

## Mechanisms of early improvement / resolution of type 2 diabetes after bariatric surgery

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### Abstract

Bariatric surgery represents the main option for obtaining substantial and long-term weight loss in morbidly obese subjects. In addition, malabsorptive (biliopancreatic diversion, BPD) and restrictive (roux-en-Y gastric bypass, RYGB) surgery, originally devised to treat obesity, has also been shown to help diabetes. Indeed, type 2 diabetes is improved or even reversed soon after these operations and well before significant weight loss occurs.

Two hypotheses have been proposed to explain the early effects of bariatric surgery on diabetes—namely, the hindgut hypothesis and the foregut hypothesis. The former states that diabetes control results from the more rapid delivery of nutrients to the distal small intestine, thereby enhancing the release of hormones such as glucagon-like peptide-1 (GLP-1). The latter theory contends that exclusion of the proximal small intestine reduces or suppresses the secretion of anti-incretin hormones, leading to improvement of blood glucose control as a consequence.

In fact, increased GLP-1 plasma levels stimulate insulin secretion and suppress glucagon secretion, thereby improving glucose metabolism. Recent studies have shown that improved intestinal gluconeogenesis may also be involved in the amelioration of glucose homeostasis following RYGB.

Although no large trials have specifically addressed the effects of bariatric surgery on the remission or reversal of type 2 diabetes independent of weight loss and/or caloric restriction, there are sufficient data in the literature to support the idea that this type of surgery—specifically, RYGB and BPD—can lead to early improvement of glucose control independent of weight loss.

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*Keywords:* Bariatric surgery; Type 2 diabetes; Insulin sensitivity; Insulin secretion; Review

### Résumé

#### *Mécanismes de l'amélioration précoce et/ou de la disparition du diabète de type 2 après chirurgie bariatrique*

La chirurgie bariatrique représente l'option majeure pour obtenir une perte de poids considérable et durable chez les sujets atteints d'obésité morbide. On a pu montrer que la chirurgie bariatrique, initialement destinée à traiter l'obésité, pouvait permettre de guérir spécifiquement le diabète. De fait, on observe après intervention une amélioration du diabète qui peut aller jusqu'à sa disparition, bien avant qu'une perte de poids significative ne soit observée. Deux hypothèses ont été proposées pour expliquer cet effet précoce de la chirurgie bariatrique sur le diabète. La première hypothèse propose que l'arrivée rapide des nutriments dans l'intestin grêle distal augmente la libération d'hormones comme le glucagon-like peptide-1 (GLP-1). La seconde propose que c'est l'exclusion du grêle proximal qui réduit ou supprime la sécrétion des hormones anti-incrétines, avec comme pour conséquence l'amélioration de l'équilibre glycémique. De son côté, l'augmentation des concentrations plasmatiques de GLP-1 stimule la sécrétion d'insuline et supprime la sécrétion de glucagon, améliorant ainsi le métabolisme du glucose. Des travaux récents ont également montré qu'une amélioration de la néogluconéogenèse intestinale pouvait être impliquée dans l'amélioration du métabolisme du glucose observée après RYGB.

Bien qu'il n'existe pas de grands essais destinés à évaluer spécifiquement les effets de la chirurgie bariatrique sur la rémission ou la disparition du diabète indépendamment de la perte de poids et/ou de la restriction calorique, il y a suffisamment de données dans la littérature

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en faveur du fait que ce type de chirurgie, et plus particulièrement les interventions de type RYGB et BPD, entraîne une amélioration précoce de l'équilibre glycémique indépendamment de la perte de poids.

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*Mots clés* : Chirurgie bariatrique ; Diabète de type 2 ; Insulino-sensibilité ; Insulinosécrétion ; Revue générale

## 1. Introduction

At present, bariatric surgery represents the main option for obtaining substantial and long-term weight loss in morbidly obese (BMI  $\geq$  40 kg/m<sup>2</sup>) or obese (BMI  $\geq$  35 kg/m<sup>2</sup>) individuals who also have other co-morbidities such as diabetes or arthritis [1].

Interestingly, although bariatric surgery was originally devised to treat obesity, it has also been found to help diabetes [2,3]. In fact, type 2 diabetes is seen to improve or even revert to normal soon after bariatric operations, and well before any significant weight loss has taken place. This observation prompted scientists to investigate the effects of bariatric surgery—now dubbed 'metabolic surgery'—on diabetic patients with a BMI < 35 kg/m<sup>2</sup> [4–7].

