

Mechanisms of improved glycaemic control after Roux-en-Y gastric bypass

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Abstract Roux-en-Y gastric bypass (RYGB) greatly improves glycaemic control in morbidly obese patients with type 2 diabetes, in many even before significant weight loss. Understanding the responsible mechanisms may contribute to our knowledge of the pathophysiology of type 2 diabetes and help identify new drug targets or improve surgical techniques. This review summarises the present knowledge based on pathophysiological studies published during the last decade. Taken together, two main mechanisms seem to be responsible for the early improvement in glycaemic control after RYGB: (1) an increase in hepatic insulin sensitivity induced, at least in part, by energy restriction and (2) improved beta cell function associated with an exaggerated postprandial glucagon-like peptide 1 secretion owing to the altered transit of nutrients. Later a weight loss induced improvement in peripheral insulin sensitivity follows.

Keywords Bariatric surgery · Beta cell function · Incretin hormones · Insulin sensitivity · Obesity · Review · Roux-en-Y gastric bypass · Type 2 diabetes mellitus

Abbreviations

AIRg	Acute insulin response to glucose
DI	Disposition index
FSIGT	Frequently sampled intravenous glucose tolerance test
GIP	Glucose-dependent insulintropic peptide
GLP-1	Glucagon-like peptide 1
HEC	Hyperinsulinaemic–euglycaemic clamp
HGP	Hepatic glucose production
HOMA-IR	HOMA of insulin resistance
IGI	Insulinogenic index
ITT	Insulin tolerance test
MMT	Mixed meal test
NGT	Normal glucose tolerance
PYY	Peptide YY _{3–36}
RYGB	Roux-en-Y gastric bypass

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Introduction

The prevalence of type 2 diabetes has increased dramatically along with the worldwide obesity pandemic. Conventional strategies to treat type 2 diabetes including lifestyle intervention and pharmacotherapy have been somewhat successful in delaying the development of cardiovascular disease and late diabetes complications through improved glycaemic control and treatment of hypertension and dyslipidaemia, but they require good treatment compliance, regular clinical check-ups and, eventually, lifelong medication. During the last decade it has been recognised that a prolonged

improvement in glycaemic control without the need for a glucose-lowering medication can be achieved in morbidly obese patients with type 2 diabetes using Roux-en-Y gastric bypass (RYGB) surgery or related bariatric procedures [1, 2]. Interestingly, the improvement in glycaemic control after RYGB often occurs within days of the surgery, before any significant weight loss [3], and even in patients with only mild obesity [4]. This points to a role for weight loss-independent mechanisms possibly related to the changes in gastrointestinal anatomy and transit of nutrients.

In this review we discuss potential mechanisms for the improved glycaemic control after RYGB, the most widespread bariatric surgical procedure at present. We focus on the effects of the operation on insulin resistance and beta cell dysfunction, as well as on the adipose tissue, the alpha cells and the secretion of incretin hormones and other gut hormones. The form of a narrative review has been chosen to give a wide and comprehensive coverage of relevant mechanisms. The reviewed studies were identified by electronic and manual literature searches, including hand-search of the reference lists of identified papers. Studies were considered relevant if they reported the impact of RYGB surgery on the pathophysiological defects of type 2 diabetes in morbidly obese ($\text{BMI} \geq 35 \text{ kg/m}^2$) adults (age ≥ 18 years). Please refer to the text box ‘Physiological indices’ for an overview of the indices mentioned in the text.

Roux-en-Y gastric bypass

RYGB is a bariatric surgical procedure that involves sectioning of the jejunum 50–100 cm from the pylorus,

anastomosis between the distal loop of the severed jejunum (the alimentary limb) to a small gastric pouch created around the oesophagus, and anastomosis between the proximal loop of the severed jejunum (the secretory limb) with the small intestine at a site that is now 150–200 cm distal relative to the position of the pylorus before the RYGB. Thus, nutrients bypass the major part of the stomach, the duodenum and the upper part of the jejunum (Fig. 1). The procedure is recommended in morbidly obese patients ($\text{BMI} \geq 40 \text{ kg/m}^2$ or $\geq 35 \text{ kg/m}^2$ in the presence of comorbidities) who have been unable to lose weight with conventional treatment strategies including diet and pharmacotherapy [5]. The weight loss induced by the surgery is, on average, 25–30% of total body weight, attaining a nadir 12–18 months postoperatively, and is maintained for at least 10 years postoperatively in most patients [6]. Individuals who undergo the operation show a significant reduction in morbidity and mortality compared with non-operated obese individuals [6], primarily due to the beneficial effects of the procedure on the comorbidities of obesity. Today, most surgeons use a laparoscopic technique and the perioperative mortality is as low as 0.3% [7].

