Published in final edited form as:

Int J Obes (Lond). 2011 September ; 35(0 3): S22–S25. doi:10.1038/ijo.2011.143.

Diabetes remission after bariatric surgery: is it just the incretins?

B Laferrère

New York Obesity Nutrition Research Center, Division of Endocrinology and Diabetes, Department of Medicine, St Luke's Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, New York, NY, USA

Abstract

Gastric bypass surgery (GBP) results in important and sustained weight loss and remarkable improvement of Type 2 diabetes. The favorable change in the incretin gut hormones is thought to be responsible, in part, for diabetes remission after GBP, independent of weight loss. However, the relative role of the change in incretins and of weight loss is difficult to differentiate. After GBP, the plasma concentrations of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucosedependent insulinotropic polypeptide increase postprandially by three- to fivefold. The postprandial incretin effect on insulin secretion, blunted in diabetes, improves rapidly after the surgery. In addition to the change in incretins, the pattern of insulin secretion in response to oral glucose changes after GBP, with recovery of the early phase and significant decrease in postprandial glucose levels. These changes were not seen after an equivalent weight loss by diet. The improved insulin release and glucose tolerance after GBP were shown by others to be blocked by the administration of a GLP-1 antagonist, demonstrating that the favorable metabolic changes after GBP are, in part, GLP-1 dependent. The improved incretin levels and effect persist years after GBP, but their long-term effect on glucose metabolism, and on hypoglycemia post GBP are yet unknown. Understanding the mechanisms by which incretin release is exaggerated postprandially after GBP may help develop new less invasive treatment options for obesity and diabetes. Changes in rate of eating, gastric emptying, intestinal transit time, nutrient absorption and sensing, as well as bile acid metabolism, may all be implicated.

Keywords

GLP-1; GIP; incretin effect; diabetes; gastric bypass

Bariatric surgery, the only efficient long-term weight loss treatment for morbid obesity, is a uniquely suited model to investigate the role of gut hormones in weight loss and diabetes remission.

© 2011 Macmillan Publishers Limited All rights reserved

Correspondence: Professor B Laferrère, New York Obesity Nutrition Research Center, Division of Endocrinology and Diabetes, Department of Medicine, St Luke's Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, 1111 Amsterdam Avenue, New York, NY 10025 USA. BBL14@columbia.edu.

Conflict of interest

B Laferrère received funding from the American Diabetes Association CR-7-05 CR-18, NIH NIDDK R01-DK67561, GCRC 1 UL1 RR024156-02, ORC DK-26687, DERC DK- 63068-05, Merck and Amylin Investigator Initiated Studies Program. B Laferrère also received lecture fees from Novo Nordisk.

One of the major benefits of surgical weight loss is the improvement or resolution of Type 2 diabetes (T2DM) in 50–80% of cases.^{1,2} The rapidity of the onset and the magnitude of the effect of gastric bypass (GBP) surgery on diabetes remain largely unexplained.

Some determinants of impaired insulin secretion in T2DM, such as glucose or lipid toxicity,^{3,4} likely improve as a result of weight loss. In contrast, the change of the gut hormone incretins after GBP,^{5,6} and their resulting effect on insulin or on glucagon secretion, could be the mediator of the greater improvement of glucose levels after GBP^{5,6} as compared with diet or gastric banding.

What are the incretins?

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are gastrointestinal hormones secreted from the duodenal K cells and ileal L cells, respectively.^{7–9} Together, the two incretins are responsible for ~50% of postprandial insulin secretion.^{10–12} The incretin effect is described as the differential insulin response after oral glucose compared with an equivalent dose of intravenous glucose.¹¹ In addition to its insulinotropic effect, GLP-1 delays gastric emptying,¹³ decreases appetite and promotes weight loss,^{13,14} inhibits glucagon¹⁵ and may improve insulin sensitivity.¹⁶ GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase 4. The incretin effect on insulin secretion is impaired in patients with T2DM.¹⁷ GLP-1 analog and dipeptidyl peptidase 4 inhibitors are currently used as anti-diabetic agents.¹⁸

