

Bariatric surgery: effects on glucose homeostasis

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Purpose of review

This article provides an overview of the effect of bariatric surgery on type 2 diabetes. It focuses on current hypotheses about the mechanism of diabetes control after Roux-en-Y gastric bypass surgery, and discusses the relationship between gastrointestinal anatomy and glucose homeostasis.

Recent findings

Along with sustained body weight loss, all bariatric operations lead to improvement or resolution of comorbid disease states, particularly type 2 diabetes. Roux-en-Y gastric bypass and biliopancreatic diversion are the most effective methods to control diabetes, resulting in persistent normal concentrations of plasma glucose, insulin, and glycosylated haemoglobin in 80–100% of cases. Resolution of diabetes after such treatment typically occurs too fast to be accounted for by weight loss alone. Recent animal investigations using duodenal–jejunal bypass, a stomach-preserving experimental model of Roux-en-Y gastric bypass, have shown that diabetes control is not a mere collateral effect of the treatment of obesity, but directly results from the exclusion of the duodenum and proximal jejunum from the flow of nutrients.

Summary

Results from clinical series and animal studies suggest that type 2 diabetes is a potentially operable disease. This indicates the need for carefully conducted clinical trials to define the ideal candidate patients and the most suitable type of operation for surgical treatment of type 2 diabetes. Understanding the exact mechanism by which Roux-en-Y gastric bypass controls diabetes is a priority because such knowledge may help us to understand the relationship between gastrointestinal physiology and insulin resistance as well as to help us identify new targets for novel antidiabetic medications.

Keywords

biliopancreatic diversion, diabetes, duodenal–jejunal bypass, gastric bypass, insulin resistance, obesity surgery

Abbreviations

| | |
|--------------|--------------------------------------|
| BPD | biliopancreatic diversion |
| DJB | duodenal–jejunal bypass |
| GLP-1 | glucagon-like peptide 1 |
| JIB | jejunoileal bypass |
| LAGB | laparoscopic adjustable gastric band |
| RYGB | Roux-en-Y gastric bypass |
| VBG | vertical banded gastroplasty |

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Introduction

It is now generally agreed that impaired insulin secretion and insulin resistance both contribute to fully established type 2 diabetes mellitus [1,2]. We still do not know, however, what causes these alterations in glucose metabolism. As a result, current therapies, including diet, exercise, behaviour modification, oral hypoglycaemic agents, and insulin, may control the hyperglycaemia but do not achieve a cure. A better understanding of the pathophysiology of type 2 diabetes will likely result in much better treatment.

In the meantime, surgery may provide new possibilities. In fact, some operations for morbid obesity not only induce significant and lasting weight loss but also lead to improvements or resolution of comorbid disease states, particularly type 2 diabetes [3–5].

Operations for obesity range from purely restrictive techniques (vertical banded gastroplasty (VBG) and adjustable gastric banding) to gastrointestinal bypass procedures such as the Roux-en-Y gastric bypass (RYGB) and the biliopancreatic diversion (BPD).

All bariatric operations result in remarkable improvement in type 2 diabetes, although with varying degrees of efficacy. RYGB and BPD are the most effective in controlling diabetes and result in sustained normal concentrations of plasma glucose, insulin, and glycated haemoglobin in 80–100% of morbidly obese patients with diabetes [6–8]. Insulin sensitivity measured by minimal modelling is increased approximately four to fivefold after RYGB-induced weight loss [9]. This surgery also prevents progression from impaired glucose tolerance to diabetes [10] and reduces mortality from this condition [11].

The remarkable resolution of diabetes after RYGB and BPD typically occurs too fast to be accounted for by weight loss alone, suggesting that these two procedures

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may have a direct and more profound impact on glucose homeostasis.

Is there a role for surgery in the management of type 2 diabetes mellitus? How does surgery control diabetes? Answering these questions has become a priority due to the current epidemic growth of this condition. Elucidating the mechanisms of action of these operations is also far reaching; this knowledge might in fact help us to understand the relationship between gastrointestinal physiology and insulin resistance and possibly to find new targets for novel antidiabetic medications.

This article presents current operative techniques for morbid obesity and reviews the effect of bariatric surgery on type 2 diabetes. Focusing on RYGB, the hypothesized mechanisms of diabetes control are also discussed in the light of recent scientific investigations.

Bariatric surgery: types of surgical procedures

Current surgical procedures for the treatment of the severely obese patient are typically categorized into restrictive, malabsorptive and mixed procedures, based on the supposed mechanism by which they cause weight loss. This classification is practical but inaccurate as growing evidence suggests that mechanisms, other than just restriction or malabsorption, play a role in determining the effects of RYGB and BPD.

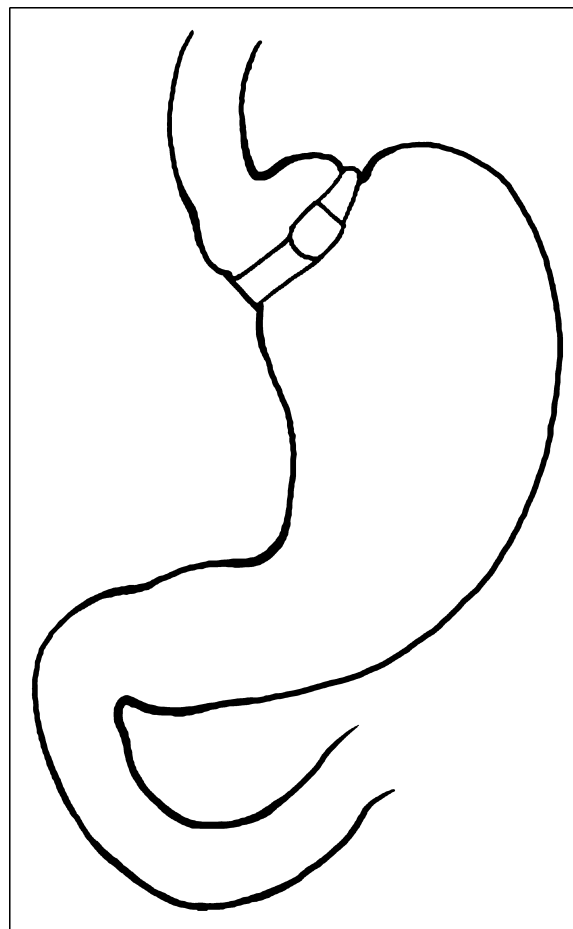
Restrictive procedures

Restrictive procedures share common features that include the use of some type of foreign material or 'band' placed circumferentially around the upper stomach in order to limit the luminal diameter and create a small gastric pouch that empties into the remainder of the stomach. These procedures include the laparoscopic adjustable gastric band (LAGB; Fig. 1) and VBG (Fig. 2). Both of these operations do not involve any re-routing of food through the gastrointestinal tract nor exclusion of intestinal segments, as in the case of RYGB and BPD.

