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REVIEW

Do we really know why diabetes remits after gastric bypass surgery?

Blandine Laferrère

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Abstract Roux-en-Y gastric bypass surgery (GBP) results in 30–40% sustained weight loss and improved type 2 diabetes in up to 80% of patients. The relative contribution of the gut neuroendocrine changes after GBP versus the weight loss has not been fully elucidated. There are clear differences between weight loss by GBP and by dietary intervention or gastric banding. One of them is the enhanced post-prandial release of incretin hormones and the recovery of the incretin effect on insulin secretion after GBP, not seen after diet-induced weight loss. The favorable changes in incretin hormones after GBP result in recovery of the early phase insulin secretion and lower post-prandial glucose levels during oral glucose administration. The enhanced incretin response may be related to the neuroglycopenia post-GBP. In parallel with changes of glucose metabolism, a larger decrease of circulating branched-chain amino acids in relation to improved insulin sensitivity and insulin secretion is observed after GBP compared to diet. The mechanisms of the rapid and long-term endocrine and metabolic changes after GBP are not fully elucidated. Changes in rate of eating, gastric emptying, nutrient absorption and sensing, bile acid metabolism, and microbiota may all be important. Understanding the mechanisms by which incretin release is exaggerated post-prandially after GBP may help develop new less invasive treatment options for obesity and diabetes. Equally important would be to identify biological predictors of success or failure and to understand the mechanisms of weight regain and/or diabetes relapse.

Keywords GLP-1 · GIP · Incretin effect · Amino acids · Diabetes · Gastric bypass

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

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 Roux-en-Y gastric bypass surgery (GBP) on diabetes remain largely unexplained.

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

What are the incretins?

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) are gastrointestinal hormones secreted, respectively, from the duodenal K cells and ileal L cells [7–9]. Together, the two incretins are responsible for ~50% of post-prandial insulin secretion [10–12]. The incretin effect is described as the differential insulin response after oral glucose compared to an

B. Laferrère (✉)
New York Obesity Nutrition Research Center, St. Luke's/Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons, 1111 Amsterdam Avenue, New York, NY 10025, USA
e-mail: BBL14@columbia.edu

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 glucagon [15], and may improve insulin sensitivity [16]. GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4). The incretin effect on insulin secretion is impaired in patients with T2DM [17]. GLP-1 analogue and DPP-4 inhibitors are currently used as anti-diabetic agents [18].

Change of incretins after bypass surgeries for weight loss

Reports of enhanced post-prandial circulating incretin concentrations after bypass surgeries started in the late 1970s and 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 in GLP-1 levels by a factor 5–10 after GBP in response to a meal [22] 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 [5] and 1 year [26] after GBP in morbidly obese patients with T2DM. In addition to the post-prandial increase of circulating incretin 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 [5] up to 1 year [27] after GBP. A study by Kindel et al. [28] in the Goto-Kakizaki (GK) rats shows that the 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 gastric bypass-like surgery is mediated, at last in part, by enhanced GLP-1 action [28]. A similar experiment in humans shows that exendin 9-39 not only decreased post-prandial insulin release [29], but also corrects the hypoglycemia [30] in patients with neuroglycopenia after GBP.

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 [31]. 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 in the 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 BMI > 35 kg/m^2, recently diagnosed with T2DM (less than five years), not on insulin, thiazolidinedione, exenatide, or DPP-4 inhibitor, with HbA1C $< 8\%$, age <60 years. The GBP group was studied first. Participants in the diet group were recruited afterwards, fit the same inclusion criteria, and were matched for body weight, BMI, age, diabetes control, and duration with patients from the surgical group. The diet consisted of meal replacement, 1,000–1,200 kcal/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 kept 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 ($\sim$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. Weight loss by either diet or GBP resulted in a significant and similar decrease of fasting glucose and fasting insulin. 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, but not after diet. These data suggest an effect of GBP independent of weight loss on glucose homeostasis. Other clinical studies after various types of bypass surgeries with or without ileal transposition in patients with BMI less than 35 kg/m^2 suggest that the diabetes may improve without weight loss [32].

Longterm changes of incretins

Data suggest that the changes in incretins observed early after GBP persist over time. Cross-sectional data from Naslund et al. [21] show persistent elevated post-prandial GLP-1 and GIP levels 20 years after duodenal jejunal bypass compared to obese non-operated controls. Our own data show persistently enhanced GLP-1 and GIP response to oral glucose up to 5 years after GBP in patients with diabetes remission, and normal incretin effect (Laferrère et al., unpublished). Parameters such as incretin levels and effect, early phase insulin release during the OGTT, and

the insulinogenic index all improve rapidly after GBP, without further change overtime in spite of continuous weight loss. On the contrary, other outcome variables, such as fasting glucose, fasting insulin, leptin, or adiponectin, continue to improve as a function of weight loss in the first year after GBP [26]. This suggests that some changes occur as a result of the surgery, independent of weight loss, while other changes are clearly weight loss related.

It remains unknown whether the exaggerated incretin response observed early after GBP, accompanied by improved post-prandial insulin and glucose levels is responsible for the later development of hyperinsulinemic hypoglycemia with [33] or without [34] nesidioblastosis. A recent human study suggests that it may. The administration of exendin 9-39, a potent GLP-1 receptor antagonist, to a selected group of individuals, improved the post-prandial hypoglycemia after GBP [30]. Although GLP-1 has been shown to preserve human islet in vitro [35] and prevent beta cell apoptosis in rodents [36] there is no human data to suggest that GLP-1 increases beta cell mass after bypass in humans. An elegant study by McLaughin et al. [37] demonstrated that hyperinsulinemic hypoglycemia post-GBP is not due to the dysfunction of the beta cell, but rather to the accelerated mode of nutrient delivery to the lower intestine. Administering a meal PO via the alimentary limb generated rapid release of GLP-1 and insulin resulting in hypoglycemia. Administering the same meal via a gastrostomy in the bypassed gastric remnant connected via the pylorus to the duodenal limb triggered neither the exaggerated insulin response nor hypoglycemia [37].

