What can bariatric surgery teach us about the pathophysiology of type 2 diabetes?

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Abstract

Bariatric surgery is indicated in cases of severe obesity. However, malabsorption-based techniques (gastric bypass and biliopancreatic diversion, both of which exclude the duodenum and jejunum from the alimentary circuit), but not restrictive techniques, can abolish type 2 diabetes within days of surgery, even before any significant weight loss has occurred. This means that calorie restriction alone cannot entirely account for this effect. In Goto-Kakizaki rats, a type 2 diabetes model, glycaemic equilibrium is improved by surgical exclusion of the proximal intestine, but deteriorates again when the proximal intestine is reconnected to the circuit in the same animals. This effect is independent of weight, suggesting that the intestine is itself involved in the immediate regulation of carbohydrate homeostasis. In humans, the rapid improvement in carbohydrate homeostasis observed after bypass surgery is secondary to an increase in insulin sensitivity rather than an increase in insulin secretion, which occurs later. Several mechanisms are involved—disappearance of hypertriglyceridaemia and decrease in levels of circulating fatty acids, disappearance of the mechanisms of lipotoxicity in the liver and skeletal muscle, and increases in secretion of GLP-1 and PYY—and may be intricately linked. In the medium term and in parallel with weight loss, a decrease in fatty tissue inflammation (which is also seen with restrictive techniques) may also be involved in metabolic improvement. Other mechanisms specific to malabsorption-based techniques (due to the required exclusion of part of the intestine), such as changes in the activity of digestive vagal afferents, changes in intestinal flora and stimulation of intestinal neoglucogenesis, also need to be studied in greater detail. The intestine is, thus, a key organ in the regulation of glycaemic equilibrium and may even be involved in the pathophysiology of type 2 diabetes.

Résumé

Que nous apprend la chirurgie bariatrique sur la physiopathologie du diabète de type 2 ?

La chirurgie bariatrique est indiquée en cas d’obésité sévère. Contrairement aux techniques restrictives, les techniques malabsorptives (by-pass gastrique ou diversion bilio-pancréatique, qui ont en commun l’exclusion du segment duodéno-jéjunal du circuit alimentaire) permettent une disparition spectaculaire du diabète de type 2, dans les jours qui suivent la chirurgie et avant même une perte de poids significative. La restriction calorique n’explique pas tout. Ainsi, chez le rat Goto-Kakizaki, modèle de diabète de type 2, l’équilibre glycémique est amélioré par l’exclusion chirurgicale de l’intestin proximal et se détériore à nouveau chez le même animal si l’intestin proximal est remis en circuit. Cet effet est indépendant du poids suggérant que l’intestin lui-même participe à la régulation immédiate de l’homéostasie glucidique. Chez l’homme, l’amélioration précoce de l’homéostasie glucidique après by-pass gastrique est secondaire à une...
amélioration de la sensibilité à l’insuline plus qu’à une amélioration de l’insulinosécrétion qui survient plus tardivement. Les mécanismes impliqués sont multiples (disparition de l’hypertriglycéridémie et réduction de la concentration des acides gras libres circulants, disparition des mécanismes de lipotoxicité dans le foie et le muscle squelettique, hausse de la sécrétion du GLP-1 et du PYY) et probablement intriqués. A moyen terme et en parallèle à la perte de poids, la réduction de l’inflammation du tissu adipeux (qui peut également s’observer avec les techniques restrictives) participe également à l’amélioration métabolique. D’autres mécanismes spécifiques des techniques malabsorptives (car nécessitant l’exclusion d’une partie de l’intestin) comme les changements d’activité des afférences vagales digestives, les modifications de la flore intestinale ou la stimulation de la néoglucogenèse intestinale doivent être étudiés plus précisément. Ainsi, l’intestin est un organe clé de la régulation de l’équilibre glycémique et pourrait même participer à la physiopathologie du diabète de type 2.