Roux-en-Y gastric bypass

The RYGB is the most commonly performed bariatric operation in the US, and is considered the 'gold standard' treatment for morbid obesity. Current techniques involve the use of a surgical stapler to create a small and vertically oriented gastric pouch, the volume of which is usually less than 30 cm³. The pouch is completely divided by the gastric remnant and is anastomosed to the jejunum (between 30 and 75 cm from the ligament of Treitz), through a narrow gastrojejunal anastomosis in a Roux-en-Y fashion (Fig. 3). Bowel continuity is restored by an entero-entero anastomosis between the excluded biliary limb and the alimentary limb. This anastomosis is usually done at 75–100 cm distal to the gastrojejunostomy,

Figure 1 (Laparoscopic) Adjustable gastric banding



although it has also been performed at 100–250 cm in patients with body mass index (BMI) greater than 50 kg/m². The latter variant is referred to as 'long-limb' RYGB or 'distal' RYGB, as opposed to the standard, 'proximal' RYGB. The long-limb RYGB is anatomically more similar to the concept of BPD (vide infra) and is aimed to induce more intestinal malabsorption than with a proximal RYGB.

After RYGB, ingested food bypasses approximately 95% of the stomach, the entire duodenum and a portion of the jejunum. RYGB usually results in 60–70% excess weight loss and most of this effect is maintained for at least 15 years [12–14].

Malabsorptive procedures

Malabsorptive procedures aim to reduce the area of intestinal mucosa available for nutrient absorption. The first attempt to obtain weight loss with this strategy was through the jejunoileal bypass (JIB), an operation that diverted enteral nutrients from most of the small intestine by anastomosing the proximal jejunum to the

Figure 2 Vertical banded gastroplasty

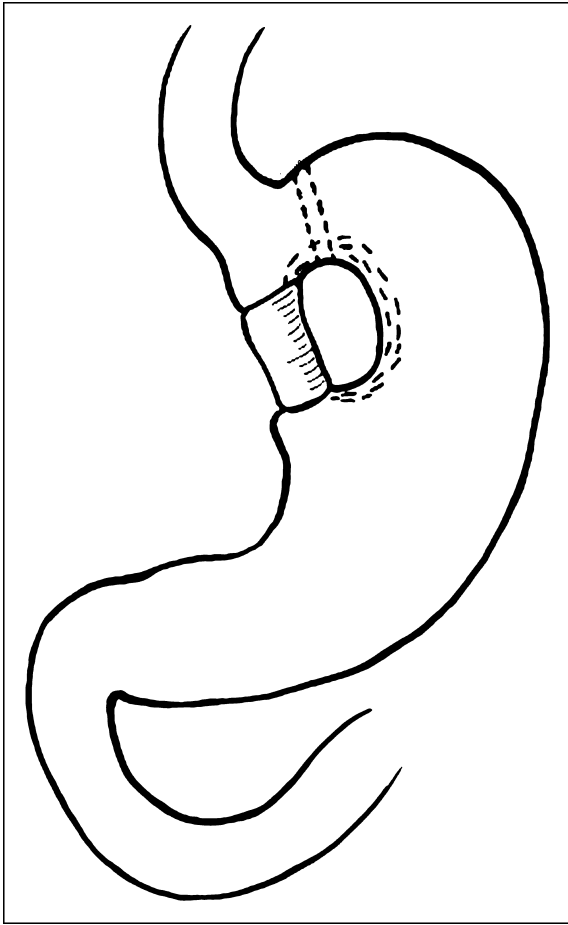
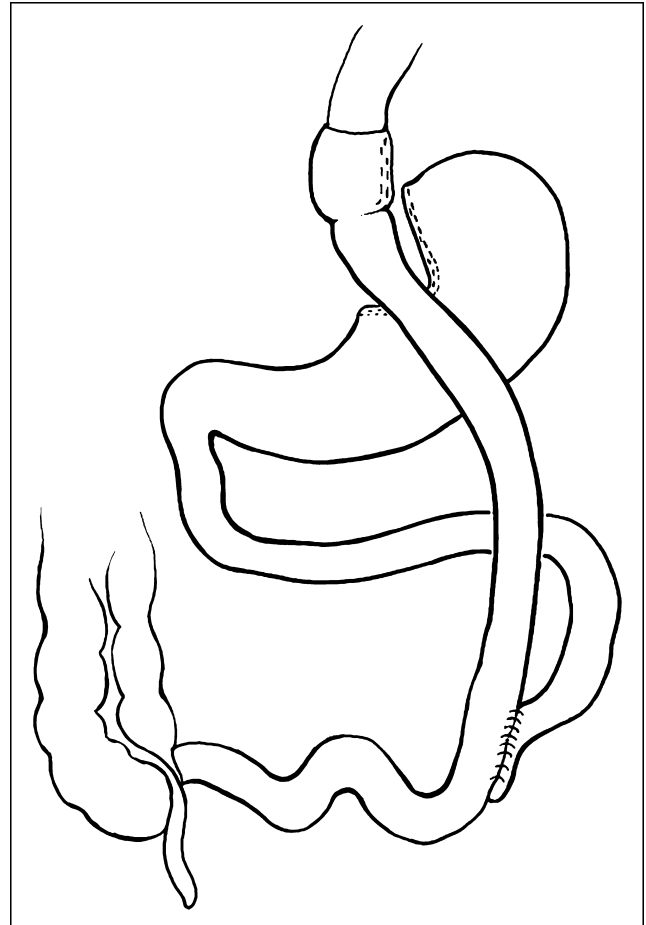


Figure 3 Roux-en-Y gastric bypass



terminal ileum (Fig. 4). The operation achieved excellent weight loss but also resulted in excessive long-term nutritional complications and hepatic cirrhosis due to bacterial overgrowth. For these reasons the JIB was ultimately abandoned.

Biliopancreatic diversion

The concept of BPD was first described by Nicola Scopinaro of Genoa, Italy in 1979 [15] in an attempt to improve the results of the JIB. Technically, the operation consists of a partial gastrectomy, which leaves behind a 200–500 ml sized upper stomach. This is anastomosed to the distal 250 cm of small intestine, whereas the excluded small intestine containing the bile and pancreatic secretions is connected to the alimentary channel 50 cm proximal to the ileocecal valve (Fig. 5). The last segment of ileum where food and bile mix is referred to as a 'common channel' and is responsible for most fat absorption.

