drained into the jejunum (alimentary limb) with no contact between nutrients and the pylorus and duodenum. The bile and pancreatic juices drain into the duodenum and jejunum as normal (biliopancreatic limb) but are only mixed with food after the anastomosis of the alimentary and biliopancreatic limbs to create the common limb. The length of the common limb is important in determining the likely risk of serious malabsorption and related nutrient deficiencies (discussed elsewhere [4]). In standard RYGB, the Roux limb is usually 0.75–1.5 metres long with a common limb of ~3 m which is adequate for absorption of macronutrients and micronutrients. A 'distal bypass' technique has been used which reduces the common limb to ~75 cm but carries a greater risk of nutrient deficiencies [5]. Although the RYGB has been widely used for successful weight loss, it can cause dumping syndrome, due to the lack of pyloric control over gastric emptying. Dumping syndrome occurs when a high osmolar load reaches the intestine rapidly, prompting fluid to enter the gut lumen and causing hypovolaemia, abdominal distension, nausea, vomiting, diarrhoea, dizziness and fatigue. In some patients, hypoglycaemia can also occur due to the strong insulin response which is likely to be stimulated by incretins upon exposure of the ileum to ingested nutrients.

3. The effects of bariatric surgery upon gut peptides

Many of the beneficial metabolic effects of bariatric surgery have been attributed to altered peptide hormone profiles, especially involving pancreatic and gut peptides. However, other mechanisms are also likely to have a role, but are beyond the scope of this review.

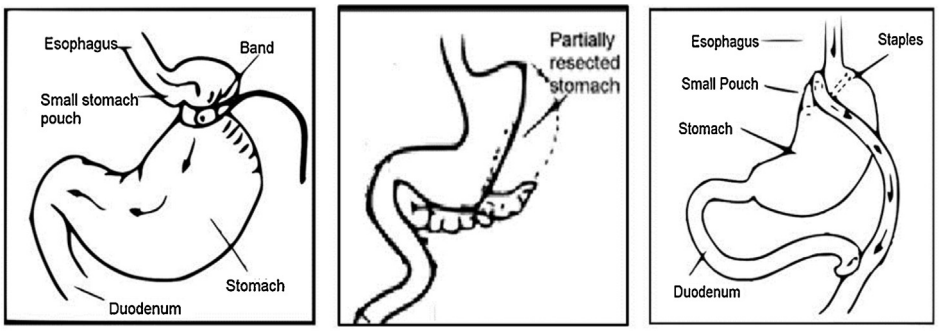
The absorption and digestion of nutrients requires a healthy gastrointestinal tract which is subject to the control by nervous and hormonal influences. Several gut hormones are responsible for regulating appetite and satiety and also control the movement of the gut and hence transit of food through the intestines (see Table 1).

4. Changes in specific gut hormones following bariatric surgery

4.1. Gastrin

Gastrin is produced in enteroendocrine G cells which predominate in the gastric antrum and duodenum and is released in response to food and gastric distension. It acts to increase the secretion of hydrochloric acid, pepsinogen and pancreatic juices and reduces appetite. Secretion appears to be highest when nutrients are in direct contact with the G cells. Rather than being a single molecular entity, gastrin is actually a family of multiple peptides of varying length with varying degrees of biological activity. Measuring and quantifying gastrin activity in a meaningful way is challenging because of this structural heterogeneity.

Theoretically, procedures (such as the RYGB) which exclude the gastric antrum or duodenum reduce contact between the nutrients and the majority of the G cells and would be likely to cause a fall in gastrin secretion. Ongoing production of hydrochloric acid in the gastric remnant without the buffering effect from ingested nutrients stimulates the production of secretin and somatostatin which further inhibit gastrin secretion. Indeed, there is some evidence that postprandial gastrin levels fall after RYGB both in the first two weeks post-operatively [6] and over the first year [7]. It has recently come to light that the remnant stomach is subject to multiple histological changes following RYGB. Common changes include chronic gastritis and atrophic gastritis. One study has demonstrated an increased proliferation rate in the epithelium of the excluded gastric antrum coupled with a reduction in the number of G cells [8]. It has been suggested that excessive gastric acid production may be involved in the pathogenesis of abnormal histological findings in the stomach after RYGB [9]. The role of gastrin secretion as either a cause or consequence of altered gastric histology is unclear. In clinical practice, many patients commence proton pump inhibitor therapy post-operatively which reduces gastric acid production, increases gastrin and prevents acid- related complications.



