REVIEW

Bariatric surgery and obesity: influence on the incretins

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The gut hormone incretins have an important physiological role in meal-related insulin release and post-prandial glucose control. In addition to weight loss, the incretin hormones have a role in glucose control after bariatric surgery. The release of incretins, and specifically of glucagon-like peptide (GLP)-1, in response to the ingestion of nutrients, is greatly enhanced after gastric bypass (RYGBP). The rapid transit of food from the gastric pouch to the distal ileum is responsible for the greater GLP-1 release after RYGBP. The incretin effect on insulin secretion, or the greater insulin response to oral glucose compared to an isoglycemic intravenous glucose challenge, is severely impaired in patients with type 2 diabetes, but is recovered rapidly after RYGBP. The improvement in insulin secretion rate and β-cell sensitivity to oral glucose after RYGBP is mediated by endogenous GLP-1, and is abolished by exendin 9–39, a specific GLP-1 receptor antagonist. While calorie restriction and weight loss have major effects on the rapid and sustained improvement of fasted glucose metabolism, the enhanced incretin effect is a key player in post-prandial glucose control after RYGBP.

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INTRODUCTION

The intestinal hormone incretins, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are responsible for 50% of post-prandial insulin secretion and have an important role in the physiology of glucose metabolism.[1] Surgical weight loss, a treatment of choice for severely obese individuals, is accompanied by the resolution or improvement of type 2 diabetes.[2,3] The predictors of diabetes remission after bariatric surgery include shorter diabetes duration, the type of surgical procedure and the amount of weight loss post-surgery.[4–6] However, improvement in glucose control after RYGBP or VSG occurs rapidly, and may involve mechanisms independent of weight loss.[7,8] Past studies suggest that some hormonal gut signals, including GLP-1 and gut-brain neuronal pathways, could be responsible for glucose control, independent of weight loss. Here, the evidence for a role of GLP-1 in glucose control after RYGBP will be reviewed, and its limitations discussed.

IMPORTANCE OF THE INCRETIN EFFECT IN PHYSIOLOGY

The incretin effect

The incretin effect is the greater insulin response to oral glucose compared to an isoglycemic intravenous glucose load. Two hormones, GLP-1 and GIP, secreted by gut endocrine cells in response to nutrient ingestion, are responsible for the incretin effect, that is, the enhancement of glucose-stimulated insulin secretion (GSIS).[9,10] In 1870, Claude Bernard was the first to discover that glucose tolerance was better after an oral glucose load than after an intravenous glucose load; he thought the liver was responsible for uptake of glucose after ingestion, to prevent hyperglycemia. La Barre and Heller[11] identified the glucose-lowering properties of duodenal extracts when administered intravenously, and La Barre named it 'incretin'. Once radio-immunoassays became available[12] the incretin effect was

characterized. McIntyre showed that a rapid infusion of 60 g of glucose in the jejunum of one man resulted in a much greater insulin response compared to the intravenous administration of an equivalent glucose load, despite of lower glycemic levels after the jejunum infusion. McIntyre concluded that factors other than arterial glycemia must be responsible for insulin secretion.[13] The incretin effect was soon quantified, with a ~ 40% greater insulin release after oral compared to a matched intravenous glucose load in healthy normal weight and obese subjects.[9] About 30 years after the term 'incretin' was coined, GIP was identified as one of the main incretins. Its original name, gastric inhibitory peptide, referring to the pharmacological role of the peptide to decrease acid secretion, was later changed to glucose-dependent insulinotropic peptide, to reflect its physiological incretin effect. About 10 years later, GLP-1 was isolated and recognize as a key incretin.[14] Thus the incretin effect, the augmented response of insulin after oral glucose compared with matched intravenous glucose, or the enhancement of GSIS, is mediated by the two incretin hormones GLP-1 and GIP, released from gut endocrine cells in response to meals and acting on the β-cell to stimulate insulin secretion.[15]

GIP and GLP-1

The release of the incretins GIP and GLP-1 is proportional to the calorie load, with fat and carbohydrate providing the main stimulants.[16–18] GIP and GLP-1 are responsible for maintaining euglycemia in spite of highly variable oral loads. The concentration of post-prandial circulating incretins is ~ 30 pM for GLP-1 and 300 pM for GIP. Incretin circulating concentrations are often not different between lean, obese and individuals with type 2 diabetes.[19] However, the incretin effect on insulin secretion is blunted in patients with diabetes.[17,20] The administration of exogenous pharmacological doses of GLP-1, or of GLP-1 analogs, restores insulin secretion and lowers blood glucose in patients with diabetes. The effect of GIP on insulin secretion can be

