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ABSTRACT

The gastrointestinal (GI) tract can play a direct role in glucose homeostasis by modulating the digestion and absorption of carbohydrates and by producing the incretin hormones. In recent years, numerous studies have focused on intestinal adaptation following bariatric surgeries. Changes in the number of incretin-(GLP-1, GIP) producing cells have been reported which could result in the modified hormonal response seen after surgery. Additionally, the rate of absorption and the intestinal regions exposed to sugars may affect the time course of appearance of glucose in the blood. This reviewgives new insightsinto the direct role of the GI tract in the metabolic outcomes of bariatric surgery,in the context of glucose homeostasis.

KEYWORDS

Intestine,Roux-en-Y gastric bypass, Vertical sleeve gastrectomy, Nutrientflow,Enteroendocrine cells,Glucose transport

Introduction

Bariatric surgeries were originally developed to treat patients with severe obesity;they were initially recommended for patients with morbid obesity (body mass index (BMI) > 40 kg/m2) or severe obesity (BMI 35.0–39.9 kg/m2) when they exhibited at least one comorbidity that had the potential of being improved by the intervention[1,2]. Today, the two most commonly performed bariatric surgeries worldwide are the Roux-en-Y gastric bypass (RYGB, Figure 1A) and the vertical sleeve gastrectomy (VSG, Figure 1B)[3].Bariatric surgeries have consistently resulted in significantimprovements on obesity-associated metabolic diseases such as type2 diabetes. This resulted in new recommendations proposing that surgery should be considered for moderately obese diabetic patients (BMI 30.0–34.9 kg/m2) if hyperglycemia is inadequately controlled despite optimal treatment with medication[4,5]. These new recommendationshave already been adopted by several medical societies all around the world and should further increase the number of operated patients in the near future.Understanding these surgeries is thus of major clinical and societal importance.

The fact that the GItract is the direct target of bariatric procedures potentially makes it a key player, although so far underestimated, in the metabolic changes observed after surgery. Indeed, the GI tract can play a direct role in glucose homeostasis by modulating gastric emptying,the digestion of carbohydrates and absorption of glucose during meals, andalso by secreting a set of hormones, includingincretins thatregulate the release of insulin[6].

In this review, we will outline the GI-dependent mechanisms responsible for the alteration of gut hormone secretion after surgery. Then, we will discuss how intestinal glucose transport (thepassage of glucose from the intestinal lumen to the blood compartment through intestinal epithelial cells), and intestinal glucose

metabolism are modified after RYGB and VSG, and describe how these changes can affect glucose homeostasis.

Altered gut hormone secretion

After bariatric surgeries, changes in the fasting and postprandial secretion of gut-derived hormones aresignificant and varied and depend on the type of GI reconstruction [7,8]. These changesare suggested to be key players in the increased postprandial secretion of insulin and improved insulin sensitivity that is reported after bariatric surgery.

Glucagon-like peptide 1 (GLP-1)

GLP-1 is an incretin hormone produced by enteroendocrinecells scattered throughout the intestinal epithelium. The density of these GLP-1 secreting cells increases across a proximal to distal gradient. GLP-1 increases insulin release and decreases glucagon production, delays gastric emptying and intestinal transit and reduces meal size[9]. Although fasting concentrations of GLP-1 do not change markedly after bariatric surgery, postprandial levels of GLP-1 have been shown to increase following most, if not all, bariatric procedures[10–13]. However, studies designed to evaluate the influence of GLP-1 *per se* on glucose regulation and weight loss, have produced varied results. Mice with genetic loss-of-function of the GLP-1 receptor respond normally to VSG [14] and RYGB [15] in terms of both weight loss and improvements in glucose regulation. Conversely, specific deletion of the GLP-1 receptor in beta cells was shown to prevent the improvement of glucose tolerance in VSG-operated mice [16]. Together these studies indicate that GLP-1 alone cannot account for the overall metabolic effect of these two surgeries but may contribute to the altered postprandial glycemic response after VSG in mice. In humans, GLP-1 antagonists (exendin-9-39) failed to impair the otherwise improved glucose tolerance after VSG [17] and had only modest effects on glycemic response after RYGB [18,19].