Mechanisms of incretin release after gastric bypass: foregut and hindgut hypotheses

GBP consists of the creation of a small gastric pouch of about 30 cc, anastomosed directly to the distal part of the jejunum (alimentary limb). The gastric remnant, including the pylorus, the duodenum, and part of the jejunum, is therefore shunted from nutrients (biliopancreatic limb) and reattached to the ileum to allow gastrointestinal and pancreatic juice to be mix with nutrients in the distal intestine (common limb).

Studies in the GK rat suggest that the exclusion of the upper gut (foregut hypothesis), rather than weight loss, benefits glucose tolerance [38, 39]. Rats after gastrojejunal bypass have better glucose tolerance than sham-operated pair-fed control animals with equivalent body weight, or rat with gastrojejuno anastomosis [38]. Recent trials with endoluminal sleeve in animals and in humans also support the foregut hypothesis [40].

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, similarly to data obtained with ileal transposition in rodents [41, 42]. After GBP, the accelerated emptying of the gastric pouch is faster for liquids and is related to the rapid release of GLP-1 [22, 43]. The study by McLaughin [37] also seems to highlight the importance of the rapid emptying on the exaggerated GLP-1 response after GBP.

Vertical sleeve gastrectomy, a procedure that does not result in shunting of the duodenum, seems to have gut endocrine effects, weight loss, and diabetes remission similar to that of GBP [44]. 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 similarly to GBP, in spite of a functional duodenum [45]. The recent study by Geloneze et al. [46] showed that a duodenal bypass procedure without gastric restriction did not improve diabetes, also dismissing the foregut hypothesis.

The relative role of duodenal exclusion (foregut hypothesis) and the rapid exposure of the distal ileum to undigested nutrients (hindgut hypothesis) [41, 42] as contributor to elevated incretin levels after GBP are not entirely clear in humans.

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, while abnormally elevated proinsulin and amylin decrease and beta cell function improves, in patients with diabetes after GBP [26].

In parallel to GLP-1, PYY_{3-36} [47] and oxyntomodulin [48], also released by the L cells, increased post-prandially after GBP, but not after diet. The changes of ghrelin after GBP are more complex than initially described [49]. Although circulating ghrelin concentrations decreased initially after GBP, they increased in proportion to weight loss 1 year after this surgery [26]. The changes of these gut hormones could favor satiety and/or appetite control after GBP.

Amino acid metabolism after GBP-lessons from metabolic studies

In a collaborative study, we have recently applied metabolic profiling in obese people with T2DM undergoing weight loss by two different methods. We showed a greater

reduction of circulating branched-chain amino acids (BCAA) and the aromatic amino acids phenylalanine (Phe) and tyrosine (Tyr) in a GBP group of patients compared to a matched group of patients who lost an equal amount of weight by diet [50]. This greater reduction in BCAA and aromatic amino acids Phe and Tyr was linked to better improvement in glycemic (blood sugar) control and greater improvement of insulin secretion in the GBP group. Although it has been known for a long time [51] that BCAA and related metabolites are linked to insulin resistance and diabetes, and can cause metabolic dysfunction [52], our study [50] shows that these metabolites are more responsive to surgical that dietary-induced weight loss. A recent epidemiological study showed that branched-chain and aromatic amino acids predict the risk for T2DM [53]. Future studies will characterize the metabolic pathways involved in the specific metabolic signature of GBP, and how it is related to changes in gut hormones, beta cell function, and changes in insulin sensitivity.

Longterm effect of GBP: not so rosy after all?

As the international community is looking with interest at the effect of GBP, longterm clinical data emerge. Most patients experience considerable improvement of co-morbidities and quality of life and reduction of mortality [54]. However, small scale long-term studies show weight regain and/or diabetes relapse in a significant percentage of patients [55, 56]. The criteria of pathological weight regain are not well defined. Similarly, establishing the diagnosis of relapse of T2DM with the value of HbA1C, a marker now used for the diagnosis of T2DM [57], is questionable. Postprandial hypoglycemia, even asymptomatic, is not infrequent in patients after GBP, likely lowers the average blood glucose, and may mask early stage of T2DM relapse. Research need to be done not only to identify biological, endocrine, and genetic markers of success, but also markers of weigh regain and diabetes relapse after GBP. Larger clinical series need to be followed and patients carefully phenotyped for years after GBP.

Conclusion

The magnitude of weight loss ($\sim$40%) and its persistence (years) in most patients are considered the major contributors to glucose control after GBP. However, the data clearly show beneficial changes of incretin levels and effect improved insulin secretion profile and decreased postprandial glucose, occurring rapidly after GBP, and for the most part independent of weight loss. Recently identified change in circulating amino acids, in parallel with the improved insulin secretion, opens new avenues for clinical investigation. Understanding the mechanisms of the change in metabolism after GBP should help define the role of the gut in the physiopathology of T2DM, and help discover new therapeutic surgical or medical intervention, and possibly prevent diabetes relapse after the surgery.

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