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restored after lowering glycemia.[21] Both GLP-1 and GIP have a trophic effect on the β-cell, as demonstrated in vitro and in vivo in rodent studies.[22–25] GLP-1 has other important physiological effects, including potentiation of GSIS in the post-prandial setting, suppression of glucagon, slowing of gastric emptying, decrease of body weight and favorable cardiovascular protection,[1,26] that makes it an attractive tool for the treatment of overweight or obese individuals with diabetes. The half-life of GLP-1 and GIP is only few minutes and both incretins are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4). DPP-4 inhibitors and long-acting GLP-1 analogs are now used in clinical practice to treat diabetes, and GLP-1 analogs were recently approved for by the Food and Drug Administration for weight loss (2014; Table 1).

RYGBP ALTERS INCRETIN PHYSIOLOGY

RYGBP enhances incretin release

With the availability of commercial kits for measuring GIP and GLP-1, publications reporting incretin levels after RYGBP abound (Table 2). Circulating concentrations of GLP-1 and GIP increase after a mixed meal and/or an oral glucose load, by a factor 10 and 1.5, to reach peak levels of ~ 100 and 300 pM, respectively, after RYGBP. The effect of RYGBP on GLP-1 is robust [27] and reported in many studies (Table 2). In over 100 participants studied after RYGBP, all were 'responders' and had large increase in GLP-1 after either a meal test or glucose tolerance test. The enhancement of GLP-1 is sustained many years after RYGBP, although the magnitude of GLP-1 levels may vary overtime.[28] The effect of RYGBP on GIP is less consistent. GIP was shown to either increase,[29] not change or decrease,[30–32] after RYGBP. GIP is secreted from the upper gastrointestinal tract, part of which is bypassed after RYGBP. The difference in GIP levels after RYGBP among studies may be related to variation in surgical techniques with different lengths of the bypass segment or bilio-pancreatic limb, or to diabetes status of study subjects.

The rate of delivery of the nutrients to the lower intestine is the main trigger of greater release of GLP-1 after RYGBP.[33–35] RYGBP surgical procedure involves the creation of a small gastric pouch (~30 ml) and a gastrojejunal anastomosis, resulting in the shunting of the larger part of the stomach, pylorus, duodenum and upper jejunum from ingested food. Gastric emptying of liquid is accelerated after RYGBP[33,36–38] and GLP-1 peak levels correlate positively with measures of gastric pouch emptying.[33] The enhanced GLP-1 release after RYGBP is blunted if the meal is administered directly in the gastric remnant[39,40] or at a slow rate directly in the jejunal alimentary limb.[41]

Recovery of the incretin effect after RYGBP

The incretin effect, blunted in patients with type 2 diabetes,[20] was shown to increase to levels of normal glucose tolerant individuals 1 month after RYGBP in patients who underwent diabetes remission.[29] However, the incretin effect was not restored in weight-matched subjects who underwent equivalent 10% total weight loss by calorie restriction, demonstrating that the improvement in the incretin effect after RYGBP is weight loss independent.[7] The release of incretins GLP-1 and GIP, and the recovery of the incretin effect, persists years after surgery in patients in diabetes remission (Laferrère, unpublished). So, interestingly, very elevated incretin levels are associated with normalization of the incretin effect after RYGBP. This raises the question of relative β-cell insensitivity to the incretins after the surgery. However, the insulinotropic effect of GIP and GLP-1 is preserved in patients with normal glucose tolerance after RYGBP.[42] Whether this is also true in patients with diabetes is unknown.

Trophic effect of GLP-1 on the β-cell

GLP-1 has been shown to have a trophic effect on the pancreas in vitro and in rodent models.[22–25] A recent study in pigs showed increased islet number and β-cell proliferation after RYGBP, in parallel with a rise in GLP-1, demonstrating the effect of RYGBP on the plasticity of the endocrine pancreas in this animal model.[43] Whether this is true in humans is unknown. It is legitimate to hypothesize that the chronic and sustained elevation of post-prandial GLP-1 after RYGBP[28,44] could have a long-term trophic effect on the human β-cells in vivo; however, this is unknown. However, there is little evidence that chronic use of GLP-1 analogs,

Table 1. Physiological effect of GLP-1 and GIP

	GIP	GLP-1
Peptide, AA	42	30/31
Released from	Duodenum (K cells)	Distal bowel, colon (L cells)
Circulating concentrations	60 pmol/l (200–500 pmol l^{-1})	5–10 pmol l^{-1} (20–40 pmol l^{-1})
NH2-inactivation/DPP-4	+	+
Effect on beta cell		
GSIS	↑	↑↑
Glucose sensitivity	?	↑
Insulin biosynthesis	↑	↑
Differentiation of precursors	↑	↑
Apoptosis	↓	↓
Alpha-cell/glucagon secretion	↔/↑	↓
Gastric emptying	↔	↓↓
Food intake	↔	↓
Body weight	↔	↓
Additional effects		
Neuroprotection	↑	↑
Cardioprotection	?	↑
Renal (diuresis, natriuresis)	?	↑
Bone formation	↑	↔
Response to T2DM	Defective/preserved under normoglycemia	Preserved

Abbreviations: AA, amino-acids; DPP-4, dipeptidyl peptidase inhibitor; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; GSIS, Glucose-stimulated insulin secretion; T2DM, type 2 diabetes.