The remission of type 2 diabetes mellitus after RYGB

In 1995 Pories et al [3] reported that among 146 morbidly obese patients with type 2 diabetes who underwent gastric bypass, 121 (83%) experienced a rapid and prolonged postoperative normalisation of plasma glucose levels without the need for glucose-lowering medication. This remarkable observation was later replicated in several other studies and

Physiological indices	
Index	Formula
HOMA-IR [100]	$(\text{Insulin}_{\text{basal}} [\mu\text{IU/ml}] \times \text{Glucose}_{\text{basal}} [\text{mmol/l}]) / 22.5$
Matsuda index (ISI_{comp}) [101]	$10,000 / \sqrt{(\text{Glucose}_{\text{basal}} [\text{mg/dl}] \times \text{Insulin}_{\text{basal}} [\mu\text{IU/ml}] \times \text{Glucose}_{\text{OGTTmean}} [\text{mg/dl}] \times \text{Insulin}_{\text{OGTTmean}} [\mu\text{IU/ml}])}$
IGI [102]	$(\text{Insulin}_{30 \text{ min}} - \text{Insulin}_{\text{basal}}) / (\text{Glucose}_{30 \text{ min}} - \text{Glucose}_{\text{basal}})$
Beta cell glucose sensitivity [103]	Model-based measure of beta cell function describing the relationship between plasma glucose and insulin secretory rate
AIRg [104]	Mean insulin secretion 0–10 min
DI [105]	Insulin secretion \times Insulin sensitivity
AIRg, acute insulin response to glucose; DI, disposition index; HOMA-IR, HOMA of insulin resistance; IGI, insulinogenic index. Where specific units are required, these are indicated	

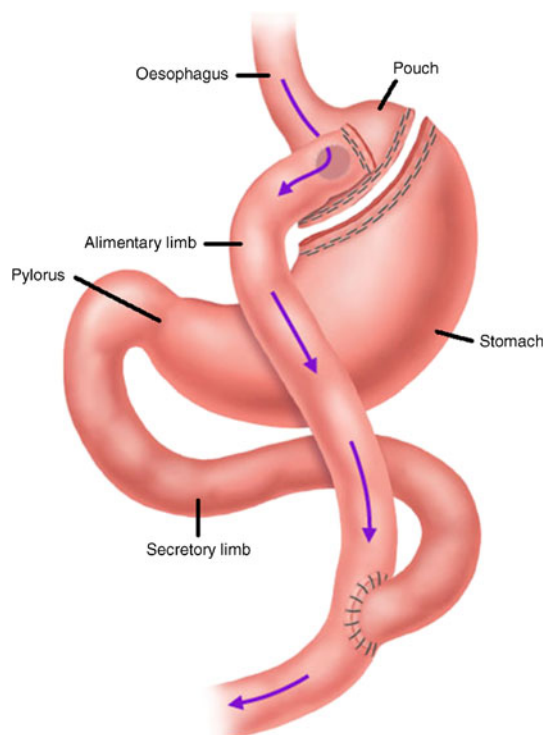


Fig. 1 The gastrointestinal anatomy after Roux-en-Y gastric bypass

confirmed in a large meta-analysis of 621 studies, including nearly 5,000 patients with type 2 diabetes, which reported that diabetes remission was seen in 80.3% after RYGB [8]. However, in a recent study of 160 patients who underwent RYGB, only 40.6% achieved complete diabetes remission as defined by the criteria from the consensus report from 2009 [1, 9]. Thus, the rate of diabetes remission after RYGB strongly depends on the definition of remission as well as on the severity of the disease, with HbA_{1c}, insulin sensitivity and beta cell function being worse in non-remitters prior to surgery [10]. For these reasons this review focuses on RYGB as a tool to improve glycaemic control rather than as a means to achieve diabetes remission.

Insulin sensitivity and RYGB

The gold standard technique of measuring insulin sensitivity is the hyperinsulinaemic–euglycaemic clamp (HEC), which primarily measures insulin sensitivity in muscle but can also be combined with isotope-labelled glucose to assess hepatic glucose production (HGP) and, thereby, hepatic insulin sensitivity. Other methods for assessing insulin sensitivity include the frequently sampled intravenous glucose tolerance test (FSIGT), the insulin tolerance test (ITT) and indices derived from a standard 75 g OGTT, e.g. the Matsuda index. However, the most frequently used measure of insulin resistance is the HOMA formula (HOMA-IR), which is primarily a surrogate index of hepatic insulin resistance.