Adjustable gastric banding
Commonly performed as a laparoscopic procedure, gastric banding is less invasive than many others options and the band can be adjusted to enhance or reduce the effect. Patients have a very small stomach pouch which reduces intake. Complications include band slippage or rupture, nausea and vomiting, stricture formation in the stomach.

Sleeve gastrectomy
Initially performed as part of a larger procedure, (see below) the sleeve gastrectomy is now increasingly performed alone. A lateral section of the stomach is removed leaving a sleeve shaped stomach with around 150-200ml capacity. Complications include wound dehissence, nausea and vomiting.

Roux-en-Y gastric bypass
A small stomach pouch is made and connected to the ileum (alimentary or digestive limb). The mixing of biliopancreatic secretions and nutrients occurs in the ileum with a shorter length of gut for absorption. The common limb is several metres long. Complications include malabsorption and dumping syndrome as the pylorus is bypassed.

Images taken from Wikimedia, licensed for unrestricted use in the public domain. Accessed 4/12/2014.

Fig. 1. A summary of common bariatric surgery procedures.

Other procedures where the G cells are still exposed to nutrients may be associated with different effects. A study in 24 patients with gastric banding demonstrated no change in fasting gastrin concentrations 6–12 months after surgery [10]. There have been reports that the gastric sleeve may be associated with increased gastrin levels in both human and animal studies [11,12]. The reasons for this are unclear.

4.2. Ghrelin

Ghrelin is produced in the stomach and pancreas in response to fasting and is associated with hunger. Ghrelin is usually considered to be most active in its acylated form, with an octanoyl group attached to its third amino acid residue, which occurs due to the action of ghrelin-O-acyltransferase (GOAT). Acylated ghrelin is then able to activate the growth hormone secretagogue receptor (GHSR) which is predominantly found in the hypothalamus and pituitary glands [13]. Acylated ghrelin is orexigenic. In obesity, both fasting and postprandial total ghrelin concentrations are lower than in normal weight individuals but the proportion of acylated ghrelin is higher in the obese [14].

Ghrelin levels rise with prolonged fasting and fall after a meal. Therefore, in general, weight loss via calorie restriction increases ghrelin levels, a phenomenon which may contribute to the poor long-term efficacy of dietary manipulation to control obesity [15]. The short and long-term effects of bariatric surgery upon ghrelin levels are still unclear, and most studies have involved relatively few participants. Different bariatric procedures appear to have different effects upon ghrelin secretion, possibly due to anatomical variations changing the degree of contact between ingested nutrients and the mucosa of the gastric fundus where the ghrelin producing cells are predominantly located. Gastric banding appears to be associated with an increase in ghrelin levels. Fruhbeck and coworkers [16] studied 24 obese men who had similar degrees of weight loss following adjustable gastric banding (GB; $n = 8$), RYGB ($n = 8$) or conventional dietary management [8]. 6 months after surgery ghrelin levels were increased to a similar degree in both the GB and conventional dietary management groups. Patients with RYGB had a significant decrease in ghrelin levels after 6 months, an effect which was comparable to that seen post-gastrectomy ($n = 6$). The authors concluded that the RYGB reduced ghrelin levels due to the exclusion of the gastric fundus, with reduced or absent contact between ghrelin-producing mucosal cells and ingested nutrients [16,17]. Similar effects have been seen by other groups. Jacobsen et al., found that fasting and postprandial ghrelin levels fell 2 weeks after RYGB [6]. Cummings and coworkers noted that gastric bypass ($n = 5$ patients) obliterated normal ghrelin diurnal and post-prandial fluctuations and was associated with a reduction in 24-h ghrelin area under the curve when compared to 5 healthy obese matched controls and 10 controls of normal weight. Similar results have been shown elsewhere [18]. There is some evidence that the effects of RYGB upon ghrelin are important for the efficacy of the operation in terms of promoting and sustaining weight loss. Dirksen et al., studied 33 patients for 12 months after RYGB and found that those who had a good weight loss response (good responders) had a higher degree of ghrelin suppression compared to poor responders [19]. However, not all studies have been able to replicate a suppressant effect of RYGB on ghrelin in human or animal work [7,20,21]. Interestingly, sleeve gastrectomy may decrease circulating acylated ghrelin concentrations [22], possibly due to the removal of ghrelin-producing cells in the stomach.