Table 2. Change of GLP-1 and GIP after bariatric surgery

Reference	Surgery	Obese/T2DM	Stimulus	GLP-1	GIP
Sarson,[71,72]	RYGBP	OB	Meal		↓
Halverson[73]	RYGBP	OB	OGTT		↑
Sirinek[69]	RYGBP	OB	OGTT		↓
Naslund[74]	JIB	OB	Meal	↑	↑
Verdich[75]	Diet	19 OB / 12 lean	Meal	↑	↓
Valverde[76]	BPD/VBG		OGTT	↑	
Korner[77]	RYGBP	OB/Lean	Meal	↑	↓
Borg[78]	RYGBP	OB	Meal	↑	
Morinigo[33]	RYGBP	OB	Meal	↑	
Laferrère[29]	RYGB	OB/T2DM	OGTT	↑	↑
Jorgensen[79]	RYGB	OB/T2DM/NGT	Meal	↑	—
Jacobsen[80]	RYGB	OB	OGTT	↑	—
Romero[81]	VSG/RYGB	OB/T2DM	Meal	↑	↑
Mallipedhi[82]	SG/BPD	IGT/T2DM	OGTT	↑	↓
Plourde[83]	BPD	T2DM/NGT	Meal	↑	↓
Kim[32]	RYGBP	Lean T2DM	OGTT	↑	↓

Abbreviations: BPD, bilio-pancreatic diversion; IGT, impaired glucose tolerant; JIB, jejuno-ileal bypass; OB, obese; OGTT, oral glucose tolerance test; NGT, normal glucose tolerant; RYGBP, Roux-en-Y gastric bypass surgery; VBG, vertical banded gastroplasty; VSG, vertical sleeve gastrectomy.

in patients with type 2 diabetes, restores and/or prevents the deterioration of β-cell function.[45] Some cases of severe hypoglycemia have been associated with nesidioblastosis after RYGBP.[46] The neuroglycopenia can be prevented by exendin 9–39, a specific GLP-1R antagonist.[47] The association of nesidioblastosis and RYGBP, and the documented effect of endogenous GLP-1 in the control of post-prandial glucose, together with animal data, suggest, but do not prove, that GLP-1 may, with other growth factors yet to be identified, be involved in the stimulation of islet growth after RYGBP. However, this remains speculative. More long-term clinical studies of β-cell function coupled with improved tools for imaging the pancreas are needed, as well as post-mortem studies of the pancreas after RYGBP.

ANTAGONISM OF GLP-1 PREVENTS THE IMPROVEMENT IN B-CELL FUNCTION AFTER RYGBP

The main effect of the incretins is enhancement of GSIS. To identify the role of endogenous GLP-1 in the amelioration of impaired β-cell function after RYGBP, the specific GLP-1 receptor antagonist exendin 9–39 has been used in four cross sectional[48–51] studies and one short-term longitudinal[52] study in post-RYGBP patients. Exendin 9–39 completely blunts the recovery of β-cell glucose sensitivity (BCGS) 1 week and 3 months after RYGBP,[52] and worsens post-prandial glucose tolerance, although only minimally.[49] Exendin 9–39 suppresses insulin secretion in response to a meal by 50%[49,50] and corrects the profound reactive hypoglycemia in patients with severe neuroglycopenia.[50] Thus, clearly, the exaggerated GLP-1 response to ingestion of food or glucose has a key role in post-prandial insulin secretion and glycemic control after RYGBP. But, whether it is the main factor driving the high rate of diabetes remission after RYGBP is perhaps less clear.[47,53–57]

LIMITS OF THE ROLE OF GLP-1 IN T2DM REMISSION AFTER RYGBP

Diabetes relapse
There is little evidence that GLP-1 is important for long-term sustained diabetes remission after RYGBP. Although GLP-1 levels remain elevated years after the surgery, diabetes relapse occurs in a large percentage of patients. In the Swedish Obese Subjects (SOS) study, the high rate of diabetes remission at 2 years, 72.3%, drops to 38.1% at 10 years and 30.4% at 15 years.[58] In another study, based on retrospective review of electronic charts, one third of patients, who initially went into diabetes remission after RYGBP, relapsed within 5 years.[6]