Results from oral tests The effect of RYGB on insulin sensitivity has been assessed in two studies using the Matsuda index based on a liquid mixed meal test (MMT) [11, 12] and in one study using mathematical modeling based on an OGTT [10]. All three studies reported significant increases in insulin sensitivity between 4 weeks and 1 year postoperatively, and in one of the studies the increase was proportional to the decrease in BMI [10]. However, the measurement of insulin sensitivity based on oral tests after RYGB has not been validated. This is important because RYGB dramatically affects the absorption rate of glucose with a more rapid uptake after surgery [13, 14], which may affect calculation of the indices. These limitations underscore the need for validation of oral tests in individuals post RYGB, as recently carried out for gastric banding, another bariatric procedure [15].

Results from intravenous tests Not surprisingly, a weight loss of 10–20 kg/m² 6–12 months after RYGB has been demonstrated to significantly improve peripheral insulin sensitivity measured by the HEC in obese patients with normal glucose tolerance (NGT) [16–22] and type 2 diabetes [20, 23, 24]. Similar results have also been found using other techniques, including FSIGT and ITT [25–30]. Furthermore, reductions in HGP or hepatic insulin resistance index have been found in four glucose tracer studies performed 6–12 months after RYGB [18, 20, 21, 31]. Whether improved insulin sensitivity also plays a role in the early improvement of glycaemic control after RYGB, which is independent of weight loss, is unclear. Several studies have shown a significant reduction in HOMA-IR within the first month after RYGB in patients with NGT and type 2 diabetes [11, 19, 26, 27, 32–38], with 4 days postoperatively being the earliest record of a significant decrease in HOMA-IR [32]. In contrast, 2–4 weeks after RYGB, studies involving HEC to measure insulin sensitivity did not find any improvement in peripheral insulin sensitivity, despite significant weight loss and a significant decrease in HOMA-IR [19, 20, 39, 40]. This discrepancy between HOMA-IR and the HEC may reflect differential effects of RYGB on peripheral and hepatic insulin sensitivity during the early postoperative period. In support of this, a recent HEC study using glucose tracer reported decreased HGP and improved hepatic insulin sensitivity without changes in peripheral insulin sensitivity in 17 patients with type 2 diabetes and 23 individuals with NGT, 1 month after RYGB [40]. However, a similar study showed no major changes on either basal HGP or peripheral insulin sensitivity 2–3 weeks after RYGB [20].

Interestingly, a similar pattern of concomitant decreases in fasting glucose and insulin, i.e. reduced HOMA-IR without changes in peripheral insulin sensitivity, has been reported after energy restriction. Kirk et al found a 40%

decrease in HOMA-IR without changes in peripheral insulin sensitivity after 48 h of low-carbohydrate energy restriction and a limited weight loss of 2 kg in obese individuals with NGT [41]. Additionally, the authors found a decrease in basal HGP, an increase in hepatic insulin sensitivity and a 20% reduction in intrahepatic lipid content. Continuation of the energy restriction for 11 weeks did not result in any further improvements in hepatic insulin sensitivity, but produced a significant increase in peripheral insulin sensitivity [41]. Similar findings, including reduced fasting glucose and insulin levels, reduced basal HGP, increased hepatic insulin sensitivity and reduced intrahepatic lipid content, have recently been reported in 11 obese patients with type 2 diabetes after 1 week of energy restriction [42]. The changes persisted at 4 and 8 weeks' follow-up, and peripheral insulin sensitivity did not change throughout the study despite a 15.3 kg weight loss after 8 weeks [42]. Thus, improved hepatic insulin sensitivity induced by postoperative energy restriction may explain the isolated reduction in HOMA-IR seen early after RYGB. In two studies that directly compared RYGB with energy restriction, a comparable decrease in HOMA-IR was found in both intervention groups [32, 33]. In contrast, other investigators have found greater decreases in HOMA-IR after RYGB than after energy restriction or gastric restrictive surgery [11, 35–37]. Foo et al used an interesting paired experimental design in which each volunteer underwent 6 days of energy restriction before and immediately after RYGB. They found a larger decrease in HOMA-IR after the combined RYGB and energy restriction, than during the pre-operative energy restriction period [37]. Thus, further studies are needed to evaluate the differential effects of RYGB on peripheral and hepatic insulin sensitivity and to clarify whether the changes in gastrointestinal anatomy after RYGB cause additional improvements in insulin sensitivity independent of energy restriction.

