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REVIEW

GIP and Bariatric Surgery

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Abstract Bariatric surgery is the most effective modality of achieving weight loss as well as the most effective treatment for type 2 diabetes mellitus (T2DM). Glucose-dependent insulinotropic polypeptide (GIP) is an incretin and is implicated in the pathogenesis of obesity and T2DM. Its role in weight loss and resolution of T2DM after bariatric surgery is very controversial. We have made an attempt to review the physiology of GIP and its role in weight loss and resolution of T2DM after bariatric surgery. We searched PubMed and included all relevant original articles (both human and animal) in the review. Whereas most human studies have shown a decrease in GIP post-malabsorptive bariatric surgery, the role of GIP in bariatric surgery done in animal experiments remains inconclusive.

Keywords GIP · GLP-1 · Bariatric surgery · TCF7L2 · RYGB · LAGB · Sleeve gastrectomy · Ileal transposition · BPD

Introduction

Bariatric surgery is currently the most effective treatment for morbid obesity. It also causes resolution of the co-morbidites associated with obesity such as type 2 diabetes mellitus (T2DM), hypertension, gastroesophageal reflux, dyslipidemias, obstructive sleep apnea, etc. The mechanism by which bariatric surgery causes weight loss as well as resolution of T2DM is a topic of ongoing research, intense debate, and controversy. Traditionally, restriction of food intake and malabsorption were thought to be the only mechanisms by which bariatric surgery caused weight loss and this weight loss ameliorated T2DM. Bariatric surgery causes changes in hormones like leptin, ghrelin, glucose-dependent insulinotropic polypeptide (GIP), glucagon-related peptide-1 (GLP-1), and adiponectin, just to name a few important ones. GIP is one such hormone whose role in the physiology of obesity and T2DM and whose changes after bariatric surgery are controversial. In this review, we make an attempt to understand the role of this hormone after bariatric surgery using available animal and human studies.

Dupré and co-workers attempted to identify insulin secretagogues in intestinal extracts and observed that similar impure preparations of CCK-PZ to those used by Brown (see below) improved glucose tolerance when infused intravenously. Brown and co-workers demonstrated that further purification of CCK-PZ resulted in the removal of a factor that powerfully inhibited acid secretion in dogs. The compound responsible was later isolated from porcine intestinal extracts and named "gastric inhibitory polypeptide" or "GIP". Later experiments showed that it has negligible action on the human stomach, and as the incretin effect was more important physiologically, it was renamed as glucose-dependent insulinotropic polypeptide [1].

Physiological Role of GIP in Humans

We have made a brief mention of the physiological role of GIP; there are other extensive reviews available on the topic [1].

- It is a physiological incretin that causes glucose-dependent insulin secretion. It acts through G protein-coupled receptors with calcium and cAMP as second messengers [2, 3].

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- GIP causes a postprandial rise of glucagon [4].
- It prevents apoptosis and causes proliferation of beta cells [5–7].
- It promotes glucose absorption in the small intestine by increasing the number of GLUT1 receptors [8–10].
- GIP causes glucose uptake, conversion of glucose to fatty acids, and deposition of fat in the adipose tissue [11–13]. It promotes lipoprotein lipase activity.
- It prevents bone resorption and increases bone formation [14, 15].
- Though initially called as gastric inhibitory peptide, later studies revealed that it has a negligible role in gastric motility or secretion [16].

GIP is a 42 amino acid polypeptide which is rapidly degraded in the plasma by the enzyme dipeptidyl peptidase 4 (DPP-4) to GIP (3–42), which is biologically inactive. DPP-4 is located on the cell surfaces of endothelial and epithelial cells. Metabolism of GIP is no different in obese diabetic subjects [17]. Minor pathways of GIP elimination, which do not affect its biological activity, include degradation by neprilysin and renal secretion [18].

Role of GIP in Type 2 Diabetes and Obesity

Impairment of GIP action is suspected to play a role in obesity and diabetes. Obese and glucose-intolerant individuals have higher levels of basal and stimulated GIP levels compared to lean subjects [19, 20]. GIP promotes obesity and increased peripheral insulin resistance as has been shown in animals [21]. Hyperinsulinemia (both fasting and postprandial) has been shown to positively correlate with increased postprandial GIP in subjects with impaired glucose tolerance [22].

Obese diabetic patients have been suspected to have resistance to action of GIP, specifically for the late phase of insulin secretion [23]. This has been shown by a higher postprandial ratio of the incremental increase in GIP to incremental increase in insulin in impaired glucose-tolerant and diabetic patients when compared to normal individuals. The cause of this GIP resistance is down-regulation of GIP receptors in type 2 diabetic patients [24]. Hyperglycemia is thought to contribute to GIP resistance directly, and reversal of hyperglycemia has been shown to reverse GIP receptor downregulation [25]. In fact, it has been shown that decreased incretin effect is not a primary phenomenon in T2DM but rather develops due to the diabetic state [26].

