Is there a place for bariatric surgery in diabetes treatment?

A symposium organized by SFD – ALFEDIAM (Société Francophone du Diabète), SOFFCO (Société Française et Francophone de Chirurgie de l’Obésité), and AFERO (Association Française d’Etude et de Recherche sur l’Obésité).

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Editorial

Time for diabetes surgery is it coming?

J. Bringer

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The theme of this program of the French-speaking Society of Diabetology (SFD) was outlined by Fabrizio Andreelli, François Pattou and myself. We wish to thank all the expert participants from France as well as other countries who have contributed to our presentations covering the most recent basic and clinical data on this innovative surgical treatment of diabetes.

Not a single diabetologist, some 15 years ago, surgical procedure has thought that an operation could be the most effective therapy for type 2 diabetes. Focusing only on HbA1c targets blinded us to the fact that an obese patient who becomes diabetic stays obese, and develops specific diabetes-related morbidities. Moreover, many patients aiming to achieve tight glycaemic control have paid 'tribute' in terms of weight increase, with all of its potentially deleterious consequences on cardiovascular risk, respiratory disorders such as a sleep apnoea and overall quality of life.

Bariatric surgery has become a potent therapeutic modality for the treatment of type 2 diabetes in obese patients because it appears able to achieve the main targets of preventing diabetic complications and improving the health impact of morbid obesity. Outcomes after surgically induced weight loss published over the past few years have been impressive. Meta-analysis show that diabetes was resolved (70%) or improved in more than 80% of patients, hyperlipidaemia improved in more than 70% of patients and hypertension was resolved in 60%, whereas sleep apnoea was improved in 80%. Among the surgically treated obese patients in the Swedish Obese Subjects (SOS) study, the benefits from the reduction of myocardial infarction and overall mortality over 10 years were almost exclusively seen in diabetic patients.

Loss of abdominal–visceral adiposity induced by surgery reduced insulin resistance and other relevant markers of chronic vascular inflammation, and improved endothelial dysfunction, and other key cardiac and atherothrombotic risk factors.

However, there is still considerable debate over the choice of operative procedure, optimal appropriate time for surgery, duration of effects, mechanisms behind the antidiabetic effects and the protective action on β cells. Some types of bariatric surgical procedures have proved not only effective for treating obesity, but also appear to be associated with endocrine changes that, independently of weight loss, give rise to remission or improvement of type 2 diabetes. The re-routing of nutrients observed in bypass surgery of the duodenum and proximal jejunum brings about significant endocrine changes (such as increased GLP-1 secretion) in the gastrointestinal system that also contribute to the glucose-lowering effects of these operations. In addition, new information from animal models and clinical research has led to a better understanding of the role of various intestinal signals in the antidiabetic effects of bariatric surgery.

Nevertheless, the risks that come with bariatric surgery need to be weighed in each prospective patient, and require the involvement of a multidisciplinary team that is experienced in patient selection, education, the operation and lifelong surveillance.

We wish to thank Novo Nordisk, which has provided the financial support that made this meeting possible. Our grateful thanks also go to Pierre-Jean Guillausseau (Editor in Chief of Diabetes & Metabolism) and Catherine Cottenceau, the SFD secretary, for their invaluable support of the organizers.
What can bariatric surgery teach us about the pathophysiology of type 2 diabetes?

F. Andreelli a,b,*, C. Amouyal a, C. Magnan c,d, G. Mithieux c,f,g,h

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.

Keywords: Bariatric surgery; Glycaemia; insulin resistance; Lipotoxicity; Intestinal neoglucogenesis; Review

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 bilo-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 prêcoce de l’homéostasie glucidique après by-pass gastrique est secondaire à une

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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 la 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 clef de la régulation de l’équilibre glycémique et pourrait même participer à la physiopathologie du diabète de type 2.

Mots clés : Chirurgie bariatrique ; Glycémie ; Insulinorésistance ; Lipotoxicité ; Néoglucogenèse intestinale ; Revue générale

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) and morbid obesity (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 viscera) 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
GLP-1 secretion is central to the early metabolic effects of RYGBP, even before BMI normalization. The intestine secretes incretins such as GLP-1, which has a crucial metabolic role through other hormonal mechanisms. Nevertheless, excluding the duodenum and jejunum may play a 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 glycaemia. It maintains glycaemia at a sufficiently high level under fasting conditions, whereas its inhibition in postprandial periods limits increases in glycaemia 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 glycaemia (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 deafferentation 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 homeostasis 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 homeostasis 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 inflammation 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 microflora 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 conflict of interests.

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The effect of bariatric surgery on gut hormones that alter appetite

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Abstract

Bariatric surgery is the only effective treatment for morbid obesity in the long term. Gut hormones are key players in the metabolic mechanisms causing obesity. Furthermore gut hormones are involved in the signalling process of hunger and satiety which leads to the control of nutrient intake. In this review, the role of these hormones as facilitators of appetite control after bariatric and metabolic surgery will be explored.

Keywords: Bariatric surgery; Gut hormones; Appetite; Review

1. Introduction

Surgical procedures are currently the most effective therapy for long-term weight loss [1]. Furthermore, some of these operations lead to the rapid remission of type 2 diabetes in a weight loss independent manner [2]. The mechanism that leads to sustained weight loss as well as diabetes remission after bariatric operations remains to be fully elucidated.

Gut hormones cause hunger and satiety effects. Therefore they play an integral role in the appetite-signalling process and are key element of the gut-brain axis. They have been implicated to play an important role in the successful outcomes after gastric bypass surgery [3]. It is becoming evident that bariatric procedures modulate the gut-brain axis by altering the anatomy of the gut and affecting gut hormones [3]. In fact some of these procedures are now considered suitable models for the study of the gut brain axis.

Bariatric procedures were designed to promote weight loss due to the reduction of stomach volume (laparoscopic adjustable gastric banding, laparoscopic sleeve gastrectomy, malabsorption of nutrients (biliopancreatic diversion, duodenal switch) or a combination of both (Roux-en-Y gastric bypass). Although there is no evidence of calorie malabsorption, (with the exception of the biliopancreatic diversion and duodenal
switch), the effects of bariatric procedures cannot be fully attributed to the reduced gastric volume. A number of studies have shown that changes in gut hormones after bariatric and metabolic surgery may be responsible for the appetite control and the resulting weight loss experienced post-operatively [4]. We review the most important peptides in terms of appetite control after bariatric and metabolic procedures: peptide YY (PYY), glucagon-like peptide-1 (GLP-1), ghrelin and cholecystokinin (CCK).

2. Peptide YY

Peptide YY is a 36-amino-acid peptide, member of the PP-fold peptide family. Y is the abbreviation for tyrosine. It is released postprandially by endocrine L-cells of the gut in response to the calories ingested, however it is not affected by gastric distension [5,6]. Although PYY is present in the whole length of the intestinal, the concentration gets higher distally [5]. PYY inhibits gastrointestinal mobility and the gastric, pancreatic and intestinal secretion [7,8]. It induces satiety and reduces nutrient intake in both the obese and the non-obese, however obese individuals appear to have a PYY deficiency that could affect satiety signals and could thus reinforce obesity [9-11].

An exaggerated postprandial PYY response after gastric bypass has been demonstrated [12]. This may contribute to the initial weight loss as well as the sustained long-term maintenance of this weight loss [12]. Another study of a human model of gastric bypass and a rodent model of jejuno-intestinal bypass showed increased PYY levels postprandially associated with increased satiety [13]. In a mechanistic investigation using the animal model an additional to the food intake effect of gastric bypass on weight loss was shown, suggesting that enhanced energy expenditure may play a role [13]. A recent prospective study of patients undergoing gastric bypass confirmed an increased postprandial PYY compared to patients undergoing gastric banding [14]. This finding suggested that differences in levels of gut hormones may play a role in promoting greater weight loss with gastric bypass compared to gastric banding [14].

Recently, we demonstrated a causative relationship between the enhanced PYY and GLP-1 response and the increased satiety following gastric bypass [15]. In this study increased postprandial PYY and GLP-1 responses were detected as early as the first week after gastric bypass, before any significant weight loss has occurred [15]. In the second part of this study good and poor responders to gastric bypass in terms of weight loss were investigated. Lower PYY and GLP-1 postprandial responses were associated with inferior weight loss [15]. Finally a comparative study of patients after gastric bypass and gastric banding was performed using a randomised double-blind saline controlled design [15]. Blockade of the gut hormone response with the somatostatin analogue octeotride increased nutrient intake and reduced satiety in the gastric bypass group, but not in the gastric banding group [15]. This finding supports the hypothesis that the enhanced gut hormone response might play a key role in the reduced food intake after gastric bypass [15]. The longer term effect of this procedure on appetite and PYY was investigated in another study, in which the enhanced response as well as the reduced appetite was sustained for 24 months postoperatively [16].

Comparative studies of patients after gastric banding and gastric bypass showed a reduced PYY response in the gastric banding group on a number of occasions [13,14,17]. A prospective study of patients undergoing vertical banded gastroplasty compared to non-obese controls demonstrated a significantly lower PYY in the preoperative, obese group [18]. Following vertical banded gastroplasty, PYY gradually increased to the control levels [18].

In a comparative study of laparoscopic sleeve gastrectomy and gastric bypass using a randomised, double-blind design, both fasting and postprandial PYY levels, were increased similarly postoperatively [19]. The markedly reduced ghrelin levels in addition to increased PYY levels after sleeve gastrectomy are associated with greater appetite suppression and excess weight loss compared with gastric bypass [19]. The authors hypothesised that the reduced ghrelin after sleeve gastrectomy has an additive to the PYY response on appetite control [19]. An animal study supports this hypothesis by demonstrating that ghrelin attenuates the inhibitory effect of PYY and GLP-1 on food intake and gastric emptying in a dose-dependent manner [20]. However the long term effects of sleeve gastrectomy remain to be elucidated.

3. Glucagon-like peptide-1 (GLP-1)

GLP-1 is released postprandially by endocrine L-cells of the gut [21]. The inhibitory effect of GLP-1 and PYY on food intake is additive [22]. Furthermore sustained GLP-1 receptor activation is associated with weight loss in both preclinical and clinical studies [23].

As in the case of PYY the postprandial GLP-1 response is enhanced after gastric bypass, but not after gastric banding [13,15]. Both fasting and postprandial levels of GLP-1 remain elevated even 20 years after jejuno-ileal bypass [24].

GLP-1 plays an important role in glucose metabolism in addition to the effect on appetite control. It is a potent incretin. GLP-1 enhances the insulin response to nutrients, delays gastric emptying and inhibits the glucagon response in a glucose-dependent manner [23].

4. Ghrelin

Ghrelin is a 28-amino acid peptide produced from the fundus of the stomach and the upper intestine [25,26]. Central and peripheral administration increases energy intake and remains the only known orexigenic gut peptide known to date [27,28]. Ghrelin increases prior to meals and is suppressed rapidly by food intake proportionally to the amount of calories...
ingested, therefore suggesting a possible role in meal initiation [29,30]. The 24-hour profile of ghrelin increases following diet-induced weight loss [31]. Furthermore obese individuals have lower fasting ghrelin levels, and reduced postprandial ghrelin suppression compared to non-obese individuals [32].