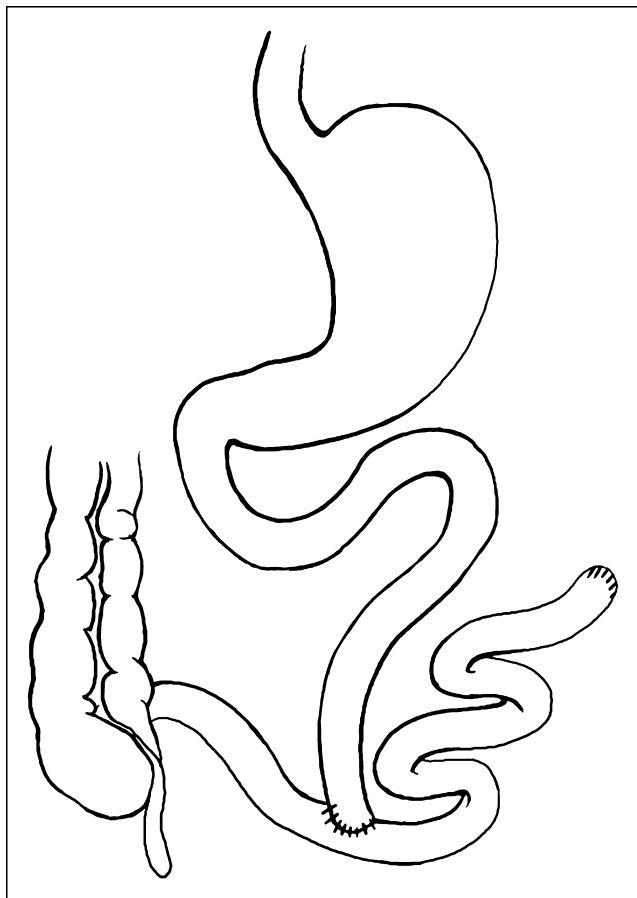
The procedure was later modified by Hess and Hess [16] and Marceau *et al.* [17] to include a 'sleeve vertical

gastrectomy' (with a maximum gastric reservoir of 150–200 ml), a duodeno-ileal switch and a longer common channel length of about 100 cm as opposed to the 50 cm in the original Scopinaro procedure (Fig. 6). In the 'duodenal switch' variant of BPD a sleeve of the stomach, pylorus and a short segment of duodenum are preserved and vagal nerve integrity is spared. This type of gastrectomy has the theoretical advantage of preserving a more physiologic digestive behaviour and diminishing the risk of dumping syndrome, ulcerogenicity and hypocalcaemia.

Antidiabetic effect of bariatric surgery

A substantial majority of patients who undergo bariatric surgery experience improvement or resolution of type 2 diabetes mellitus. The prospective, controlled Swedish Obese Subjects Study [18] involved obese patients who underwent gastric surgery and contemporaneously matched, conventionally treated obese controls, with follow-up data at 2 years (4047 participants) or 10 years (1703 participants). Two- and 10-year rates of recovery

Figure 4 Jejunio-ileal bypass

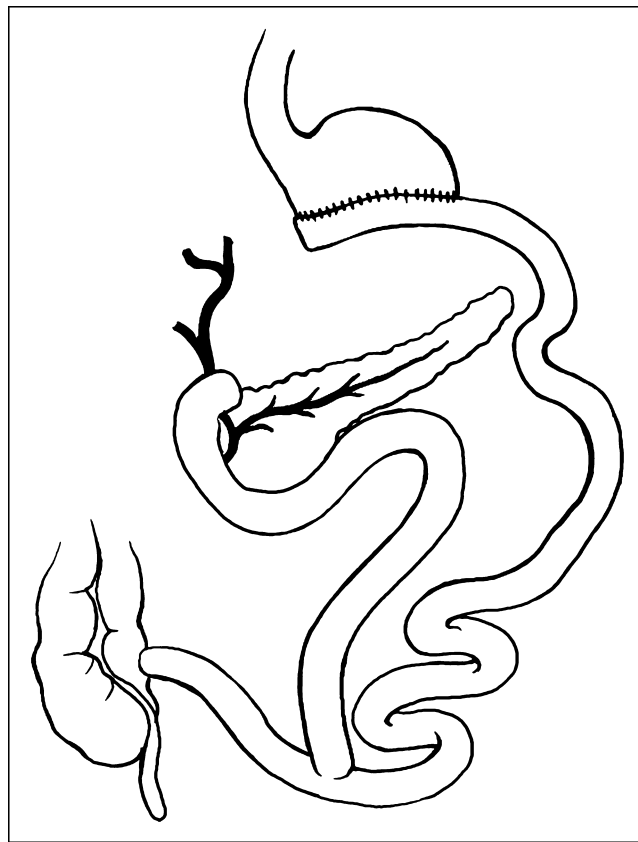


from diabetes were more favourable in the surgery group than in the control group.

A recently published metaanalysis [19] involving 136 studies with a total of 22 094 patients focused on the effect of bariatric surgery on obesity comorbidities. This study showed that type 2 diabetes was completely resolved in 76.8% of patients and resolved or improved in 86.0%. Bariatric surgery has also been shown to lower the rate of progression from impaired glucose tolerance to diabetes by 30-fold [20].

Gastrointestinal bypass procedures are more effective than purely restrictive procedures in controlling diabetes. Although diabetes control is described after all types of bariatric operations, the rate and rapidity of this effect varies significantly across different procedures. With respect to diabetes resolution (ability to discontinue all diabetes-related medications and maintain normal fasting glycaemia and glycosylated haemoglobin levels), the metaanalysis from Buchwald and co-workers [19] found a gradation of effect from 98.9% (95% confidence interval (CI), 96.8–100%) for BPD or duodenal switch to 83.7% (95% CI, 77.3–90.1%) for RYGB to 71.6% (95% CI, 55.1–

Figure 5 Classic biliopancreatic diversion



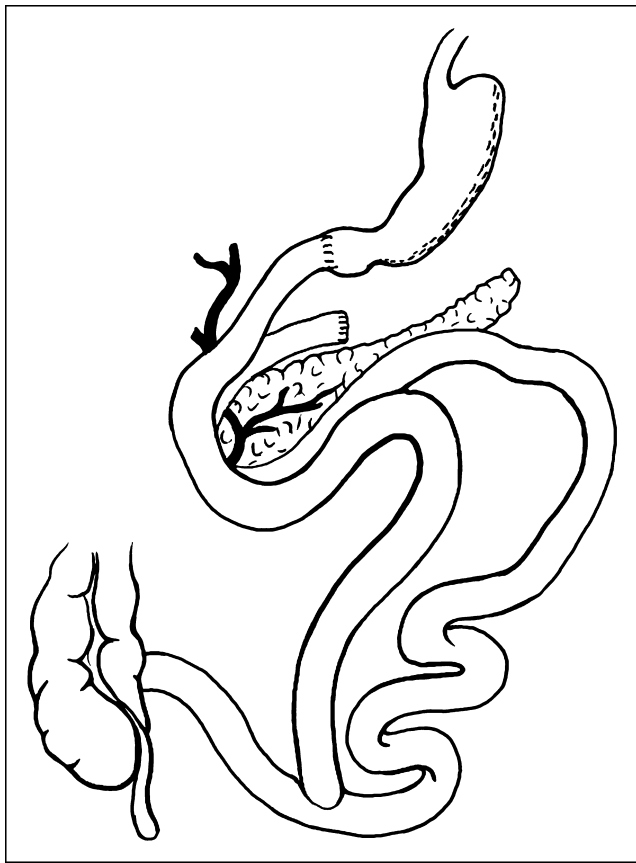
88.2%) for VBG, and to 47.9% (95% CI, 29.1–66.7%) for LAGB.