Hepatic insulin sensitivity improves immediately after RYGB in response to the energy restriction, whereas peripheral insulin sensitivity is improved later in response to the postoperative weight loss

Islet cell dysfunction and RYGB

An important distinction should be made between intravenous and oral tests when measuring beta cell function. Intravenous tests address 'intrinsic' regulation of insulin secretion, while oral tests combine 'intrinsic' and 'extrinsic' regulation, i.e. they include the potentiating effects of the hormonal and neural responses elicited by meal ingestion (the entero-insular axis). The most frequently applied intravenous tests include the FSIGT, the hyperglycaemic glucose

clamp and the arginine test, while oral tests can be performed using an OGTT or MMT. Since insulin secretion during any of these tests is, in part, determined by the prevailing insulin sensitivity, beta cell function usually is expressed as the disposition index (DI).

Results from oral tests Insulin secretion in response to an oral stimulus is significantly altered after RYGB, with an earlier and exaggerated postprandial rise in insulin concentration that reaches a higher peak level than that achieved before RYGB [11, 13, 14, 33, 35, 38, 43–52]. However, the total postprandial AUC for insulin is unchanged or even decreased, consistent with the improved insulin sensitivity and a more rapid return of insulin concentrations to fasting levels [14, 19, 33, 38, 43, 44]. Recently, two studies from the same research group described no change, or even a significant decrease, in peak insulin concentrations after RYGB [32, 53]. However, these contradictory findings may be explained by the lack of blood sampling in the first 60 min after the end of the meal, which is the time period when insulin levels usually peak [54]. In a study of ten patients with type 2 diabetes, early insulin secretion during an oral stimulus, measured by the insulinogenic index (IGI), was significantly increased 30 and 90 days after RYGB, but unchanged at 7 days postoperatively [38]. A significant increase in IGI, irrespective of glucose tolerance, has also been reported by other investigators 4–6 weeks after RYGB [11, 55], but not after gastric restrictive surgery [11]. One year postoperatively, the increase in IGI seems to level off, probably in response to the increase in peripheral insulin sensitivity [51, 55]. Accordingly, in the only study to adjust IGI for changes in insulin sensitivity, there was a non-significant increase in the unadjusted IGI 1 year after RYGB, and a significant increase in DI [51]. Also, beta cell glucose sensitivity in response to both an OGTT and an MMT has been shown to increase early after RYGB [10, 11, 52] but does not fully normalise even 3–12 months postoperatively in patients with type 2 diabetes [10, 52].

Results from intravenous tests Insulin secretion after RYGB in response to an intravenous stimulus has been reported in five studies, four of which used the FSIGT [25, 30, 52, 55, 56] and one the more laborious hyperglycaemic clamp [11]. The FSIGT studies found a gradual increase in first phase insulin secretion (acute insulin response to glucose; AIRg) (see text box 'Physiological indices') in patients with type 2 diabetes during the first 12 months after RYGB, while AIRg declined in individuals with NGT [25, 30, 52, 55, 56]. Accordingly, large significant increases in DI (8.5- to 83-fold) were observed in patients with type 2 diabetes, while patients with NGT experienced no change in DI [25, 30, 55, 56]. The results from the hyperglycaemic clamp did not show any change in AIRg or DI during the first

postoperative month, the latter despite a significant doubling in insulin sensitivity, suggesting a lack of statistical power [11]. Second phase insulin secretion appears to decline postoperatively, with changes apparent within the first month [11, 30].

Postprandial insulin secretion is altered immediately after RYGB—secretion is more rapid and exaggerated, but is shorter lasting. Intrinsic beta cell function gradually recovers in patients with type 2 diabetes and is unchanged in individuals with NGT

Alpha cell function In a study including 12 volunteers with NGT who underwent an MMT before and at various times after RYGB, fasting glucagon concentrations were unchanged [14]. Postprandial glucagon concentrations were increased significantly 3 days and 2 months after surgery, but returned to preoperative levels 1 year postoperatively [14]. A similar postprandial increase in plasma glucagon without changes in fasting plasma glucagon has been reported in patients with type 2 diabetes 1 month after surgery [33]. This temporary increase in postprandial glucagon levels during the first months after surgery is a paradoxical increase given the concomitant decrease in plasma glucose and increase in glucagon-like peptide 1 (GLP-1) secretion, but may reflect biologically inactive proglucagon forms derived from the gut that interfere with glucagon assays [57]. Taken together, the available results suggest that changes in circulating glucagon do not contribute to the improvements in glucose metabolism observed after RYGB.

Gut hormones and RYGB

Changes in the fasting and postprandial secretion of gut-derived hormones from the enteroendocrine cells located in the gut epithelium, possibly resulting from the altered postoperative nutrient transit, have been suggested as potential mechanisms for the improvement in glycaemic control after RYGB [3, 58]. A large number of studies have subsequently supported this hypothesis by demonstrating extensive alterations in the release of hormones that regulate glucose homeostasis and appetite [59].