Cummings et al showed a profound suppression of the 24-hour profile of ghrelin following gastric bypass [31]. Since this landmark study the findings of other studies have been conflicting. Studies demonstrated a decrease in fasting and postprandial ghrelin [33-40], no change in fasting and postprandial ghrelin [12-15,19,41-46] and an increase in fasting ghrelin after gastric bypass [47-51]. The reason for this heterogeneity remains to be elucidated. One possible explanation is that even in the studies which showed increased fasting ghrelin, it does not reach the levels reported with diet-induced weight loss or controls [12]. In a study which investigated the intraoperative changes in ghrelin during a gastric bypass procedure, the complete division of the stomach and the formation of the vertical pouch, was associated with the decline in the perioperational ghrelin [37]. We have previously demonstrated that an intact vagus nerve is required for ghrelin to have an appetite effect as shown in a study including vagotomised patients [52]. Differences in the technical aspects of the operations may affect the function or the preservation of the vagus nerve, which in turn could alter the ghrelin effect. Reversible vagal nerve dysfunction caused intraoperatively might play a role, as shown by a study which showed decreased ghrelin levels on the postoperative day 1 after gastric bypass, followed by increased preoperative levels at 1 month [49]. Porries suggested that the different configuration of the pouch might explain the inconsistency in the available results regarding the ghrelin response after gastric bypass [53]. Using a vertical pouch, ghrelin producing cells are more likely to be excluded, compared to a horizontal pouch [53]. Hyperinsulinaemia and insulin resistance are associated with ghrelin suppression in obese individuals [54]. Therefore an alternative hypothesis is that the preoperative differences as well as insulin sensitivity in the postoperative improvement of glycemic control might be the cause for the different results reported.

A study on patients prior to and 5 days and 2 months after bilipancreatic diversion showed a similar response with an initial reduction in fasting ghrelin, followed by a return to the preoperative levels when food consumption resumed to almost preoperative levels [55]. This finding supports the hypothesis that although the primary source of ghrelin is the gastric mucosa, exposure of the small bowel to food is sufficient for ghrelin suppression in humans [56]. Furthermore exposure of the stomach to food is not a prerequisite for suppression [56].

Weight loss following gastric banding is independent of circulating plasma ghrelin as evidenced by an increase in fasting ghrelin accompanied by a paradoxical decrease in hunger [57]. Studies of the ghrelin response after restrictive procedures (gastric banding and vertically banded gastroplasty) demonstrated increased basal ghrelin [58] and a blunted postprandial suppression of ghrelin [14,36].

The role of ghrelin in the effects of bariatric and metabolic surgery has not been fully characterised. So far there has been an inconsistency in the available data. However there is no doubt that has played an integral role in the in the development of the concept of metabolic surgery by bringing interest on gut hormones and changes of them following metabolic surgery.

5. Cholecystokinin (CCK)

CCK induces postprandial satiety [59]. No changes in the CCK response to a meal have been detected after bariatric surgery [60,61]. However in a different, prospective study patients undergoing vertically-banded gastroplasty were investigated. The postprandial peak CCK was significantly higher postoperatively compared to preoperatively, suggesting a possible role for CCK in the appetite control following restrictive procedures [61].

6. Conclusion

Bariatric and metabolic surgery leads to successful weight loss. This is achieved with successful appetite control. These surgical procedures affect gut hormones and modify the gut brain-axis, altering satiety signals. In fact the mode of action of some of these operations is associated with gut hormone pathways.

Conflicts of interests

The authors have reported no conflict of interests.

References


Effect of gastric bypass surgery on the incretins

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Abstract

Aims. Our studies were designed to understand the role of the gut hormones incretins GLP-1 and GIP on diabetes remission after gastric bypass surgery (GBP).

Methods. Morbidly obese patients with type 2 diabetes (T2DM) were studied before and 1, 6, 12, 24 and 36 months after GBP. A matched group of patients were studied before and after a diet-induced 10 kg weight loss, equivalent to the weight loss 1 month after GBP. All patients underwent an oral glucose tolerance test and an isoglycaemic glucose intravenous challenge to measure the incretin effect.

Results. Post-prandial GLP-1 and GIP levels increase after GBP and the incretin effect on insulin secretion normalizes to the level of non diabetic controls. In addition, the pattern of insulin secretion in response to oral glucose changes after GBP, with recovery of the early phase, and post-prandial glucose levels decrease significantly. These changes were not seen after an equivalent weight loss by diet. The changes in incretin levels and effect observed at 1 month are long lasting and persist up to 3 years after the surgery. The improved insulin release and glucose tolerance after GBP were shown by others to be blocked by the administration of a GLP-1 antagonist in rodents, demonstrating that these metabolic changes are, in part, GLP-1 dependent.

Conclusion. Although sustained and significant weight loss is likely to be the key mediator of diabetes remission after GBP, the changes of incretins improve the early phase of insulin secretion and post-prandial glucose levels, and contribute to the better glucose tolerance.

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Keywords: GLP-1; GIP; Incretin effect; Diabetes; Gastric bypass; Review

Résumé

Effet de la chirurgie bypass sur les incrétines

Objectifs. Les études que nous avons menées avaient pour but de comprendre le rôle des incrétines GLP-1 et GIP dans la rémission du diabète après chirurgie bariatrique (GBP).

Méthodes. Des patients atteints d’obésité morbide et de diabète de type 2 (DT2) ont été étudiés avant puis 1, 6, 12, 24, 26 mois après GBP. Un groupe de patients comparables a été étudié avant et après un régime alimentaire, après une perte de poids de 10 kg équivalente à celle observée 1 mois après GBP. Chez tous les participants a été réalisé un test d’hypoglycémie provoquée par voie orale (HGPO) suivi par un test intraveineux isoglycémique pour évaluer l’effet incrétine.

Résultats. Les concentrations plasmatiques post-prandiales d’incrétines étaient plus élevées après bypass, avec normalisation de l’effet incrétine sur l’insulinosécrétion. De plus, la courbe de sécrétion d’insuline se normalisait après bypass avec restauration de la phase rapide, et diminution de la glycémie post-prandiale. Ces modifications n’ont pas été observées après une perte de poids équivalente obtenue grâce au régime alimentaire. L’augmentation des concentrations plasmatiques d’incrétines et de leur effet sur l’insulinosécrétion, observée 1 mois après chirurgie bypass persiste jusqu’à 3 ans après chirurgie. D’autres auteurs ont montré que l’amélioration de l’insulinosécrétion et de la tolérance au glucose après bypass était bloquée par l’administration d’un antagoniste de la GLP-1 chez le rat, preuve que ces modifications métaboliques dépendent, en partie, du GLP-1.

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Conclusion. Bien que la perte de poids massive et durable joue probablement un rôle essentiel dans la rémission du diabète après bypass, les modifications des incrétines améliorent la phase rapide de l’insulinosécretion, diminuent la glycémie post-prandiale et contribuent à l’équilibre glycémique.

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Mots clés : GLP-1 ; GIP ; Effet incrétine ; Diabète ; Chirurgie bariatrique ; Revue générale

1. Introduction

One of the major benefits of surgical weight loss is the resolution of type 2 diabetes (T2DM) in 50-80% of cases [1,2]. The rapidity of the onset and the magnitude of the effect of gastric bypass surgery on diabetes remain largely unexplained.

Some determinants of impaired insulin secretion in T2DM, such as glucose or lipid toxicity [3,4], likely improve as a result of weight loss per se. In contrast, the change of the gut hormone incretins after GBP [5,6], and their resulting effect on insulin or on glucagon secretion, could be the mediator of the greater improvement of glucose levels after GBP [5,6] compared to diet or to gastric banding.

2. What are the incretins?

Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), secreted respectively from the upper (duodenum K cells) and the lower intestine (ileum L cells) [7-9], are the two incretins responsible for approximately 50% of post-prandial insulin secretion [10-13]. The incretin effect is described as the greater insulin response after oral glucose compared to an equivalent dose of intravenous glucose [11,14]. In addition to its insulotropic effect, GLP-1 delays gastric emptying [15], decreases appetite and promotes weight loss [15,16], inhibits glucagon [17], and improves insulin sensitivity [18]. GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV). The incretin effect on insulin secretion is impaired in patients with T2DM [19]. GLP-1 analogues and DPP-IV inhibitors are currently used as anti-diabetic agents [20].

3. Change of incretins after bypass surgeries for weight loss

Reports of increase incretin levels after bypass surgeries started in the late 1970’s early 1980’s, at a time when no commercial assays were available. GLP-1 consistently increased after jejuno ileal bypass, biliopancreatic diversion or gastric bypass [21-23]. More recent reports, including ours, confirm a significant increase of GLP-1 levels by a factor 5 to 10 after a meal [24] or oral glucose [5] after GBP. The results of bypass surgeries on changes of GIP levels are less consistent with either elevated or decreased levels after the same types of surgery [21,23,25-27]. In morbidly obese patients with T2DM, we reported an increase of GIP levels 1 month after GBP [5]. In addition to the increase post-prandial levels of incretins, we have shown that the incretin effect on insulin secretion, blunted in patients with diabetes, normalized to the levels of non-diabetic controls as early as 1 month after gastric bypass surgery [5]. These patients had diagnosed diabetes for less than 5 years, were well controlled (mean HbA1c 6%) and on minimum therapy. Recent data in Gato-Kakizaki (GK) rats show that the increased GLP-1 secretion and improved glucose tolerance after duodeno jejunal bypass (DBJ), is reversed by the administration of a GLP-1 receptor antagonism. This proof-of-concept study provides direct evidence that improvement of glucose tolerance following a gastric bypass-like surgery is mediated, at least in part, by enhanced GLP-1 action [28].

4. Effect of weight loss versus bypass on incretins

Previous data suggested that a diet-induced weight loss (-18.8 kg) increase the incretin levels in response to a test meal [29]. To address the question of the possible role of weight loss on the change in incretin levels and effect after GBP surgery, we designed a prospective study with a surgical group studied before and 1 month after GBP and a matched diet group studied before and after a diet-induced equivalent weight loss. Our working hypothesis was that the increase in incretin levels and incretin effect would be greater after GBP surgery than after equivalent weight loss by diet.

The inclusion criteria for the surgical group and the diet group were identical: morbidly obese patients with BMI >35kg/m2, with T2DM of less than 5 years duration, not on insulin, thiazolidinedione, exenatide or DPP-IV inhibitor, with HbA1c <8%, age <60 years, of all ethnic background. The GBP group was studied first. Participants in the diet group were recruited afterwards, fit the same inclusion criteria, and were matched for body weight, BMI, age, diabetes control and duration with patients from the surgical group. The diet consisted of meal replacement, about 1000 to 1200 kcal/d, given on weekly outpatient visits. The duration of weight loss was not set but the expectation was that the participants would lose 10 kg of weight in 4 to 8 weeks. The patients were kept on negative energy balance while retested after diet weight loss. The diabetes management during diet included self glucose monitoring by the patients and the adjustment of medications to avoid hypoglycaemia. At baseline and after weight loss, patients were
studied off diabetes medications for 72 hours. The results of these experiments have been published elsewhere [6]. In brief, patients in GBP and diet group lost the same amount of weight (~10 kg). Diabetes medications were discontinued at the time of surgery for all GBP patients, and were decreased or stopped for diet patients, using algorithm based on American Diabetes Association (ADA) criteria of target glucose control. There was a significant and similar decrease of fasting glucose and fasting insulin after diet and after GBP. However, the recovery of the early phase insulin secretion in response to oral glucose and the improvement in incretin levels and effect were observed only after GBP and not after diet. Recent clinical studies of various types of bypass surgeries and/or ileal transposition in humans with BMI less than 35 kg/m² suggest that the diabetes can be improved without weight loss [30]. Data on gut hormones in these patients has not been provided.