In a landmark experiment by Vilsboll et al., it was found that only the late phase of insulin secretion by GIP was affected while the early phase was normal. Both early and the late phases of insulin secretion were normal when GLP-1 was administered. Hence, it may be possible that there is no decrease in the functional GIP receptors in impaired glucose tolerance and diabetes. The defect in just the late phase of insulin secretion may be due to a post-receptor defect. Many authorities hypothesize that this may be genetically acquired as the reduced insulinotropic effect of GIP has been found in first degree relatives of type 2 diabetic patients [27, 28].

It is important to note that certain polymorphisms of TCF7L2 protein are associated with GIP resistance [29]. GIP resistance causes high GIP levels. Patients consuming greater amount of fat in their food have been shown to have a longer GIP postprandial response. Animal experiments have shown that high fat diet causes a proliferation of GIP producing K cells in the duodenum. Hence, the type of diet may influence the development of obesity and insulin resistance mediated by GIP [30, 31].

When impaired glucose tolerance leads to clinical diabetes, there is both a decreased beta cell function and insulin release and also a decreased K cell function and GIP release. This indicates that there is a common pathway of resistance that eventually leads to a failure of glucose responsiveness in beta and GIP cells [22].

To summarize, GIP is elevated in obesity and T2DM and contributes to insulin resistance and defective glucose stimulated insulin secretion seen in this condition. Thus, a decrease in GIP or a blockade in its action will be useful for an obese type 2 diabetic patient. The pathophysiology of obesity and T2DM with respect to GIP is summarized in Fig. 1.

How Is the GIP Different from the Better Known Incretin GLP-1?

The differences are summarized in Table 1.

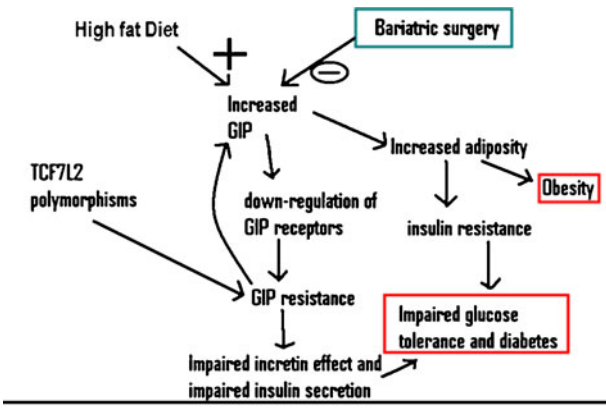

Fig. 1 Role of GIP in the pathogenesis of obesity and type 2 diabetes—bariatric surgery acts by decreasing GIP levels

Table 1 Differences in the administration of GIP and GLP-1

	GIP	GLP-1
Source	K cells in proximal small bowel	L cells in distal small bowel
Half life in plasma [64]	7 min	2 min
Increase after food	>10 times	2–3 times
Glucagon secretion [65]	Increase	Decrease
Gastric motility [66]	No significant effect	Decrease
Effect on adipose tissue [67]	Lipogenesis	Lipolysis
Late phase of insulin secretion in diabetes	Administration of GIP unable to normalize[a]	Administration of GLP-1 can normalize
Action on GLUT2 transporters in small intestine [10]	Increased in number	No effect
Altered physiology in type 2 diabetes	GIP resistance of islet cells	Preservation of GLP-1 action on islets
Pharmacotherapy	Not proven to be useful in T2DM	Proven to be useful in T2DM

[a] It is interesting to note that GIP and GLP-1 administration can both normalize the first phase of insulin secretion

How Does Bariatric Surgery Cause a Change GIP?

GIP is secreted by the K cells present in maximum concentration in the duodenum and jejunum (though GIP is secreted throughout the small intestine). The duodenum and a part of the jejunum are excluded in Roux-en-Y gastric bypass (RYGB). The whole of duodenum and jejunum is bypassed in biliopancreatic diversion (BPD-DS). This results in a lack of exposure of the K cells to nutrients and less secretion of GIP. This correlates with decreased GIP seen after malabsorption procedures (see later). In a study by Rudnicki et al. on rats, it was found that the presence of food and bile is necessary for the secretion of GIP. This was accomplished by doing a Roux-en-Y cholangiojejunostomy in one group of rats and doing a jejunal bypass in another group. The former group had a higher insulin response while the latter had a lesser insulin response to oral glucose when compared to sham-operated animals. This experiment highlights the importance of bile in mediating secretion of a factor from the proximal intestine. In both RYGB and BPD, the food in the alimentary limb is not exposed to bile, thus possibly preventing the secretion of the factor from the proximal intestine. GIP can explain the findings of this experiment as preventing exposure of the proximal gut to digested food (food + bile) causes decreased secretion of GIP. GIP as explained before causes insulin resistance, hyperinsulinemia, and increased glucose levels, all of which are ameliorated in animals undergoing just a jejunal bypass [32].

Role of GIP in Bariatric Surgery—Is It the Hormone Behind Foregut Theory?