Incretin hormones The large number of studies that have examined changes in the release of incretin hormones after RYGB consistently find that fasting levels of GLP-1 are unchanged, whereas postprandial secretion increases by several fold [11, 13, 14, 21, 32, 36, 38, 43, 44, 46, 47, 50, 52, 60, 61]. Fasting levels of glucose-dependent insulinotropic peptide (GIP) are also unchanged, but reports as to the changes in postprandial release have been more

inconsistent, with some studies finding an increase [33, 46] and others no change, or even a decline, in GIP secretion [11, 13, 14, 47]. These results are consistent with the change in gastrointestinal anatomy induced by the surgery, whereby nutrients bypass the proximal part of the small intestine, where most of the GIP-producing K cells are located, and are delivered directly into the distal small intestine, which has a high density of GLP-1-producing L cells. The inconsistent findings in GIP secretion are likely to reflect differences in the length of the limbs of the Roux anastomosis, with shorter limbs possibly being associated with higher GIP responses.

The incretin effect, i.e. greater insulin secretion in response to an oral stimulus than to an isoglycaemic intravenous stimulus, has been further investigated in patients with type 2 diabetes before and 4 weeks after surgery [44]. There was a fivefold increase in the incretin effect after RYGB and, moreover, the postoperative incretin effect did not differ statistically from that of unoperated matched controls. In another study by the same authors, similar changes in incretin effect were found in a group of patients with type 2 diabetes undergoing RYGB, but not in a matched group of patients with type 2 diabetes who achieved a comparable diet-induced weight loss [33]. These observations seem to confirm the increased insulinotropic action of GLP-1 in the postprandial period after RYGB.

Further evidence for the role of GLP-1 after RYGB has recently been provided by a study in which an MMT was performed during a hyperglycaemic clamp with and without infusion of the GLP-1 receptor antagonist exendin 9–39 in RYGB-operated participants and controls [62]. As expected, insulin secretion in response to the meal was elevated in the RYGB operated group compared with the control subjects, but was reduced to about half during blockade of GLP-1 by exendin 9–39.

The importance of the post-RYGB gastrointestinal anatomy on glucose metabolism and the release of gut hormones has been demonstrated in two case reports that examined the effect of peroral feeding vs gastroduodenal feeding in RYGB-operated patients with a gastrostomy catheter inserted in the gastric remnant [48, 49]. In both reports, an MMT was performed on two consecutive days. On the peroral day, with nutrients passing through the gastric bypass pathway, typical postoperative exaggerated insulin and GLP-1 responses were found, while on the gastroduodenal day, with nutrients passing through the excluded pathway, insulin and GLP-1 responses mimicked those seen preoperatively. Hence, the postoperative changes in insulin and gut hormone secretion are closely related to the changes in gastrointestinal nutrient transit, possibly resulting from a more rapid delivery of nutrients to the distal parts of the small intestine, as implicated by studies of paracetamol absorption before and after RYGB [14, 63].

Appetite-regulating gut hormones Gut hormones also play a role in appetite regulation, with anorexigenic hormones such as GLP-1, peptide YY_{3–36} (PYY), oxyntomodulin, and cholecystokinin being released postprandially, in addition to increases in levels of ghrelin, an orexigenic hormone, preprandially. Like GLP-1, PYY is released from the intestinal L cells and levels of PYY are elevated postprandially after RYGB [13, 45, 50, 63, 64]. Levels of oxyntomodulin, another L cell product, have been reported to be elevated postoperatively [65], but the reported concentrations of oxyntomodulin were much higher than those of other L cell products (glicentin, GLP-1 and GLP-2), throwing doubt on the accuracy of the assays, given that oxyntomodulin is a product of the intestinal processing of proglucagon [66]. Nevertheless, significantly increased postprandial levels of enteroglucagon have been found after RYGB [14], 30–40% of which may be oxyntomodulin. In the only available study on cholecystokinin, fasting cholecystokinin concentrations did not change postoperatively in ten patients 3 weeks after RYGB [58]. In contrast to the increase in ghrelin levels observed after diet-induced weight loss, levels were initially reported to be markedly reduced after RYGB [67], but subsequent studies have not been able to reproduce this finding, with most studies reporting modest decreases in fasting and postprandial ghrelin levels during the first 6–12 months after RYGB [59]. However, recent studies have found that ghrelin levels return to preoperative values, or even increase, years after RYGB [14, 68].