The antidiabetic effect of bariatric surgery is long lasting. Long-term control of glycaemia and normal levels of glycosylated haemoglobin after RYGB have been documented in large series with up to 16 years of follow up [21,22]. Furthermore, in the experience of MacDonald and co-workers, mortality risk from diabetes over a 10-year follow-up after RYGB was less than that in a cohort of patients with diabetes matched for age, weight and BMI who were not operated on (1.0% versus 4.5% for every year of follow-up; $P < 0.0003$) [11].

Scopinaro and co-workers [23*] have recently reported the long-term outcomes of BPD in a series of 312 obese patients with type 2 diabetes. These authors observed that fasting serum glucose concentration fell to within normal values in all but two of the patients and remained in the physiological range in all but six for a mean follow up of 10 years.

Surgery as a cure for type 2 diabetes?

The extraordinary control of diabetes by obesity surgery has led to some intriguing questions.

Figure 6 Biliopancreatic diversion with duodenal switch

Is diabetes control a primary and direct result of the surgical procedures or simply a secondary outcome of obesity treatment?

In 2004 we reported an experimental study providing evidence that the control of diabetes after gastrointestinal bypass surgery is not secondary to the treatment of obesity [24]. Using Goto–Kakizaki rats, a spontaneous, nonobese model of type 2 diabetes mellitus, we found that duodenal–jejunal bypass (DJB) (a stomach-sparing experimental model of RYGB) significantly improves glucose tolerance compared with sham-operated controls, despite equivalent food intake rates and body weights in the two groups. Furthermore, DJB was more effective than either rosiglitazone therapy or greater weight loss from food restriction in matched controls. This study also allowed the effects of intestinal bypass to be isolated from those related to gastric restriction as the DJB model leaves the stomach unperturbed. These findings suggest that diabetes control should no longer be regarded as a mere collateral effect of operations for morbid obesity, but rather as a specific outcome of gastrointestinal bypass surgery, implicating that type 2 diabetes is a potentially operable disease.

Should patients with type 2 diabetes be considered for surgical treatment regardless of their BMI?

Current indications for bariatric surgery include BMI equal to or greater than 40 kg/m² or between 35 and 40 kg/m² with obesity-related comorbidities. These selection criteria were first issued by the National Institutes of Health (NIH) Consensus Development panel in 1991 [25,26] and have been substantially adopted by all major surgical societies. As bariatric operations have been performed nearly universally in patients selected with the NIH criteria, the antidiabetic effects of bariatric procedures are well documented in either severely or morbidly obese patients.

Bariatric operations, however, have occasionally been performed in nonmorbidly obese individuals. In 1997, Mingrone *et al.* [27] reported a case of a young woman of normal weight with diabetes who underwent BPD for chylomicronaemia and whose plasma insulin and blood glucose levels were normalized within 3 months, despite the fact that she increased her weight due to an unrestricted diet rich in sugar and lipids. Noya *et al.* [28] reported remission of type 2 diabetes in nine out of 10 moderately obese (mean BMI 33.2) patients with diabetes who underwent BPD.

Sporadic but consistent observations of diabetes remission have also been reported even before the advent of bariatric surgery as a serendipitous outcome of gastric resections for peptic ulcer in nonobese patients. In 1955, Friedman and co-workers [29] reported on three patients with diabetes mellitus who had poor glycaemic control in spite of high daily doses of insulin. As early as 3–4 days after subtotal gastrectomy all three patients showed a remarkable improvement in their diabetes with a sudden reduction in their insulin requirement, before patients developed weight loss. Interestingly, these patients later regained their weight without an associated recrudescence of glycosuria. Bittner *et al.* [30] similarly reported improvement in diabetes with lowered plasma glucose and insulin after subtotal gastrectomy and gastrointestinal reconstructions that excluded duodenal passage (Billroth II and Roux-en-Y type of reconstruction). These reports show an intriguing similarity with the typical remission of type 2 diabetes seen after RYGB or BPD for morbid obesity: plasma glucose and insulin fall rapidly and antidiabetic medications can be reduced or suspended shortly after the operation.

Experimental studies in nonobese rats and these clinical observations are consistent in showing that amelioration of diabetes can occur not only in morbidly obese patients but also in nonobese individuals after different types of operations that share the common feature of duodenal–jejunal exclusion (RYGB, BPD, DJB,

subtotal gastrectomy with RY or Billroth II reconstruction).

The possibility of a surgical option in the treatment of patients with type 2 diabetes is significant as we face a worldwide epidemic with limited efficacy of conventional therapeutic strategies [31]. Indeed, the potential of surgery to achieve diabetes resolution is attractive when compared with the evidence that oral antidiabetic agents and insulin have limitations, side effects and limited long-term efficacy due to poor patient compliance [32–34].

Despite the fact that these and other arguments support the use of surgery as an alternative antidiabetic treatment, this concept will inevitably face significant opposition from both surgeons and physicians. In fact, the risk of mortality and morbidity from surgery may seem disproportionate for a condition that has always been considered a ‘medical’ disease. Diabetes is not a benign disease, however, and is associated with significant reduction of both life expectancy and quality of life. In current clinical practice there are many diseases for which surgical treatment is widely accepted although they are far more benign than diabetes. Such diseases can benefit from medications that are much more effective than current antidiabetic drugs, while in the long term many patients will still experience recurrence of symptoms and the need for medication after surgery (e.g. gastrointestinal reflux disease) [35]. Considering the evidence that nearly all patients who have undergone RYGB or BPD maintain diabetes remission without the need for medication over 10 and more years, there is a definite rationale for surgical treatment of type 2 diabetes.

Clinical experience with bariatric surgery as well as data from animal investigations now suggest that surgical indication in patients with type 2 diabetes should not be on the basis of the current arbitrary cut-off at BMI 35 kg/m², but rather on the evaluation of the risk/benefit ratio as for any invasive therapeutic modalities. There is a definite need for carefully conducted clinical trials to define the ideal candidate patients and the most suitable type of operation.