Change of incretins after bypass surgeries for weight loss

Reports of increased incretin levels after bypass surgeries started in the late 1970s/early 1980s, at a time when no commercial assays were available. GLP-1 consistently increased after jejunoileal bypass, biliopancreatic diversion or GBP.^{19–21} More recent reports confirm a significant increase of GLP-1 levels by a factor 5–10 after GBP, in response to a meal²² or to oral glucose.⁵ The effect of bypass surgeries on changes in GIP levels are less consistent with either elevated or decreased levels.^{19,21,23–25} We reported an increase of GIP levels 1 month after GBP in morbidly obese patients with T2DM.⁵ In addition to the postprandial increase of circulating incretins concentration, we have shown that the incretin effect on insulin secretion, blunted in patients with diabetes, normalized to the levels of non-diabetic controls as early as 1 month after GBP surgery.⁵ These patients, who had diagnosed diabetes for less than 5 years, were well controlled (mean hemoglobin A1C, 6%) and on minimum oral therapy. Recent data in the Goto–Kakizaki rats show that improved glucose tolerance after duodenojejunal bypass is reversed by the administration of the GLP-1 receptor antagonist exendin 9–39. This elegant proof-of-concept study provides direct evidence that improvement of glucose tolerance following a GBP-like surgery is mediated, at least in part, by enhanced GLP-1 action.²⁶

Effect of weight loss versus bypass on incretins

Previous data suggested that a diet-induced weight loss (–18.8 kg) increased GLP-1 levels in response to a test meal.²⁷ To address the question of the possible role of weight loss on the change in incretin levels and effect after GBP surgery, we designed a prospective study with a surgical group studied before and 1 month after GBP and a matched diet group studied before and after a diet-induced equivalent weight loss. Our working hypothesis was that the increase in incretin levels and incretin effect would be greater after GBP surgery than after equivalent weight loss by diet.

The inclusion criteria for the surgical group and the diet group were identical: morbidly obese patients with body mass index >35 kgm⁻², with T2DM of <5 years duration, not on

insulin, thiazolidinedione, exenatide or dipeptidyl peptidase 4 inhibitor, with hemoglobin A1C<8%, age<60 years, of all ethnic background. The GBP group was studied first. Participants in the diet group were recruited afterward, fit the same inclusion criteria and were matched for body weight, body mass index, age, diabetes control and duration with patients from the surgical group. The diet consisted of meal replacement, 1000–1200 kcal per day, given on weekly outpatient visits. The duration of weight loss was not set but the expectation was that the participants would lose 10 kg of weight in 4–8 weeks. The patients were maintained on negative energy balance while retested after diet weight loss. Diabetes management during diet included self-glucose monitoring by the patients and the adjustment of medications to avoid hypoglycemia. At baseline and after weight loss, patients were studied off diabetes medications for 72 h. The results of these experiments have been published elsewhere.⁶ In brief, patients in the GBP and diet groups lost the same amount of weight (~10 kg). Diabetes medications were discontinued at the time of surgery for all GBP patients, and were decreased or stopped for diet patients, using an algorithm based on standard criteria of target glucose control. There was a significant and similar decrease of fasting glucose and fasting insulin after diet and after GBP. Recovery of the early-phase insulin secretion in response to oral glucose and the improvement in incretin levels and effect were, however, observed only after GBP and not after diet. Recent clinical studies of various types of bypass surgeries and/or ileal transposition in humans with body mass index <35 kgm⁻² suggest that diabetes can be improved without weight loss.²⁸ Data on gut hormones in these patients have not been provided.

Long-term changes of incretins

Data suggest that the changes observed early after GBP persist over time. Cross-sectional data from Naslund *et al.*²⁹ show persistent elevated postprandial GLP-1 and GIP levels 20 years after duodenal–jejunal bypass compared with obese non-operated controls. Our own data show persistently increased GLP-1 response to oral glucose and GIP up to 3 years after GBP in patients with diabetes remission and normal incretin effect. With GBP weight loss, some parameters, such as fasting glucose, fasting insulin, leptin or adiponectin, improve as a function of weight loss in the first year.³⁰ Other parameters, such as incretin levels and effect, early-phase insulin release during the oral glucose tolerance test, and the insulinogenic index all improve rapidly 1 month after GBP without further change at 6 and 12 months, in spite of continuous weight loss. This suggests that some changes occur as a result of the surgery, independent of weight loss, whereas other changes are clearly weight-loss related.