Two theories have been proposed to explain the resolution of T2DM after bariatric surgery. The hindgut theory is based on the secretion of a hormone secreted due to exposure of the hindgut to nutrients: this hormone is believed to be GLP-1. The foregut theory is based on the change in secretion of a putative hormone due to exclusion of the foregut, which is responsible for resolution of diabetes. GIP due to its site of secretion has been regarded as one of the hormones possibly involved in the foregut theory.

The foregut theory was originally proposed by Walter J. Pories and Albrecht in 1998. They suggested that diabetes was due to overstimulation of the foregut in vulnerable individuals which led to hyperinsulinemia, insulin resistance, and hyperglycemia [22]. Further research on the topic was done by Dr. Francisco Rubino and Dr. Michael Gagner. They proposed an anti-incretin theory—stimulation of the proximal gut led to production of unknown factors which antagonized the production and/or action of incretins. They suggested that this anti-incretin is a yet unidentified substance which counteracted the action of GIP, the proximal bowel incretin. This is plausible as diabetic patients have a defective action of GIP [33].

There may also be a biologic basis for the hindgut and foregut theories. It may be noted that the carnivores have bigger abdomens and larger intestines than their carnivore counterparts. This is because carnivores eat a more enriched and easily absorbed diet and need to have a shorter gut to prevent excessive absorption in the proximal gut and absence of any nutrients in the distal gut which predispose the animal to diabetes. If a person with a longer gut suddenly switches to a diet which is easily absorbable, it will result in excessive stimulation of the proximal gut and inhibition of the distal gut (due to absence of nutrients reaching it), thus resulting in diabetes and the metabolic syndrome. Thus, surgeons are now faced with the problem of "long gut syndrome".

There has been a debate whether the foregut theory or the hindgut theory is relatively more important for the control of diabetes after bariatric surgery. In an experiment using Wistar rats by de Campos Martin et al., it was found

that glucose tolerance was improved with the "hindgut" operation but not with the "foregut" operation [34]. In a human experiment, nutrients were infused into only the proximal small intestine (<60 cm—short segment infusion) on 1 day and the entire intestine (long segment infusion) the next day. There was increased GLP-1 along with increased insulin secretion during long segment infusion only, but increases in GIP levels were not different between the 2 days. This again favors the hindgut theory and GLP-1 as the cause of resolution of diabetes post-bariatric surgery. Interestingly, ghrelin levels were decreased on the second day when the entire intestine was infused [35]. In an experiment by Rubino et al. using Goto Kakizaki rats, it was found that a duodenojejunal bypass improved glucose tolerance compared to a gastrojejunostomy without bypass of any intestine [36].

Further evidence to support the foregut theory has come in the form of the endoluminal sleeve device. The device is composed of a self-expanding implant that is placed in the duodenum and is attached to a 60-cm plastic sleeve that extends into the proximal jejunum. This device has been able to decrease Hb1Ac levels in obese diabetic subjects [37].

Wang et al. showed in an experiment using a non-obese rat model that the duodenojejunal bypass (a foregut operation) and the ileal transposition (a hindgut operation) are equivalent in terms of weight loss and decrease in blood glucose levels. Ileal transposition produced a more rapid and a greater increase in GLP-1 when compared to duodenojejunal bypass [38].

It is possible that the hindgut and foregut hypotheses work in tandem to cause diabetes remission after bariatric surgery and both theories may be true. Further studies may help in elucidating this. Applying the hindgut and foregut theories, it is possible to attribute the current obesity epidemic to the modern diet. Meals containing easily digestible nutrients and less of fiber are primarily absorbed in the proximal gut resulting in an empty distal gut. The modern diet is an example of such a diet which has caused overstimulation of the proximal gut and understimulation of the distal gut [39, 40].

Evidence from Animal Models

Duodenojejunal bypass is a variation of human Roux-en-Y gastric bypass and has been done in rat models. In the recent experiment by Kindel et al. using Wistar rats, it was found that GIP levels in plasma and lymphatics did not significantly change. But they found increased GIP levels in the jejunum, the new site of nutrient absorption, and found no change in the level of GIP in the bypassed segment [41]. Strader et al. found no change in plasma GIP levels after ileal transposition in rats [42]. Rubino et al. found that GIP levels decreased after duodenojejunal bypass in Goto Kakizaki rats, but these hormone levels were not different from sham-operated controls [43]. Pacheco et al. also found no change in post-glucose overload levels of GIP after gastrojejunal bypass [44]. Thus, there are conflicting data in animal experiments that do allow one to draw any firm conclusions.

Animal (mice) studies have also revealed that GIP antagonism can be useful for the treatment of obesity and diabetes. No human studies using GIP pharmacotherapy are available [45, 46].