4.3. Cholecystokinin (CCK)

CCK is secreted by I cells in the duodenal mucosa and acts to promote contraction of the gallbladder which propels bile into the gut lumen. It also promotes the release of digestive enzymes from the pancreas, slows gastric emptying and is associated with satiety. Several studies have shown an increase in CCK levels postprandially after RYGB in response to a mixed meal [6,19]. This is perhaps surprising, since the main physiological stimulant of CCK release is the presence of amino acids and fatty acids within the duodenum, which is excluded from contact with nutrients following RYGB. However, there are other stimulants of CCK release, such as parasympathetic impulses and intra-luminal releasing factors which may be important following bariatric surgery [23]. Another

Table 1
A summary of peptide hormones which act upon the gut and their likely roles.

Hormone	Site of production	Stimulus for secretion	Likely actions
Gastrin	G cells in the gastric antrum and duodenum	Gastric distension & food in the stomach	• Increases production of hydrochloric acid, pepsinogen, intrinsic factor, pancreatic secretions and bile. • Promotes satiety
Ghrelin	Predominantly stomach and pancreas.	Empty stomach	• Stimulates appetite, increases hunger • Increases gastric emptying and gastrointestinal motility in preparation for eating • Induces growth hormone release • Inhibits glucose-stimulated insulin production
Cholecystokinin (CCK)	I cells in duodenal mucosa	Fatty acids or amino acids in the duodenum	• Contraction of the gallbladder releasing bile • Pancreatic enzyme secretion • Secretion of insulin, glucagon and PP • Slows gastric emptying • Promotes satiety
Secretin	S cells in duodenal mucosa	Low pH in the lumen	• Increases production of pancreatic bicarbonate • Reduces gastric acid production and inhibits gastrin release • Promotes insulin release • Reduces gastric and duodenal motility
Vasoactive intestinal polypeptide (VIP)	Enteric nerves and parasym-pathetic efferent nerve fibres	Vagal stimulation	• Increases the secretion of water and electrolytes out of cells and into the gut lumen • Relaxation of smooth muscle in the vasculature, gut and genitourinary system. • Reduces gastric acid production • Promotes hormone release from the pancreas, gut and hypothalamus
Pancreatic polypeptide (PP)	Produced by PP cells in the pancreas	Meal, especially high protein content.	• Regulates production of both exocrine and endocrine pancreatic secretions • Associated with satiety.
Gastric inhibitory peptide (GIP)	K cells in the gastrointestinal mucosa (ileum)	Nutrients in the gut lumen	• Incretin hormone, promoting insulin production and release in the pancreas • Promotes satiety • Promotes a postprandial rise in glucagon • Prevents beta cell apoptosis • Promotes the conversion of glucose to fatty acids and their storage in adipose, by increasing the activity of lipoprotein lipase.
Glucagon-like peptide -1 (GLP-1)	L cells in the gastrointestinal mucosa (ileum)	Nutrients in the gut lumen	• Incretin hormone, promoting insulin production and release in the pancreas • Reduces gastric emptying and intestinal motility • Promotes satiety
Glucagon-like peptide -2 (GLP-2)(99)	L cells in the gastrointestinal mucosa (ileum)	Nutrients in the gut lumen	• Promotes gut hypertrophy • Possible role in glucose homeostasis • Possible role in slowing gut motility to promote absorption
Oxyntomodulin	L cells in the gastrointestinal mucosa (ileum)	Nutrients in the gut lumen	• Promotes satiety • Agonist of glucagon receptor and GLP-1 receptors • Increases energy expenditure
Peptide YY (PYY)	L cells in the gastrointestinal mucosa (colon)	Nutrients in the gut lumen	• Promotes satiety • Reduces gastric emptying and intestinal motility • Ileal brake

possible explanation is that surgery may increase stimulation of CCK cells in the more distal small intestine or alter the number of CCK-producing cells within duodenal mucosa [24,25] leading to higher CCK production for a given level of stimulus.

The role of CCK in the efficacy of bariatric surgery is unclear. Theoretically, high CCK levels may contribute to the increased satiety and improved glucose homeostasis following RYGB. However, Dirksen et al., found that CCK levels were higher in poor responders compared to good responders after RYGB [19].

Few studies have examined the changes in CCK which occur following other bariatric procedures. Peterli et al. [26] assessed patients up to 1 year after RYGB or sleeve gastrectomy. While both groups showed increased postprandial CCK levels compared to pre-operative concentrations, the sleeve gastrectomy was associated with a much larger CCK increase compared to the RYGB group. This difference was evident at one week post-operatively, and gained in magnitude over the first year [26]. The effect of gastric banding on CCK concentrations is unknown.