It remains unknown whether the improved postprandial insulin and glucose levels observed 1 month after GBP are responsible for the later development of hyperinsulinemic hypoglycemia with³¹ or without³² nesidioblastosis. Although GLP-1 has been shown to preserve human islet *in vitro*³³ and prevent β -cell apoptosis in rodents,³⁴ there are no human data to suggest that GLP-1 increases β -cell mass after bypass in humans. An elegant study by McLaughlin *et al.*³⁵ demonstrated that hyperinsulinemic hypoglycemia post GBP is not due to the dysfunction of the β cell, but rather due to the accelerated mode of nutrient delivery to the lower intestine. Administering the same meal PO via the alimentary limb, generated rapid release of GLP-1 and insulin resulting in hypoglycemia. Administering the same meal via a gastrotomy in the bypassed gastric remnant connected to the duodenal limb did not trigger this exaggerated insulin response and hypoglycemia.³⁵

Mechanisms of incretin release after GBP: foregut and hindgut hypotheses

As a result of GBP, a small gastric pouch of about 30 cc is anastomosed directly to the distal part of the jejunum (alimentary limb). The rest of the stomach, including the pylorus,

duodenum and part of the jejunum is shunted from nutrients (biliopancreatic limb) and reattached to the ileum to allow gastrointestinal and pancreatic juice to be mixed with nutrients in the distal intestine (common limb).

Studies in the Goto–Kakizaki rat suggest that the exclusion of the upper gut (foregut hypothesis), rather than weight loss, benefits glucose tolerance.^{36,37} Rats after gastrojejunal bypass have better glucose tolerance than sham-operated pair-fed control animals with equivalent body weight, or rats with gastrojejunal anastomosis.³⁶ The hindgut hypothesis suggests that the rapid stimulation of the distal ileum by nutrients is responsible for increased GLP-1 and beneficial effect on glucose tolerance, similar to data obtained with ileal transposition in rodents.^{38,39} There are few data in humans to support these hypotheses. After GBP, the emptying of the gastric pouch is faster for liquids but delayed for solids.^{22,40} Accelerated gastric emptying and intestinal transit time for liquid²² may result in rapid release of GLP-1 by the distal ileum, which is rapidly put in contact with nutrients. It is likely that both duodenal exclusion (foregut hypothesis) and the rapid exposure of the distal ileum to undigested nutrients (hindgut hypothesis)^{38,39} are possible mechanisms that may contribute to elevated incretin levels after GBP; however, this has not yet been carefully studied in humans. The duodenal exclusion hypothesis is, to a degree, proven invalid by the results of vertical sleeve gastrectomy, which results in diabetes remission in a large percentage of patients and an increase in gut hormones, very similar to GBP, in spite of a functional duodenum.⁴¹

Other hormones

The incretins are not the only factors contributing to diabetes improvement after GBP surgery. We have shown that adiponectin increases and leptin decreases with weight loss after GBP, whereas abnormally elevated proinsulin and amylin decrease, as β -cell function improves, in patients with diabetes after GBP.³⁰ In parallel to GLP-1, PYY3–36^(ref. 42) and oxyntomodulin,⁴³ also released by the L cells, increased postprandially after GBP but not after diet. The changes of ghrelin after GBP are more complex than initially described.⁴⁴ We have recently shown that although circulating ghrelin concentration decreased initially after GBP, it increased in proportion to weight loss 1 year after this surgery.⁴⁵

Conclusion

The magnitude of weight loss (~40%) and its persistence (years) are considered as the major contributors to glucose control after GBP. However, the data clearly show that secondary to the bypass procedure, beneficial changes of incretin levels and effect occur rapidly after GBP, resulting in an improved insulin secretion profile and decreased post-prandial glucose. Understanding the mechanisms of diabetes remission after GBP surgery should help understand the role of the gut in the pathophysiology of T2DM, and help discover new therapeutic surgical or medical intervention.

References

1. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA*. 2004; 292:1724–1737. [PubMed: 15479938]
2. Dixon JB, O'Brien PE, Playfair J, Chapman L, Schachter LM, Skinner S, et al. Adjustable gastric banding and conventional therapy for type 2 diabetes: a randomized controlled trial. *JAMA*. 2008; 299:316–323. [PubMed: 18212316]
3. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care*. 1990; 13:610–630. [PubMed: 2192847]