Postprandial GLP-1 release is exaggerated after RYGB and potentiates postprandial insulin secretion. The increased release of GLP-1, PYY and possibly other anorexigenic hormones, such as oxyntomodulin and cholecystokinin, may contribute to the postoperative weight loss and thereby indirectly to improved insulin sensitivity

Adipose tissue and RYGB

The massive weight loss after RYGB comprises a 50% reduction in whole body fat mass including a 60% decrease in visceral adipose tissue as assessed 12 months after the procedure by dual-energy X-ray absorptiometry and computer tomography, respectively. During the same time period, lean body mass is reduced by 15–20% [69–71].

NEFA Fasting NEFA concentrations have been reported to be elevated 1 month after RYGB in patients with various degrees of glucose tolerance [20, 34, 39]. However, at 3 months postoperatively, NEFA levels have already returned to preoperative values and do not show any further

alterations at 6 and 12 months follow-up [20, 34, 72]. Postprandial NEFA concentrations 2–3 years after RYGB are similar to those of matched controls during an 8 h fatty meal test [73]. Using the HEC with a glycerol tracer and indirect calorimetry, a large increase in lipolysis and lipid oxidation rates has also been shown during the first 2–3 weeks after RYGB, with normalisation at the 1 year follow-up [20]. In another study, insulin-mediated suppression of NEFA in RYGB-operated patients was comparable to that in lean controls and was significantly greater than that in obese controls more than 1 year postoperatively [74].

Adipokines Changes in adipokines after RYGB are primarily characterised by a decrease in leptin [14, 34, 39, 58, 73, 75] and an increase in adiponectin levels [75–77] that appear to be associated with the degree of postoperative weight loss, and thus may reflect the amount of remaining adipose tissue. Furthermore, levels of IL-6 and visfatin are reduced postoperatively [34] and resistin levels are unchanged [78]. The decreasing plasma leptin levels and the increasing plasma adiponectin levels that occur after surgery favour an anti-inflammatory state and reduced levels of insulin resistance [14, 26].

In summary, body fat content, including visceral fat, is substantially reduced as part of the large postoperative weight loss. NEFA levels are increased early after surgery, probably reflecting fat mobilisation during the fast weight loss, but return to normal levels when the weight loss levels off. The concentration of leptin is reduced along with the reduction in adipose tissue, while adiponectin levels increase.

Bile acids and RYGB

A study comparing non-diabetic post-RYGB patients with morbidly obese and overweight controls found a more than twofold elevation of fasting bile acids in the post-RYGB group [79]. Moreover, bile acid concentrations were correlated with key metabolic variables, including inverse relationships with 2 h post-meal glucose, triacylglycerols, and thyroid-stimulating hormone levels, while correlations with adiponectin and peak postprandial GLP-1 concentrations were positive. The authors suggested that postoperative alterations in bile acid recirculation may contribute to improved glucose and lipid metabolism after RYGB [79].