4.4. GIP

Glucose-dependent insulinotropic polypeptide (GIP) is secreted from K cells in the small intestine. Like GLP-1, GIP is associated with an insulinogenic effect following ingestion of oral glucose (historically this has been known as the incretin effect). GIP was originally called gastric inhibitory polypeptide and was first identified as a factor which dramatically inhibited gastric acid secretion in dogs. However, this effect was found to be negligible in humans and the hormone was later renamed glucose-dependent insulinotropic polypeptide (GIP) [27]. The role of GIP in the development of diabetes and obesity is unclear, but hyperglycaemia may act to directly downregulate GIP receptors in pancreatic β-cells [28] leading to a defect in late-stage insulin release [29,30]. GIP is secreted from K cells found throughout the small intestine but in highest proportions in the duodenum and jejunum [27]. Bariatric procedures which reduce or prevent nutrient exposure to the duodenum and jejunum, such as the RYGB, have been found in some studies to result in a reduction in postprandial GIP secretion [31], an effect which may be more pronounced in diabetic subjects [32,33]. Reductions in fasting GIP have also been found after surgery [34] but reduced fasting or postprandial GIP levels have not been described in all reports [6,35,36]. Altered fasting and postprandial GIP responses to bariatric surgery may be affected by the presence or absence of diabetes [35–37].

The role of GIP in other procedures is even less clear. After gastric banding, there appears to be no change in fasting GIP concentrations 6–12 months after surgery [10,38], however, postprandial GIP levels may be reduced [38].

4.5. GLP-1

Glucagon-like peptide 1 (GLP-1) is secreted from L cells which predominate in the distal ileum and colon. Although fasting concentrations of GLP-1 do not appear to change markedly after bariatric surgery [10,39], there is a large body of evidence suggesting that postprandial levels are increased compared to the pre-surgical state following many different bariatric procedures including gastric banding, sleeve gastrectomy and RYGB [6,19,22,40]. The reasons for this sustained increase in GLP-1 post-surgery are unclear but have been attributed to the greater delivery of intact nutrients to the ileum through anatomical changes or increased intestinal transit (hindgut hypothesis) [41–44]. An alternative hypothesis, the foregut hypothesis, suggests that exclusion of the upper small intestine is responsible for the beneficial aspects of bariatric surgery, possibly through decreased secretion of an 'anti-incretin' factor [37,45,46].

The beneficial effects of bariatric surgery upon appetite and glucose homeostasis have been attributed, at least in part, to the increased secretion of GLP-1. GLP-1 is an attractive candidate for this role as potential mediator of these beneficial effects as it is an incretin hormone and has an insulinogenic effect following ingestion of oral glucose [47]. Binding of GLP-1 to the GLP-1 receptor on pancreatic beta cells activates adenylate cyclase and increases cAMP concentrations which augment glucose-dependent insulin secretion. The ability of GLP-1 to promote insulin secretion is dependent upon the glucose concentration, with reduced or absent effect at low glucose concentrations. This has made GLP-1 agonists an attractive target for pharmacological intervention to reduce hyperglycaemia with no undue tendency for hypoglycaemia. GLP-1 agonists or mimetics such as liraglutide have been approved for pharmacological use in the treatment of diabetes and obesity [49,50].

GLP-1 is also thought to have centrally-mediated effects upon appetite by interacting with vagal afferent nerve fibres. In rodents, GLP-1 administration appears to activate neurones in the brainstem, including the arcuate nucleus and paraventricular nucleus to promote satiety [51–53]. Performing a vagotomy with bariatric surgery attenuates these effects [51]. There is also some evidence to support an increase in energy expenditure in rodents [19,53] but this is less clear in humans [19]. GLP-1 may also mediate altered food choices, for example, with increased palatability of less calorie-dense foods in rats [54,55] but work in humans has shown fewer clear effects [54].

Although GLP-1 is widely believed to account for at least some of the beneficial effects of RYGB upon weight and glucose tolerance [56], it is unlikely to account for all of the effects. Jorgensen et al., found that the beneficial metabolic effects of RYGB upon beta-cell sensitivity were obliterated by infusion of exendin-9, a GLP-1 receptor antagonist (GLP1R) [57] suggesting that GLP-1 action is fundamental in achieving improved glucose tolerance after surgery. There is also some evidence that GLP-1 concentrations may be directly related to a patient's individual outcome following bariatric surgery. In their study of 33 patients for one year after RYGB, Dirksen et al., found that levels of GLP-1 were higher in patients who had lost large amounts of weight post-surgery (good responders) compared to those with poor weight loss (poor responders) [19]. However, Wilson-Pérez et al., found that sleeve gastrectomy was still effective in GLP-1 receptor knockout mice suggesting that the GLP-1 receptor is not necessary for benefit and that alternative pathways must also be involved [58]. Mokadem et al., found that RYGB has beneficial metabolic effects in two mouse models of GLP-1 deficiency, and that the results were comparable to RYGB treated control mice [59]. Taken together, this evidence suggests that while GLP-1 may have a role in promoting the beneficial effects of bariatric surgery upon metabolic health, other mechanisms are also likely to play a role and GLP1R agonism alone is not responsible for the complete effect.