Mechanism of diabetes control after gastrointestinal bypass operations

One might think that surgically induced weight loss and decreased food intake are the most obvious methods for remission of diabetes after obesity surgery; however, evidence suggest that the mechanisms involved are not so straightforward.

The role of weight loss and decreased food intake

Many clinical observations and findings from our animal studies are consistent in showing that decreased food

intake and weight loss are not primary mediators of the control of diabetes after RYGB and BPD.

Indeed, most reported series of RYGB show that return to euglycaemia and normal insulin levels occurs within days after surgery, long before there is any significant weight loss [8,36]. In 1998, Scopinaro *et al.* [37] reported normalization of glucose levels in 100% of their morbidly obese patients after BPD with no need for medication and on a totally free diet as early as 1 month after the operation, when excess weight was still more than 80%. Hickey and co-workers [36] demonstrated significantly lower levels of fasting plasma glucose, plasma insulin and serum leptins in a group of patients maintaining stable weight after RYGB compared with a group of patients matched in weight, age and percentage of fat, who did not undergo surgery.

Furthermore, restrictive techniques result in lower rates of diabetes remission compared with RYGB and BPD (48% for LAGB versus 82–98% for RYGB and BPD) [19] and while diabetes resolution takes place very rapidly after gastrointestinal bypass techniques, it occurs more gradually after restrictive procedures. In fact, in a recent study by Ponce and co-workers [38] the rate of diabetes resolution after LAGB was greater at 2 years postoperatively compared with the first year after surgery and was correlated to the degree of weight loss.

Hence, whereas diabetes control after restrictive procedures may be explained by weight loss alone, this is not a sufficient explanation for the magnitude and rapidity of diabetes resolution after BPD and RYGB.

Against a dominant role of decreased caloric intake also stands the observation that a very low-calorie diet fails to improve diabetes in patients who later experience diabetes resolution from RYGB surgery [39]. Furthermore, patients undergoing BPD show only temporary food intake limitation; over time, their eating capacity is fully restored or even increased [37], while blood glucose levels remain under control.

One may argue, however, that a timely combined action of decreased energy intake and weight loss could explain the antidiabetic effect of surgery. In fact, postoperative starvation may be responsible for the early fall in blood glucose while subsequent weight loss could explain maintenance of the effect, even when normal food intake behaviour is later resumed, such as after BPD. To rule out this hypothesis we performed animal studies in which DJB rats were pair-fed with sham-operated controls [40]. In these experiments, DJB-treated rats with diabetes showed better glucose tolerance than matched, pair-fed sham-operated animals with the same food intake and body weight, showing that diabetes control after

gastrointestinal bypass surgery is not primarily mediated by changes in energy intake or body weight.

The role of intestinal malabsorption

Intestinal malabsorption may improve diabetes in many ways. By determining weight loss it could reduce insulin resistance. Glucose malabsorption may also reduce overall stress on islet cells whereas fat malabsorption may reduce circulating free fatty acids (FFAs) and, consequently, improve insulin sensitivity. Indeed it is known that high levels of FFAs can induce insulin resistance [41] and lowered FFAs are associated with improved insulin sensitivity in individuals with hyperlipidaemia [42].

Whereas intestinal malabsorption is clinically evident after BPD, however, clinically significant malabsorption is not observed after standard RYGB [43–45].

Studies in animals with diabetes undergoing D-xylose testing and faecal fat assessment showed no reduction in carbohydrate or lipid absorption after DJB, although this experimental model does improve diabetes [40]. Because the proportion of intestine removed from digestive continuity after our DJB procedure matches that bypassed in a typical proximal RYGB, our data also support clinical evidence arguing against a major role for malabsorption in the effects of human RYGB [43–45].

The role of hormonal changes

It has been hypothesized that the significant re-routing of food through the gastrointestinal tract may alter the dynamic of gut-hormone secretion, especially in response to meal stimuli. In support of this hypothesis are some clinical observations showing substantial changes in gut-hormone levels after gastrointestinal bypass procedures. In 2002, Cummings and co-workers [46] reported inappropriate suppression of ghrelin, an orexigenic hormone, after weight loss from RYGB. Several investigations have consistently documented a decrease in plasma levels of leptin and insulin, and increased levels of adiponectin and peptide YY3-36 after RYGB and BPD, supporting the possibility of an endocrine effect of these operations [47–49,50*].

Increased levels of glucagon-like peptide 1 (GLP-1) have also been suggested to play a role in the mechanism of appetite and diabetes control after RYGB. While few studies have shown an increase in GLP-1 levels after RYGB [50*], however, other investigations have not yielded consistent findings [49,51].

For any hormonal change to play a role in the mechanism of action of a surgical procedure it is necessary that it occurs before the effects of the operation take place. Preliminary clinical studies [49] have shown that some

hormonal changes can occur within days after RYGB, supporting the hypothesis that this procedure may work through an endocrine mechanism.

In recent investigations using obese animals with diabetes (Zucker ZDF rats), we found that exclusion of the intestinal foregut from the transit of nutrients by DJB is sufficient to restore physiologic ghrelin regulation (which is altered in such animals) and decrease appetite without restriction of gastric volume [52*]. As the DJB does not prevent stimulation of the ghrelin-rich gastric fundus by ingested nutrients, these findings also show that intestinal signals are involved in ghrelin regulation and that the bowel rearrangement typical of DJB (and RYGB) may influence these signals.

Further investigations are needed to elucidate which of the hormonal changes that occur after RYGB are actually involved in the efficacy of this operation.

Rearrangement of gastrointestinal anatomy and diabetes control

Regardless of the molecular explanation, which still remains to be elucidated, it is important to understand which part of the typical anatomical rearrangement of RYGB is essential for the effect on diabetes. Two hypotheses have been proposed. The ‘hindgut hypothesis’ holds that diabetes control results from the expedited delivery of nutrient chyme to the distal intestine, enhancing a physiologic signal that improves glucose metabolism [53–56]. A potential candidate mediator of this effect is GLP-1 or other distal gut peptides. An alternative hypothesis is that the exclusion of the duodenum and proximal jejunum from the transit of nutrients may prevent secretion of a putative signal that promotes insulin resistance and type 2 diabetes (‘foregut hypothesis’) [57,58]. Although no obvious candidate molecules can be identified with our current knowledge, if proven true, this hypothesis may open new avenues in the search for the cause and cure of diabetes.

The hindgut and the foregut hypothesis

The hindgut hypothesis has been suggested due to reports showing that GLP-1 levels are increased after JIB [59] and ileal transposition [56]. The latter is an experimental procedure that consists of the transposition of an isolated segment of ileum to the jejunum, and has been associated with increased synthesis and release of GLP-1 and peptide YY in rats [60*]. The hindgut hypothesis derives its rationale from the assumption that RYGB expedites delivery of nutrients to the distal small bowel in a similar way as after JIB and ileal transposition [54,56].