Evidence from Human Studies

RYGB

In the study by Whitson et al., it was found that there was no change in GIP levels 6 months postoperatively in both diabetic and non-diabetic patients after RYGB. It is notable that this study did not detect any postoperative change in diabetic patients with respect to ghrelin and GLP-1, which is definitely untrue given studies with better design. Nevertheless, equal weight loss was found in diabetic and non-diabetic patients. The samples were non-fasting and post-prandial samples were not measured which can partially explain the results obtained. Patients were used as their own controls. Hormone assays were done 6 months postoperatively. The assay used had a sensitivity of 0.7 and a specificity of 91% [47].

In a cross-sectional study by Korner et al., it was found that GIP secretion was decreased postprandially after a liquid meal in gastric bypass patients compared to overweight controls and gastric banding (LAGB) patients as was shown by a decreased area under the curve for GIP and blunted peak response in RYGB patients. Even though the fasting GIP levels were lower in RYGB patients compared to overweight controls, they did not reach statistical significance. The mean postoperative period was 24.6± 2 months. Unlike in a previous study, obese patients were used as controls. All the patients were non-diabetic and were weight stable. For the GIP radioimmunoassay, they used the C terminally directed antiserum R 65, which cross-reacts fully with human GIP, but not with the so-called GIP 8000, whose chemical nature and relationship to GIP secretion is uncertain. The antiserum reacts equally with intact GIP and GIP 3–42, the primary metabolite [48].

Rubino et al. found that fasting GIP levels were reduced after RYGB only in diabetics but not in non-diabetics. Postoperative values were measured 3 weeks after surgery. Patients were used as their controls and only fasting samples were measured [49].

Clements et al. found that GIP started decreasing at 2 weeks postoperatively to attain statistical significance at

6 weeks and remained significantly decreased at 12 weeks. Only fasting samples were measured. All patients were diabetic and separate controls were not used [50].

Meal (50 g glucose)-stimulated GIP levels were found to be increased 1.5 times after RYGB in a study by Laferrere et al. [51]. Another study by the same authors showed similar results after 1 month post surgery [52]. Assays were done 1 month post surgery and all patients were diabetic. Matched patients who had diet-induced weight loss were used as controls. Only postprandial levels were reported. The assay used cross-reacts 100% with GIP 1–42 and GIP 3–42 but does not cross-react with GLP-1, GLP-2, oxyntomodulin, or glucagon. The intraassay and interassay CVs were 3.0–8.8% and 1.8–6.1%, respectively. These are the only studies reporting an increase in GIP levels postoperatively. To summarize, postprandial GIP levels were found to be reduced in most studies and a decrease in fasting GIP has been reported in some studies.

Biliopancreatic Diversion

Guidone et al. found both fasting and postprandial GIP significantly reduced 1 and 4 weeks after BPD. All patients were morbidly obese and diabetic [53].

Mingrone et al. reported that there was a diurnal variation of GIP levels. The amplitude of the diurnal variations was decreased in both normal glucose-tolerant and diabetic patients but more so in diabetic patients after BPD. Postoperative tests were done within 2 weeks of BPD. BPD caused a significant decrease in area under the curve (AUC) for GIP and this was more so in diabetic subjects [54]. Salinari et al. found that area under the curve for GIP was decreased by fourfold 1 month after BPD in diabetic patients. This was not statistically different from normal weight controls. They, however, found no correlation between insulin sensitivity and a decrease in GIP/increase GLP-1 change independent of the route of glucose administration, prompting them to suggest the existence of another intestinal factor in the control of insulin action in peripheral tissues whose secretion is altered by BPD [55].

All the above studies used patients as their own controls except the one by Salinari et al. who used normal weight controls. It is also important to note that all surgeries in the above studies included a distal gastric resection and thus were not duodenal switch procedures. Thus, GIP to decrease postoperatively has been more consistent across studies in those involving BPD when compared to those involving RYGB.

Adjustable Gastric Band

Shak et al. showed that GIP was unchanged after LAGB at 6 and 12 months post surgery. The number of diabetic patients was not reported in this prospective study. Only fasting samples were measured. Baseline incretins and change in incretins after surgery were not correlated with excess weight loss [56].

In the study by Korner et al., the AUC for GIP (fasting to 180 min after meal) was greater than that for RYGB and this was statistically significant. There was no correlation between GIP and peak insulin levels. All patients were non-diabetic [48].

GIP changes have not been measured after sleeve gastrectomy alone. However, DePaula et al. reported GIP changes associated with ileal transposition/interposition (II) with sleeve gastrectomy (II-SG) (with or without duodenal diversion) in type 2 diabetic patients who had diabetes for at least 3 years and had stable glycemia with oral hypoglycemics or insulin. It was found that fasting levels as well as overall area under the curve of GIP were greater in II-SG with or without duodenal diversion. Of note, they had a large sample size (58). They did not use a separate control. Mean postoperative period was 21.7 months [57].