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1. Introduction

Bariatric surgery is indicated in cases of morbid [body mass index (BMI) > 40 kg/m²] and severe (BMI > 35 kg/m²) obesity with at least one other severe co-morbidity such as arterial hypertension, type 2 diabetes or sleep apnoea. Bariatric surgery has become increasingly popular in recent years due to the growing rates of obesity in the general population and the occurrence of obesity in younger patients. Although not all of the favourable and unfavourable effects of the various surgical techniques for treating obesity are yet known, the efficacy of such surgical techniques for reducing excess weight in the medium term is indisputable. These operations are also associated with improvements in certain co-morbid conditions linked to excess weight, including, in particular, metabolic conditions such as hypertriglyceridaemia, insulin resistance and type 2 diabetes. However, what do we currently know of the improvement in carbohydrate metabolism associated with bariatric surgery?

2. Bariatric surgery involves different techniques

The techniques used in bariatric surgery can be classified into two major types. Purely restrictive techniques limit the volume of food that can be ingested, and involve stomach stapling (‘calibrated vertical gastroplasty’) to reduce the volume of the upper part of the stomach, using a reversible technique (adjustable gastric bands). One newly developed restrictive technique—sleeve gastrectomy—involves resectioning of the greater curvature of the stomach. On the other hand, malabsorption-based techniques reduce both food intake and absorption of nutrients, and involve both reducing gastric volume while creating an intestinal circuit that cuts out pancreatic exocrine secretion. Two malabsorption-based techniques are currently widely used: biliopancreatic diversion (BPD; Scopinaro’s method); and the roux-en-Y gastric bypass (RYGBP) technique. Gastric bypass involves isolation of the upper section of the stomach (to create a gastric ‘pouch’), which is then anastomosed to the upper jejunum and ileum, bypassing the rest of the stomach, duodenum and proximal jejunum. Worldwide, the two most practised methods of gastric bypass involve the use of gastric bands and the RYGBP method.

3. Bariatric surgery decreases co-morbidity associated with obesity

The SOS (Swedish Obese Subjects) Study is the only investigation to compare the long-term effects of surgery with those of lifestyle and dietary changes [1]. This multicentre open study looked at the active management of both severe obesity (BMI > 35 kg/m²) and at least one co-morbid condition (BMI > 40 kg/m²). On inclusion, patients were given a choice between a strategy based on lifestyle changes (with dietary and lifestyle follow-up) and one based on bariatric surgery (with a choice between gastric bypass and gastroplasty). One of the strong points of the study was the regular follow-up of patients for more than 12 years, with regular evaluations of weight loss and changes in quality of life, and of co-morbid conditions initially associated with excess weight. The mean age of the subjects at inclusion was 40 years in both groups, with a mean BMI of 40 kg/m².

One year after surgery, more weight loss was observed with gastric bypass than with gastroplasty [1]. Metabolic co-morbidities, such as type 2 diabetes and hypertriglyceridaemia, showed significantly greater improvement following surgery (with no comparisons made between gastric bypass and gastroplasty) than after lifestyle modifications during the first year. The favourable effects on glycaemic equilibrium were marked, with a particularly large number of cases of type 2 diabetes remission. Furthermore, hypertriglyceridaemia also disappeared soon after bariatric surgery, with an increase in high-density lipoprotein (HDL)-cholesterol levels. However, bariatric surgery had little effect on low-density lipoprotein (LDL) cholesterol. Also, arterial hypertension was improved in some cases, but did not generally resolve.

After the first year of follow-up, a gradual increase in weight was observed in the patients who underwent surgery. This increase was proportionally larger in the bypass group than in the gastroplasty group, but the two curves did not meet [1]. In parallel with this weight increase, a recurrence
or worsening of co-morbid conditions was noted. Thus, the study found that patients can regain weight after bariatric surgery. This had already been shown for gastroplasty, but this was the first report of the effect (which has since been confirmed by other teams) with gastric bypass surgery. This suggests that there is no ‘definitive’ surgical solution for severe and morbid obesity, and also showed that the progression of co-morbid conditions is largely influenced by fluctuations in the patient’s weight, as a clear gradual increase in the incidence of diabetes and dyslipidaemia was observed with increasing weight after bariatric surgery.