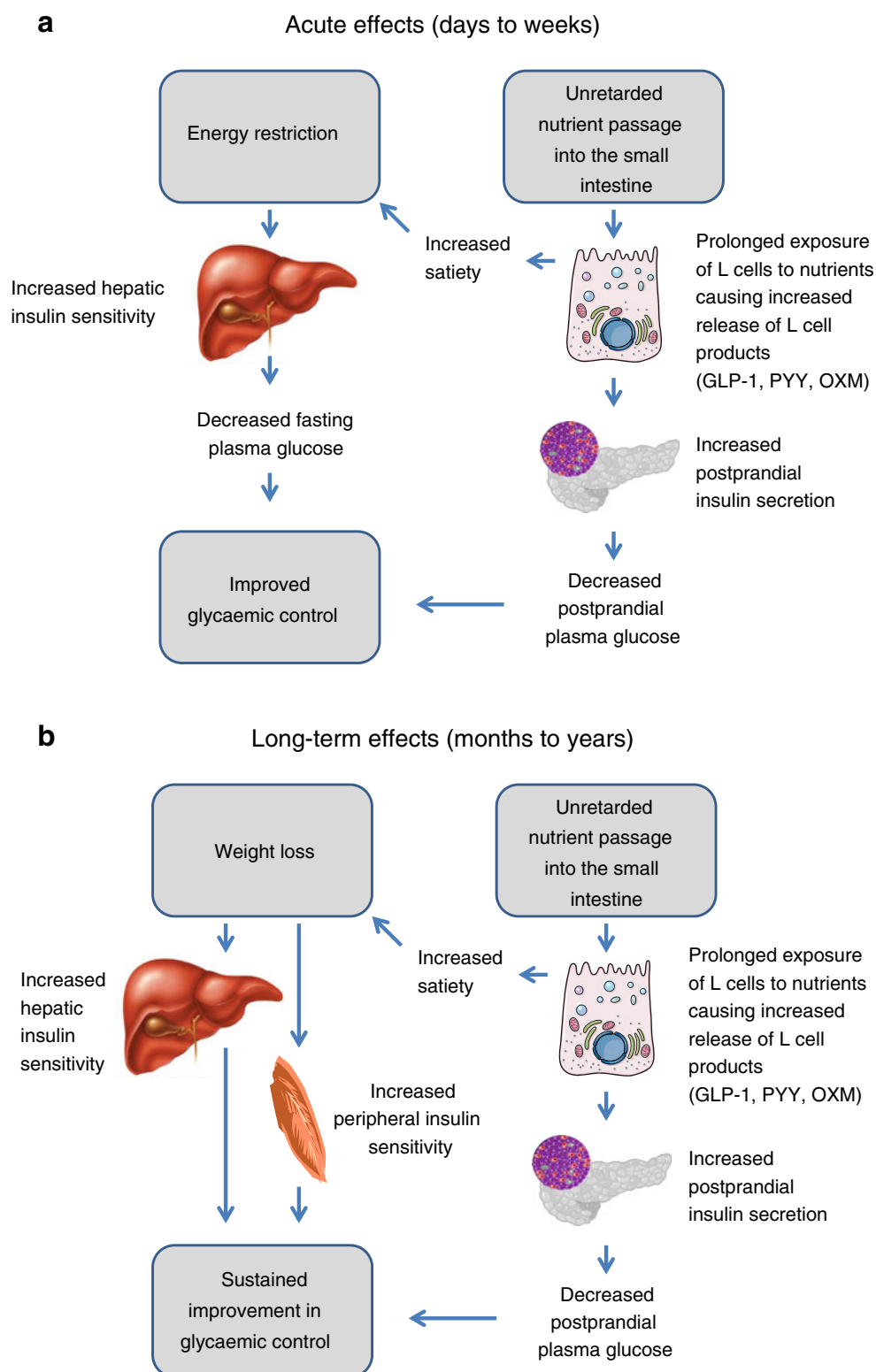
Discussion

Prompt improvement in glycaemic control after RYGB surgery, measurable just a few days postoperatively, is a clinical reality [3, 8]. Understanding the mechanisms behind this remarkable improvement in glucose metabolism may

lead to a better understanding of the pathophysiology of type 2 diabetes and, hence, the identification of new drug targets and/or improved surgical techniques. In this article we have reviewed a large number of RYGB-related pathophysiological studies and, taken together, two main mecha-

nisms seem to be responsible for the improvement in glycaemic control after RYGB: (1) an early increase in insulin sensitivity in the liver and later in skeletal muscle, and (2) improved beta cell function associated with an exaggerated postprandial GLP-1 secretion (Fig. 2).

Fig. 2 **a** Mechanisms responsible for the early improvement in glycaemic control after Roux-en-Y gastric bypass. **b** Mechanisms responsible for the sustained improvement in glycaemic control after Roux-en-Y gastric bypass. OXM, oxyntomodulin



The early improvement in hepatic insulin sensitivity, demonstrated by the significant and consistent reduction in HOMA-IR during the first postoperative week, but yet to be conclusively confirmed using more specific clamp and tracer techniques, could be explained by postoperative energy restriction, as described above. Obese patients undergoing other forms of surgery do not experience a similar improvement in glycaemic control, but, rather, a temporary deterioration in glucose tolerance, supposedly due to low-grade inflammation, high NEFA levels in response to fat mobilisation and surgical stress with the activation of cortisol, catecholamines, glucagon and growth hormone during the first days after surgery [80]. A study meticulously comparing changes in glycaemic control during the first 1–2 postoperative weeks in type 2 diabetes patients treated with either gastric bypass or other forms of abdominal surgery during identical feeding schedules would be of major interest.

Beta cell function also seems to improve early after RYGB, particularly in response to oral stimuli. This is seen by a down- and leftward shift in the postprandial glucose concentration curve after RYGB compared with a parallel downshift after energy restriction [33] or gastric banding [11], e.g. resulting in larger reductions in 2 h postprandial glucose value after RYGB. These changes in postprandial glucose tolerance after RYGB are related to an exaggerated postprandial insulin response, i.e. a brisk rise and higher peak concentration of insulin, which is in sharp contrast to the low and late insulin response profile characterising patients with type 2 diabetes before surgery. Note that the improvement in insulin secretion is already apparent during the first meal after RYGB [49].