Bariatric operations, which are effective for weight loss as well as diabetes reversal, alter the anatomical connections between the stomach and small intestine, thereby changing the normal pathway for food. This observation suggests that the intestine plays a part in the pathogenesis of type 2 diabetes.

The tight physiological relationship between the intestine and endocrine pancreas has been extensively reported in the literature. During ontogenesis, the septum transversum generates two pancreatic buds at the level of the junction between the foregut and midgut, involving dorsal and ventral endoderm, which then fuse to form the pancreas. The dorsal bud arises first and generates most of the pancreas. The ventral bud arises next to the bile duct, and makes up only part of the head and uncinate process of the pancreas [8]. The small intestine shares with the pancreas the same endodermal derivation and probably many endocrine functions as well.

The term 'enteroinsular axis' arises from the fact that the gastrointestinal tract plays a major role in controlling glucose metabolism [9–11]. Glucose ingestion stimulates insulin secretion 50% more than glucose infusion even in the presence of similar circulating levels of glucose [12].

The reason(s) for the diabetes improvement/reversibility—and, in particular, the greater insulin sensitivity—are currently unknown. However, it has been speculated that, in addition to altered incretin secretion, other, unknown factors regulating insulin sensitivity may be involved that are altered by the surgical treatment [13–15]. Clearly, identification of such mechanisms are of major importance, as that might lead to the development of effective new treatments for type 2 diabetes and, specifically, reversal of insulin resistance. Also, it is worth noting that the improvement in insulin sensitivity after bariatric surgery can be as much as 70% or more [13,16], a figure far above that achieved by the currently available therapies.

At present, it is not clear which aspect of the surgical procedure is responsible for the observed increase in insulin sensitivity. It has, however, been suggested that certain surgical procedures are more effective than others, as it appears that not all operations are equal. In a recent meta-analysis and review of the literature looking at all types of bariatric surgery together [17], resolution of the clinical manifestations of diabetes occurred in 78.1% of patients, while diabetes control improved in 86.6% of the cases. Indeed, biliopancreatic diversion (BPD), or the so-called 'duodenal switch', had the best results with 95.1% of diabetes resolution, followed by roux-en-Y gastric bypass (RYGB) with 80.3%, gastroplasty with 79.7% and laparoscopic adjustable gastric banding (LAGB) with 56.7%.

In the present review, the available data in the literature on the early effects of bariatric surgery on type 2 diabetes are reviewed in an effort to elucidate the mechanisms through which glucose disposal is improved or normalized independent of weight loss.

## 2. Effect of gastric banding on type 2 diabetes

Laparoscopic gastric banding (Fig. 1) appears to be effective in improving the metabolic syndrome and type 2 diabetes [18,19]. A recent randomized trial comparing LAGB-induced weight loss with conventional therapy for management of type 2 diabetes in obese participants showed better glycaemic control and diabetes remission rates with adjustable gastric banding. However, the data reported in this trial covered the later effects of LAGB at 2 years, when weight loss was at its maximum point.

In contrast, the efficacy of the operation for early improvement of type 2 diabetes has been found in few studies. In one involving 93 subjects, the first effects on glucose control appeared 6 months after LAGB, when the percentage of excess weight lost was about 29% [19]. However, a close correlation between weight loss and reduction of circulating levels of glucose was observed, suggesting that the mechanism of glucose metabolism improvement was essentially related to the weight loss.

## 3. Early effects of RYGB and BPD on type 2 diabetes

RYGB is a mostly restrictive operation that reduces gastric volume to about 30 ml, and excludes the duodenum and of a portion of the jejunum from food transit by creating a gastrojejunum anastomosis (Fig. 2). In contrast, BPD is mainly a malabsorptive procedure, leaving a gastric remnant of 300–400 ml