Duodenojejunal Bypass

After the initial success of the stomach preserving duodenojejunal bypass (DJB) in a rat model in causing resolution diabetes, the same procedure was attempted in humans by Cohen et al. and Lee et al. Cohen et al. reported that laparoscopic DJB in non-morbidly obese diabetic humans

Table 2 Summary of animal studies involving GIP and bariatric surgery

Author/year	Animal model	Intervention	Results
Kindel et al.—2010	Non-obese non-diabetic (Wistar rats)	Duodenojejunal bypass	No change in plasma GIP levels
Strader et al.—2009	Diabetic non-obese rat model (streptozotocin-treated Long Evans rat)	Ileal transposition	No change in GIP levels
Rubino et al.—2008	Diabetic non-obese rat model (Goto Kakizaki)	Duodenojejunal bypass	Decreased GIP which was not different statistically from sham group
Pacheco et al.—2007	Diabetic non-obese rat model (GK rats)	Gastrojejunal bypass	No change in post-glucose overload GIP

Table 3 Summary of human studies involving GIP and bariatric surgery

Author/year	Subjects	Surgery	Period after surgery	Controls	Timing of assay	Result
Lee et al.—2010	6 non-obese T2DM	Laparoscopic DJB	6 months	None	Fasting and postprandial	No change in AUC of GIP
Salinari et al.—2009	9 obese T2DM	BPD	1 month	6 normal weight	Fasting and postprandial	Decreased AUC of GIP
Depaula et al.—2009	58 non-obese diabetic	II-SG and II-DSG	19.2 months (mean)	None	Fasting and postprandial	Increase in GIP levels
Ockander et al.—2009	37 obese	JIB	1–30 years	5 unoperated obese and 20 normal weight	NA	Increased density of GIP cells in JIB group
Mingrone et al.—2009	10 obese—5 with T2DM	BPD	2 weeks	None	Fasting and postprandial	Decrease in AUC of GIP more in diabetic
Gulstrand et al.—2008	12 severely obese–non-diabetic	VBG=7; JIB=5	1 year	None	Fasting and postprandial	Increased AUC of GIP in VBG compared to JIB
Laferrere et al.—2008	9 obese women with T2DM	RYGB	1 month	10 matched patients with diet-induced weight loss	Postprandial	Increase in GIP
Shak et al.—2008	24 obese patients	LAGB	6 and 12 months	None	Fasting	No change in GIP
Whitson et al.—2007	10; 5 diabetic	RYGB	6 months	None	Non-fasting	No change in GIP postoperatively
Korner et al.—2007	10 patients with gastric banding and 13 with RYGB. All non-diabetic	RYGB and banding	24.6±2 months	13 overweight controls	Fasting and postprandial	Blunting of postprandial peak GIP compared to RYGB and overweight group
Rubino et al.—2006	10 patients 6 with T2DM	RYGB	3 weeks	None	Fasting	Decrease in GIP only in diabetics
Guidone et al.—2006	10 obese with T2DM	BPD	1 week	None	Fasting and postprandial	Decrease in fasting and postprandial GIP
Clements et al.—2004	20 obese with T2DM	RYGB	2, 6, and 12 weeks	None	Fasting	Decrease in GIP
Naslund et al.—1998	12 obese–non-diabetic	JIB	6 after 9 months; 6 after 20 years	6 lean and 6 non-operated obese–non-diabetic	Fasting and postprandial	Elevation of GIP—more in the 20-year group

was safe and effective in causing resolution of diabetes [58]. Lee et al. reported the changes in incretins after following patients 6 months after DJB. All patients had body mass index of <30 kg/m^2, a history of T2DM for ≤10 years, and fasting C-peptide ≥0.3 nmol/l. The AUC of glucose, peak glucose levels during OGTT, and HbA1c also declined until 3 months postoperatively. The AUC of C-peptide and insulin tended to increase postoperatively. The AUC of glucagon had a significant increase at 6 months postoperatively. The AUC of active GLP-1 increased at 1 and 6 months postoperatively. There was no change in the AUC of total GIP [59]. Though further studies are needed, it may be possible that GIP is not the mediator of the "foregut theory".

Jejunoileal Bypass

Though the jejunoileal bypass (JIB) is of historical interest only, its unique rearrangement of the small bowel might have been able to shed light on the mechanisms related to gut hormone secretion. However, there is no definite pattern of change in GIP after JIB [60–62]. The animal and the human studies have been summarized in Tables 2 and 3, respectively.

Future Directions

The change in GIP levels after the currently performed bariatric surgeries namely, RYGB, BPD-DS, and gastric banding, has been well established with a decrease demonstrated in malabsorptive surgery and no change after restrictive surgery. It would be interesting to measure GIP levels post-sleeve gastrectomy especially since this surgery has been shown to increase postprandial GLP-1 in the study by Peterli et al. This has led to a debate as to whether bowel rearrangement is mandatory to produce changes in gastrointestinal hormones when a simpler gastric procedure could accomplish the same [63].

Since GIP decrease has been found to be beneficial for obese and diabetic patients, trials of GIP antagonists may result in a new way of treating diabetic/obese people. Well-designed controlled studies are necessary to further elucidate the role of this hormone in bariatric surgery. Such studies must measure both fasting and postprandial samples. Results of surgery need to be reported separately for diabetic and non-diabetic patients.