To answer this provocative question, surgical reports have focused in recent years on the effects of obesity-related surgery on carbohydrate metabolism [2]. This treatment strategy has increasingly come to the fore with the advent of malabsorption-based surgical techniques, such as RYGBP, which comes with fewer side-effects (such as loss of nutrition, in particular) than do older techniques, such as BPD, using the technique of Scopinaro. Since the 1990s, RYGBP has been shown to be more effective than gastric bands or gastroplasty for controlling glycaemia, with many cases of complete type 2 diabetes reversal reported with the technique [2-7]. The superiority of RYGBP over other methods for controlling glycaemia may be partly accounted for by the greater weight loss obtained with the technique than with a gastric band (50% of excess weight lost in 12 months with RYGBP vs 30% with gastric bands, and >80% excess weight lost in 24 months with RYGBP vs 40% with bands) [8].

In addition, surgical studies have established that one determining factor for the disappearance of type 2 diabetes is a known duration of diabetes of <10 years [5]. Indeed, in cases of diabetes of longer duration, even in cases with weight loss that significantly improved glycaemic equilibrium, the diabetes has not disappeared completely. This finding reveals the limitations of the weight-dependent effects of bariatric surgery on glycaemic equilibrium, and have subsequently led surgical teams to operate on patients with type 2 diabetes as soon as possible after the diagnosis.

5. Confounding factors

It is clear from previous reports on the effects of bariatric surgery on the progression of type 2 diabetes that certain confounding factors have been taken into account either inadequately or not at all.

The first such confounding factor is the type 2 diabetes patient per se. Those described as ‘immediately cured’by bariatric surgery are different from the population of patients generally followed by diabetes specialists. The former patients usually have a much higher BMI than most patients with type 2 diabetes (at least 40 kg/m² vs 32 kg/m² for the type 2 diabetic population followed by diabetes specialists). Analyses of HbA₁c also show that the population undergoing surgery generally has better-controlled diabetes with the use of milder treatment (insulin treatment is rare in this population). In addition, the surgical population presents with no diabetes complications.

Another confounding factor is the assertion that diabetes has been reversed. Most surgical reports assess whether diabetes has been cured on the basis of a decrease in HbA₁c levels over time in the absence of glycaemia-lowering treatment. Indices of insulin sensitivity (such as HOMA or glucose utilization during euglycaemic–hyperinsulinaemic clamp tests), and analyses of insulin secretion (in response to an oral glucose load challenge or calibrated test meal) are only rarely reported. Similarly, changes in daily food intake and body composition during post-surgical follow-up are only occasionally analyzed, and only changes in weight are systematically reported. Surgical reports, therefore, ignore explanatory mechanisms and have, above all, sought to describe the factors predictive of long-term diabetes cure, such as duration of diabetes of >10 years, a key factor now recognized to be associated with a poor prognosis [5].

6. Gastric bypass has particular effects on carbohydrate homoeostasis

The day-to-day experience of bariatric surgery teams (confirmed by published results) shows that RYGBP can completely normalize the glycaemic cycle in type 2 diabetic patients in the week following the intervention, even before any significant weight loss has occurred [2-7]. This acute effect of RYGBP, not seen with gastroplasty or gastric band-based techniques, suggests that the surgical procedure itself—designed to exclude most of the stomach, duodenum and part of the jejunum from the alimentary circuit—directly affects carbohydrate homoeostasis.