Glucose-dependent insulinotropic polypeptide (GIP)

GIPis another incretin hormonesecreted byenteroendocrinecells located mostly in the duodenum and proximal jejunum and released in response to nutrients (notably lipids) [9].GIP promotes the conversion of glucose to fatty acids and their storage in adipose tissues[20]. While some studies report similar enhancements ofGIP secretion following RYGB and VSG surgery [21], others have documented GIP levels to be unchanged [10,22]or reduced [23,24]following RYGB surgery.Although not yet formally demonstrated, it is possible that since GIP is produced by cells of the proximal intestine, differences in the length of the intestinal limb bypassed by the surgery could differentially affect meal-induced GIP secretion in patients. Moreover,the presence or the absence of type-2 diabetes in patients before bariatric surgerymightaffectthe alteration of GIP secretion after surgery[25,26]. A recent study investigated the combined and separate effects of endogenously secreted GLP-1 and GIP on glucose tolerance after RYGB [27]. GLP-1 increased insulin and attenuated glucagon secretion in the postprandial state, whereas amplification of the GIP signal aggravated postprandial hyperglucagonemia and did not contribute to the improved glucose tolerance[27].The role of GIP in theimproved glucose tolerance following RYGBis still an open questionand also remains to be addressed in detail in the context of VSG.

Ghrelin

Ghrelin is an orexigenic hormone produced mainly in the stomach and duodenum thatexerts gluco-regulatory functions[28].Resection of the fundic region in VSG leads to a decrease in ghrelin-expressing cells and concomitant ghrelin-circulating levels in rats [29,30] and humans[11,31,32]. Body weight and glucose tolerance measurements after VSG, however, showed similar results in ghrelin-deficient and in wild-type mice [33]. Moreover,while postprandial ghrelin levels are reduced after VSG[11,31,32], they have been reported to either decrease[34], increase [32,35]or remainunchanged[11,36]after RYGB

compared to obese patients.Post-operativemodifications ofghrelin levels after surgery are,therefore,unlikely to determine metabolic improvement.

Other digestive hormones

Hormones, such ascholecystokinin[10],PYY[37]and others [7], have also been found to be modulated after some bariatric procedures andhave thus been proposedas importantfactors contributing to the post-surgery metabolic improvement.Hormonal changes are certainlyinvolvedin the positive outcomes of surgery, but all simplistic views aiming to identify "the" determinant hormone responsible for the beneficial effect of bariatric surgeries are probably shortsighted and futile, sinceGI surgerieslead to a profound alteration of the entire gut's hormonal response, following a meal.After surgery, a new homeostatic state is institutedand thus hormone levels should be considered in relation to each other rather than compared to their pre-operative values. For instance, physiologically, glucagon secretion decreases after a meal, but it has been shown that postprandial glucagon release is increased following RYGB and VSG compared to pre-operative states [21,38]. Interestingly,one study reported that GIP, GLP-1, and GLP-2 differently affect glucagon responses to orally ingested glucose in patients with diabetes [39].Indeed, in non-operated diabetic patients, intravenous infusion of GIP increasedthe glucagon response and thus counteracted the reduction of glucagon secretion associated with intravenous infusion of GLP-1. Since postprandial levels of GLP-1 and GIP are modified after bariatric surgery, these hormonal interactions could explain how postprandial glucagon levels are increased. Understanding how all these hormonal signals act together to mediate the effects of surgery is an important but ambitious research goal, particularly considering that we are far from understanding how they are integrated together, even in physiological conditions.

The origin of these modified hormonal secretions is still debated.Historically, altered nutrient flow, either by foregut exclusionor by accelerated hindgut delivery of nutrients,wasconsidered responsible for the improved hormonal responseand the success of derivative procedures like RYGB[40].The modified postprandial hormonal response observed after VSG, a purely gastric surgery in which the food path is not modified, however, has somewhat weakened these assumptions. More recent studies have nevertheless revealed that gastric emptying rates were indeed very rapid after VSG [41–43].