4. Leahy JL, Bonner-Weir S, Weir GC. Beta-cell dysfunction induced by chronic hyperglycemia. Current ideas on mechanism of impaired glucose-induced insulin secretion. *Diabetes Care*. 1992; 15:442–455. [PubMed: 1559411]
5. Laferrière B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, 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; 30:1709–1716. [PubMed: 17416796]
6. Laferrière B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, 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; 93:2479–2485. [PubMed: 18430778]
7. Kreyman B, Williams G, Ghatei MA, Bloom SR. Glucagon-like peptide-1 7–36: a physiological incretin in man. *Lancet*. 1987; 2:1300–1304. [PubMed: 2890903]
8. Holst JJ, Orskov C. Incretin hormones Fan update. *Scand J Clin Lab Invest Suppl*. 2001; 234:75–85. [PubMed: 11713984]
9. Theodorakis MJ, Carlson O, Michopoulos S, Doyle ME, Juhaszova M, Petraki K, et al. Human duodenal enteroendocrine cells: source of both incretin peptides, GLP-1 and GIP. *Am J Physiol Endocrinol Metab*. 2006; 290:E550–E559. [PubMed: 16219666]
10. Ebert R, Creutzfeldt W. Gastrointestinal peptides and insulin secretion. *Diabetes Metab Rev*. 1987; 3:1–26. [PubMed: 3552520]
11. Nauck MA, Homberger E, Siegel EG, Allen RC, Eaton RP, Ebert R, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab*. 1986; 63:492–498. [PubMed: 3522621]
12. Preitner F, Ibberson M, Franklin I, Binnert C, Pende M, Gjnovci A, et al. Gluco-incretins control insulin secretion at multiple levels as revealed in mice lacking GLP-1 and GIP receptors. *J Clin Invest*. 2004; 113:635–645. [PubMed: 14966573]
13. Flint A, Raben A, Ersboll AK, Holst JJ, Astrup A. The effect of physiological levels of glucagon-like peptide-1 on appetite, gastric emptying, energy and substrate metabolism in obesity. *Int J Obes Relat Metab Disord*. 2001; 25:781–792. [PubMed: 11439290]
14. Gutzwiller JP, Drewe J, Goke B, Schmidt H, Rohrer B, Lareida J, et al. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. *Am J Physiol*. 1999; 276:R1541–R1544. [PubMed: 10233049]
15. Naslund E, Bogefors J, Skogar S, Gryback P, Jacobsson H, Holst JJ, et al. GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. *Am J Physiol*. 1999; 277:R910–R916. [PubMed: 10484511]
16. D'Alessio DA, Prigeon RL, Ensink JW. Enteral enhancement of glucose disposition by both insulin-dependent and insulinin-dependent processes. A physiological role of glucagon-like peptide I. *Diabetes*. 1995; 44:1433–1437. [PubMed: 7589851]
17. Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 1986; 29:46–52. [PubMed: 3514343]
18. Holst JJ. Glucagon-like peptide-1: from extract to agent. The Claude Bernard Lecture, 2005. *Diabetologia*. 2006; 49:253–260. [PubMed: 16416146]
19. Sarson DL, Scopinaro N, Bloom SR. Gut hormone changes after jejunoileal (JIB) or biliopancreatic (BPB) bypass surgery for morbid obesity. *Int J Obes*. 1981; 5:471–480. [PubMed: 6796532]
20. Naslund E, Gryback P, Hellstrom PM, Jacobsson H, Holst JJ, Theodorsson E, et al. Gastrointestinal hormones and gastric emptying 20 years after jejunoileal bypass for massive obesity. *Int J Obes Relat Metab Disord*. 1997; 21:387–392. [PubMed: 9152741]
21. Naslund E, Backman L, Holst JJ, Theodorsson E, Hellstrom PM. Importance of small bowel peptides for the improved glucose metabolism 20 years after jejunoileal bypass for obesity. *Obes Surg*. 1998; 8:253–260. [PubMed: 9678192]
22. Morinigo R, Moize V, Musri M, Lacy AM, Navarro S, Marin JL, et al. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab*. 2006; 91:1735–1740. [PubMed: 16478824]