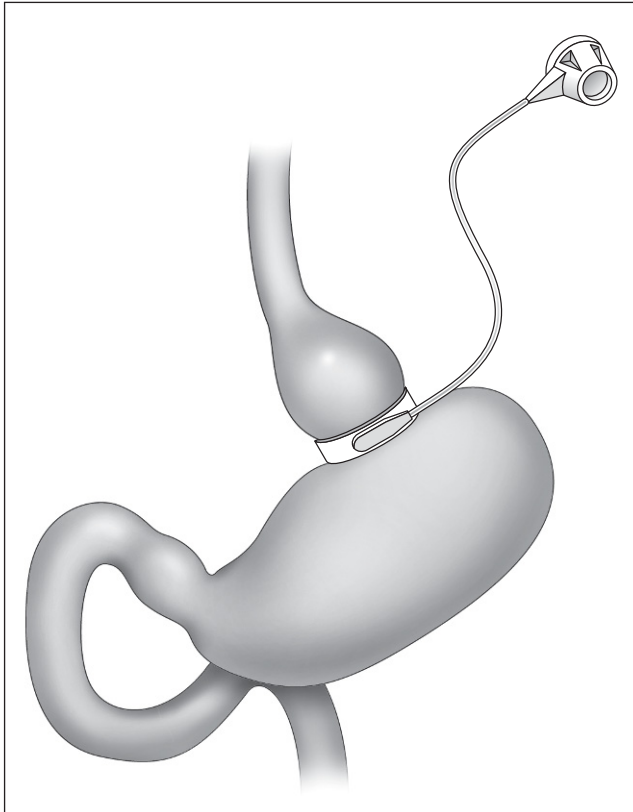


Fig. 1. Laparoscopic adjustable gastric banding: the gastric circumference is adjusted (narrowed) by a band of plastic material using an inflatable fluid-filled balloon that is connected, via a catheter, to a subcutaneous reservoir.

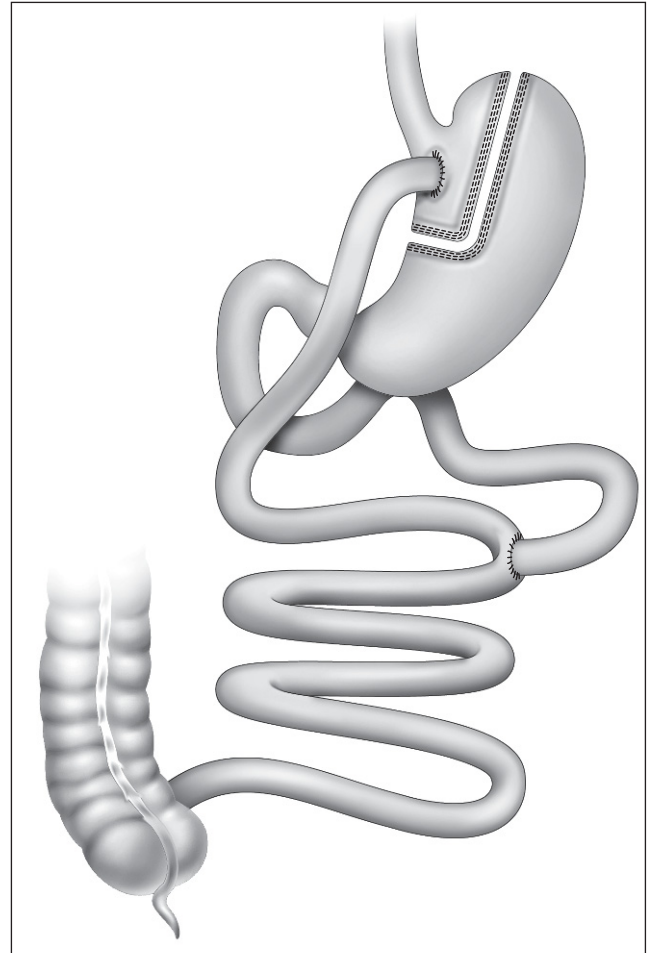


Fig. 2. Roux-en-Y gastric bypass (RYGB): the stomach is divided along the lesser curvature, creating a small reservoir of about 30 ml that is anastomosed to the distal end of the jejunum, which is divided at about 75 cm from the ligament of Treitz. The proximal end of the transected bowel is then sutured to the jejunum at about 100 cm from the gastrojejunal anastomosis.

and bypassing a major portion of the small intestine—namely, the duodenum, the whole of the jejunum and the proximal ileum (Fig. 3). Thus, BPD is characterized by lipid malabsorption with frank steatorrhea. The early effects of RYGB and BPD on type 2 diabetes are summarized in Table 1.

The literature includes data from diabetic patients with BMIs that are either  $> 35\text{--}40\text{ kg/m}^2$  or  $< 35\text{ kg/m}^2$  [7,13,16,20–30] and, with the exception of Smith *et al.* [23], who found a 42% diabetes remission, and Scopinaro *et al.* [28], who found a figure of 74%, all the other studies reported a 97–100% improvement/remission of diabetes within 1 month of the operation. It is worth noting that these effects of metabolic surgery were seen before any significant weight loss. Also, at least in those who underwent a malabsorptive procedure such as BPD, the patients were subject to no food energy restrictions, but were following a free, *ad libitum* diet.