Accelerated nutrient flow and increasedintestinal surface exposure

GI remodeling leads to a drastic acceleration of food arrival in the intestine, by pyloric exclusion after RYGB [12,44]and also by an increase in gastric emptying rate after VSG[42,43]. Increasing evidence shows that the modified dynamics of the nutrient flow is likely to contributeto both the modified glycemic response to a meal andthe concomitant altered gut hormone secretion in patients.

The total intestinal surface that is almost immediately exposed to a liquid meal is drastically different between operated and control individuals, and affects the entry of glucose into the blood[44]. A study, using radiolabeled tracer, found that only five minutes after a nutrient gavage, the stomachs of RYGB and VSG rats were completely emptied, whereas only 6.1% of the nutrient mixture had emptied from sham animals [41]. The accelerated gastric emptying and food delivery to the intestine increases the total intestinal surface exposed to the luminal content. This could have a direct effect on the rate of glucose entry into the blood during a sugar-rich meal. Indeed, this hypothesis was illustrated by a recent study using multiple intestinal clamp sites in minipigs with RYGB [45].The study demonstrated a direct relationship between the exposed intestinal area and the transfer of glucose to the blood. More interestingly, the insulin

response and secretion of GLP-1 significantly increased only when the total intestinal surface was accessible by the liquid meal. Even if one cannot discriminate whether the stimulation of the distal intestine by the meal or the increase in blood glucose *per se* is responsible for the hormonal response, these experiments suggest that the hormonal response to a meal after RYGB is highly dependent on the altered nutrient flow caused by GI reconstruction.

Two human studies confirmed the role of altered nutrient flow in the hormonal response observed after surgery[12,44]. In the first, RYGB patients received either a glucose drink or the same solution infused into the proximal Roux limb at 4 kcal/min, a rate equivalent to physiologic gastric emptying[44]. Blood glucose, insulin, glucagon, GIP and GLP-1 were then measured during the test.The glycemic response was delayed in RYGB patients receiving the solution at 4 kcal/min compared to when the same solution was received orally. Moreover, the infusedpatients' hormonal responses were similar to those observed in non-operated subjects receiving the oral drink, thus supporting the effect of rapid nutrient exposure on the exaggerated incretin responses. The second study evaluated GI motility with a scintigraphic technique, andgut hormone secretion in RYGB patients [12]. The authors found a statistically significant association between gastric pouch emptying and hormone responses during a multiple meal test. In contrast, no relation was found between gut hormone release and gastric pouch emptying when they used a solid radiolabeled marker, further strengthening the role of rapid nutrient flow in hormone secretion, sincetransit of solids is much slower than liquids.

Interestingly, a study in rats showed that intestinal infusion of a glucose solution at an identical rate led to a greater GLP-1 secretion in VSG rats relative to sham-operated controls [41]. This suggests the existence of delivery-independent mechanisms that alter the gut hormonal response, at least in VSG rats.

In summary, the altered glycemic and hormonal response to a liquid meal in RYGB and VSG patients is likely to be mediated by the accelerated nutrient

flow after both surgeries, which increases the surface of contact between the meal and the intestine. However, it is worth noting that amixed meal test may differ in many ways with the daily diet pattern of patients[46] and that thehormonal responses observed experimentally may not occur during small solid meals[47,48].

The altered nutrient flow and subsequent modified nutritional stimulation of the intestine after surgery could causetheintestinal adaptation that in turn might affect hormonal secretion and the glycemic response to a meal.

Intestinal adaptation and enteroendocrine cell number

Due to the difficulty of directly studying the GI tract of bariatric patients, most of the studies aiming to describe intestinal adaptations after RYGB or VSG procedureshave been conducted in experimental models such as rodents. In 2009, Stearns et al. were the first to report changes in intestinal structure and function in a rat model of RYGB [49]. They showed an increased villus size and crypt depth in the Roux limb and common limb of operated rats. This hyperplasia has been confirmed and further characterized by several subsequent studies [50–55].