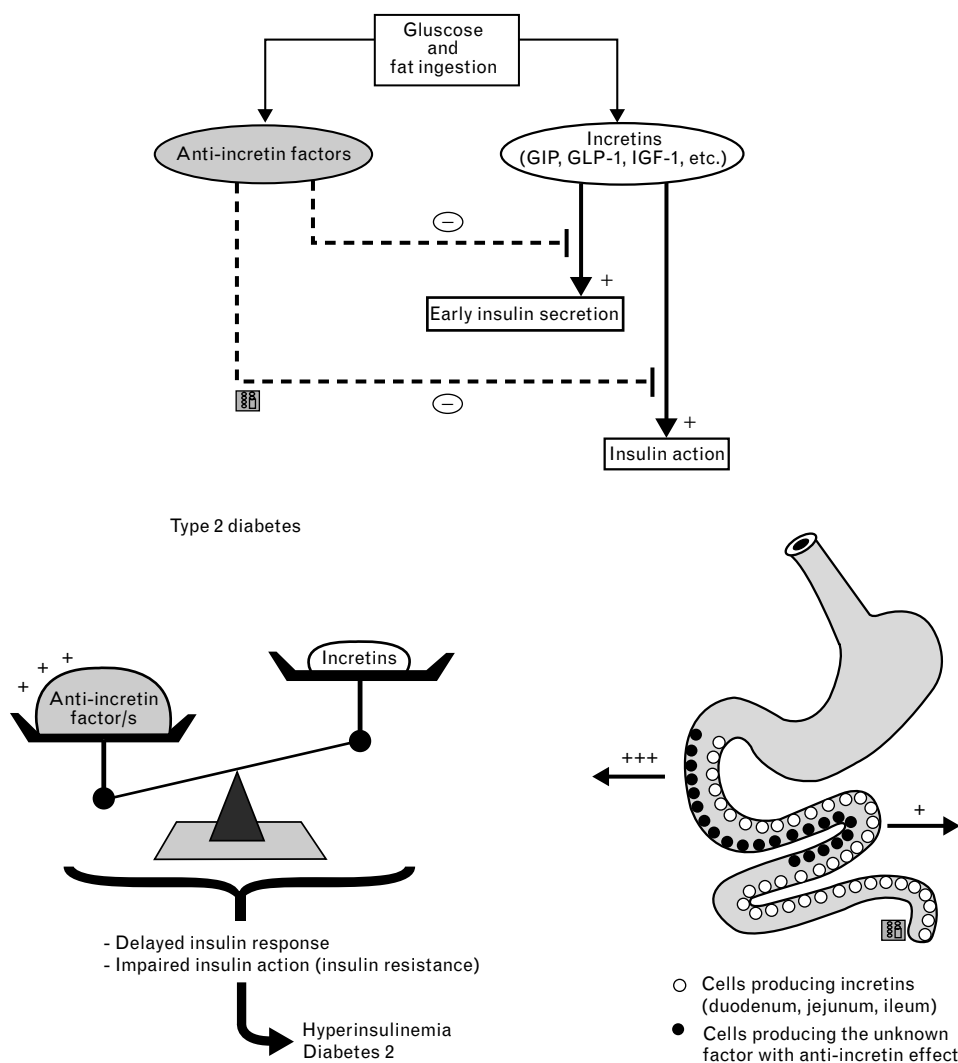
Likening RYGB to JIB or ileal transposition, however, is a conceptual mistake. Indeed, while both JIB and ileal

transposition maintain the duodenum and proximal jejunum en route with the transit of food, this is not the case with RYGB, BPD and DJB. Duodenal passage of nutrients hardly represents a minor physiological difference and, therefore, in our opinion, JIB and ileal transposition should not be used as a model of RYGB, BPD and DJB.

We recently performed a study that supports the foregut hypothesis as a dominant mechanism in improving glucose homeostasis after RYGB [40]. In fact, we found that, whereas DJB (gastro-jejunostomy + duodenal exclusion as in RYGB) greatly improves diabetes in Goto-Kakizaki rats, performing an equivalent shortcut for ingested nutri-

ents to the hindgut, without excluding nutrient flow through the proximal intestine (via a simple gastro-jejunostomy), does not improve diabetes in the same animal model. In addition, diabetic abnormalities of glucose tolerance return in DJB-treated animals when nutrient flow through the proximal intestine is surgically re-established via the normal gastro-duodenal route, despite preserving the gastro-jejunostomy. Similarly, in animals that originally underwent a simple gastro-jejunostomy without benefits, diabetes is greatly improved by a re-operation in which the proximal intestine is excluded from nutrient flow, but the gastro-jejunostomy is left intact.

Figure 7 Hypothesis regarding the possible contribution of the proximal intestine to the alterations of glucose metabolism in type 2 diabetes



The passage of nutrients through the intestinal foregut might trigger, in addition to the known incretin response, a concomitant counter-regulatory signal ('anti-incretin factor') aimed to prevent hypoglycaemia. This signal may interfere with pathways of the incretin system or act downstream to inhibit insulin action. In predisposed individuals, chronic stimulation with particular nutrients might create an imbalance between incretin and 'anti-incretin' signals, resulting in insulin resistance and type 2 diabetes. Adapted from Rubino and Gagner [58]. GIP, gastric inhibitory peptide; GLP-1, glucagon-like peptide 1; IGF-1, insulin-like growth factor 1.

These findings demonstrate that isolating a segment of proximal intestine from nutrient flow is important in mediating the improvement of glucose tolerance in animals with diabetes.

Gastrointestinal bypass surgery: more of a good thing or less of a bad thing for glucose homeostasis?

Regardless of anatomic considerations and possible molecular explanations, there are additional basic questions that need to be answered. In fact, when looking at the big picture, there are only two possible ways by which gastrointestinal bypass surgery can control type 2 diabetes: this surgery enhances a signal with positive influence on glucose homeostasis (i.e. GLP-1, reduced glucose absorption, weight loss etc.); this surgery contrasts a factor that negatively influences glucose homeostasis or is implicated in the pathophysiology of insulin resistance and diabetes.

If the first hypothesis were correct, one would expect improved (or at least unchanged) glucose tolerance in both normal and diabetic individuals, as a result of increased secretion of signals exerting a positive influence on glucose metabolism. We observed that when DJB is performed in animals without diabetes (Wistar rats), glucose tolerance is worse than that of matched sham-operated controls, in striking contrast with the marked improvement seen in rats with diabetes after DJB [40]. Our data are consistent with results of clinical investigations showing a similar impairment of glucose tolerance in individuals without diabetes who have undergone operations that, like DJB, include duodenal–jejunal exclusion. In fact, several clinical studies, including a randomized trial [61] comparing gastrectomy with duodenal exclusion (such as the Roux-en-Y reconstruction) versus gastrectomy with preservation of duodenal passage, showed that the former impairs glucose tolerance in patients without diabetes and results in lower plasma gastric inhibitory peptide and insulin levels [30,62].