One proposed mechanism of action is that the beneficial effects of GLP-1 are mediated through altered gastric motility. Physiologically and pharmacologically, GLP-1 and GLP-1 mimetics have been associated with delayed gastric emptying [60,61], resulting in a more gradual supply of nutrients to the gut, a phenomenon which has been linked to improved glucose tolerance [62]. However, there is some evidence from human studies that GLP-1 may actually be associated with increased gastric transit for liquid calories [44].

A second possible mechanism is that GLP-1 and GIP promote diabetes remission due to their functions as incretin hormones [56]. The incretin effect is the ability of intra-intestinal glucose to stimulate greater insulin production than a similar quantity of intra-venous glucose, and has been attributed to the direct insulinotropic effects of GLP-1 and GIP. In fact, these incretin hormones are likely to account for at least 50% of the postprandial insulin response in humans and animals and appear to be particularly important for the first phase insulin response [63,64].

However, while the incretin effect might account for the improved glucose tolerance after bariatric surgery, increased insulin secretion might be expected to produce weight gain, rather than weight loss. Although GLP-1 is associated with satiety, its role in promoting weight loss following bariatric surgery remains poorly understood.

4.6. GLP-2

L cells are also capable of secreting glucagon like peptide 2 (GLP-2) which is much less clearly understood compared to GLP-1. GLP-2 appears to have a role in stimulating gut hypertrophy by ileal cell hyperplasia and reducing apoptosis [65] and has been used therapeutically in patients with short gut syndrome [66].

Following bariatric surgery, concentrations of GLP-2 appear to be increased in rodents and humans [67,68]. Le Roux et al., found that this increase in GLP-2 was accompanied by crypt cell prolifer-

ation [67]. However, other studies have failed to show any effect of bariatric surgery upon GLP-2 [69].

4.7. PYY

Like GLP-1, PYY_{1-36} is produced by enteroendocrine L cells in the distal small intestine and colon. Following cleavage in the circulation by the enzyme dipeptidyl-peptidase-IV (DPP-IV), PYY_{1-36} is converted to PYY_{3-36} which is considered to promote satiety through its agonism of the Y2 receptor [70]. Although PYY_{3-36} has many effects upon the body including delaying gastric emptying [71], reducing postprandial insulin production [71] and altering colonic motility [72], its main role appears to involve the central regulation of appetite [73]. Observations that postprandial PYY_{3-36} levels appear to be reduced in obese patients compared to healthy volunteers and that PYY_{3-36} infusion reduces caloric intake have led to suggestions that obesity is a state of PYY_{3-36} deficiency [73,74].

Following bariatric surgery, levels of PYY increase postprandially, an effect which is evident two weeks post-surgery and still present after a year [6,75]. This increase in postprandial PYY appears to occur following many different types of bariatric procedure including gastric banding [76], sleeve gastrectomy [40] and RYGB [75]. Rodent knockout models suggest that PYY is an important contributor to weight loss following bypass surgery [77].

4.8. Oxyntomodulin

Oxyntomodulin and glicentin are additional L cell products which, like GLP-1, originate from the proglucagon gene by alternative post-translational processing pathways. Oxyntomodulin is a 37-amino acid peptide hormone which is structurally similar to glucagon with an additional C-terminal octapeptide. However, very little is known about the role of oxyntomodulin in bariatric surgery. Laferrère et al., studied ten obese women with type 2 diabetes before and 1 month after RYGB who were matched with ten women who achieved 10 kg of weight loss through dietary means. Patients who had the RYGB demonstrated a marked increase in oxyntomodulin levels following a 50 g glucose test meal. Fasting levels were similar in the surgical and diet-induced weight loss groups [78]. Other studies have shown similar findings [79]. However, the role of oxyntomodulin in the aetiology of weight loss in other bariatric surgery procedures is still to be elucidated.