Before going further into the specific mechanisms of RYGBP, it is necessary to determine whether or not the technique rapidly improves type 2 diabetes by decreasing insulin resistance or by increasing insulin secretion. Insulin sensitivity is rarely evaluated by a gold-standard method (euglycaemic–hyperinsulinaemic clamp test) in patients with morbid obesity due to the complexity of the procedure. Indeed, HOMA determination and the use of simpler exploratory methods, such as monitoring the decrease of glycaemia following intravenous injection of a single dose of fast-acting insulin, are more frequently reported in studies of bariatric surgery. RYGBP significantly increases insulin sensitivity in patients with morbid obesity from the sixth day after surgery, when weight loss remains modest [9]. In the short term, RYGBP yields greater improvement in insulin sensitivity than do gastric bands [10]. The improvement in insulin sensitivity observed with gastric bands is strictly dependent on weight loss [11-13] whereas, with RYGBP, changes in HOMA after
surgery are independent of weight loss, but correlated with the extent of insulin resistance prior to surgery [10]. This reflects the weight-loss-independent effects of RYGBP on insulin sensitivity. Furthermore, the near-normalization of insulin sensitivity (to levels generally observed in normal-weight subjects) may be seen with RYGBP, even when the BMI fails to return to normal values in the postoperative follow-up and the patient remains obese [11, 14]. These data strongly suggest that RYGBP has effects independent of weight loss on insulin sensitivity.

Less clear-cut results have been obtained for insulin secretion. Most teams have shown that insulin secretion in insulin-resistant obese patients decreases in proportion to the increase in insulin sensitivity [15]. Thus, fasting HOMA rapidly normalizes after gastric bypass [15]. In contrast, restoration of insulin secretion—in terms of both its physiological levels for each phase and its pulsatility—during caloric challenge is much more unusual [16, 17]. However, these data remain controversial, as the groups of patients studied were not homogeneous and many confounding factors were present, including: duration of diabetes (and, thus, the extent of impaired insulin secretion); differences in techniques used to study insulin secretion (hyperglycaemia induced in oral challenge or a calibrated test meal); absence of an early peak of insulin secretion; variable duration of postoperative follow-up; and not taking into account the medium-term weight loss. Obese hyperinsulinaemic patients display adaptation towards lower levels of insulin secretion. In contrast, in a population of type 2 diabetes patients with low levels of insulin production (a population rarely described in published studies), stimulation of secretion of incretins such as glucagon-like peptide-1 (GLP-1) during meals after bypass surgery might play a major role in controlling postprandial glycaemia (see below). It is currently thought that improvement in insulin sensitivity, at least in the short term, is the cornerstone of the early metabolic effects of RYGBP in all patients, including those with type 2 diabetes [18]. In the longer term, insulin secretion appears to adapt itself to weight loss, as the vast majority of obese type 2 diabetic patients are insulin-resistant and hyperinsulinaemic prior to surgery.

7. How does RYGBP specifically improve insulin sensitivity?

The mechanisms by which RYGBP rapidly increases insulin sensitivity remain unclear. One of the first mechanisms to be considered was strict calorie restriction. Indeed, in the first few weeks after RYGBP, caloric restriction is especially severe (< 500 kcal/d on average). High-protein diets that are low in calories have been shown to have favourable effects in the short term in patients with type 2 diabetes [19]. However, post-bypass restrictions involve a diet particularly low in protein, leading to a risk of protein malnutrition after RYGBP. In contrast to typical high-protein diets, the food restrictions following gastric bypass are severe and known to induce a decrease in insulin sensitivity in obese subjects [20]. Thus, food restriction itself cannot account for the early metabolic effects of bariatric surgery.

Ghrelin, an orexigenic hormone secreted by the stomach, is increased before meals and decreased after meals [21]. Cummings et al. [22] were the first to show that ghrelin secretion collapses after RYGBP, which led them to suggest that the decrease in ghrelin might account for the substantial decrease in appetite observed after the surgical procedure. However, other teams have reported different results, with no change in the concentrations of active ghrelin in the bloodstream. These variable results may be accounted for by the recent finding that a number of different circulating forms of ghrelin are present, and the active form (octanoyl) was not measured by the older test kits. Thus, the role of ghrelin as a satiety factor after RYGBP surgery remains a matter of debate [23, 24].

The same is true of the possible effects of ghrelin on insulin sensitivity. Several studies have suggested that ghrelin may modify insulin sensitivity, establishing a link between digestive hormone signalling and insulin susceptibility [25, 26]. However, these studies were based on statistical correlations (serum ghrelin concentration is inversely proportional to the degree of insulin resistance) and, thus, do not provide sufficient proof. For this reason, the role of ghrelin as a direct regulator of insulin sensitivity remains entirely hypothetical at this time.