5. Long-term changes of incretins

Do the incretin changes observed early after gastric bypass persist overtime? Cross sectional data from Naslund show a persistent increase fasting and post-prandial GLP-1 and GIP levels 20 years after DJB compared to obese non-operated controls [31]. Our own data show persistent increased GLP-1 response to oral glucose and GIP up to 3 years after GBP, after ~30kg weight loss, in patients with diabetes remission and normal incretin effect (Fig. 1). Off notes, the incretin levels and effect, the early phase insulin release during the OGTT and the incretinogenic index all improve rapidly (1 month) after GBP without further change at 6 and 12 months, in spite of continuous weight loss. On the contrary, other variables such as glucose levels improve as a function of weight loss up to one year. This suggests that some changes occur as a result of the surgery, independently of weight loss, while other changes are clearly weight loss related.

Whether the improved post-prandial insulin and glucose levels observed one month after GBP is responsible for the later development of hyperinsulinemic hypoglycaemia with [32,33] or without [34] nesidioblastosis is unknown. Although GLP-1 has been shown to preserve human islet in vitro [35] and prevent beta cell apoptosis in rodents [36] there is no human data to suggest that GLP-1 increases beta cell mass after gastric bypass in humans.

6. Mechanisms of incretin release after gastric bypass (Fig. 2)

As a result of GBP, a small gastric pouch of about 30cc is anastomosed directly to the distal part of the ileum (alimentary limb). The rest of the stomach, including the pylorus, with the duodenum and part of the jejunum is shunted from the nutrients and reattached to the very distal part of the ileum to allow gastrointestinal and pancreatic juice to be excreted (biliopancreatic (BP) limb). Elegant studies in a rat model of diabetes suggest that the exclusion of the upper gut (foregut
hypothesis), rather than weight loss, benefits glucose tolerance [37,38]. Rats after gastrojejunal bypass have better glucose tolerance than sham-operated pair-fed control animals with equivalent body weight [37]. The hindgut hypothesis suggests that the rapid stimulation of the distal ileum by nutrients is responsible for increased GLP-1 and beneficial effect on glucose tolerance, as suggested by studies of ileal transposition in rodents [39-41]. There are few data in humans to support these hypotheses. After GBP, the emptying of the gastric pouch is faster for liquids but delayed for solids [24,42]. The increased GE and intestinal transit time for liquid [24] may result in rapid release of GLP-1 by the distal ileum rapidly in contact with nutrients GLP-1. It is likely that both duodenal exclusion (foregut hypothesis) [43] and the rapid exposure of GLP-1. It is likely that both duodenal exclusion (foregut hypothesis) [43] and the rapid exposure of GLP-1 by the distal ileum rapidly in contact with nutrients GLP-1. It is likely that both duodenal exclusion (foregut hypothesis) [43] and the rapid exposure of nutrients GLP-1 are possible mechanisms that may contribute to incretin levels increase after GBP, but this has not yet been studied in humans.

What is the place of incretins in the remission of type 2 diabetes after gastric bypass surgery? Data show clearly beneficial changes of incretin levels and effect after GBP, resulting in better profile of insulin secretion and decreased post-prandial glucose. However it is likely that weight loss by its magnitude (~40%) and its duration (years) is the major contributor to glucose control after GBP, via mechanisms other than incretins, such as decreased inflammation, decreased liver fat, intramyocellular fat, insulin resistance and changes in adipokines.

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Conflicts of interests

The authors have reported no conflict of interests.

References

[4] Holst JJ, Theodorsson E, et al. Gastrointestinal hormones and gastric emptying beneficial changes of incretin levels and effect after GBP, via mechanisms other than incretins, such as decreased inflammation, decreased liver fat, intramyocellular fat, insulin resistance and changes in adipokines.

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

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Abstract

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

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

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

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

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

Résumé

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

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

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

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

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

1. Introduction

At present, bariatric surgery represents the main option for obtaining substantial and long-term weight loss in morbidly obese (BMI ≥ 40 kg/m²) or obese (BMI ≥ 35 kg/m²) individuals who also have other co-morbidities such as diabetes or arthritis [1].

Interestingly, although bariatric surgery was originally devised to treat obesity, it has also been found to help diabetes [2,3]. In fact, type 2 diabetes is seen to improve or even revert to normal soon after bariatric operations, and well before any significant weight loss has taken place. This observation prompted scientists to investigate the effects of bariatric surgery—now dubbed ‘metabolic surgery’—on diabetic patients with a BMI < 35 kg/m² [4–7].

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

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

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

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

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

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

2. Effect of gastric banding on type 2 diabetes

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

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

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

RYGB is a mostly restrictive operation that reduces gastric volume to about 30 ml, and excludes the duodenum and a portion of the jejunum from food transit by creating a gastrojejunum anastomosis (Fig. 2). In contrast, BPD is mainly a malabsorptive procedure, leaving a gastric remnant of 300–400 ml...
and bypassing a major portion of the small intestine—one, the duodenum, the whole of the jejunum and the proximal ileum (Fig. 3). Thus, BPD is characterized by lipid malabsorption with frank steatorrhoea. The early effects of RYGB and BPD on type 2 diabetes are summarized in Table 1.

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

4. Mechanisms of improvement/reversibility of diabetes

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

Recently, it was shown that gastric bypass can also bring about significant improvement in hepatic insulin sensitivity, most likely through reduced hepatic gluconeogenesis and without affecting peripheral insulin sensitivity [35]. Moreover, gastric bypass promotes intestinal gluconeogenesis and stimulates the hepatoportal glucose sensor via a GLUT2-dependent pathway, while the lack of gluconeogenic response is associated with absence
of the anti-diabetic effects following the operation. This finding suggests that, to some extent at least, intestinal gluconeogenesis is involved in the improvement of glucose homoeostasis after RYGB. Interestingly, RYGB differs from BPD in terms of effects on insulin sensitivity and secretion. While BPD results in rapid improvement of insulin sensitivity, with a consequent reduction of insulin secretion [13,30], RYGB improves diabetes control through increased insulin secretion. Indeed, it has been repeatedly shown that RYGB stimulates gastric inhibitory peptide (GIP) and GLP-1 secretion, with stimulation of insulin secretion as a consequence. Thus, insulin oversecretion together with the quicker absorption of ingested glucose and other carbohydrates could explain the reported postabsorptive episodes of hypoglycaemia. Also, sporadic cases of nesidioblastosis have been reported after RYGB for morbid obesity [36,37]. Nesidioblastosis refers to inappropriate insulin secretion resulting in recurrent severe hypoglycaemia, and is related to hypertrophy and hyperplasia of the islets of Langerhans. Patients who develop nesidioblastosis after RYGB often experience severe hypoglycaemia that, in a few instances, may require total pancreatectomy [37].

### Table 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Source</th>
<th>Subjects (n)</th>
<th>BMI (kg/m²)</th>
<th>Diabetes /IGT</th>
<th>Time since operation</th>
<th>Diabetes improvement/remission/IGT reversal</th>
<th>Type of operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pories WJ et al.</td>
<td>Ann Surg 1987</td>
<td>141</td>
<td>≥40</td>
<td>88/53</td>
<td>10 days</td>
<td>100%</td>
<td>RYGB</td>
</tr>
<tr>
<td>Rubino F et al.</td>
<td>Ann Surg 2004</td>
<td>6</td>
<td>≥40</td>
<td>6</td>
<td>3 weeks</td>
<td>100%</td>
<td>RYGB</td>
</tr>
<tr>
<td>Cohen R et al.</td>
<td>Surg Obes Relat Dis 2006</td>
<td>37</td>
<td>&lt;35</td>
<td>37</td>
<td>6 months</td>
<td>97%</td>
<td>RYGB</td>
</tr>
<tr>
<td>Smith BR et al.</td>
<td>Am Surg 2008</td>
<td>59</td>
<td>≥40</td>
<td>59</td>
<td>1 month</td>
<td>42%</td>
<td>RYGB</td>
</tr>
<tr>
<td>Laferrère B et al.</td>
<td>Diabetes Care 2007</td>
<td>8</td>
<td>&gt;35</td>
<td>8</td>
<td>1 month</td>
<td>100%</td>
<td>RYGB</td>
</tr>
<tr>
<td>Laferrère B et al.</td>
<td>JCEM 2008</td>
<td>9</td>
<td>≥35</td>
<td>9</td>
<td>1 month</td>
<td>100%</td>
<td>RYGB</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>207/53</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mingrone et al.</td>
<td>Diabetologia 1997</td>
<td>7</td>
<td>≥40</td>
<td>7</td>
<td>3 months</td>
<td>100%</td>
<td>BPD</td>
</tr>
<tr>
<td>Mingrone et al.</td>
<td>Diabetes 1999</td>
<td>2</td>
<td>21/20.1</td>
<td>2</td>
<td>3 weeks</td>
<td>100%</td>
<td>BPD</td>
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<tr>
<td>Guidone C et al.</td>
<td>Diabetes 2006</td>
<td>10</td>
<td>≥40</td>
<td>10</td>
<td>1 week–1 month</td>
<td>100%</td>
<td>BPD</td>
</tr>
<tr>
<td>Mari A et al.</td>
<td>Diabetologia 2006</td>
<td>20</td>
<td>≥40</td>
<td>11/9</td>
<td>1 week</td>
<td>100%</td>
<td>BPD</td>
</tr>
<tr>
<td>Scopinaro N et al.</td>
<td>Obes Surg 2008</td>
<td>443</td>
<td>≥40</td>
<td>443</td>
<td>1–2 months</td>
<td>74%</td>
<td>BPD</td>
</tr>
<tr>
<td>Briatore L et al.</td>
<td>Obesity 2008</td>
<td>9</td>
<td>≥40</td>
<td>9</td>
<td>1 month</td>
<td>100%</td>
<td>BPD</td>
</tr>
<tr>
<td>Salinari S et al.</td>
<td>Diabetes Care 2009</td>
<td>9</td>
<td>≥40</td>
<td>9</td>
<td>1 month</td>
<td>100%</td>
<td>BPD</td>
</tr>
<tr>
<td>Chieffini C et al.</td>
<td>Diabetologia 2009</td>
<td>5</td>
<td>&lt;35</td>
<td>5</td>
<td>1 month</td>
<td>100%</td>
<td>BPD</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>496/9</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### 5. Effects of energy restriction on diabetes

One of the most relevant challenges in the study of the pathophysiology of metabolic surgery and, in particular, its rapid effect on glucose disposal, is to differentiate the role of the operation per se from the effects of energy restriction. A number of studies have shown marked improvement of plasma glucose in type 2 diabetics that was disproportionate to the weight loss and after only short periods of energy restriction [38]. However, the factors responsible for the early benefits of energy restriction on glycaemia are still not clear, partly because of the difficulty in isolating the effects of energy restriction from those of weight loss when the first measurements are taken 7–10 days into the diet [38]. Nevertheless, one study demonstrated clear glycaemic benefits with energy restriction [39], including an associated improvement in insulin sensitivity, but failed to address the hepatic vs peripheral contributions or the determinants of basal glycaemia. Similarly, it is difficult to isolate the effects of weight loss from those of energy restriction. Four days of dieting (reducing energy intake by around 1000 kcal/d) led to a large increase in insulin suppression of hepatic glucose output and, thus, increased hepatic insulin sensitivity [40], and continuation of the diet for
28 days showed significant weight loss associated with increased insulin sensitivity. This suggests that energy restriction and weight loss may have independent effects on glucose control. Although few studies have compared energy restriction with metabolic surgery in type 2 diabetes, they have shown that the effect of metabolic surgery on glucose control is significantly better than that of diet alone. However, randomized studies of larger cohorts are needed to better clarify this important issue.