#### 4. Mechanisms of improvement/reversibility of diabetes

Two main hypotheses have been proposed to explain the early effects of metabolic surgery on diabetes: the hindgut hypothesis; and the foregut hypothesis. The former states that

diabetes control results from the more rapid delivery of nutrients to the distal small intestine, thereby enhancing the release of hormones such as glucagon-like peptide-1 (GLP-1) [31], a physiological sign of improved glucose metabolism. On the other hand, the foregut hypothesis contends that the exclusion of the proximal small intestine reduces or suppresses the secretion of anti-incretin hormones [13–15], with a consequent improvement in blood glucose control. Indeed, increased GLP-1 plasma levels stimulate insulin secretion and suppress glucagon secretion, thereby improving glucose metabolism [32–34].

Recently, it was shown that gastric bypass can also bring about significant improvement in hepatic insulin sensitivity, most likely through reduced hepatic gluconeogenesis and without affecting peripheral insulin sensitivity [35]. Moreover, gastric bypass promotes intestinal gluconeogenesis and stimulates the hepatoportal glucose sensor *via* a GLUT2-dependent pathway, while the lack of gluconeogenic response is associated with absence

Table 1

Reports in the literature on the early effects of roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion (BPD) on type 2 diabetes control and impaired glucose tolerance (IGT)

Authors	Source	Subjects (n)	BMI (kg/m <sup>2</sup> )	Diabetes /IGT	Time since operation	Diabetes improvement/remission/IGT reversal	Type of operation
Pories WJ et al.	Ann Surg 1987	141	~40	88/53	10 days	100%	RYGB
Rubino F et al.	Ann Surg 2004	6	~40	6	3 weeks	100%	RYGB
Cohen R et al.	Surg Obes Relat Dis 2006	37	<35	37	6 months	97%	RYGB
Smith BR et al.	Am Surg 2008	59	~40	59	1 month	42%	RYGB
Laferrère B et al.	Diabetes Care 2007	8	>35	8	1 month	100%	RYGB
Laferrère B et al.	JCEM 2008	9	~35	9	1 month	100%	RYGB
TOTAL 207/53 RYGB							
Mingrone et al.	Diabetologia 1997	7	~40	7	3 months	100%	BPD
Mingrone et al.	Diabetes 1999	2	21/20.1	2	3 weeks	100%	BPD
Guidone C et al.	Diabetes 2006	10	~40	10	1 week–1 month	100%	BPD
Mari A et al.	Diabetologia 2006	20	~40	11/9	1 week	100%	BPD
Scopinaro N et al.	Obes Surg 2008	443	~40	443	1–2 months	74%	BPD
Briatore L et al.	Obesity 2008	9	~40	9	1 month	100%	BPD
Salinari S et al.	Diabetes Care 2009	9	~40	9	1 month	100%	BPD
Chiellini C et al.	Diabetologia 2009	5	<35	5	1 month	100%	BPD
TOTAL 496/9 BPD							

of the anti-diabetic effects following the operation. This finding suggests that, to some extent at least, intestinal gluconeogenesis is involved in the improvement of glucose homeostasis after RYGB.

Interestingly, RYGB differs from BPD in terms of effects on insulin sensitivity and secretion. While BPD results in rapid improvement of insulin sensitivity, with a consequent reduction of insulin secretion [13,30], RYGB improves diabetes control through increased insulin secretion. Indeed, it has been repeatedly shown that RYGB stimulates gastric inhibitory peptide (GIP) and GLP-1 secretion, with stimulation of insulin secretion as a consequence. Thus, insulin oversecretion together with the quicker absorption of ingested glucose and other carbohydrates could explain the reported postabsorptive episodes of hypoglycaemia.

Also, sporadic cases of nesidioblastosis have been reported after RYGB for morbid obesity [36,37]. Nesidioblastosis refers to inappropriate insulin secretion resulting in recurrent severe hypoglycaemia, and is related to hypertrophy and hyperplasia of the islets of Langerhans. Patients who develop nesidioblastosis after RYGB often experience severe hypoglycaemia that, in a few instances, may require total pancreatectomy [37].