An important consequence of Roux limb overgrowth after RYGB is an increase in the total number of enteroendocrine cells, including GLP-1-, GIP-,CCK- and PYY-producing cells within the intestinal mucosa[52,54,56,57]. This adaptation was reported in both human and rodent RYGB subjects and could contribute to the modified hormonal profileafter surgery. Whether the increased number of enteroendocrine cellsdue to Roux limb overgrowth is associated with an additionalincrease in their density,is still a matter of debate[54,57,58].

To date, no study has directly investigated intestinal adaptation after VSG in humans. However, two recent reports using rat models of VSG described an absence ofhypertrophy of the jejunum mucosa after this surgery [54,59]. The distribution of enteroendocrine cells producing GLP-1 was also examinedin these studies but contradictory results were obtained. The first study reported that GLP-1 cell numbers were not modified at 3 month post-VSG [59].In contrast, a second studyreported an increase in the number and density of GLP-1 cells14 days after surgery[54].It remains to be determined whether this discrepancy results from the different time pointstaken foranalysis, or differences in other variables such as post-operative diet or surgical techniques.An increase in the density of GLP-1 cellswould,however, be a reasonable explanationfor the higher delivery-independent GLP-1 secretion observed after VSGin rats [21,37].

Whether modified numbers of enteroendocrine cells actually affect the release of gut hormone after surgery remains to be determined. An increase in hormone productionby or an exacerbated nutrient sensitivity of the enteroendocrine cells after the surgery could also be involved. Assaying the sensitivity of enteroendocrine cells to nutrients before and after surgery will be a challenging task in the future but development of enteroids from human biopsies couldoffer a unique opportunity to evaluate it[60,61].

Intestinal adaptation and glucose transport

The idea that bariatric surgeries could lead to alterations in intestinal glucose transport has been the subject of several studies.To be absorbed by the intestine, polysaccharides must be hydrolyzed into their monosaccharide components (glucose, galactose and fructose) by saccharidases. Glucose and galactose are transported across the apical membrane into the enterocyte by the sodium/glucose cotransporter 1 (SGLT1)[62], whereas fructose is taken up by

the fructose transporter 5 (GLUT5)[63]. Monosaccharides are partly metabolized in the enterocytes but most of them exit the cells*via* glucose transporter 2 (GLUT2) in the basolateral membrane, a process that delivers them to the blood before reaching the liver for further metabolism and regulation of glucose production[64]. During sugar-rich meals or in the case of insulin resistance, monosaccharide absorption might be exacerbated after translocation of GLUT2 to the apical membrane [65].Thus, the appearance of glucose in the blood follows a time course that is affectedby theintestinal surface exposed to nutrients, but also by the number of functional enterocytes and the expression of their glucose transporters.

Molecular analyses have produced heterogeneous results regarding the expression pattern of intestinal sugar transporters after RYGB in rats[49,51,53,54].SGLT1, GLUT2 and GLUT5 mRNA or protein levels were reported to be increased[51], decreased [49,51,53]or not modified[54][53] in the alimentary Roux limb of RYGB animals, compared to the jejunum of sham animals.The heterogeneity of these molecular analyses could be due to experimental differences such as differentpostoperative time points, variable surgical procedures or pre- and post-operative diets. Additionally,thepresence of different steps in the adaptive process[54],or alterations in expression levels following diurnal rhythms [49] also likely influence the results.One study reported no difference for SGLT1, GLUT2 or GLUT5 mRNA levels between the Roux limb, the biliopancreatic limb or the common limbof a RYGB minipig model [45]. In humans,increased mRNA expression of SGLT1 and GLUT2has been reported more than a year after surgery[66].Thus species-related differences might also exist.

It is worth highlighting thatthe activity of SGLT1 does not always correlate with its mRNA expression [49,54].The growth of the intestinal mucosa, following RYGB,and therefore the increased numbers of enterocytes could affect the total absorptive capacity of the intestine, beyond the expression of sugar transporters.

In fact, it is hard to demonstrate the relationship between transporter expression and the glycemic response to an oral glucose tolerance test *in vivo*. Accordingly, differences in the glycemic response of rats between 14 and 40 days post-RYGB have not been observed despitesignificant variation in the expression of their intestinal sugar transporters [30]. Direct assessments of intestinal glucose transport capacity before and after surgeryare,therefore,still needed to evaluate the existing functional changes.