6. Conclusion

Although no large trials have specifically addressed the effects of bariatric or metabolic surgery on remission or reversal of type 2 diabetes, independent of weight loss and/or caloric restriction, there are sufficient data from the literature to suggest that this type of surgery—and, specifically, RYGB and BPD—can bring about early improvement of glucose control that is independent of weight loss. Although the specific mechanism of action underlying this early consequence of the RYGB and BPD procedures has yet to be elucidated, at present at least, it appears that the major players are probably incretins and, possibly, anti-incretins and intestinal gluconeogenesis.

Conflicts of interests

The authors have reported no conflict of interests.

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Drucker DJ. Biological actions and therapeutic potential of the glucagon-like peptides. Gastroenterology 2002;122:531-44.


Laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy: which has a place in the treatment of diabetes in morbidly obese patients?

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Abstract

Laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy (LSG) are two bariatric procedures approved for the management of morbidly obese patients.

According to a meta-analysis of all obese patients who underwent bariatric procedures, 11% also had type 2 diabetes mellitus (T2DM) before surgery, and improvement or resolution of this co-morbidity was highlighted in many of the studies. However, the mechanism(s) of action underlying such an effect with the various types of bariatric procedure remain unclear. Also, in terms of weight loss, the most efficient operations are those that come with a high rate of morbidity. This means that the choice of procedure is best done after a multidisciplinary team discussion with the patient in an effort to predict the beneficial effects and risks of each possible procedure. However, for years now, the bariatric team at Montpellier Hospital has preferred either LSG or LGBP as the treatment of choice for morbidly obese patients with T2DM, given the higher rates of failure with LAGB over time compared with the excellent results achieved by both LSG and LGBP in many studies.

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Keywords: Gastric banding; Sleeve gastrectomy; Bariatric surgery; Obesity; Type 2 diabetes mellitus; Review

Résumé

Gastroplastie par anneau ajustable ou gastrectomie en manchon laparoscopiques: quelle technique pour traiter les diabétiques de type 2 atteints d’obésité morbide ?

La gastroplastie par anneau ajustable et la gastrectomie en manchon sont deux techniques chirurgicales validées pour la prise en charge de patients obèses morbidès.

11 % de patients qui bénéficient de ce type de chirurgie présente un diabète de type 2. De nombreuses études ont souligné l’efficacité de ces opérations sur la résolution ou l’amélioration du diabète de type 2. Cependant les mécanismes d’actions sont mal connus. Les procédures les plus efficaces étant les plus morbidès, le choix de la technique opératoire doit être réalisé en concertation pluridisciplinaire après information et accord du patient. L’équipe du CHU de Montpellier a décidé au vue de l’analyse de la littérature et de son expérience importante dans ce domaine de proposer la gastrectomie longitudinale et le court circuit gastrique comme procédure de choix dans cette indication en raison des effets hormonaux digestifs décrits après ces opérations, et d’un taux d’échec à long terme de la gastroplastie par anneau jugé trop important.

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Mots clés : gastroplastie par anneau, gastrectomie longitudinale, chirurgie bariatrique, obésité, diabète de type 2, revue générale.
1. Introduction

Laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy (LSG) are two bariatric procedures approved for the management of morbidly obese patients [1]. The gastric band is an inflatable silicone device that is placed around the upper part of the stomach to create a 20-cc gastric pouch that is distended during every meal. The gastric band is connected by tubing to a reservoir inserted under the skin that changes the pouch diameter and, thus, regulates the transit of food [2]. The result is early and complete satiety. This is a solely restrictive procedure that has no direct impact on ghrelin regulation [3]. In contrast, LSG consists of permanently removing two-thirds of the stomach using longitudinal partial gastrectomy, a procedure approved by the French Ministry of Health ever since the Haute Autorité de Santé (HAS; National Authority for Health) report in 2008 considered it another purely restrictive procedure [4]. However, hormonal variations [in ghrelin, glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)] have recently been described [5,6]. Resection of the fundus (site of ghrelin secretion) and quicker gastric emptying that, in turn, propels food more rapidly into the bowel may be explanations for the hormonal effects. Both surgical procedures are effective in terms of weight loss [1], as both can achieve an average of 50–65% excess weight loss in the mid-term [7–9]. In the long term, however, the results for LAGB are less impressive (35–50%) [1,9] whereas, for LSG, there is a complete lack of data so far.

According to a meta-analysis of all obese patients who underwent bariatric procedures, 11% also had type 2 diabetes mellitus (T2DM) before surgery [9], and improvement or resolution of this co-morbidity was highlighted in many of the studies [1,10–19]. In addition, the efficacy of biliopancreatic diversion (BPD), with or without duodenal switch (DS), and gastric bypass (GBP) are well established, and may be explained by several hormonal effects (decreased ghrelin, and increased PYY and GLP-1) that may be due to the duodenopancreatic shunt and/or the rapid arrival of food in the bowel as well as the weight loss of the patient.

However, the impact of LAGB on T2D is more controversial. On the basis of reports in the literature from 1990 to 2006 considered in a recent meta-analysis, Buchwald et al. [10] observed remission of T2DM in 56.7% of patients who underwent LAGB that was maintained for some time: 55% for up to 2 years of surgery; and 58.3% for more than 2 years after the operation). Although adequate, these results are not as good as those for GBP (80.3%) or BPD/DS (95.1%) and, given the very recent validation of LSG for this indication, no data have as yet been reported. However, a prospective randomized study by Dixon et al. [13] described a higher rate of resolution of T2DM with LAGB. The study compared the impact of medical treatment with that of LAGB in patients with T2DM and a body mass index (BMI) > 30 kg/m², but < 40 kg/m², and introduced the idea of a major role of the proximal small intestine and/or the effects of incretins in the regulation of glycaemia. Indeed, after 2 years, 73% of the surgery group vs only 13% in the drug-treatment group saw a resolution of their T2DM in this study. Parikh et al. [14] presented the post-bariatric-surgery results of 282 diabetic patients [218 LAGB, 53 laparoscopic GBP (LGBP) and 11 BPD/DS]. With LAGB, the percentages of excess weight loss after 1 and 2 years were 43% and 50%, respectively, while the percentages of patients still using antidiabetic agents were 39% and 34%, respectively, and the percentages of patients treated with insulin were 14% and 18%, respectively.

As for LSG, intermediate-term studies have reported on the effects of this procedure on T2D resolution. In a comparative study of 39 patients who underwent LSG vs 52 who underwent LGBP, Vidal et al. [15] found that the two procedures were similarly effective after 1 year (84.6% rate of T2D cure). In addition, Silecchia et al. [16] reported resolution of non-insulin-dependent diabetes in 69.2% and improvement in 15.4% at 12 months, and in 76.9% and 15.4%, respectively, at 18 months, in super-obese patients after LSG. Furthermore, the bariatric centre at Montpellier Hospital presented to the 2009 Congress of the International Federation for the Surgery of Obesity (IFSO) the results of a prospective multicentre study comparing the impact of LSG and LGBP on HbA₁c levels and the treatment of T2DM in severely or morbidly obese patients after 1 year [17]. The study included 35 patients in the LGBP group and 33 in the LSG group, and all had been treated with either oral antidiabetic drugs (OADs) or insulin before the operation (32 were taking OADs and three were taking insulin in the LGBP group, while 27 were taking OADs and six were taking insulin in the LSG group). The average BMI in the LGBP group was 47.9 kg/m² and, in the LSG group, 50.6 kg/m². At 1 year after surgery, the operation was successful (defined as stopping or reducing the use of medications, or HbA₁c levels < 7%) in 100% of the LGBP group and in 93.94% of the LSG group. T2DM had resolved (drugs were no longer needed) in 60% of patients in the LGBP group and in 75.8% of the LSG group. The average HbA₁c decreases were −2.537% with LGBP and −2.175% with LSG, while the number of patients with HbA₁c levels > 7% fell from 24 to 4 in the LGBP group, and from 23 to 4 in the LSG group. No statistical differences were found between the two types of surgery in terms of effects on HbA₁c levels (P = 0.552) and evolution of pharmacological treatment (P = 0.231). However, preoperative HbA₁c levels were found to be correlated with stopping medical treatment, as better results were achieved in patients who had HbA₁c levels < 7% prior to surgery (P = 0.037). Nevertheless, no differences were found on analyses according to age, gender, BMI and duration of diabetes. Furthermore, no correlation was found between excess weight loss and reduction of HbA₁c (P = 0.681).

In a retrospective study by Rosenhaim et al. [18], the results at 2 and 6 months after LSG in 30 patients with T2DM, for which 22 (73%) had been taking medications preoperatively, showed that resolution of T2DM occurred in 27% at 2 months and in 63% at 6 months of follow-up. HbA₁c levels decreased from 6.36 ± 0.82% (n = 14) before surgery to 6.02 ± 0.57
(n = 11) at 2 months and to 5.92 ± 0.33 (n = 12) at 6 months after surgery. BMI decreased from 46.12 ± 10.86 kg/m² (n = 30) before the operation to 38.27 ± 6.59 kg/m² (n = 30) at 2 months and to 35.78 ± 5.11 kg/m² (n = 29) at 6 months after it. Patients with a shorter duration of T2DM (< 5 years) and greater weight loss after surgery achieved higher resolution rates.

A comparative study of LAGB and partial gastrectomy (n = 27), LSG (n = 53) and LAGB (n = 100), by Frezza et al. [19], found that, at 12 and 18 months, LSG led to greater excess weight loss (P < 0.05) and lower blood glucose levels (P < 0.05) than did LAGB. The authors concluded that LSG offers better weight loss and glucose control at both 1 and 1.5 years post-surgery than does LAGB, suggesting that gastric fundus resection plays an important—albeit not yet well-defined—role. Shah et al. [20] evaluated the impact of LSG on glycaemic control in obese Indian patients with T2D, with emphasis on its speedy resolution. At 1 month after surgery, 81.2% of patients had stopped their antidiabetic medications and, at 1 year after surgery, 100% of patients had improved and 96.2% had resolved their diabetes. Such a rapid resolution of T2DM appears to be due to a number of changes in digestive-hormone regulation. In a randomized, prospective, parallel-group study, Peterli et al. [21] evaluated the effects of laparoscopic roux-en-Y gastric bypass (LGBP) and LSG on fasting and meal-stimulated insulin, glucose and GLP-1 levels. Both body weight and BMI decreased markedly (P < 0.002) and similarly with either procedure. Excess BMI loss was similar at 3 months (43.3 ± 12.1% vs 39.4 ± 9.4%; P > 0.36). Also, after surgery, the patients had markedly increased postprandial plasma insulin and GLP-1 levels (P < 0.01) after either surgical procedure, thereby leading to improved glucose homoeostasis. However, compared with LSG, LGBP patients showed early augmented insulin responses (within 1 week of surgery), thus potentially mediating greater early glycaemic control. Nevertheless, after 3 months, no significant differences were observed in terms of insulin and GLP-1 secretion between the two procedures. These results do not support the idea that the proximal small intestine mediates improvement in glucose homoeostasis.

2. Conclusion

Bariatric surgery has demonstrated unquestionable efficacy in the treatment of T2DM in patients who are also morbidly obese. However, the mechanism(s) of action underlying such an effect with the various types of bariatric procedure remain unclear. Also, in terms of weight loss, the most efficient operations are those that come with a high rate of morbidity. This means that the choice of procedure is best done after a multidisciplinary team discussion with the patient in an effort to predict the beneficial effects and risks of each possible procedure. However, for years now, the bariatric team at Montpellier Hospital has preferred either LSG or LGBP as the treatment of choice for morbidly obese patients with T2DM, given the higher rates of failure with LAGB over time compared with the excellent results achieved by both LSG and LGBP in many studies.