23. Sarson DL, Besterman HS, Bloom SR. Radioimmunoassay of gastric inhibitory polypeptide and its release in morbid obesity and after jejuno-ileal bypass [proceedings]. *J Endocrinol.* 1979; 81:155P–156P.
24. Lauritsen KB, Christensen KC, Stokholm KH. Gastric inhibitory polypeptide (GIP) release and incretin effect after oral glucose in obesity and after jejunoileal bypass. *Scand J Gastroenterol.* 1980; 15:489–495. [PubMed: 7001614]
25. Halverson JD, Kramer J, Cave A, Permutt A, Santiago J. Altered glucose tolerance, insulin response, and insulin sensitivity after massive weight reduction subsequent to gastric bypass. *Surgery.* 1982; 92:235–240. [PubMed: 7048596]
26. Kindel TL, Yoder SM, Seeley RJ, D'Alessio DA, Tso P. Duodenal- Jejunal exclusion improves glucose tolerance in the diabetic, Goto-Kakizaki rat by a GLP-1 receptor-mediated mechanism. *J Gastrointest Surg.* 2009; 13:1762–1772. [PubMed: 19488823]
27. Verdich C, Toubro S, Buemann B, Lysgard MJ, Juul HJ, Astrup A. The role of postprandial releases of insulin and incretin hormones in meal-induced satiety—Effect of obesity and weight reduction. *Int J Obes Relat Metab Disord.* 2001; 25:1206–1214. [PubMed: 11477506]
28. Cohen RV, Schiavon CA, Pinheiro JS, Correa JL, Rubino F. Duodenal-jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22–34 kg/m²: a report of 2 cases. *Surg Obes Relat Dis.* 2007; 3:195–197. [PubMed: 17386401]
29. Naslund E, Backman L, Holst JJ, Theodorsson E, Hellstrom PM. Importance of small bowel peptides for the improved glucose metabolism 20 years after jejunoileal bypass for obesity. *Obes Surg.* 1998; 8:253–260. [PubMed: 9678192]
30. Bose M, Teixeira J, Scherer PE, Pi-Sunyer FX, Bawa B, Laferrère B. Weight loss and incretin responsiveness improve glucose control independently after gastric bypass surgery. *J Diabetes.* 2010; 2:47–55. [PubMed: 20676394]
31. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med.* 2005; 353:249–254. [PubMed: 16034010]
32. Kellogg TA, Bantle JP, Leslie DB, Redmond JB, Slusarek B, Swan T, et al. Postgastric bypass hyperinsulinemic hypoglycemia syndrome: characterization and response to a modified diet. *Surg Obes Relat Dis.* 2008; 4:492–499. [PubMed: 18656831]
33. Farilla L, Bulotta A, Hirshberg B, Li CS, Khoury N, Noushmehr H, et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology.* 2003; 144:5149–5158. [PubMed: 12960095]
34. Cornu M, Yang JY, Jaccard E, Poussin C, Widmann C, Thorens B. Glucagon-like peptide-1 protects beta-cells against apoptosis by increasing the activity of an IGF-2/IGF-1 receptor autocrine loop. *Diabetes.* 2009; 58:1816–1825. [PubMed: 19401425]
35. McLaughlin T, Peck M, Holst J, Deacon C. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. *J Clin Endocrinol Metab.* 2010; 95:1851–1855. [PubMed: 20133462]
36. 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. [PubMed: 14685093]
37. Pacheco D, de Luis DA, Romero A, Gonzalez SM, Conde R, Izaola O, et al. The effects of duodenal-jejunal exclusion on hormonal regulation of glucose metabolism in Goto-Kakizaki rats. *Am J Surg.* 2007; 194:221–224. [PubMed: 17618808]
38. Patriti A, Facchiano E, Anneti C, Aisa MC, Galli F, Fanelli C, et al. Early improvement of glucose tolerance after ileal transposition in a non-obese type 2 diabetes rat model. *Obes Surg.* 2005; 15:1258–1264. [PubMed: 16259883]
39. Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. *Am J Physiol Endocrinol Metab.* 2005; 288:E447–E453. [PubMed: 15454396]
40. Horowitz M, Collins PJ, Harding PE, Shearman DJ. Gastric emptying after gastric bypass. *Int J Obes.* 1986; 10:117–121. [PubMed: 3721699]
41. Gill RS, Birch DW, Shi X, Sharma AM, Karmali S. Sleeve gastrectomy and type 2 diabetes mellitus: a systematic review. *Surg Obes Relat Dis.* 2010; 6:707–713. [PubMed: 20947447]

42. Olivan B, Teixeira J, Bose M, Bawa B, Chang T, Summe H, et al. Effect of weight loss by diet or gastric bypass surgery on peptide YY3-36 levels. *Ann Surg.* 2009; 249:948–953. [PubMed: 19474685]
43. Laferrière B, Swerdlow N, Bawa B, Arias S, Bose M, Olivan B, et al. Rise of oxyntomodulin in response to oral glucose after gastric bypass surgery in patients with type 2 diabetes. *J Clin Endocrinol Metab.* 2010; 95:4072–4076. [PubMed: 20501690]
44. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, et al. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med.* 2002; 346:1623–1630. [PubMed: 12023994]
45. Bose M, Machineni S, Olivan B, Teixeira J, McGinty JJ, Bawa B, et al. Superior appetite hormone profile after equivalent weight loss by gastric bypass compared to gastric banding. *Obesity (Silver Spring).* 2010; 18:1085–1091. [PubMed: 20057364]