Another possible mechanism is a change in the profile of adipocytokine secretion with RYGBP. These hormones are secreted by the adipose tissues involved in various types of physiological regulation, including insulin sensitivity [27] and, possibly, cardiovascular risk [28]. Some of these molecules (such as visfatin and leptin) are secreted in excess in the obese, while others (such as adiponectin) are produced in smaller amounts in patients with insulin resistance than in normal-weight subjects [29]. Adipose tissue (particularly of the viscer) is also the site of synthesis of inflammatory factors such as interleukin (IL)-6 and tumour necrosis factor (TNF)-α, which alter insulin sensitivity [30]. Following RYGBP, the secretion profiles of these factors change. RYGBP decreases circulating concentrations of visfatin, leptin, TNF-α, IL-6 and C-reactive protein (CRP), while increasing adiponectin and improving insulin sensitivity [12, 31]. Furthermore, it has been shown that macrophage infiltration of human adipose tissue (reflecting inflammation) decreases after RYGBP [32, 33].

These perfectly coordinated elements may be involved in the improvement in metabolic status observed after RYGBP. However, their contribution to the early metabolic effects of RYGBP remains unclear. Indeed, it could be argued that such effects are not specific to RYGBP, as such changes are also observed with gastroplasty [34] and lifestyle (diet and physical activity) modifications [35]. For this reason, changes in adipocytokine profiles are currently interpreted as additional effects in the long term and as dependent on weight loss rather than a specific effect of RYGBP.

One recently described mechanism involves a decrease in tissue lipotoxicity as a key factor in the metabolic effects of
RYGBP: Triglycerides stored outside of adipocytes (also known as ‘ectopic lipids’) are particularly damaging to the insulin-signalling pathway [36]. Insulin resistance in the muscle and liver has been shown to be strongly correlated with triglyceride storage in these two tissues [37]. The excess lipid within cells leads to intracellular accumulation of diacylglycerol, which activates certain isoforms of protein kinase-C (PKC) that, in turn, phosphorylate serine residues in insulin receptor substrate (IRS)-1. This type of phosphorylation is known to decrease intracellular insulin signalling [38].

Many experimental studies have shown that ectopic lipid depletion from tissues increases the sensitivity of those tissues to insulin, highlighting the importance of lipotoxicity in the pathophysiology of insulin resistance [39]. Yet, are such mechanisms observed in bariatric surgery? The team of Ferrannini investigated this in insulin-resistant obese patients by studying insulin sensitivity and changes in intramuscular triglyceride content (muscle biopsies) following RYGBP (with determinations made just before, and six months after, surgery) and a low-calorie diet [40]. They found that RYGBP, by inducing poor digestive absorption of fats, led to rapid normalization of triglyceridaemia and of circulating fatty-acid concentrations, considered high before surgery. The decrease in circulating fatty acids may limit glucose–lipid competition and increase insulin sensitivity [40]. The study also showed that RYGBP can trigger the complete elimination of ectopic lipids from muscle tissue. The insulin sensitivity of these patients (determined by euglycaemic–hyperinsulinaemic clamp) was also normalized, even though the patients remained obese (mean BMI fell from 51 kg/m$^2$ to 39 kg/m$^2$). These beneficial effects of RYGBP were correlated with reductions in waist circumference and in excess abdominal visceral adipose tissue. Such effects were not seen, however, in obese patients following an intense diet and physical-activity programme whose mean BMI fell from 51 kg/m$^2$ to 48 kg/m$^2$.

Similar conclusions were made in a recent non-invasive nuclear magnetic resonance (NMR) spectroscopy analysis of changes in intramuscular triglyceride concentrations in a cohort of patients undergoing BPD surgery [41]. These studies found that malabsorption-based techniques have a specific effect on ectopic lipids and their role in the regulation of insulin resistance. Further evidence of this was revealed by the lack of effect of liposuction of subcutaneous adipose tissue on metabolic parameters despite considerable weight loss [42]. The near-disappearance of tissue lipotoxicity particularly in muscle and of hepatic steatosis plays a key role in the specific mechanisms of RYGBP, even before BMI normalization.