Ex vivo, glucose transport can be measuredby radioactive methods with isolated intestinal segments from rats that have undergone bariatric surgery. Entry of glucose into the enterocytes (from the mucosal or serosal side)is referred to asintestinal glucose uptake but is often misnamed as intestinal glucose transport, which is actually thepassage of glucose from the intestinal lumen to the blood compartment through enterocytes. Of note, in a recent study,no alteration in glucose transport in the Roux limb of RYGB rats compared to the jejunum of sham ratswas observed, whereas glucose uptake wasmarkedly increased in RYGB ratsregardless of the entry site (mucosal or serosal side) [54].After RYGB, some studies report a reduction in intestinal glucose uptake[45,49]whereas others report no changes [54,67].It has also been reported that RYGB may abolish the diurnal rhythm associated SGLT1-mediated glucose uptake, with a 63% reduction specifically prior to the onset of feeding [49]. Finally,a study in humans reported that RYGB was followed by an increase in SGLT-1 expression and showed a positive association between SGLT-1 expression and glucose absorption [66].Once again, the methods used to evaluate the glucose uptake, the intestinal segments, and the exact time-points at which measurements were made after surgery differed widely among studies, probably contributing to the heterogeneity of the results.

To the best of our knowledge, only one group has evaluated glucose transport and uptake after VSG [54]. In this study, glucose transport from the luminal to the serosal side was markedly decreased in the jejunum of VSG rats, compared

to sham-operated rats. Expression of the sugar transporters SGLT1, GLUT2 or GLUT5 did not reflect the modification in intestinal transport capacity. The mechanism of this regulation is still unknown, but VSG could improve glucose tolerance by delaying the entry of alimentary glucose. This would be in agreement with the delayed glycemic response observed after an oral load of glucose in rats [54]or in VSGsubjectscomparedto RYGBsubjects[68].

It is difficult to transpose these *ex vivo* findings upon what actually happens during a glucose gavage or a meal, since the dynamic aspect of nutrient flow is lost. In addition,whilst intestinal glucose transport may be reflected by the early slope of an oral tolerance test, glucose clearance after the peak is the reflection of glucose disposal by peripheral organs such as liver, muscles and adipose tissue but also, as described below, the intestine itself.

Intestinal adaptation and glucose disposal

It has been shown recently that hyperplasia in the Roux limb after RYGB is associated with a reprogramming of glucose metabolism towards increased intestinal glucose uptake and consumption by intestinal cells[53,54]. The remodeled intestine could thus increase wholebody glucose disposal and contribute to the glucose lowering effect of derivative bariatric procedures.

The reprogramming of glucose metabolism is characterized by increased mRNA and protein levels of enzymes involved in glycolysis,and by the appearance of the glucose transporter GLUT1 at the basolateral membrane of enterocytes [53,59,54]. The GLUT1 transporter is widely expressed during development but its expression is decreased in adults and becomes very low in mature jejunum [69]. The overexpression of intestinal GLUT1 after RYGB might be a consequence of the increased energy demand to support the intestinal hyperplasia that occurs very early after surgery. Accordingly, there is no reprogramming of glucose metabolism and no overexpression of GLUT1 in the jejunum of VSG-operated rats that does not display any hyperplasia[54,59].

In vivo, using positron emission tomography-computed tomography (PET-CT) scanning and intravenous administration of [^{18}F]-FDG, it has been demonstrated that RYGB surgery increases intestinal glucose disposal in rats [53]. Similarly, another study reported increased metabolic activity in the Roux limb of humansfollowing bariatric surgery using the same techniques[54].