Oxyntomodulin appears to be an agonist on both GLP-1 receptors (GLP1R) and glucagon receptors (GCGR) and is considered to be a promising pharmacological agent in the treatment of obesity. Rodent studies confirm that the dual agonism upon GLP1R and GCGR is responsible for more potent metabolic effects compared to GCGR or GLP1R agonism alone [80]. This has given rise to further work identifying alternative GLP1R–GCGR co-agonists with structural similarities [81]. As a weight loss agent, Oxyntomodulin has shown promise in both rodent and human studies. Subcutaneous administration of oxyntomodulin over 4 weeks promotes weight loss in humans and appears to be associated with both an increase in energy expenditure and reduction in food intake with no change in food palatability [82,83].

4.9. Other gut hormones

There are several other gut hormones which may be involved in mediating the effects of bariatric surgery, or which may be altered in secretion rates or function following gastrointestinal surgery. Secretin is a 27 amino acid peptide hormone which is produced by S cells in the duodenal mucosa in response to a low intraluminal pH. It works to promote pancreatic bicarbonate production and reduce the production of gastric acid. Vasoactive intestinal polypeptide (VIP) is a 28 amino acid peptide released by the enteric nervous system and parasympathetic efferent nerve fibres, which acts to increase the secretion of water and electrolytes into the pancreatic juices and the gut itself. It also causes relaxation of gastrointestinal smooth muscle and reduces the production of gastric acid. Pancreatic polypeptide (PP) is a 36 amino acid peptide hormone, production of which is normally attributed to PP cells in the pancreas, but also likely involves gut endocrine cells. It acts to regulate both exocrine and endocrine pancreatic activities via central mechanisms following the ingestion of a meal, especially a high protein meal. PP is thought to play a role in satiation following the observation that infusing PP to human volunteers resulted in a reduction in food intake [6]. Unfortunately very little is known about the effect of bariatric surgery upon these hormones Table 2.

4.10. Insulin

Insulin is a 51-amino acid peptide hormone produced in the pancreatic beta cells which reduces blood glucose concentrations postprandially. Type 2 diabetes mellitus is a disorder of deficient insulin release, often developing in obese individuals who have increased insulin requirements resulting from obesity. Different bariatric procedures have different effects upon insulin secretion. Shak et al., found that fasting insulin levels were unchanged after gastric banding [10]. RYGB and sleeve gastrectomy both seem to have more pronounced effects upon insulin. Mallipedhi et al., found that fasting insulin levels fell one and six months after sleeve gastrectomy [84]. Insulin concentrations also appear to fall after RYGB, an effect which appears to be accompanied by an increase in insulin sensitivity, as measured by the homeostasis model assessment score (HOMA) [79]. Although many studies have demonstrated an increase in insulin sensitivity with the RYGB [6,79,85], there also appears to be evidence of improved beta cell function [85,86]. Jorgensen and coworkers studied 13 patients with obesity and type 2 diabetes following RYGB surgery. Within one week post-surgery, there was a significant reduction in fasting insulin and glucose with improvements in beta-cell sensitivity [86], effects which have been attributed to the beneficial effects of GLP-1 [57].

The ability of bariatric surgery to cause remission or cure of diabetes is presumably related to its ability to improve insulin sensitivity and beta cell function, but the precise mechanisms are imperfectly understood. Undoubtedly, some of the benefit of bariatric surgery on insulin and glucose homeostasis is mediated by weight loss. Indeed, Lim et al., demonstrated that a calorie-restricted diet of 600 kcal/day has the ability to normalise fasting glucose concentrations and improve the first phase insulin secretion in a group of non-surgical patients with type 2 diabetes [87]. Although all forms of bariatric surgery have the potential to exert beneficial effects upon glucose tolerance through weight loss, some procedures, particularly RYGB, are associated with greater improvements in metabolic health than can be explained by weight loss alone [88]. Other procedures, such as gastric banding, have more modest effects upon insulin and glucose which might be explained by weight loss alone [10]. Other studies have found similar beneficial effects upon glucose tolerance following RYGB in non-diabetic subjects [6].

Many studies report different remission rates according to the definitions used [89]. Pories et al., reviewed 298 patients with pre-existing impaired glucose tolerance or type 2 diabetes. Following RYGB, 91% of these patients attained normal glucose tolerance, an effect which persisted for many years for the majority or patients [88]. The achievement of normal glucose tolerance for 1 year without the assistance of active pharmacological therapy or other ongoing procedures is consistent with remission of diabetes, according to the American Diabetes Association (see Table 3) [90].

Short-term, RYGB is associated with around 52% remission of type 2 diabetes. Sleeve gastrectomy is associated with 26% remis-

Table 2
Effects of bariatric surgery procedures upon gut peptides.