Conflicts of interests

D. Nocca is consultant for Ethicon and for Tutogen.

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Gastric bypass and glucose metabolism

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Abstract

Gastric bypass (GBP) surgery was originally developed to treat patients with severe obesity. Nevertheless, in those with type 2 diabetes, GBP also exerts a spectacular effect on glucose metabolism, leading to remission of the diabetes in many cases. In this report, the basic principles of the surgical procedure are outlined together with a summary of the potential mechanisms that might explain the remarkable effects of this type of operation on glucose metabolism.

Keyword: Gastric bypass; Bariatric surgery; Glucose metabolism; Review

Résumé

Bypass gastrique et métabolisme du glucose

La chirurgie bariatrique a été développée à l’origine pour traiter les patients atteints d’obésité morbide. Cependant, chez les patients obèses atteints diabète de type 2, le bypass gastrique a aussi des effets spectaculaires sur le métabolisme du glucose, effets qui conduisent à la rémission du diabète dans de nombreux cas. Dans cette revue, les principes de base de l’intervention chirurgicale sont rappelés, ainsi que les mécanismes qui peuvent expliquer les résultats remarquables de ce type d’intervention sur le métabolisme du glucose.

Mots clés : Bypass gastrique ; Chirurgie bariatrique ; M étabolisme du glucose ; Revue générale

1. Introduction

Gastric bypass (GBP) is the preferred operation for treating severe obesity in North America [1]. The use of the procedure is also rapidly growing in Europe, accounting for approximately 20% of all bariatric operations performed last year in France. One likely explanation for the widespread enthusiasm over the rather complex procedure is its efficacy in terms of weight loss compared with rapid exclusively restrictive procedures such as gastric banding [2]. Another appealing feature of GBP is its spectacular effect on glucose metabolism, even in patients with overt type 2 diabetes (T2D) [3]. Initially reported by Pories et al. [4], this specific and initially unexpected benefit of GBP is now well established. In a recent meta-analysis of the outcome of T2D after bariatric surgery, more than 80% of patients achieved diabetes remission following GBP [5]. Several studies also suggest that GBP can markedly reduce diabetes-related mortality [6, 7]. We outline here the basic principles of the surgical procedure, and summarize the potential mechanisms that might explain the outstanding effects of this operation on glucose metabolism.
2. The GBP operation

The basic idea of bypassing the stomach, duodenum and proximal jejunum for treating severe obesity was first suggested by Mason and Itó in 1969 [8]. This operation was later refined by Griffin et al. [9], who described the basics of the procedure that are still in use today, known as the ‘roux-en-Y gastric bypass’. As illustrated in Fig. 1, GBP can be divided into three distinct components: (1) construction of a small gastric pouch (30 ml or less) along the small curvature of the stomach that is divided from the gastric remnant, which is left in place, but disconnected from the upper alimentary tract; (2) sectioning of the jejunum approximately 50 cm from the ligament of Treitz, with reanastomosis of the distal jejunal (alimentary) limb to the gastric remnant (gastrojejunal anastomosis); and (3) reconnection of the proximal jejunal limb (excluding the biliopancreatic limb) to the alimentary limb (jejunojejunal anastomosis). Following GBP, ingested food travels directly from the gastric pouch to the alimentary limb, where it comes into contact with biliopancreatic juice after merging with the common limb, downstream of the jejunojejunal anastomosis. The vagus nerves are carefully preserved during the procedure by most surgeons, although many of the distal neural tributaries along the small curvature may be disrupted. However, with the ongoing improvements in the available technologies and surgical skills, this operation can now be performed by laparoscopy in the vast majority of patients, including many of those with massive obesity or a past history of previous abdominal surgery.

3. Effects of GBP on glucose metabolism

3.1. Calorie restriction

Even in the absence of surgery, the dramatic metabolic effect of calorie restriction alone on T2D is well documented in the short term, but also in the longer term in cases where it can be prolonged [10]. By design, GBP is a severely restrictive operation that enforces calorie restriction by at least three mechanisms that work in synergy. The first is mechanical, and related to the limited volume of the gastric pouch and its reduced outlet. This is why anatomical restriction per se (such as gastric bands) can also induce significant metabolic improvement. However, GBP can also significantly modulate satiety by perturbing neurointestinal cross-talk, and favouring the postprandial induction of satiety signals such as an increase of the anorexigen peptide YY [11] (ileal break) or of intestinal neoglucogenesis [12]. In addition—and albeit still a controversial point—GBP also appears to decrease levels of orexigen peptides such as ghrelin [13]. The final mechanism that may contribute to restricted caloric intake after GBP is the selective food eviction spontaneously adopted by patients to limit the burden of postprandial dumping syndrome [14].
3.2. Insulin sensitivity

As expected, the rapid and dramatic weight loss induced by GBP is associated with a major improvement in peripheral insulin sensitivity. This rapid restoration of insulin sensitivity is not totally explained by weight loss, and may also be related to enhanced insulin signalling in muscle [15]. Another landmark of surgical weight loss is the marked decrease in non-alcoholic fatty liver disease [16], a condition commonly seen in T2D patients [17]. As regression of liver steatosis appears to be closely related to insulin resistance [18], GBP may have specific hepatic benefits beyond weight loss.

3.3. Insulin secretion

In contrast to purely restrictive operations, GBP significantly affects the secretion of insulin. Restoration of a near-normal postprandial insulin response after GBP in patients with T2D has been documented in longitudinal studies. It presents early after the operation [19], and is independent of weight loss [20]. Insulin secretion is only modestly stimulated by intravenous glucose, and the postprandial insulin response appears to be intimately related to a rise in circulating glucagon-like peptide-1 (GLP-1) levels (incretin effect). However, the precise stimulus for such an exaggerated postprandial secretion of GLP-1 remains a subject of debate. It might be provoked by direct stimulation of L cells in the distal ileum, or mediated by earlier jejunal stimuli through neurointestinal cross-talk [21]. The role of the modulation of other incretins, such as glucose-dependent insulinotropic polypeptide (GIP) [22], hyperglycaemic peptides such as glucagon or some still undiscovered anti-incretin peptides potentially increased by jejunoileal bypass are classically associated with a decrease in jejunal glucose absorption [25], but the picture is less clear with GBP. An early and transient rise in absorbed glucose has been directly measured after GBP in humans [26]. On the other hand, in rats, Rubino et al. [23] could find no changes in nutrient absorption after duodenoejejunal bypass, and a recent study showed a decrease in the expression of the intestinal active sodium-dependent glucose transporter 1 (SGLT1) after GBP [27]. These apparently discordant observations need to be reconciled by further clinical studies. In addition, GBP might also significantly modulate energy metabolism by bringing about changes in the microbial intestinal microflora and proinflammatory lipopolysaccharides [28].

3.4. Beta-cell mass

In many cases, GBP appears to fully reverse the diabetic phenotype. Basal insulin and the proinsulin-to-insulin ratio are decreased, while beta-cell sensitivity, as estimated by homeostatic model assessment (HOMA), increases markedly after GBP. The drastic reduction of both hyperglycaemia and dyslipidaemia, two highly toxic conditions for beta cells, must surely contribute to the long-term favourable effects of all bariatric operations on beta-cell function [24]. Alternatively, another hypothesis to explain this apparent reversal of diabetic phenotype is that GBP can truly restore the endocrine cell mass through proliferation and decreased apoptosis. The occurrence of inappropriate postprandial hyperinsulinism after GBP, which may eventually lead to symptomatic hypoglycaemia in some cases, supports this theory [3]. However, it is worth remembering that, despite being well established in rodent models, the trophic effects of GLP-1 and its pharmacological counterparts remain elusive in human islet cells. Thus, the potential restoration of the beta-cell mass in humans after GBP remains highly speculative.

3.5. Other intestinal changes

GBP also induces several non-hormonal changes in intestinal physiology that might contribute to the modulation of glucose metabolism. Malabsorptive procedures such as jejunoileal bypass are classically associated with a decrease in jejunal glucose absorption [25], but the picture is less clear with GBP. An early and transient rise in absorbed glucose has been directly measured after GBP in humans [26]. On the other hand, in rats, Rubino et al. [23] could find no changes in nutrient absorption after duodenoejejunal bypass, and a recent study showed a decrease in the expression of the intestinal active sodium-dependent glucose transporter 1 (SGLT1) after GBP [27]. These apparently discordant observations need to be reconciled by further clinical studies. In addition, GBP might also significantly modulate energy metabolism by bringing about changes in the microbial intestinal microflora and proinflammatory lipopolysaccharides [28].

4. GBP limitations

The main limitations of GBP are related to its associated risks over both the short and long term. Laparoscopic GBP in patients with T2D and, often, other related co-morbidities, represents a major surgical procedure. The most frequent severe adverse events after GBP include Anastomotic leaks, haemorrhage and thromboembolic events. Although the postoperative mortality rate remains < 1% in experienced centres, the overall risk of serious complications reaches 5% [29]. GBP also carries a long-term risk of various medical hazards such as vitamin deficiencies, malnutrition, osteoporosis and psychiatric disorders. Furthermore, despite its favourable effects on overall survival, GBP may increase the risk of accidental death [7]. Eventually, partial weight regain is often observed over time, and the long-term outcome for glucose metabolism after GBP is not well known. This indicates that careful multidisciplinary evaluation and follow-up need to be organized and put in place prior to the operation, and enforced for life thereafter.

5. Conclusion

Initially proposed for severely obese patients as an effective surgery for weight loss, GBP has also brought unexpected benefits in glucose metabolism, including the apparent remission of overt diabetes in many cases. GBP can modulate various metabolic pathways such as calorie intake, insulin sensitivity and beta-cell function as well as glucose intestinal
absorption, all of which are beneficial for glucose control and potentially synergistic. It is likely that further studies will unravel additional mechanisms of actions related to such major anatomical change. Understanding these mechanisms will help in the development of alternative and potentially less-invasive interventions [30], as well as in the identification of new pharmacological targets for treating diabetes [31].

Conflicts of interests

The authors have reported no conflict of interests.

References

Bariatric surgery in young massively obese diabetic patients

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Abstract

Obesity is the most important lifestyle-related risk factor for type 2 diabetes (T2DM). The prevalence of T2DM in adolescents is increasing in parallel with the increasing incidence of major obesity. In adult obese subjects, the greatest degree of T2DM prevention, improvement or recovery has been reported in patients who have undergone bariatric surgery. However, few studies are available on the benefits and risks of bariatric surgery in adolescents with T2DM. The indications for obesity surgery in this population are unusual, and should only be considered in academic settings after comprehensive interdisciplinary evaluation.

Keywords: Bariatric surgery; Adolescents; Diabetes; Morbid obesity; Review

Résumé

Chirurgie bariatrique chez les diabétiques jeunes avec obésité morbide

L’obésité est le principal facteur de risque modifiable du diabète de type 2. La prévalence du diabète de type 2 augmente dans la population des adolescents, en liaison avec l’épidémie d’obésité morbide. Chez l’adulte, la chirurgie bariatrique a fait la preuve de son efficacité dans la régression voire la disparition du diabète de type 2 ; peu de données sont disponible sur les bénéfices et les risques de la chirurgie de l’obésité chez l’adolescent atteint de diabète de type 2. En toute hypothèse, cette mesure exceptionnelle ne peut être envisagée que dans un cadre académique après une évaluation interdisciplinaire experte et globale.