Recent studies have shown that the intestine itself probably plays an important role in the metabolic effects of RYGBP. Indeed, the intestine secretes incretins such as GLP-1, which has been studied in detail in investigations of the effects of RYGBP. GLP-1 is secreted by the L cells of the ileum and has many physiological (including increasing insulin secretion) and central effects, through which it improves insulin sensitivity and hepatic glucose production [43]. GLP-1 secretion is stimulated during the digestive absorption of glucose, fructose, certain peptides and free fatty acids. GLP-1 also restores the early phase of insulin secretion in patients with type 2 diabetes and has beneficial effects on pancreatic beta-cell mass [44]. GLP-1 secretion is reduced by type 2 diabetes [45] and by low-calorie diets [46]. RYGBP excludes the duodenum and jejunum from the alimentary circuit, and brings the ileum and stomach closer together, thereby increasing GLP-1 secretion [47-49].

Thus, RYGBP may improve carbohydrate metabolism by acting on both insulin secretion and insulin sensitivity. This effect is observed immediately after surgery and may account for the early metabolic effects of RYGBP [50]. However, the increase in GLP-1 secretion is only observed during meals and lasts for less than an hour, whereas GLP-1 concentrations between meals are low due to tight caloric restriction (F. Andréelli, personal data; and reference 47). As most patients have only two meals a day during the first 6 weeks after surgery, the increase in GLP-1 levels during the day is only transient. This situation is therefore different from the therapeutic effects of GLP-1 analogues, with which high plasma GLP-1 concentrations can be obtained around the clock [44]. The transient increase in GLP-1 concentration observed after a gastric bypass may, however, be of major importance in the short term for stimulating insulin secretion during meals and avoiding an increase in postprandial glycaemia. In the longer term, it may also be important for preservation (or even restoration) of the pancreatic beta-cell mass.

Nevertheless, no evidence has yet been obtained to either confirm or reject these hypotheses. Other incretins have been implicated in the early metabolic effects of RYGBP, including peptide YY (PYY) and pancreatic polypeptide (PP), which belong to the same family as neuropeptide Y (NPY). PYY is widely distributed throughout the entire length of the digestive tract and is co-localized with GLP-1, and secreted during meals, particularly if the meal is rich in lipids. It has a satiety-generating effect, induced via the Y2 receptors expressed in the hypothalamus. The principal peripheral action of PYY is to reduce lipolysis. By decreasing circulating fatty-acid concentrations, PYY increases insulin sensitivity. Plasma PYY concentration is low in obese subjects and increases considerably after RYGBP [51, 52].

8. Perspectives for future research

The results presented above suggest interesting avenues of research into the mechanisms of metabolic change observed shortly after RYGBP. These factors probably act simultaneously to different extents to restore insulin sensitivity soon after surgery. Although other mechanisms have also been proposed, they have yet to be investigated in humans. Nevertheless, excluding the duodenum and jejunum may play a crucial metabolic role through other hormonal mechanisms. In Goto-Kakizaki rats, a model of type 2 diabetes, glucose intolerance is improved by surgical exclusion of the proximal intestine and deteriorates again when the proximal intestine...
is reconnected to the rest of the digestive circuit [53]; and the effect is independent of weight. The mechanisms involved remain unclear, but suggest that this type of surgery has intrinsic properties that make it a useful therapeutic tool in itself. However, we cannot exclude the possibility that some of the effects are linked to changes in vagal tone in the excluded part of the intestine. The digestive tract is among the most innervated organs of the body [54], and the electrical activity of the digestive afferents of the vagal nerve is known to be affected by the type of nutrients ingested, even before their effective absorption [55, 56]. By way of such detection before absorption by enterocytes, the afferents of the vagal nerve can modify both insulin sensitivity and hepatic glucose production before any changes in circulating insulin and glucose concentrations occur [57, 58]. Thus, major changes in the intestinal circuit due to bypass surgery can modify the neuronal physiology of the digestive tract, leading to changes in carbohydrate homeostasis.