Hormone	Obesity (without surgery)	Gastric banding	Sleeve Gastrectomy	Roux-en-Y gastric bypass
Gastrin (7, 10–12)		↔	↑	↓ postprandial
Ghrelin (total) (6, 7, 14, 16–19, 22, 100, 101)	↔ or ↓ fasting ↔ or ↓ postprandial	↑	↓ fasting ↓ postprandial	↓ fasting ↓ postprandial
Cholecystokinin (CCK) (6, 19, 26, 101)	↔ fasting ↔ or ↓ postprandial		↔ fasting ↑postprandial	↔ fasting ↑postprandial
Gastric inhibitory peptide (GIP) (10, 31, 38, 84)	↔	↔ fasting ↔ or ↓ postprandial	↑ postprandial	↔ or ↓ fasting ↔ or ↓ postprandial
Glucagon-like peptide -1 (GLP-1) (6, 19, 22, 40)	↔ or ↓	↔ or slight ↑ fasting Slight ↑postprandial	↔ or slight ↑ fasting ↑postprandial ↑ postprandial	↔ or slight ↑ fasting ↑postprandial ↔ or ↑ postprandial
Glucagon-like peptide -2 (GLP-2)(67, 69)				
Peptide YY (PYY) (6, 73, 74, 76, 77)	↓	↔ or slight ↑ fasting Slight ↑postprandial	↔ or slight ↑ fasting ↑postprandial	↔ or slight ↑ fasting ↑postprandial
Oxyntomodulin(78)				↔ fasting ↑postprandial
Insulin (86, 102)	↔, ↑ or ↓ depending on diabetes status	↔ fasting	↓ fasting ↔ or ↓ postprandial	↓ fasting ↔ or ↓ postprandial
Glucagon (85, 95, 96)	↔ or ↑			↑or ↓ fasting ↔ or ↓ postprandial
Somatostatin (6)				↑ fasting ↑ postprandial

Note that this information is based upon several studies but many areas are controversial and studies have had conflicting results. The table below aims to give a summary of the most consistent patterns. Cells were left blank if evidence was lacking.

Table 3
definitions of diabetes status after bariatric surgery(90).

Definition	Criteria
Improved diabetic control	• A significant reduction in A1C (by >11 mmol/mol or 1%) or • A significant reduction in fasting blood glucose (by >1.4 mmol/l or 25 mg/dL) or • A significant reduction in A1C and FBG accompanied by a decrease in antidiabetic medication requirement • At least 1year's duration
Partial remission	• Hyperglycemia below diagnostic thresholds for diabetes (HbA1c 42–47 mmol/mol; fasting glucose 100–125 mg/dL (5.5–6.9 mmol/)) • At least 1 year's duration • No active pharmacologic therapy or ongoing procedures
Complete remission	• Normal glycemic measures (HbA1c <48 mmol/mol; fasting glucose <125 mg/dl (7.0 mmol/l)) • At least 1 year's duration • No active pharmacologic therapy or ongoing procedures
Prolonged remission	• Complete remission of at least 5 years' duration

sion and gastric banding with 6% remission of type 2 diabetes [91]. Among patients who do not achieve complete remission, many achieve partial remission or an improvement in their diabetic control (Table 3) or improved quality of life [92]. Of patients following RYGB, sleeve gastrectomy and gastric banding respectively, 1%, 4% and 31% have unchanged glucose tolerance [91]. Bariatric surgery also reduces the likelihood of a future diagnosis of diabetes compared to matched controls [93].

4.11. Glucagon

Glucagon is a 29 amino acid peptide hormone produced in the alpha cells of the pancreatic islets. It is released during the fasting state and acts to increase blood sugar levels by promoting glycogenolysis and gluconeogenesis. In general, weight loss leads to reduced circulating concentrations of glucagon [94]. Very few studies have assessed the effect of bariatric surgery upon circulating glucagon concentrations. Korner et al., studied glucagon concentrations in women after gastric banding, RYGB and in a group of overweight control patients ($n = 36$ in total) [95]. Patients were studied at around 24 months post-surgery and were weight stable at the time of the study. The investigators found no difference between fasting glucagon and area under the curve from 0 to 180 min after a liquid meal, but glucagon concentrations at 180 min were significantly lower in patients who had the RYGB compared to the control group. However, different groups have found dif-

ferent effects of surgery upon glucagon concentrations. Umeda et al., studied patients before and up to 3 months after RYGB. Fasting glucagon concentrations increased and postprandial glucagon levels decreased following surgery in response to a liquid meal [85]. Conversely, Swarbrick et al., found low fasting glucagon levels after surgery but their data suggests that reductions in circulating glucagon occur in a gradual manner and only became significantly different to baseline levels at three months [96]. It is unclear if this reduction occurred independently of weight loss.