Considering the contribution of increased intestinal glucose disposal to the glucose lowering effect of RYGB surgery, a study on rats using PET-CT scanning reported a 90% higher [^{18}F]-FDG uptake by the intestine of RYGB-treated rats and a 30% reduction in [^{18}F]-FDG signal in the blood,compared to sham animals[53]. This suggests that intestinal glucose utilization is key to the improvement of wholebody glucose disposal in rats. To date, intestinal blood glucose disposal has not been quantified in human patients, but a recent study measured GI retention and presumably metabolism of ingested glucose in obese subjects before and after RYGB [70]. Using a mixed meal containing labeled [$^{6,6\text{-}2}$H2]-glucose, the authors demonstrated that GI clearance of ingested glucose is increased after RYGB surgery. However, the difference effected by the bariatric procedure was low (from 10% ± 8% before to 15% ± 9% after surgery), showing that intestinal glucose diversion during meals is not likely to largely contribute to the postprandial improvement in glycemic control.

Studies directly measuring the intestinal clearance of intravenously administrated glucose are needed to evaluate whether the reprogramming of glucose metabolism and subsequent increase in intestinal glucose disposal makes a real contribution to the glucose lowering effect of RYGB surgery in humans.

Concluding Remarks and Future Perspectives

Glucose excursion after a meal depends onintestinal transport of glucose to the blood, secretion of gut hormones and glucose handling by peripheral organs. The remodeledGI tract after bariatric surgery plays a major role in altering all

these processes. Complementing the associated accelerated nutrient flow and increased intestinal surface exposure, the two main types of bariatric surgeries, RYGB and VSG, differently alter gut morphology, gut hormone secretions, and intestinal glucose transport and metabolism (**Key Figure**) and these factors may all contribute to glucose homeostasis. The biggest challenge now is to evaluate the relative contribution of all these mechanisms (**Outstanding questions box**) and to find a way to recapitulate the important ones in non-surgical or less invasive treatments.

FIGURES AND KEY FIGURE

Figure 1: Two common types of bariatric surgeries

(A) The Roux-en-Y gastric bypass (RYGB) consists of creating a small gastricpouch below the esophagus (25-50mL in humans) that is connected directly to the middle portion of the jejunum, bypassing the rest of the stomach, the pylorus and the upper portion of the small intestine (duodenum and proximal jejunum), which is anastomosed distally. The operation creates three anatomically distinct gut segments: an alimentary limb (or Roux limb), which receives only undigested food (red arrows); a biliopancreatic limb, which drains gastric secretions, bile and pancreatic enzymes (blue arrows); and a common limb that connects the two aforementioned limbs together. This operation is very efficient, with an important and sustained weight loss accompanied by a reduction in obesity-associated comorbidities such as hypertension, hyperlipidemia and type 2 diabetes in most patients. **(B)** The vertical sleeve gastrectomy (VSG) involves a longitudinal resection of the stomach starting from the antrum and ending at the fundus close to the cardia; the remaining volume of the gastric compartment is about 150 mL in humans. This intervention has been proven to be an effective procedure at middle term with an important weight loss accompanied by a reduction in obesity-associated

comorbidities such as hypertension, hyperlipidemia and type 2 diabetes in many patients.

<u>Figure 2, Key Figure</u>: **Differential intestinal adaptations after RYGB versus VSG and their putative contributions to the resulting altered hormone secretion and improved glucose tolerance**.

Both bariatric surgeries reduce the transit time of the meal and increase the exposure of the intestinal mucosa that acts to modify secretion by enteroencrine cells and also glucose entry.In response to RYGB, the Roux limb becomes hyperplasic, with the number of incretin secreting cells increasing. Additionally, a shift in glucose metabolism increases the intestinal glucose consumption.In response to VSG, despite no intestinal hyperplasia, the number of GLP-1 positive cells mayincrease due to increased cell density. Moreover, studies in rats suggest that glucose transport from the lumen to the blood decreases delaying alimentary glucose absorption. To date, no study has directly investigated intestinal adaptation after VSG in humans.