Most studies involving GIP have been performed in rats and these have been inconclusive. It is possible that these have a different physiology compared to humans and a different model (like mice) needs to be chosen. There have also been efforts to design large animal models for bariatric surgery.

Conclusion

GIP is an incretin hormone, which is closely linked to obesity and T2DM. It is increased in overweight and glucose-intolerant people. The changes seen in this hormone in animal models of bariatric surgery have not been consistent. Most human studies have reported a decrease in this hormone post-malabsorptive surgery. GIP promotes insulin resistance and a decrease in GIP is beneficial. For the same reason, GIP antagonists would be more beneficial which opens up an avenue for research into GIP antagonists in the treatment of obese diabetic patients.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. McIntosh CH, Widenmaier S, Kim SJ. Glucose-dependent insulinotropic polypeptide (gastric inhibitory polypeptide; GIP). Vitam Horm. 2009;80:409–71.
2. Lu M, Wheeler MB, Leng XH, et al. The role of the free cytosolic calcium level in beta-cell signal transduction by gastric inhibitory polypeptide and glucagon-like peptide I (7–37). Endocrinology. 1993;132:94–100.
3. Siegel EG, Creutzfeldt W. Stimulation of insulin release in isolated rat islets by GIP in physiological concentrations and its relation to islet cyclic AMP content. Diabetologia. 1985;28:857–61.
4. Ross SA, Dupre J. Effects of ingestion of triglyceride or galactose on secretion of gastric inhibitory polypeptide and on responses to intravenous glucose in normal and diabetic subjects. Diabetes. 1978;27:327–33.
5. Ehses JA, Casilla VR, Doty T, et al. Glucose-dependent insulinotropic polypeptide promotes beta-(INS-1) cell survival via cyclic adenosine monophosphate-mediated caspase-3 inhibition and regulation of p38 mitogen-activated protein kinase. Endocrinology. 2003;144:4433–45.
6. Kim SJ, Winter K, Nian C, et al. Glucose-dependent insulinotropic polypeptide (GIP) stimulation of pancreatic beta-cell survival is dependent upon phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) signaling, inactivation of the forkhead transcription factor Foxo1, and down-regulation of bax expression. J Biol Chem. 2005;280:22297–307.
7. Kim SJ, Nian C, Widenmaier S, et al. Glucose-dependent insulinotropic polypeptide-mediated up-regulation of beta-cell antiapoptotic Bcl-2 gene expression is coordinated by cyclic AMP (cAMP) response element binding protein (CREB) and cAMP-responsive CREB coactivator 2. Mol Cell Biol. 2008;28:1644–56.
8. Creutzfeldt W. The entero-insular axis in type 2 diabetes—incretins as therapeutic agents. Exp Clin Endocrinol Diabetes. 2001;109 Suppl 2:S288–303.
9. Cheeseman CI, O'Neill D. Basolateral D-glucose transport activity along the crypt–villus axis in rat jejunum and upregulation induced by gastric inhibitory peptide and glucagon-like peptide-2. Exp Physiol. 1998;83:605–16.
10. Cheeseman CI, Tsang R. The effect of GIP and glucagon-like peptides on intestinal basolateral membrane hexose transport. Am J Physiol. 1996;271:G477–82.