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Mots clés : Chirurgie bariatrique ; Adolescent ; Obésité massive ; Diabète ; Revue générale

1. Introduction

Type 2 diabetes (T2DM) is now much more frequently being observed in childhood, although its prevalence is not yet truly epidemic in proportion [1]. In the US in high-risk ethnic populations, the incidence of cases approaches 50% of all new cases of diabetes diagnosed in adolescents [2]. In Europe up to now, T2DM in children and adolescents has remained a rare disease [3, 4].

The nosology and pathogenic mechanisms of T2DM in children and adolescents are still a matter of debate, and vary depending on genetic, environmental and behavioural determinants [3–6]. However, diabetes develops mainly in young people who are obese, and particularly within groups that are prone to insulin resistance (such as African-Americans). In the very obese, diabetes is often associated with other complications of excess fat mass such as hypertension, low-grade chronic inflammation, joint disorders and non-alcoholic hepatic steatosis, and also with changes in quality of life and self-esteem. Treatment of T2DM in youths includes weight management, increases in physical activity and drug therapy (such as metformin) to reduce insulinresistance,
or insulin when oral hypoglycaemic agents fail to control glycaemia. As in adults, weight loss is the most important aspect in T2DM management, as it reduces both morbidity and mortality [6–9].

In adult obese subjects, the most successful T2DM prevention, improvement or recovery has been reported in patients who underwent bariatric surgery. However, little is known of the effects of bariatric surgery in adolescents with T2DM.

2. Risks and benefits of bariatric surgery in adults

Bariatric surgery includes restrictive procedures such as adjustable gastric banding (AGB), sleeve gastrectomy (SG) and malabsorptive techniques (biliopancreatic diversion/duodenal switch), which are less commonly used, and combination techniques such as roux-en-Y gastric bypass (GBP). In most cases, the procedures are laparoscopic [10]. AGB, the easiest procedure to perform, preserves the natural anatomy and is easily reversible, but often requires adaptation and repeat intervention. An adjustable band is wrapped around the stomach, creating a pouch that empties into the remaining stomach through a narrowed outlet. The main complications of the technique are band slippage, port problems and erosion. Excess weight loss averages 50% over 3 years, with a tendency to regain weight in the long term. GBP is a procedure that creates a small stomach pouch that is isolated from the rest of the stomach and attached to a loop of jejunum. This procedure is both restrictive (due to the gastrectomy) and malabsorptive (due to the bypass). Solely malabsorptive procedures based on major anatomical rearrangement of the intestine, albeit efficient in terms of weight loss, are associated with the higher rate of morbidty, and are not recommended for use in children and adolescents because of their high rate of complications and their impact on nutritional status.

In adults, the effects of bariatric surgery have been studied in a series of investigations including the prospective controlled Swedish Obese Subjects (SOS) study, involving 4047 subjects with an average follow-up period of 10.9 years. The average weight loss in the controls was < 2% over a 15-year follow-up. In the surgical group, the maximum weight loss was observed after 1 to 2 years, and was 32% with GBP and 20% with AGB; at 10 years, weight loss had stabilized at 25% and 14%, respectively. There were 129 deaths in the control group and 101 deaths in the surgery group. Surgery resulted in a significant decrease in cardiovascular- and cancer-related deaths. In the postoperative period (90 days), 0.25% of the surgery group and 0.1% of the control group died. The 2- and 10-year rates of recovery from diabetes, low-density lipoprotein (HDL) cholesterol and hypertension were significantly higher in the surgery group. Indeed, the surgery group had lower rates of diabetes than did the controls [11]. In the Longitudinal Assessment of Bariatric Surgery (LABS) study, the 30-day rate of death among patients who underwent Roux-en-Y GBP or laparoscopic AGB was 0.3%, and a total of 4.3% of patients had at least one major adverse outcome [12]. In a retrospective study of 7925 GBP patients and their matched controls, Adams et al. [13] observed a 40% reduction in overall mortality in the GBP patients (decreases in cancer and cardiovascular mortality, and increases in sudden death).

The risk of death and adverse outcomes after bariatric surgery depend on the patients’characteristics. The LABS observational study of consecutive patients undergoing bariatric surgery in the US evaluated the outcomes of patients undergoing first-time bariatric surgery, using a composite 30-day endpoint of major adverse events (death, venous thromboembolism, repeat intervention, prolonged hospitalization). The rate of deaths was 0.3% among patients who underwent either GBP or AGB, with 4.3% of patients having at least one major adverse outcome. The patient’s history of venous thrombosis or pulmonary embolism, obstructive sleep apnoea and impaired functional status was each independently associated with an increased risk of the composite endpoint. Extreme values of body mass index (BMI) were also associated with increased risk. Given that these data were obtained from highly skilled, high-volume bariatric centres, the composite endpoint occurred in 1.0% of the AGB group and in 4.8% of the GBP group [13].

3. Bariatric surgery and type 2 diabetes in adults

The most successful T2DM prevention, amelioration or recovery in adult obese subjects has been reported in patients who underwent bariatric surgery [14,15]. The conclusion of a recent meta-analysis of the impact of bariatric surgery on T2DM in adults was that 78.1% of diabetic patients had complete resolution of their disease, while it was improved or resolved in 86.6% of patients. Weight loss and diabetes resolution were greatest for patients undergoing biliopancreatic diversion/duodenal switch, followed by those undergoing GBP, and was least for banding procedures. Insulin levels declined significantly postoperatively, as HbA1c and fasting glucose values. Weight and diabetes parameters showed little differences at both < 2 years and ≥ 2 years [14]. However, long-term weight loss and improvement or remission of metabolic and respiratory complications has been well documented in two major studies [12, 13]. In the SOS study, the rate of recovery of diabetes was 72% at 2 years and 36% at 10 years. Moreover, the incidence of diabetes at 2 years was 30 times lower than in the controls, a benefit that was still evident at 10 years.

Based on such results, bariatric surgery in now considered a therapeutic option for the treatment of T2DM. In fact, T2DM is among the indications for bariatric surgery in patients with a BMI < 40 kg/m² [15–17]. It also appears that malabsorptive bariatric procedures are the most efficient: in the meta-analysis by Buchwald et al. [14], the highest rate of T2DM recovery was observed in the biliopancreatic diversion/duodenal switch and GBP groups (98% and 83%, respectively) compared with AGB (49%). Nevertheless, the issue remains debatable: in the meta-analysis by Parikh et al. [16] of only diabetic patients,
the rate of patients requiring antidiabetic drugs at 1 and 2 years was 39% and 34%, respectively, for AGB, and 22% for GBP with no significant differences.

The mechanism of metabolic improvement after bariatric surgery is currently under study. Weight loss certainly plays a role: in the SOS study, weight relapse was associated with a higher risk of diabetes relapse. Reduction of food intake may also play a role. However, after GBP, the improvement in metabolic control is seen early after the intervention, whereas it takes several weeks after AGB. Clearly, the kinetics of such an improvement suggest other explanations. The unusual improvement in T2D after GBP compared with equivalent weight losses due to medical treatment suggests a specific effect of surgery on glucose homeostasis that is independent of weight loss. The surgical procedure itself may explain the differences observed, with exclusion of the proximal part of the duodenum necessary for rapid metabolic improvement to occur. Other potential mechanisms include the effect of the surgical procedure on adiponecin, ghrelin, incretins (such as glucagon-like peptide-1, or GLP-1) and intestinal nutrient-sensing. In animals, the beneficial effects of enterogastric-anastomosis (EGA) procedures on food intake and glucose homeostasis involve intestinal gluconeogenesis and its detection via the GLUT2 and hepatoporal sensory pathway. In addition, ghrelin levels are decreased following GBP despite decreases in weight loss and food intake in some studies. Higher levels of GLP-1, an intestinal peptide involved in the control of food intake and insulin secretion, may also play a role. Furthermore, modification of the gut flora may be yet another potential explanation for the observed metabolic improvement [18–20].

4. Benefits and risks of bariatric surgery in adolescents

Little is known of the benefits and risks of bariatric surgery in children and adolescents. For this reason, the data from 17 studies, involving 553, mostly consecutive, morbidly obese adolescent patients, were reviewed by Treadwell et al. [21] as part of a health-technology assessment for the Washington State Health Care Authority. The panel of experts concluded that: (1) GBP and AGB both resulted in clinically significant weight loss—defined as a loss of 7% of body weight—corresponding to a decrease in BMI of 4 kg/m² after roux-en-Y GBP (follow-up of 1–6.3 years) and of 3.5 kg/m² after AGB (follow-up of 1.7–3.3 years); (2) laparoscopic AGB resolved the co-morbid conditions of diabetes and hypertension, whereas Roux-en-Y GBP resolved hypertension, with insufficient data to rate the evolution of other co-morbidities; (3) the safety profile (moderate evidence) for laparoscopic AGB after a follow-up period of 1–85 months revealed no peri- or postoperative deaths, although 26 of 328 patients required repeat surgery to correct complications (band slippage, intragastric migration and port/tubing problems); (4) the safety profile (moderate evidence) for Roux-en-Y GBP after a follow-up period of 2 weeks to 6 years revealed a combination of mild (slight malnutrition) and severe (pulmonary embolism, severe malnutrition, postoperative bleeding and gastrointestinal obstruction) complications [21,22].

In a longitudinal assessment of clinical characteristics in 61 adolescents who underwent laparoscopic roux-en-Y GBP, Inge et al. [23] showed that it resulted in improvement or reversal of cardiovascular risk factors and a decrease in BMI in approximately 37% of all patients, regardless of the initial BMI, at 1 year after the surgery. They also concluded that ‘late’ referral for bariatric surgery in those with the highest BMI values may preclude reversal of obesity. This suggests that the timing of referral for and the decision to undergo bariatric surgery in adolescents is a key issue.

Nevertheless, a number of questions have yet to be answered: Are the improvements in quality of life and co-morbid conditions due to surgery-induced weight loss long-lasting? Are the results collected in academic centres using multidisciplinary teams representative of the general population? What are the predictors of bariatric surgery success and safety?

Given these uncertainties, it appears necessary to be extremely prudent before considering bariatric surgery in younger patients. Indeed, bariatric surgery in such cases should only be considered in the presence of obesity-related health-threatening co-morbidities (BMI > 40 kg/m² plus a severe co-morbidity, or a BMI > 50 kg/m² and a less severe co-morbidity) after failure of a well-conducted medical treatment that includes psychological and social support. Also, the decision should involve a skilled, multidisciplinary team, and the patient needs to demonstrate good compliance with a family-based lifestyle-modification programme. It must be made clear that obesity surgery is a trade-off: surgery creates a new lifelong ‘digestive disorder’ in the hopes that the altered gastrointestinal tract will improve the primary behavioural disorder (obesity) and its consequences without inducing new risks (such as malnutrition, micronutrient deficiency and osteopenia). It should also be clear that bariatric surgery is not a cure, but merely an intervention that only helps the patient to keep a commitment to lifestyle changes. To create anatomical and functional changes in developing children is not a harmless act, and a lifelong exposure to such changes may result in unforeseen complications [22–27].