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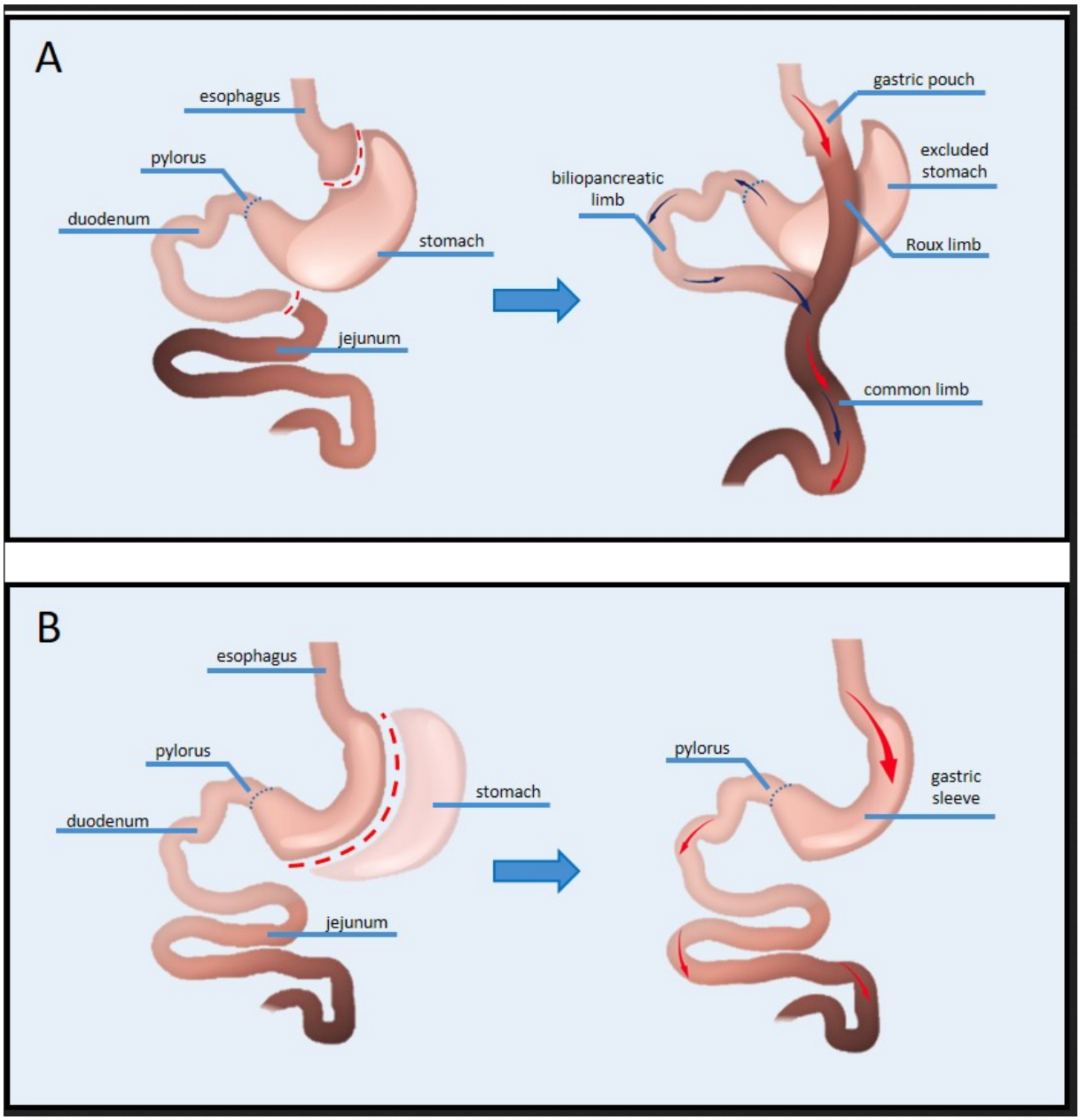
A
esophagus
pylorus
duodenum
stomach
jejunum
gastric pouch
excluded stomach
biliopancreatic limb
Roux limb
common limb
B
esophagus
pylorus
duodenum
stomach
jejunum
pylorus
gastric sleeve