4.12. Somatostatin

Somatostatin is peptide hormone produced by delta (or D) cells in the pancreas, stomach and duodenum. The preprohormone can be cleaved at two different locations giving two forms of 14 and 28 amino acids in length which both have biological activity. Somatostatin regulates the secretion of multiple other hormones. In the gastrointestinal tract, it reduces the secretion of gastrin, secretin, CCK, GIP and GLP-1. In the pituitary, it reduces secretion of growth hormone, thyroid stimulating hormone and prolactin. In the pancreas, it reduces production and secretion of insulin and glucagon and inhibits exocrine secretion. A somatostatin analogue, Octreotide, has been found to cause reduced adiposity in rats fed a high-fat diet [97]. A human study has suggested that somatostatin infusion inhibits release of PYY in obese women [98].

The role of somatostatin following bariatric surgery is unclear. Jacobsen et al., found that fasting and postprandial levels of somatostatin in venous blood were unchanged in 8 obese non-diabetic patients two weeks after undergoing RYGB [6]. However, as somatostatin exerts some of its actions in a paracrine manner, circulating venous concentrations may not adequately represent altered physiological actions, and two weeks may be too early to see any effect. The contribution of gastrointestinal somatostatin secretion to circulating somatostatin concentrations is also unclear. Other reports have suggested that an older procedure, jejunoileal bypass, affects somatostatin cell density [25].

5. Conclusions

Bariatric surgery remains the only treatment with proven effect at inducing rapid and sustained weight loss with related beneficial metabolic effects such as remission of type 2 diabetes. A range of different surgical approaches have been attempted in the past, but current practice centres around gastric banding, sleeve gastrectomy and RYGB.

Studies of peptide hormone concentrations after bariatric surgery have often found conflicting results. This may in part relate to differences of timing after the procedure, as it may take up to a year or more to reach a steady state (for example, [96]). Weight loss itself can cause changes in peptide hormone secretion, even in the absence of bariatric surgery [87] and it is difficult to evaluate the effects of surgery independently of weight loss in the initial months after surgery. Many studies measure either fasting or postprandial concentrations of hormones and a wide variety of meal tests have been used in the literature. It is quite likely that different meal tests will have slightly different effects upon hormone secretion due to different nutrient composition. Assays for many peptide hormones are challenging due to the structural heterogeneity of the molecules. A range of different assays are in use for measuring peptide hormone concentrations and this may also contribute to the differences between studies.

The beneficial effects of bariatric surgery are still poorly understood, but are most likely to be multifactorial in aetiology. Increases in satiety-promoting hormones, reductions in hunger-promoting hormones, reduced food intake (at least in the early post-surgery phase), central effects, altered bile acid metabolism and altered intestinal microbiota may all play a role. Indeed, weight loss itself is associated with beneficial metabolic effects [87] and altered gut hormone secretion but bariatric surgery appears to create circumstances where weight loss can be maintained in the long term.

The effect of bariatric surgery upon glucose tolerance is likely to be related to increased production of the incretin hormone, GLP-1, which has a profound insulinotropic action, coupled to the improved insulin sensitivity resulting from weight loss. The effect of bariatric surgery upon weight loss is less clear. It is possible that the acute calorie restriction which occurs immediately post-surgery, coupled with a beneficial hormonal milieu promotes weight loss which, unusually, can be maintained over the long-term. This may, at least in part, be related to sustained increases in satiety-promoting peptides (GLP-1, GIP, PYY_{3-36}, oxyntomodulin, gastrin) and reductions in hunger-promoting factors (ghrelin).

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Glossary

CCK: Cholecystokinin
DPP-IV: Dipeptidyl-peptidase-IV
GCGR: Glucagon receptor
GHSR: Growth hormone secretagogue receptor
GIP: Gastric inhibitory peptide
GLP-1: Glucagon like peptide-1
GLP1R: Glucagon like peptide-1 receptor
GOAT: Ghrelin-O-acyltransferase
HOMA: Homeostasis model assessment
PP: Pancreatic polypeptide
PYY: Peptide YY
RYGB: Roux-en-Y gastric bypass
T2DM: Type 2 diabetes mellitus
VIP: Vasoactive intestinal polypeptide