Lessons from rodent models
Although data in humans and pigs support a role for GLP-1 in controlling glucose metabolism after RYGBP, experiments with knock-out animal models challenge the role of GLP-1 in the control of body weight and glucose after RYGBP or vertical sleeve gastrectomy (VSG). Berthoud et al.[59] showed that obese GLP-1R-deficient mice lost the same amount of body weight and fat mass and maintained similarly lower body weight compared with wild-type mice after a RYGBP-like procedure.[59] GLP-1 levels are also enhanced after VSG in humans[60] and rodents,[61] and are thought to be a mediator of diabetes remission after this surgery.[62] However, VSG-operated GLP-1R-deficient mice respond similarly to wild-type controls in terms of body weight loss, improved glucose tolerance, food intake reduction, and altered food selection.[63] These data demonstrate that GLP-1 receptor activity is not necessary for the metabolic improvements induced by VSG or RYGBP surgery in these animal models. As these experiments were conducted in whole body knockouts from birth, developmental compensation could be a reason for these

conflicting results. The relevance of these knockout experiments to clinical observations is therefore unclear.

Small and identical improvement in β-cell response to IV glucose after RYGBP and caloric restriction
To assess β-cell function, BCGS and the disposition index (DI), or the simplified relationship between insulin secretion and insulin sensitivity, were measured. Both measures were calculated using data from an oral glucose load and from a matched isoglycemic IV glucose load, collected on separate days, in patients with type 2 diabetes and severe obesity. Data were collected before surgery, and at one month, then yearly for three years after RYGBP. Prior to surgery, BCGS after either an oral or an IV isoglycemic glucose challenge, was, as expected, significantly impaired in patients with T2DM compared to lean controls, and to obese controls with normal glucose tolerance (NGT), matched for BMI. After RYGBP, all patients were in diabetes remission (HbA1C < 6.5%, fasting glucose < 7.0 mmol l^{-1} (or 126 mg dl^{-1}), on no diabetes medications). The BCGS and DI measured with the oral glucose test parameters improved rapidly at 1 month and normalized to the levels of the lean and the obese NGT controls at one year.[64] However, BCGS and DI measured after IV glucose administration improved only minimally and remained greatly impaired compared to that of the lean and obese NGT non-operated controls.[64] This experiment highlights the role of the incretins and other gut-mediated factors in the amelioration of β-cell response to oral nutrients after RYGBP. It also clearly shows a persistent β-cell defect that cannot be rescued with an IV glucose challenge, 3 years after the surgery, even in persons who are in clinical diabetes remission. In humans, there is no evidence to date for a full recovery of β-cell function to IV stimuli after RYGBP.[64] This goes against a trophic role of GLP-1 on human β-cell after RYGBP.

Weight loss by either calorie restriction[65,66] or by RYGBP[67,68] improves insulin sensitivity. In a separate study, individuals studied before and after RYGBP were compared to individuals studied before and after an equivalent 10% weight loss by caloric restriction, with or without laparoscopic adjustable gastric banding (LAGB). BCGS and DI after IV glucose stimulus improved significantly and similarly after the two modes of weight loss. Others also have shown that a matched 20% weight loss by either RYGBP or adjustable gastric banding (LAGB) result in similar improvement of insulin sensitivity.[67,68] These data demonstrate that the amount rather than the method of weight loss is important for the increase in insulin sensitivity. However, the greater improvement in β-cell function measured during an oral glucose challenge, after RYGBP compared with diet weight loss [7,69] underscores the importance of the engagement of the gut and the incretin effect, rather than weight loss, in the metabolic response to nutrient ingestion after RYGBP.[70]

CONCLUSION
Surgical weight loss is associated with a remarkably high rate of type 2 diabetes remission. Decreased calorie intake and weight loss, together with β-cell reserve, are likely to be the major determinants of long-term glucose control after any bariatric surgery. The effect of bariatric surgery on insulin sensitivity is highly dependent on weight loss. The effect of the incretin hormones on post-prandial insulin secretion and glucose control is amplified after RYGBP, as a result of the accelerated transit of ingested nutrients. The enhanced GLP-1 secretion rescues β-cell function during meals, independent of weight loss, after RYGBP. The incretin effect, observed only during meals, may only have a limited role in diabetes remission after RYGBP. Future studies may shed light on the link between other factors such as bile acids, gut microbiota, gut remodeling and the incretins with weight and metabolic outcomes after RYGBP.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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