## 5. Effects of energy restriction on diabetes

One of the most relevant challenges in the study of the pathophysiology of metabolic surgery and, in particular, its rapid effect on glucose disposal, is to differentiate the role of the operation *per se* from the effects of energy restriction. A number of studies have shown marked improvement of plasma glucose in type 2 diabetics that was disproportionate to the weight loss and after only short periods of energy restriction [38]. However, the factors responsible for the early benefits of energy restriction on glycaemia are still not clear, partly because of the difficulty in isolating the effects of energy restriction from those of weight loss when the first measurements are taken 7–10 days into the diet [38]. Nevertheless, one study demonstrated clear glycaemic benefits with energy restriction [39], including an associated improvement in insulin sensitivity, but failed to address the hepatic vs peripheral contributions or the determinants of basal glycaemia.

Similarly, it is difficult to isolate the effects of weight loss from those of energy restriction. Four days of dieting (reducing energy intake by around 1000 kcal/d) led to a large increase in insulin suppression of hepatic glucose output and, thus, increased hepatic insulin sensitivity [40], and continuation of the diet for

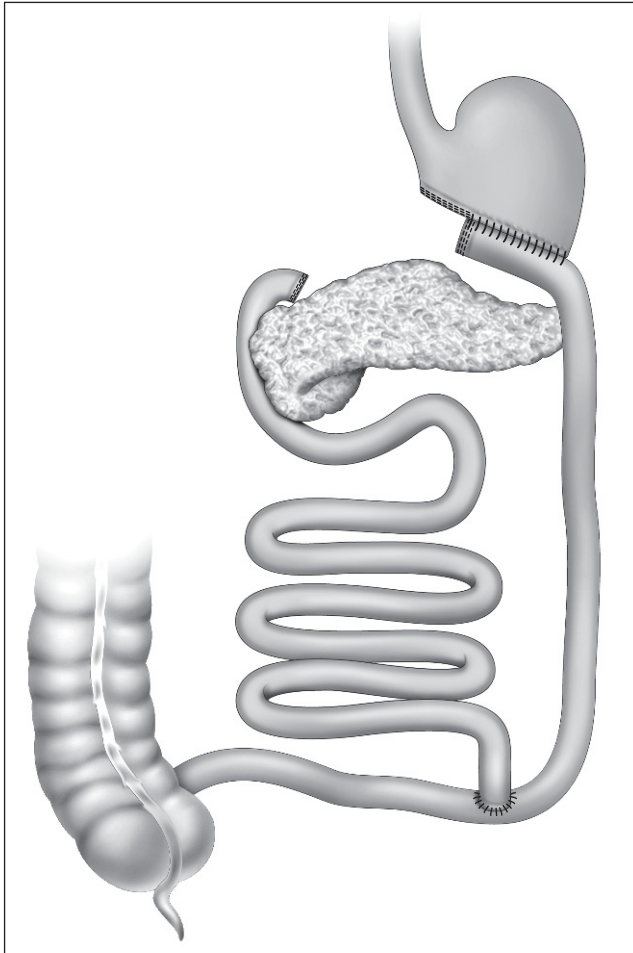


Fig. 3. Biliopancreatic diversion (BPD): this procedure comprises partial gastrectomy (about 50–60%) and gastroentero-anastomosis. The ileum is then divided 250-cm proximal to the ileocaecal valve and its distal end anastomosed to the resected stomach (alimentary tract). The proximal end of the small bowel, which carries the biliopancreatic juice (biliary tract), is then sutured to the distal ileum at about 50 cm from the ileocaecal valve (common tract).

28 days showed significant weight loss associated with increased insulin sensitivity. This suggests that energy restriction and weight loss may have independent effects on glucose control.

Although few studies have compared energy restriction with metabolic surgery in type 2 diabetes, they have shown that the effect of metabolic surgery on glucose control is significantly better than that of diet alone. However, randomized studies of larger cohorts are needed to better clarify this important issue.

## 6. Conclusion

Although no large trials have specifically addressed the effects of bariatric or metabolic surgery on remission or reversal of type 2 diabetes, independent of weight loss and/or caloric restriction, there are sufficient data from the literature to suggest that this type of surgery—and, specifically, RYGB and BPD—can bring about early improvement of

glucose control that is independent of weight loss. Although the specific mechanism of action underlying this early consequence of the RYGB and BPD procedures has yet to be elucidated, at present at least, it appears that the major players are probably incretins and, possibly, anti-incretins and intestinal gluconeogenesis.

## Conflicts of interests

The authors have reported no conflict of interests.

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