11. Girard J. The incretins: from the concept to their use in the treatment of type 2 diabetes. Part A: incretins: concept and physiological functions. Diabetes Metab. 2008;34:550–9.
12. Oben J, Morgan L, Fletcher J, et al. Effect of the entero-pancreatic hormones, gastric inhibitory polypeptide and glucagon-like polypeptide-1(7–36) amide, on fatty acid synthesis in explants of rat adipose tissue. J Endocrinol. 1991;130:267–72.
13. Hauner H, Glatting G, Kaminska D, et al. Effects of gastric inhibitory polypeptide on glucose and lipid metabolism of isolated rat adipocytes. Ann Nutr Metab. 1988;32:282–88.
14. Yamada C, Yamada Y, Tsukiyama K, et al. The murine glucagon-like peptide-1 receptor is essential for control of bone resorption. Endocrinology. 2008;149:574–79.
15. Tsukiyama K, Yamada Y, Yamada C, et al. Gastric inhibitory polypeptide as an endogenous factor promoting new bone formation after food ingestion. Mol Endocrinol. 2006;20:1644–51.
16. Meier JJ, Nauck MA, Schmidt WE, et al. Gastric inhibitory polypeptide: the neglected incretin revisited. Regul Pept. 2002;107:1–13.
17. Vilsboll T, Agerso H, Lauritsen T, et al. The elimination rates of intact GIP as well as its primary metabolite, GIP 3–42, are similar in type 2 diabetic patients and healthy subjects. Regul Pept. 2006; 137:168–72.
18. Hupe-Sodmann K, McGregor GP, Bridenbaugh R, et al. Characterisation of the processing by human neutral endopeptidase 24.11 of GLP-1(7–36) amide and comparison of the substrate specificity of the enzyme for other glucagon-like peptides. Regul Pept. 1995; 58:149–56.
19. Elahi D, Andersen DK, Muller DC, et al. The enteric enhancement of glucose-stimulated insulin release. The role of GIP in aging, obesity, and non-insulin-dependent diabetes mellitus. Diabetes. 1984;33:950–57.
20. Vilsboll T, Krarup T, Sonne J, et al. Incretin secretion in relation to meal size and body weight in healthy subjects and people with type 1 and type 2 diabetes mellitus. J Clin Endocrinol Metab. 2003;88:2706–13.
21. Miyawaki K, Yamada Y, Ban N, et al. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nat Med. 2002; 8:738–42.
22. Theodorakis MJ, Carlson O, Muller DC, et al. Elevated plasma glucose-dependent insulinotropic polypeptide associates with hyperinsulinemia in impaired glucose tolerance. Diabetes Care. 2004;27:1692–8.
23. Knop FK, Vilsboll T, Hojberg PV, et al. The insulinotropic effect of GIP is impaired in patients with chronic pancreatitis and secondary diabetes mellitus as compared to patients with chronic pancreatitis and normal glucose tolerance. Regul Pept. 2007; 144:123–30.
24. Lynn FC, Pamir N, Ng EH, et al. Defective glucose-dependent insulinotropic polypeptide receptor expression in diabetic fatty Zucker rats. Diabetes. 2001;50:1004–11.
25. Piteau S, Olver A, Kim SJ, et al. Reversal of islet GIP receptor down-regulation and resistance to GIP by reducing hyperglycemia in the Zucker rat. Biochem Biophys Res Commun. 2007;362: 1007–12.
26. Knop FK, Vilsboll T, Hojberg PV, et al. Reduced incretin effect in type 2 diabetes: cause or consequence of the diabetic state. Diabetes. 2007;56:1951–9.
27. Meier JJ, Hucking K, Holst JJ, et al. Reduced insulinotropic effect of gastric inhibitory polypeptide in first-degree relatives of patients with type 2 diabetes. Diabetes. 2001;50:2497–504.
28. Vilsboll T, Krarup T, Madsbad S, et al. Defective amplification of the late phase insulin response to glucose by GIP in obese type II diabetic patients. Diabetologia. 2002;45:1111–9.
29. Pilgaard K, Jensen CB, Schou JH, et al. The T allele of rs7903146 TCF7L2 is associated with impaired insulinotropic action of incretin hormones, reduced 24 h profiles of plasma insulin and glucagon, and increased hepatic glucose production in young healthy men. Diabetologia. 2009;52:1298–307.
30. Gniuli D, Calcagno A, Dalla LL, et al. High-fat feeding stimulates endocrine, glucose-dependent insulinotropic polypeptide (GIP)-expressing cell hyperplasia in the duodenum of Wistar rats. Diabetologia. 2010;53:2233–40.
31. Rijkelijkhuizen JM, McQuarrie K, Girman CJ, et al. Effects of meal size and composition on incretin, alpha-cell, and beta-cell responses. Metabolism. 2010;59:502–11.
32. Rudnicki M, Patel DG, McFadden DW, et al. Proximal jejunal and biliary effects on the enteroinsular axis. Surgery. 1990;107:455–60.
33. Rubino F. Is type 2 diabetes an operable intestinal disease? A provocative yet reasonable hypothesis. Diabetes Care. 2008;31 Suppl 2:S290–6.
34. de Campos Martins MV, Peixoto AA, Schanaider A, et al. Glucose tolerance in the proximal versus the distal small bowel in Wistar rats. Obes Surg. 2009;19:202–6.
35. Little TJ, Doran S, Meyer JH, et al. The release of GLP-1 and ghrelin, but not GIP and CCK, by glucose is dependent upon the length of small intestine exposed. Am J Physiol Endocrinol Metab. 2006;291:E647–55.
36. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244:741–9.
37. Cote GA, Edmundowicz SA. Emerging technology: endoluminal treatment of obesity. Gastrointest Endosc. 2009;70:991–9.
38. Wang TT, Hu SY, Gao HD, et al. Ileal transposition controls diabetes as well as modified duodenal jejunal bypass with better lipid lowering in a nonobese rat model of type II diabetes by increasing GLP-1. Ann Surg. 2008;247:968–75.
39. Pories WJ, Albrecht RJ. Etiology of type II diabetes mellitus: role of the foregut. World J Surg. 2001;25:527–31.
40. Santoro S. Is the metabolic syndrome a disease of the foregut? Yes, excessive foregut. Ann Surg. 2008;247:1074–5.
41. Kindel TL, Yoder SM, D'Alessio DA, et al. The effect of duodenal-jejunal bypass on glucose-dependent insulinotropic polypeptide secretion in Wistar rats. Obes Surg. 2010;20:768–75.
42. Strader AD, Vahl TP, Jandacek RJ, et al. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab. 2005;288: E447–53.
43. Rubino F, Marescaux J. Effect of duodenal–jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg. 2004;239:1–11.
44. Pacheco D, de Luis DA, Romero A, et al. The effects of duodenal–jejunal exclusion on hormonal regulation of glucose metabolism in Goto–Kakizaki rats. Am J Surg. 2007;194:221–4.
45. McClean PL, Irwin N, Hunter K, et al. (Pro(3))GIP[mPEG]: novel, long-acting, mPEGylated antagonist of gastric inhibitory polypeptide for obesity-diabetes (diabesity) therapy. Br J Pharmacol. 2008;155:690–701.
46. Flatt PR. Dorothy Hodgkin Lecture 2008. Gastric inhibitory polypeptide (GIP) revisited: a new therapeutic target for obesity-diabetes? Diabet Med. 2008;25:759–64.
47. Whitson BA, Leslie DB, Kellogg TA, et al. Entero-endocrine changes after gastric bypass in diabetic and nondiabetic patients: a preliminary study. J Surg Res. 2007;141:31–9.
48. Korner J, Bessler M, Inabnet W, et al. Exaggerated glucagon-like peptide-1 and blunted glucose-dependent insulinotropic peptide secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis. 2007;3:597–601.
49. Rubino F, Gagner M, Gentileschi P, et al. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg. 2004;240:236–42.