Figure 1A,B

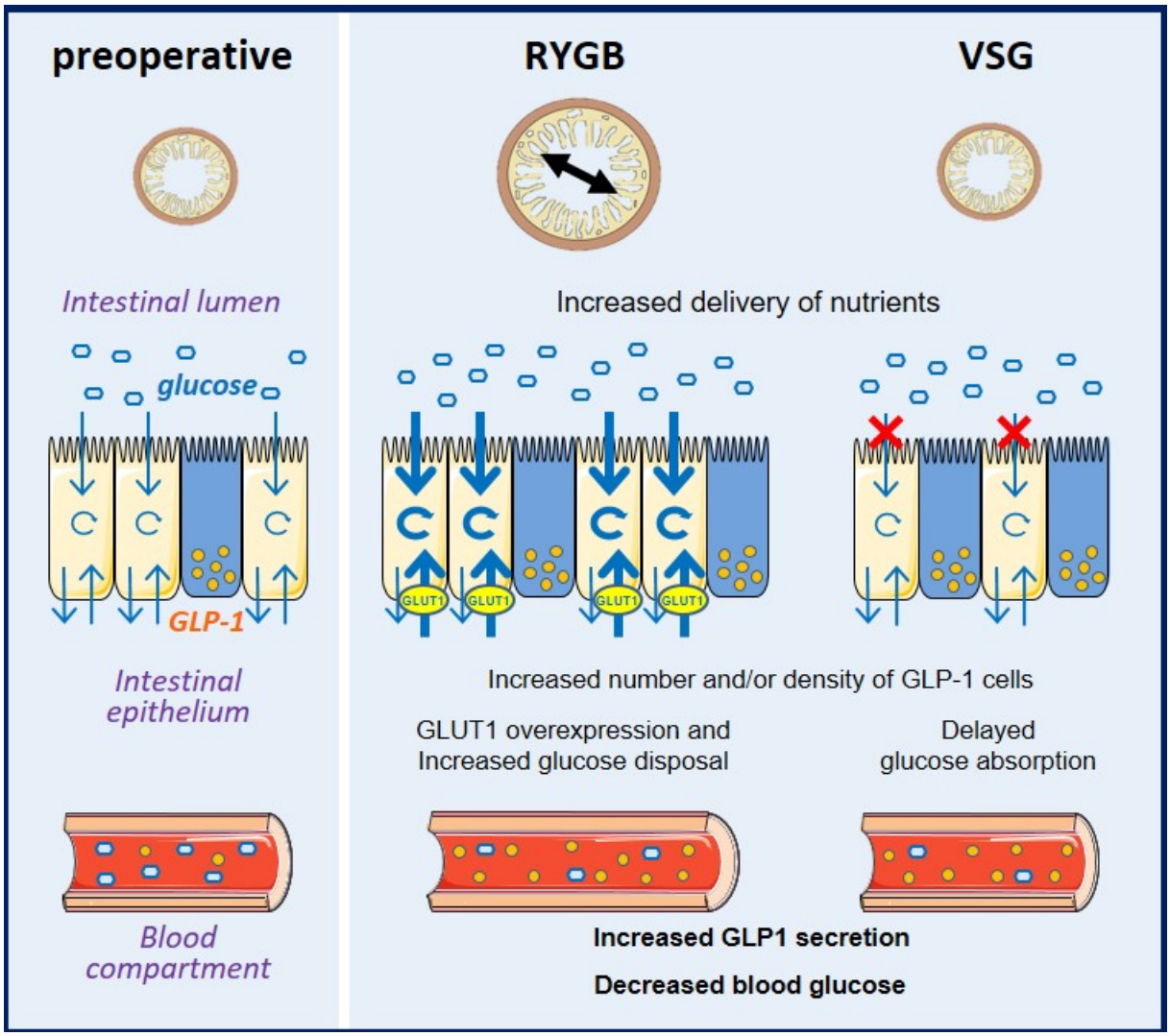
preoperative
RYGB
VSG
Intestinal lumen
Increased delivery of nutrients
glucose
GLP-1
GLUT1
Intestinal epithelium
Increased number and/or density of GLP-1 cells
GLUT1 overexpression and Increased glucose disposal
Delayed glucose absorption
Blood compartment
Increased GLP1 secretion
Decreased blood glucose

Figure 2