In summary, our animal investigations together with these clinical observations support the following findings:

1. in normal individuals, duodenal passage of nutrients is necessary to maintain normal glucose tolerance, whereas duodenal–jejunal exclusion seems to disrupt the physiologic entero-insular axis;
2. in individuals with diabetes, duodenal–jejunal exclusion improves glucose tolerance.

These data are consistent with the hypothesis that surgical bypass of the proximal small intestine reverses a humoral mechanism originating in the bowel that impairs glucose tolerance in individuals with diabetes. This hypothesis characterizes type 2 diabetes as a possible duodenal–jejunal illness.

We speculate that under normal conditions, stimulation of the proximal bowel with nutrients triggers both an incretin response that increases insulin secretion, as well as a concomitant counter-regulatory signal that controls insulin action in order to prevent hypoglycaemia. In predisposed individuals, chronic stimulation with particular nutrients may create an imbalance between incretin and ‘anti-incretin’ signals, resulting in insulin resistance and type 2 diabetes (Fig. 7).

This hypothesis is consistent with the discrepancy seen in the effect of duodenal–jejunal exclusion in normal controls versus individuals with diabetes. Indeed, according to this model, duodenal exclusion weakens the physiologic ‘incretin effect’ in normal individuals but can also tackle an exaggerated production of the ‘anti-incretin’ signal, thus explaining why this anatomical condition is beneficial only in individuals with diabetes.

Conclusion

Bariatric surgery, and in particular RYGB and BPD, induces a remarkable resolution of type 2 diabetes that typically occurs too fast to be accounted for by weight loss alone. Clinical observations and animal experiments suggest that a key component of these operations in ameliorating diabetes is the bypass of the proximal small intestine. Thus proximal intestinal bypass is a potential therapeutic approach for diabetes and there is the possibility that potentially undiscovered factors in the proximal bowel may play an important role in the pathophysiology of insulin resistance and type 2 diabetes.

Acknowledgement

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 524–525).

- 1 Cavaghan MK, Ehrmann DA, Polonsky KS. Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. *J Clin Invest* 2000; 106:329–333.
- 2 Mahler RJ, Adler ML. Clinical review 102: type 2 diabetes mellitus: update on diagnosis, pathophysiology, and treatment. *J Clin Endocrinol Metab* 1999; 84:1165–1171.
- 3 Foley EF, Benotti PN, Borlase BC, *et al.* Impact of gastric restrictive surgery on hypertension in the morbidly obese. *Am J Surg* 1992; 163:294–297.
- 4 Smith S, Edwards CB, Goodman GN. Changes in diabetic management after Roux en-Y gastric bypass. *Obes Surg* 1996; 6:345–348.
- 5 Cowan GS, Buffington CK. Significant changes in blood pressure, glucose, and lipids with gastric bypass surgery. *World J Surg* 1998; 22:987–992.
- 6 Scopinaro N, Adami GF, Marinari GM, *et al.* Biliopancreatic diversion. *World J Surg* 1998; 22:936–946.
- 7 Schauer PR, Ikramuddin S, Gourash W, *et al.* Outcomes after laparoscopic roux-en-Y gastric bypass for morbid obesity. *Ann Surg* 2000; 232:515–529.