50. Clements RH, Gonzalez QH, Long CI, et al. Hormonal changes after Roux-en Y gastric bypass for morbid obesity and the control of type-II diabetes mellitus. Am Surg. 2004;70:1–4.
51. Laferrere B, Teixeira J, McGinty J, et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. J Clin Endocrinol Metab. 2008;93:2479–85.
52. Laferrere B, Heshka S, Wang K, et al. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care. 2007;30:1709–16.
53. Guidone C, Manco M, Valera-Mora E, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. Diabetes. 2006;55:2025–31.
54. Mingrone G, Nolfe G, Gissey GC, et al. Circadian rhythms of GIP and GLP1 in glucose-tolerant and in type 2 diabetic patients after biliopancreatic diversion. Diabetologia. 2009;52:873–81.
55. Salinari S, Bertuzzi A, Asnaghi S, et al. First-phase insulin secretion restoration and differential response to glucose load depending on the route of administration in type 2 diabetic subjects after bariatric surgery. Diabetes Care. 2009;32:375–80.
56. Shak JR, Roper J, Perez-Perez GI, et al. The effect of laparoscopic gastric banding surgery on plasma levels of appetite-control, insulinotropic, and digestive hormones. Obes Surg. 2008;18: 1089–96.
57. DePaula AL, Macedo AL, Schraibman V, et al. Hormonal evaluation following laparoscopic treatment of type 2 diabetes mellitus patients with BMI 20–34. Surg Endosc. 2009;23:1724–32.
58. Cohen RV, Schiavon CA, Pinheiro JS, et al. Duodenal–jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22–34 kg/m^2: a report of 2 cases. Surg Obes Relat Dis. 2007;3:195–7.
59. Lee HC, Kim MK, Kwon HS, et al. Early changes in incretin secretion after laparoscopic duodenal–jejunal bypass surgery in type 2 diabetic patients. Obes Surg. 2010;20:1530–5.
60. Naslund E, Backman L, Holst JJ, et al. Importance of small bowel peptides for the improved glucose metabolism 20 years after jejunoileal bypass for obesity. Obes Surg. 1998;8:253–60.
61. Ockander L, Hedenbro JL, Rehfeld JF, et al. Jejunoileal bypass changes the duodenal cholecystokinin and somatostatin cell density. Obes Surg. 2003;13:584–90.
62. Guldstrand M, Ahren B, Naslund E, et al. Dissociated incretin response to oral glucose at 1 year after restrictive vs. malabsorptive bariatric surgery. Diabetes Obes Metab. 2009;11:1027–33.
63. Peterli R, Wolnerhanssen B, Peters T, et al. Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg. 2009;250:234–41.
64. Deacon CF, Nauck MA, Meier J, et al. Degradation of endogenous and exogenous gastric inhibitory polypeptide in healthy and in type 2 diabetic subjects as revealed using a new assay for the intact peptide. J Clin Endocrinol Metab. 2000;85:3575–81.
65. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. J Clin Endocrinol Metab. 2002;87:1239–46.
66. Imeryuz N, Yegen BC, Bozkurt A, et al. Glucagon-like peptide-1 inhibits gastric emptying via vagal afferent-mediated central mechanisms. Am J Physiol. 1997;273:G920–27.
67. Sancho V, Trigo MV, Martin-Duce A, et al. Effect of GLP-1 on D-glucose transport, lipolysis and lipogenesis in adipocytes of obese subjects. Int J Mol Med. 2006;17:1133–37.