5. Effect of bariatric surgery on diabetes in adolescents

The balance between the benefits and risks of bariatric surgery in adolescents is poorly documented, particularly in the long term, with little data available on the effects of bariatric surgery on diabetes in this patient population. However, Inge et al. [23] studied T2D reversal after surgery-induced weight loss in 11 adolescents who had undergone GBP and whose metabolic outcomes were compared with those of 67 diabetic adolescents treated medically. After surgery, there was evidence of diabetes remission associated with massive weight loss in all but one patient in the surgery group. In comparison, adolescents who were followed during 1 year of medical treatment demonstrated stable weight and no significant change in diabetic medication use. In addition, in the surgery
group, HbA1c decreased from 7.3% to 5.6% compared with 7.8% to 7.1% in the medical group. Furthermore, in another series of 30 cases, GBP resulted in improvement of fasting blood glucose and insulin after 1 year [27]. Interestingly, bariatric surgery also brought about major improvement in sleep apnoea syndrome in adolescents [28,29].

In a retrospective study in 76 adolescents who underwent biliopancreatic diversion (BPD) with a mean follow-up period of 11 years (range 2–23 years), Scopinaro et al. [29] found that the mean percentage of initial excess weight loss at each patient’s longest follow-up was 78%. Prior to surgery, two patients had T2DM but, at the longest follow-up period after surgery, none were diabetic. However, 11 patients developed protein malnutrition 1–10 years after BPD, and the long-term mortality rate was 4%.

6. Practical guidelines

Considering the effects of bariatric surgery on the overall co-morbidities linked with obesity, the expert panel of the health technology assessment for the Washington State Health Care Authority concluded that: (1) AGB and GBP for morbidly obese patients aged 21 or less can resolve co-morbid conditions (diabetes and hypertension) compared with non-surgical approaches (strength of evidence: weak), and two studies of AGB indicate a diabetes resolution rate of 80% and 100%, respectively (strength of evidence: weak); and (2) the evidence is insufficient to permit quantitative estimates of the likelihood of co-morbidity resolution and survival [21].

Pratt et al. [30] carried out a systematic search to update the evidence-based best-practice guidelines for paediatric/adolescent bariatric surgery, and recommended the inclusion of adolescents with BMI scores > 35 kg/m² plus specific obesity-related co-morbid conditions for which there is clear evidence of serious short-term morbidity (such as T2DM, severe steatohepatitis, pseudotumour cerebri and moderate-to-severe obstructive sleep apnoea), and those with extreme obesity (BMI ≥ 40 kg/m²) plus other co-morbidities associated with long-term risks. On identifying more than 1085 reports, and reviewing 186 of the most relevant in detail, they recommend that the preoperative multidisciplinary evaluation should take into consideration carefully designed criteria for patient selection, choice of appropriate procedure, thorough screening and management of co-morbidities, optimization of long-term compliance and age-appropriate, fully informed consent.

In patients with genetic disorders associated with major obesity such as Prader–Willi syndrome, the fact that bariatric surgery yields a high risk of complications is problematic [31].

7. Conclusion

Should bariatric surgery be considered for young, massively obese, diabetic patients? The answer to the first part of the question is that, in exceptional circumstances, bariatric surgery can be considered in young obese patients with a BMI > 35 kg/m² with life-threatening complications as a result. This means that diabetes that is inadequately controlled by medical treatment is one co-morbid condition that justifies a discussion on the appropriateness of bariatric surgery, especially in a young patient who has not responded to intensive obesity care. Albeit based on scant data, it appears that bariatric surgery may be just as effective for T2DM improvement or recovery in adolescents as it is in adults. However, it is not yet known, in the absence of long-term data, whether or not bariatric surgery can cure T2DM in such patients in the long term.

Bariatric surgery in children and adolescents should only be performed in reference academic centres with long-term follow-ups and in relation to clinical research. The multidisciplinary paediatric team should include medical (nutritional, endocrinological, metabolic, gastrointestinal, sleep and pulmonary) expertise, as well as psychological and surgical expertise, and an anaesthetic-care team experienced in obesity management. Also, only strongly motivated and well-informed patients (and their families) capable of providing favourable social and psychological support, and good preoperative care and counselling, should be considered for such surgery. In addition, both patients and their families need to be well informed as to the risks and complications of bariatric surgery.

The postoperative follow-up should take into account growth and development. Compliance is also essential to prevent and treat the potential risks of the procedure, adapt the treatment (insulin, antidiabetic drugs), and manage the physical and psychosocial responses to any dramatic weight loss. In addition, lifelong surveillance of micro- and macronutrient intakes, and nutritional, weight and digestive status has to be undertaken postoperatively.

Data on the effects and complications of bariatric surgery in children and adolescents are currently scanty, so the multidisciplinary teams involved in the management of these patients are encouraged to contribute their findings to a database.

Conflicts of interests

The authors have reported no conflict of interests.

References


Bariatric surgery in patients with Type 2 diabetes: benefits, risks, indications and perspectives

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Abstract

Obesity plays a key role in the pathophysiology of type 2 diabetes (T2DM), and weight loss is a major objective, although difficult to achieve with medical treatments. Bariatric surgery has proven its efficacy in obtaining marked and sustained weight loss, and is also associated with a significant improvement in glucose control and even diabetes remission. Roux-en-Y gastric bypass appears to be more effective in diabetic patients than the restrictive gastroplasty procedure. This may be explained not only by greater weight reduction, but also by specific hormonal changes. Indeed, increased levels of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) may lead to improved β-cell function and insulin secretion as well as reduced insulin resistance associated with weight loss. The presence of T2DM in obese individuals is a further argument to propose bariatric surgery, and even more so when diabetes is difficult to manage by medical means and other weight-related complications may occur. Bariatric surgery is associated with a better cardiovascular prognosis and reduced mortality, even though acute and long-term complications are present. The observation that surgical rerouting of nutrients triggers changes in the release of incretin hormones that, in turn, ameliorate the diabetic state in the absence of weight loss has led to the recent development of innovative surgical procedures. Thus, bariatric surgery may be said to be progressing towards so-called ‘metabolic surgery’, which merits further evaluation in patients with T2DM within a multidisciplinary approach that involves both surgeons and endocrinologists.

Keywords: Bariatric surgery; Gastric bypass; Gastroplasty; Obesity; Type 2 diabetes; Review

Résumé

Chirurgie bariatrique chez les patients atteints de diabète de type 2: bénéfices, risques, indications et perspectives

L’obésité joue un rôle-clé dans la physiopathologie du diabète de type 2 (DT2) et l’obtention d’une perte de poids est un objectif majeur, bien que difficile à atteindre avec les moyens médicaux. La chirurgie bariatrique a apporté la preuve de son efficacité pour induire un amaigrissement marqué et soutenu, qui s’accompagne d’une amélioration du contrôle glycémique et assez souvent d’une rémission du diabète. La dérivation gastrique avec l’anse de Roux-en-Y apparaît être plus efficace chez les patients diabétiques que la simple technique restrictive qu’est la gastroplastie calibrée. Ceci peut s’expliquer non seulement par une perte pondérale supérieure, mais aussi par des modifications hormonales spécifiques. En effet, une augmentation des concentrations de GLP-1 (glucagon-like peptide-1) et de GIP (glucose-dependent insulinotropic polypeptide) avec la dérivation permet d’améliorer la fonction de la cellule β et la réponse insulinosécrétoire, en plus de la diminution de l’insulinorésistance consécutive à l’amaigrissement. La présence d’un DT2 chez un sujet obèse est un argument supplémentaire pour proposer une chirurgie bariatrique, d’autant plus que le diabète est difficile à gérer avec les moyens médicaux et qu’il existe d’autres complications liées à l’excès de poids. La chirurgie bariatrique est associée à un meilleur pronostic cardiovasculaire et à une diminution de la mortalité, même si cette chirurgie peut également occasionner des complications à court et à long terme. L’observation que la dérivation gastro-intestinale des aliments stimule la sécrétion des hormones incrétines, susceptibles d’améliorer le diabète en l’absence de perte de poids, a conduit récemment au développement de nouvelles procédures chirurgicales. Ainsi, la chirurgie bariatrique pourrait évoluer vers une chirurgie métabolique.

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1. Introduction

Obesity is a major independent risk factor for the development of type 2 diabetes mellitus (T2DM) and is also associated with the rapidly increasing prevalence of diabetes [1, 2]. The majority of patients (> 80%) diagnosed with T2DM are overweight [body mass index (BMI) > 25 kg/m²], and roughly 50% are obese (BMI > 30 kg/m²) and almost 10% are morbidly obese (BMI > 40 kg/m²). This twin epidemic of obesity and diabetes has serious consequences with increased cardiovascular morbidity and premature mortality. However, studies have shown that weight loss, even when modest, can reduce the incidence of T2DM in patients with impaired glucose tolerance and improve blood glucose control (and other cardiovascular risk factors) in patients with T2DM, while marked weight loss can even lead to resolution/remission of diabetes [2].

Lifestyle interventional programmes including diet therapy, behavioural modification, exercise regimens and pharmacotherapy are widely used in various combinations [3, 4]. Unfortunately, clinically significant weight loss is uncommon and mostly transient, particularly in patients with severe obesity and with T2DM, for whom sustained weight reduction is even more difficult to achieve.

Bariatric surgery is a rapidly evolving branch of surgical science [5-7]. The aim is to induce major weight loss in those whose obesity places them at high risk of severe health problems, including T2DM [7-9]. In an attempt to balance the risks of surgery against the benefits of weight loss, bariatric operations are currently performed only in the morbidly obese (BMI > 40 kg/m²) and in those with a BMI > 35 kg/m² and co-morbidities such as T2DM [10]. In the mid-1990s, Pories et al. [11] proposed the provocative theory that T2DM might be a surgical disease, as bariatric surgery proved to be the most effective approach for treating and even resolving this type of diabetes [12]. Over the past 10 years, bariatric surgery has gained an increasing place in the management of obese patients with T2DM [13-16]. Moreover, the suggestion that the foregut plays an important role in the pathophysiology of T2DM opens up new possibilities for a surgical approach in patients with T2DM, even in absence of severe obesity, as well as a nominal shift from ‘bariatric’ to ‘metabolic’ surgery [17, 18].

The present review focuses mainly on the benefit–risk profile of bariatric surgery in the management of obese patients with T2DM, but also includes a discussion of the mechanisms of action of various surgical procedures, the factors influencing prognosis and validated indications in clinical practice. In addition, new perspectives for metabolic surgery in non-obese patients with T2DM are also briefly discussed.

2. Surgical techniques

A number of surgical approaches to induce weight loss have been developed, and several are also currently used in the management of obese patients with T2DM [5, 6]. In general, these procedures can be classified as: solely restrictive [laparoscopic adjustable gastric banding (LAGB) and its variant, vertical banded gastroplasty (VGB)] [19]; mostly restrictive [Roux-en-Y gastric bypass (RYGB)] [20]; and mostly malabsorptive [biliopancreatic diversion with duodenal switch (BPDS)] [21]. In the first group, the mechanism essentially hinges upon generating effective satiety signals with only small amounts of ingested food [19]. In the second group, a degree of gastric restriction is coupled with bypass of the duodenum and upper jejunum, a procedure that may also result in important hormonal changes for glycaemic control (see below) [20]. In the third group of procedures, only the final 50 cm of the total length of the bowel is available for ingested food and biliopancreatic juices to mix, leading to consistent nutrient malabsorption [21].

These techniques have all been proven effective in the management of obese patients with or without T2DM. However, as these surgical procedures are different, their efficacy-to-safety balance may also differ. Techniques with a component of malabsorption generally lead to more pronounced and more sustained weight loss compared with solely restrictive procedures [22]. As for tolerability and safety, patients treated with LAGB had lower short-term morbidity than those treated with RYGB, but repeat-operation rates are higher among patients who undergo LAGB. However, according to a recent Cochrane review, although certain procedures result in greater weight loss, well-validated comparative data are nevertheless limited. The evidence for safety is even less clear. Because of the limited evidence and poor quality of trials, the reviewers concluded that caution is required when interpreting comparative safety and effectiveness [23].