- 8 Pories WJ, Swanson MS, MacDonald KG, *et al*. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg* 1995; 222:339–350.
- 9 Pender C, Goldfine ID, Tanner CJ, *et al*. Muscle insulin receptor concentrations in obese patients post bariatric surgery: relationship to hyperinsulinemia. *Int J Obes Relat Metab Disord* 2004; 28:363–369.
- 10 Pories WJ, MacDonald KG, Morgan EJ, *et al*. Surgical treatment of obesity and its effect on diabetes: 10-y follow-up. *Am J Clin Nutr* 1992; 55 (2 Suppl): 582S–585S.
- 11 MacDonald KG, Long SD, Swanson MS, *et al*. The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. *J Gastrointest Surg* 1997; 1:213–220.
- 12 DeMaria EJ, Sugerman HJ, Kellum JM, *et al*. Results of 281 consecutive total laparoscopic Roux-en-Y gastric bypasses to treat morbid obesity. *Ann Surg* 2002; 235:640–647.
- 13 Fobi MA, Lee H, Holness R, Cabinda D. Gastric bypass operation for obesity. *World J Surg* 1998; 22:925–935.
- 14 Higa KD, Boone KB, Ho T, Davies OG. Laparoscopic Roux-en-Y gastric bypass for morbid obesity: technique and preliminary results of our first 400 patients. *Arch Surg* 2000; 135:1029–1034.
- 15 Scopinaro N, Gianetta E, Civalieri D, *et al*. Bilio-pancreatic bypass for obesity. II: Initial experience in man. *Br J Surg* 1979; 66:618–620.
- 16 Hess DS, Hess DW. Biliopancreatic diversion with a duodenal switch. *Obes Surg* 1998; 8:267–282.
- 17 Marceau P, Hould FS, Simard S, *et al*. Biliopancreatic diversion with duodenal switch. *World J Surg* 1998; 22:947–954.
- 18 Sjostrom L, Lindroos AK, Peltonen M, *et al*. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004; 351:2683–2693.
- 19 Buchwald H, Avidor Y, Braunwald E, *et al*. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004; 292:1724–1737.
- 20 Long SD, O'Brien K, MacDonald KG Jr, *et al*. Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type II diabetes: a longitudinal interventional study. *Diabetes Care* 1994; 17:372–375.
- 21 Pories WJ. Diabetes: the evolution of a new paradigm. *Ann Surg* 2004; 239:12–13.
- 22 Schauer PR, Burguera B, Ikramuddin S, *et al*. Effect of laparoscopic Roux-en-Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 2003; 238:467–484.
- 23 Scopinaro N, Marinari GM, Camerini GB, *et al*. Specific effects of biliopancreatic diversion on the major components of metabolic syndrome: a long-term follow-up study. *Diabetes Care* 2005; 28:2406–2411.
- The authors of this article reviewed the files of 312 obese patients with type 2 diabetes who had undergone BPD between June 1984 and January 1993. Soon after the operation, fasting serum glucose concentration fell to within normal values in all but two of the patients and remained in the physiological range in all but six up until 10 years. This article shows that diabetes resolution after BPD is sustained and that long-term recurrence of diabetes is rare.
- 24 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.
- 25 National Institutes of Health Conference. Gastrointestinal surgery for severe obesity. Consensus Development Conference Panel. *Ann Intern Med* 1991; 115:956–961.
- 26 Gastrointestinal surgery for severe obesity: National Institutes of Health Consensus Development Conference Statement. *Am J Clin Nutr* 1992; 55:615–619.
- 27 Mingrone G, De Gaetano A, Greco AV, *et al*. Reversibility of insulin resistance in obese diabetic patients: role of plasma lipids. *Diabetologia* 1997; 40:599–605.
- 28 Noya G, Cossu ML, Coppola M, *et al*. Biliopancreatic diversion preserving the stomach and pylorus in the treatment of hypercholesterolemia and diabetes type II: results in the first 10 cases. *Obes Surg* 1998; 8:67–72.
- 29 Friedman NM, Sancetta AJ, Magovern GJ. The amelioration of diabetes mellitus following subtotal gastrectomy. *Surg Gynecol Obstetr* 1955; 100:201–204.
- 30 Bittner R, Bittner B, Beger HG. Homeostasis of glucose and gastric resection: the influence of the food passage through the duodenum (article in German). *Z Gastroenterol* 1981; 19:698–707.
- 31 Liebl A, Neiss A, Spannheimer A. Costs of type 2 diabetes in Germany: results of the CODE-2 study. *Dtsch Med Wochenschr* 2001; 126:585–589.
- 32 Liebl A. Challenges in optimal metabolic control of diabetes. *Diabetes Metab Res Rev* 2002; 18 (Suppl 3):S36–S41.
- 33 Evans A, Krentz AJ. Benefits and risks of transfer from oral agents to insulin in type 2 diabetes mellitus. *Drug Saf* 1999; 21:7–22.
- 34 DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131:281–303.
- 35 Spechler SJ, Lee E, Ahnen D, *et al*. Long-term outcome of medical and surgical therapies for gastroesophageal reflux disease: follow-up of a randomized controlled trial. *JAMA* 2001; 285:2331–2338.
- 36 Hickey MS, Pories WJ, MacDonald KG, *et al*. A new paradigm for type 2 diabetes mellitus: could it be a disease of the foregut? *Ann Surg* 1998; 227: 637–643; discussion 643–644.
- 37 Scopinaro N, Adami GF, Marinari GM, *et al*. Biliopancreatic diversion. *World J Surg* 1998; 22:936–946.
- 38 Ponce J, Haynes B, Paynter S, *et al*. Effect of lap-band-induced weight loss on type 2 diabetes mellitus and hypertension. *Obes Surg* 2004; 14:1335–1342.
- 39 Lima J, Helena L, Oliveira S, *et al*. Rapid resolution of diabetes after gastric bypass. *Obes Surg* 2005; 15:448–449.
- 40 Rubino F, Forgione A, Cummings D, *et al*. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the roximal small intestine in the pathophysiology of type 2 diabetes. *Ann Surg* (in press).
- 41 Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev* 2002; 23:599–622.
- 42 Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev* 2002; 23:201–229.
- 43 Brolin RE, LaMarca LB, Kenler HA, *et al*. Malabsorptive gastric bypass in patients with superobesity. *J Gastrointest Surg* 2002; 6:195–205.
- 44 Faraj M, Jones P, Sniderman AD, *et al*. Enhanced dietary fat clearance in postobese women. *J Lipid Res* 2001; 42:571–580.
- 45 MacLean LD, Rhode BM, Nohr CW. Long- or short-limb gastric bypass? *J Gastrointest Surg* 2001; 5:525–530.
- 46 Cummings DE, Weigle DS, Frayo RS, *et al*. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 2002; 346:1623–1630.
- 47 Korner J, Bessler M, Cirilo LJ, *et al*. Effects of Roux-en-Y gastric bypass surgery on fasting and postprandial concentrations of plasma ghrelin, peptide YY, and insulin. *J Clin Endocrinol Metab* 2005; 90:359–365.
- 48 Holdstock C, Engstrom BE, Ohrvall M, *et al*. *J Clin Endocrinol Metab* 2003; 88:3177–3183.
- 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; 240:236–242.
- 50 le Roux CW, Aylwin SJ, Batterham RL, *et al*. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. *Ann Surg* 2006; 243:108–114.
- The authors of this recent study examined meal-stimulated responses of insulin, ghrelin, peptide YY, GLP-1, and pancreatic polypeptide in humans and rodents following different bariatric surgical techniques. They show that patients who undergo RYGB have increased postprandial plasma levels of peptide YY and GLP-1.
- 51 Suzuki S, Ramos EJ, Goncalves CG, *et al*. Changes in GI hormones and their effect on gastric emptying and transit times after Roux-en-Y gastric bypass in rat model. *Surgery* 2005; 138:283–290.
- 52 Rubino F, Zizzari P, Tomasetto C, *et al*. The role of the small bowel in the regulation of circulating ghrelin levels and food intake in the obese Zucker rat. *Endocrinology* 2005; 146:1745–1751.
- This study shows an independent contribution of the small bowel to the regulation of ghrelin and appetite in obese animals with diabetes. These findings suggest the possibility that defective signalling from the proximal bowel could be involved in the pathogenesis of obesity/hyperphagia.
- 53 Cummings DE, Overduin J, Foster-Schubert KE. Gastric bypass for obesity: mechanisms of weight loss and diabetes resolution. *J Clin Endocrinol Metab* 2004; 89:2608–2315.
- 54 Mason EE. The mechanism of surgical treatment of type 2 diabetes. *Obes Surg* 2005; 15:459–461.
- 55 Patriri A, Facchiano E, Sanna A, *et al*. The enteroinsular axis and the recovery from type 2 diabetes after bariatric surgery. *Obes Surg* 2004; 14:840–848.

- 56** Mason EE. Ileal transposition and enteroglucagon/GLP1 in obesity (and diabetic?) surgery. *Obes Surg* 1999; 9:223–228.
- 57** Pories WJ, Albrecht RJ. Etiology of type II diabetes mellitus: role of the foregut. *World J Surg* 2001; 25:527–531.
- 58** Rubino F, Gagner M. Potential of surgery for curing type 2 diabetes mellitus. *Ann Surg* 2002; 236:554–559.
- 59** Naslund E, Gryback P, Hellstrom PM, *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.
- 60** 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–E453.
- The transposition of an isolated segment of ileum to the jejunum caused increased synthesis and release of GLP-1 and peptide YY in rats.
- 61** Schwarz A, Buchler M, Usinger K, *et al.* Importance of the duodenal passage and pouch volume after total gastrectomy and reconstruction with the Ullm pouch: prospective randomized clinical study. *World J Surg* 1996; 20:60–67.
- 62** Schattenmann G, Ebert R, Siewert R, Creutzfeldt W. Different response of gastric inhibitory polypeptide to glucose and fat from duodenum and jejunum. *Scand J Gastroenterol* 1984; 19:260–266.