It has been suggested that the enhanced insulin secretion after RYGB is caused by a factor released from the gut in response to the rapid passage of nutrients into the small intestine, the so-called hindgut hypothesis [3]. It is therefore interesting that the peripheral plasma GLP-1 responses to a meal, which increase 10- to 20-fold after RYGB, are closely associated with postprandial insulin secretion [38, 44, 49, 62]. It may be argued that these peripheral GLP-1 levels are not much higher than those observed during treatment with GLP-1 receptor analogues, but several lines of evidence support the notion that endogenous as opposed to exogenous GLP-1 may influence insulin secretion via mechanisms other than direct interaction with the beta cells. From animal studies, GLP-1 is known to activate afferent sensory neurones, as well as hypothalamic nuclei regulating glucose metabolism, and to reflexly stimulate pancreatic insulin secretion [81, 82]. These sensory mechanisms are exposed to much higher local concentrations of endogenous GLP-1 [83]. Therefore, although postprandial peripheral GLP-1 concentrations are not much higher than those observed after the administration of therapeutic GLP-1 agonists,

much higher intrainestinal and intraportal concentrations may explain why endogenous GLP-1 might be more effective than peripherally administered GLP-1. It is possible that the high portal GLP-1 concentrations might also have insulin-independent effects on glucose metabolism via neural reflexes, e.g. HGP [84]. Further support for the importance of GLP-1 for the improvement in glycaemic control comes from experimental surgery in both animals and humans involving ileal interposition, where a segment of ileum is interposed within the upper jejunum, thereby increasing the exposure of the L cells to ingested nutrients without bypassing the duodenum. In rats, the operation significantly improves glucose metabolism without weight loss and increases the secretion of GLP-1 and PYY [85, 86]. In humans, the procedure combined with sleeve gastrectomy induced improved insulin sensitivity and beta cell function [87] and consequently improved glycaemic control [88].

The dramatic effect of RYGB on postprandial glucose tolerance was highlighted in 2005, when Service et al described six postoperative cases of hyperinsulinaemic hypoglycaemia with apparent nesidioblastosis severe enough to require partial pancreatectomy to control the symptoms [89]. Later, other investigators found no change in beta cell mass in the same tissue specimens as compared with better matched controls [90]. The pathogenesis of this syndrome is not clarified, but an imbalance between improved insulin sensitivity and exaggerated GLP-1 responses resulting in an excessive postprandial insulin secretion might be partly responsible. Indeed, prevention of the exaggerated release of GLP-1 in a patient with severe postoperative hypoglycaemia by feeding through a gastrostomy catheter inserted in the gastric remnant was shown to prevent hypoglycaemia [48].

Whether exclusion of nutrients from the duodenum also contributes to the improvement in glucose tolerance after RYGB via an unknown factor has also been a point of considerable interest, the so-called foregut hypothesis [3]. This hypothesis is supported by an experimental design in Goto-Kakizaki rats in which duodenal–jejunal bypass that excludes nutrient passage through the duodenum is compared with gastrojejunostomy with intact duodenal nutrient passage [91]. In these animals, only duodenal–jejunal bypass results in a significant improvement in glucose metabolism, despite no difference in food intake, nutrient absorption or weight loss between the two operations. Studies in humans after duodenal–jejunal bypass also show improvements in glycaemic control with little or no weight loss [92–95]. Additional support for the hypothesis comes from experiments involving a duodenal–jejunal plastic sleeve, causing nutrients to move from the stomach to the jejunum without coming into contact with the duodenal mucosa, a procedure that also improves glucose tolerance in patients with type 2 diabetes [96–99]. Interestingly, changes in the secretion of gut

hormones including GLP-1 are observed both after duodenal–jejunal bypass and implantation of the plastic sleeve [95, 99].

In conclusion, we suggest that improvements in hepatic insulin sensitivity induced by energy restriction, which are appreciable only a few days after the operation, and an exaggerated GLP-1 response, inducing a normalised or exaggerated insulin secretion profile after ingestion of a meal, explain the majority of the early improvement in glycaemic control that occurs after RYGB (Fig. 2a). The exaggerated GLP-1 response is likely to result from the unretarded passage of nutrients to more distal parts of the small intestine that have a higher density of L cells. The interplay between the intestine–brain–islets of Langerhans demonstrated in rodents may also exist in humans and may also contribute to the improvement in glycaemic control, although documentation is needed. Thus, RYGB remains an inspiration in the search for new drug targets for the treatment of type 2 diabetes.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement CD, NBJ, KNBM and SHJ have contributed to the drafting of the manuscript. All authors have contributed to the interpretation and analysis of the reviewed studies and have critically revised and given final approval of the present version of this manuscript.

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