The intestinal microflora also appear to have an important role in weight homeostasis. The bacterial microflora in human stools belong principally to two families: Bacteroidetes and Firmicutes. These two families predominate in the human intestine, accounting for more than 90% of the gut microflora. In the stools of obese subjects before calorie restriction, bacteria of the Firmicutes family account for a greater proportion than in normal-weight subjects [59, 60]. However, during calorie restriction leading to weight loss—and regardless of the type of diet—the abundance of Bacteroidetes increases in the stools of obese subjects while that of Firmicutes decreases significantly to proportions similar to those observed in subjects of normal weight. Changes in the relative proportions of these two bacterial populations in the obese population induced by changes in diet are correlated with the percentage of weight loss, but not with changes in the calorie contents of the diet. This demonstrates that the intestinal microflora species are determined by what we eat and that simple dietary changes in the obese can restore the microflora to those generally found in the normal-weighted. Similar results (increased Firmicutes-to-Bacteroidetes ratio) have been reported for obese ob/ob mice [61]. The genome of the Firmicutes family of bacteria contains genes encoding enzymes not present in mammals that increase the absorptive capacity of the digestive tract, thereby accounting for weight gain. If the microflora of obese ob/ob mice are transplanted by gavage into mice with no intestinal microflora (germ-free C57B16 mice), an increase in fat mass is observed in the latter mice with no increase in food intake. In contrast, germ-free mice receiving the (Bacteroidetes-predominant) microflora of thin mice display no significant weight gain. This underscores the importance of the intestinal microflora, at least in rodents, in regulating weight and fat mass. Changes in the intestinal microflora induced by gastric bypass remain unknown.

Endogenous glucose production (EGP) is a crucial physiological function in the regulation of glycemia. It maintains glycemia at a sufficiently high level under fasting conditions, whereas its inhibition in postprandial periods limits increases in glycemia due to glucose intake [62]. The key enzyme in EGP is glucose-6-phosphatase (Glc6Pase), which catalyzes the final step in the process: hydrolysis of glucose-6-phosphate to glucose. Until the mid-1990s, based on determinations of enzyme activity, this enzyme was thought to be active only in the liver and kidneys, which were therefore thought to be the only organs capable of EGP. Real-time PCR experiments, however, showed that the small intestines of rats and humans also produced Glc6Pase [63]. There is a decreasing gradient of Glc6Pase gene expression from the duodenum to the distal jejunum in rats, whereas the gene is expressed all the way through to the ileum in humans [64].

Highly efficient nutritional regulation (not all hormonal) has now been demonstrated to occur in the small intestine. Expression of the Glc6Pase gene in the intestine, as in the liver, is controlled by insulin, leading to its expression being strongly induced by hypoinsulinism such as under fasting conditions and in diabetic patients with low insulin levels. An approach combining the ratio of arterial and venous glycemia (to estimate the net result of glucose production and use) with the dilution of a tritiated tracer (to estimate glucose use) has shown that intestinal glucose production is induced after 24 h of fasting and, in rats, accounts for around 20% of EGP after 48 h of fasting and about 33% of EGP after 72 h of fasting [65]. Glucose enrichment of portal blood may also modify hepatic glucose production and insulin sensitivity in peripheral tissues [66]. Thus, stimulation of intestinal gluconeogenesis may be a major mechanism underlying regulation of insulin sensitivity, particularly under conditions such as fasting.

Mithieux et al. [67] have also shown that induction of intestinal gluconeogenesis in rats by protein intake, and the resulting increase in glucose release into the portal blood, was sufficient to modify activity in hypothalamic regions via a vagal reflex arc, thereby decreasing food intake. Gluconeogenesis in the intestine may be rapidly induced after gastric bypass, accounting for both satiety and the improvement in carbohydrate metabolism seen after surgery. To address this issue, food intake and glucose homeostasis were monitored in mouse models of gastric bypass [gastroentero-anastomosis (GEA), a model of gastric bypass without size reduction of the stomach] and gastric lap-band (GLB) [68]. Despite a full-sized stomach, GEA mice decreased their food intake for some time by about 70% compared with their food intake before surgery, while food intake was reduced for only 5 days in GLB mice. GEA mice partially recovered GLP-1 secretion in response to oral glucose. This suggests the importance of a possible role of GLP-1 in decreasing food intake, which was addressed in a study of mice infused with exendin-(9-39), a potent GLP-1 antagonist. In fact, the GEA mice treated with exendin-(9-39) continued to exhibit markedly decreased food intakes, ruling out GLP-1 as a possible key factor in the suppression of food intake induced by GEA. It was further observed that marked induction of the expression of both Glc6Pase and PEPCK (phosphoenolpyruvate carboxykinase) enzymes occurred in the distal jejunum and ileum only in GEA mice, and not the GLB mice. This translated to glucose
release into the portal blood during the postabsorptive period, as observed in protein-fed rats [67]. The contribution of hepatoportal sensing to the decreased food intake of GEA mice was determined by deafferentiation of the portal vein in mice performed at the time of surgery. The mice recovered their normal food intake within days. In addition, GEA had no effect on food intake in Glut2-null mice, which are devoid of portal glucose-sensing capacity [68]. This confirmed the causal role of intestinal gluconeogenesis in the decreased food intake seen in GEA mice.

In addition, Troy et al. [68] have also addressed the question of the rapid recovery of insulin sensitivity after the gastric bypass procedure. Interestingly, GEA mice recovered quasi-normal insulin sensitivity within 10 days of surgery, as observed in humans. However, improvement of glucose homoeostasis was not cancelled in GEA mice infused with exendin-(9-39), thus ruling out GLP-1 as a key factor in the phenomenon. Furthermore, euglycaemic– hyperinsulinaemic clamp experiments showed that the metabolic improvement observed in GEA mice probably occurred in the liver, as hepatic Glc6Pase activity was diminished in GEA mice, but not in Glb or sham-operated mice. As observed with changes in food intake, no improvement was found in Glut2-null mice or in mice in which the portal vein was deafferentiated at the time of surgery. This strongly suggests that intestinal gluconeogenesis was a causal factor in the rapid and dramatic amelioration of insulin sensitivity specific to ‘bypass’ surgery [68].

9. Conclusion

It is now widely accepted that RYGBP yields a much greater improvement in carbohydrate homoeostasis than does treatment with a gastric band, and that the phenomenon is at least partly independent of weight loss. Calorie restriction alone cannot account for the metabolic effects of the surgery. However, the mechanisms involved are complex, and lead to improvement in insulin sensitivity rather than increases in insulin secretion (although changes in GLP-1 secretion following RYGBP have raised questions as to the use of this surgery to restore long-term insulin secretion in type 2 diabetes patients). A decrease in lipotoxicity (in both skeletal muscle and the liver) plays an important role and accounts for the beneficial effects of RYGBP observed before BMI normalization. A decrease in adipose tissue inöammation also contributes to the improvement in glycaemic equilibrium in the longer term. Other mechanisms that include changes in the activity of digestive vagal afferents, changes in the intestinal microöora and stimulation of intestinal gluconeogenesis may also be involved. However, these mechanisms require more detailed study in the context of gastric bypass, although it is likely that the intestine (particularly the duodenojejunal segment) plays an important role in regulating insulin sensitivity. This possibility raises questions concerning the possible role of the intestine in the pathophysiology of type 2 diabetes.

Conflicts of interests

The authors have reported no conöict of interests.

References


[26] Purnell JQ, Weigle DS, Breen P, Cummings DE. Ghrelin levels correlate with insulin levels, insulin resistance, and high-density lipoprotein cholesterol, but not with gender, menopausal status, or cortisol levels in humans. J Clin Endocrinol Metab 2003;88:5747-52.


[52] Chan JL, Mun EC, Stoynova V, Mantzoros CS, Goldfine AB. Peptide YY levels are elevated after gastric bypass surgery. Obesity (Silver Spring) 2006;14:194-8.


[54] Furness JB. The organisation of the autonomic nervous system: peripheral connections. Auton Neurosci 2006;130:1-5.