Innovative bariatric surgical procedures continue to be under investigation. The gastric sleeve, or sleeve gastrectomy, is certainly among the more advanced and already in routine use in some centres [24, 25]. The procedure results in a narrow gastric tube through excision of most of the stomach. The operation does more than just limit intake, but also removes...
most—or perhaps all—of the ghrelin-producing cells in the gastric mucosa. In addition, two new procedures—the duodenoejunal bypass stomach-sparing operation [26] and ileal transposition [27-29]—have been tested in attempts to induce remission of diabetes without weight loss in lean or only modestly overweight patients with T2DM. However, both are still in the early stages of human trials (see Perspectives below). Nevertheless, there is little doubt that the mechanism of action on glucose metabolism differs depending on the type of bariatric surgery [30].

3. Mechanisms of metabolic improvement

Bariatric surgery is a highly effective means of inducing diabetes remission in very obese patients with T2DM [31]. Diabetes remission results from improvements in both insulin resistance and β-cell dysfunction. Better insulin action on glucose metabolism relieves secretory pressure on the β-cell, resulting in reduced insulin output [32, 33]. However, significant improvements in dynamic β-cell responses may also play a role. This may be the result of reduced glucotoxicity and/or specific incretin effects favouring β-cell function. By rank order of increasing efficacy in glucose control, the most common surgical procedures go from the solely restrictive to the mostly restrictive and to the mostly malabsorptive, thus paralleling their weight-reducing effects. The mechanisms responsible for glycaemic improvement and resolution/remission of diabetes after bariatric surgery also depend on the type of surgical procedure used.

Calorie restriction and weight loss are the dominant mechanisms of improved glucose metabolism when solely restrictive procedures are applied [8, 19]. The former appears to account for the early post-surgical recovery of insulin sensitivity and secretory dynamics, while the latter is the final determinant of outcome once weight and caloric balance have stabilized [32, 33]. In general, when analyzing the effect of solely restrictive procedures, the sustained improvement of glucose control is directly proportional to the final amount of weight loss. However, even with RYGB, the percentage of weight lost is a predictive factor of diabetes remission [34].

When food transit is surgically altered, changes in the pattern of gastrointestinal hormone release may support early adaptation of β-cell function, but this is unlikely to make a major contribution to insulin action. Weight-independent antidiabetic effects with RYGB are evident from the rapid resolution of T2DM (before weight loss occurs), the greater improvement of glucose homeostasis after RYGB than after equivalent weight loss by other means and the occasional development of very-late-onset pancreatic β-cell hyperfunctioning. Several mechanisms probably mediate the direct antidiabetic impact of RYGB, including: enhanced nutrient stimulation of L-cell peptides [for example, glucagon-like peptide-1 (GLP-1)] from the lower intestine (‘hindgut hypothesis’); the intriguing, but as yet uncharacterized, phenomena related to exclusion of the upper intestine from contact with ingested nutrients (‘foregut hypothesis’); compromised ghrelin secretion; and most likely other effects that have yet to be identified [30, 35, 36]. Indeed, a role for glucagon or gut-derived glucagonotropic signalling as putative diabetogenic signals from the foregut has been recently proposed [37]. Research designed to prioritize these mechanisms and identify potential additional mechanisms promises to help in the optimization of surgical design (see Perspectives below) and may also reveal novel pharmaceutical targets for antidiabetes drug treatments [36].

4. Clinical benefits

The dataset of a recent systematic review and meta-analysis included 621 studies with 888 treatment arms and 135,246 patients; of these studies, 103 treatment arms, involving 3188 patients, reported resolution of diabetes—that is, resolution of the clinical and laboratory manifestations of T2DM [38]. In addition, 19 studies with 43 treatment arms and 11,175 patients reported both weight loss and diabetes resolution in 4,070 diabetic patients. At baseline, the patients’ mean age was 40.2 years, BMI was 47.9 kg/m², 80% were female and 10.5% had undergone previous bariatric procedures. Meta-analysis showed an overall loss of 38.5 kg or 56% of excess body weight. Also, 78% of the diabetic patients enjoyed complete resolution of their disease, while diabetes was improved or resolved in nearly 87%. Weight loss and diabetes resolution were greatest for patients undergoing BPDS, followed by RYGB, and was lowest with LAGB. Insulin levels declined significantly postoperatively, as did glycated haemoglobin (HbA₁c) and fasting glucose values. Weight and diabetes parameters showed little differences within 2 years, or after 2 or more years, of follow-up. The conclusion was that the clinical and laboratory manifestations of T2DM were resolved or improved in the vast majority of patients after bariatric surgery, and these responses are more pronounced with procedures that led to a greater percentage of excess weight loss maintained for 2 or more years.

Besides the effect on glucose control, bariatric surgery also leads to significant improvement of cardiovascular risk factors, especially those linked with the metabolic syndrome, including inflammation markers [39]. The prospective Swedish Obese Subjects (SOS) study confirmed that bariatric surgery significantly improves glucose, lipid and blood pressure control in surgically compared with medically treated obese individuals [40]. Recently, the 10.9-year follow-up of the SOS study reported a significant 30% risk reduction in overall mortality in 2,010 obese patients (7.4% with T2DM) who had undergone bariatric surgery [41]. Likewise, in a retrospective US cohort of 7,925 surgical patients mostly treated with RYGB, mortality from any cause was significantly 40% lower than in 7,925 non-surgical obese patients [42]. However, mortality data for a specific diabetic cohort are scanty. In an early retrospective analysis of two groups of obese diabetic patients, the mortality rate (including perioperative deaths) in the control medical group was 28% after 6.2 years compared
with only 9% in the RYGB surgical group after 9 years. For every year of follow-up, patients in the control group had a 4.5% risk of dying vs 1.0% for those in the surgical group. The improvement in mortality with surgery was primarily due to a decrease in the number of cardiovascular deaths [43].

Recently, a systematic review concluded that bariatric surgery appears to be a clinically and cost-effective intervention for moderate-to-severely obese people compared with non-surgical interventions [44]. However, uncertainties persist and further research is required. In particular, new research needs to investigate the resolution and/or development of T2DM and, more important, the duration of T2DM remission, so that the potential benefits of early intervention may be better assessed.

5. Prognostic factors

Studies of postoperative outcomes for bariatric surgery have provided information on the predictors of success. Indeed, the surgeon's and institution's experience, and patients' behaviour after surgery, are key determinants of its success or failure in all obese subjects, including those with T2DM [45].

Rates of total diabetes remission and glycaemic improvement essentially depend on the type of surgical intervention, as already stated. Although physiological (hormonal) mechanisms probably contribute to RYGB outcomes, early rapid weight loss and the percentage of excess weight lost were also significant factors associated with diabetes remission in a multivariate analysis [34]. In addition, in that study, the preoperative insulin dose was another predictor, suggesting that the severity of diabetes plays a crucial role. This may be indexed by disease duration, HbA1c level, intensity of treatment and presence of complications [46]. Diabetes duration is generally related to a progressive reduction in β-cell function and/or mass, which may hinder remission of diabetes even after marked weight loss if surgery is performed too late. HbA1c is a classical marker not only of glucose control, but also, indirectly, of diabetes severity. The higher the initial HbA1c level, the lower the chances of diabetes remission after bariatric surgery. Similarly, the intensity of treatment also plays a major part. Insulin-treated patients are less prone to complete remission of diabetes compared with patients taking oral treatment, and recovery of adequate glucose control despite stopping insulin therapy would be an alternative—and perhaps more realistic—efficacy criterion in such a diabetic subgroup. Among patients using oral therapy, the rate of complete diabetes remission is higher in those treated with monotherapy compared with those already receiving the maximum oral combined treatment. The presence of diabetic complications (such as nephropathy and retinopathy) should probably be considered an indirect marker of longstanding, poorly controlled diabetes rather than a direct contributor to surgical treatment failure.

Other factors, such as adiposity topography, T2DM family history, interaction with previous antidiabetic therapies and evidence of autoimmunity (late-onset type 1 diabetes) have not been specifically analyzed and merit further evaluation.

6. Risks

The risk and type of complications related to bariatric surgery among diabetic patients are not much different from those in a non-diabetic population, although some (such as infections) are more prevalent in diabetics. Surprisingly, bariatric surgery is remarkably safe, especially given the large body size of patients, and the frequency and seriousness of co-morbidities. Nevertheless, the operative mortality rate is low: the 30-day mortality rates reported in a recent meta-analysis were LAGB = 0.1%, VBG = 0.1%, RYGB = 0.5% and BPDS = 1.1% [47]. However, death may also occur after discharge from hospital, possibly due to pulmonary embolism and arrhythmias [6].

Surgical complications are either acute or long term [6]. Acute complications occur in 5–10% of patients—depending on the procedure, and the patient's risk, age and condition—and mirror those following other abdominal operations, including haemorrhage, obstruction, anastomotic leaks, infection, arrhythmias and pulmonary emboli. Long-term complications are miscellaneous and mostly include neuropathies due to nutritional deficiencies, internal hernias, anastomotic stenoses and emotional disorders. Although nutritional deficits can be avoided with daily multivitamin and mineral supplements, compliance with this recommendation is not universal, and dramatic complications due to severe deficiencies may occur, albeit rarely. In general, however, the complications do not differ in diabetic, compared with non-diabetic, patients [48].

The risk of hypoglycaemia sometimes reported in non-diabetic individuals late after RYGB (attributed to the development of neisidioblastosis) does not appear to affect diabetic patients. However, calorie restriction, weight loss and incretin-related mechanisms may dramatically improve glucose control and lead to early hypoglycaemia if no appropriate reduction in glucose-lowering therapies is made soon after surgery. Ideally, this should be performed as a preventative rather than waiting for hypoglycaemic episodes to occur before considering adjustment of any antidiabetic treatment [7]. Similarly, antihypertensive therapy, commonly used in obese patients with T2DM, should be frequently adjusted after bariatric surgery to avoid hypotension leading to orthostatic dizziness.

7. Indications

The first indications and contraindications for bariatric surgery were established in 1991 by the US National Institutes of Health (NIH) Consensus Conference on surgery for obesity [10]. In 2004, the American Society for Bariatric Surgery (ASBS; now the American Society for Metabolic and Bariatric Surgery, or ASMBS), updated that statement with a follow-up Consensus Conference [49]. In practical terms, most physicians, surgeons and carers consider patients eligible for bariatric surgery if their BMI is at least 40 kg/m², or at least 35 kg/m² if accompanied by co-morbidities.
such as T2DM, hypertension, severe arthritis (limiting daily function) and cardiopulmonary failure. In the past, the age limit was 18–65 years, but recent data show that teenagers and patients over 65 can benefit from surgery with little or no increases in risk. Other inclusion criteria include the patient’s ability to understand the surgery and its consequences, and to comply with long-term follow-up, and the patient’s agreement to maintain vitamin and mineral supplementation, and to report problems promptly to specialists familiar with the complications of bariatric surgery. Similar recommendations were made in the 2007 Interdisciplinary European guidelines for surgery for those with severe (morbid) obesity [50].

Thus, T2DM as a complication of obesity is a further argument to propose bariatric surgery even when BMI is 35–40 kg/m², as stated in the official recommendations [10, 49, 50]. From a practical point of view, it is reasonable to consider as major indications either those patients whose T2DM is difficult to manage or poorly controlled mainly because of the presence of severe obesity, or those who, in addition to diabetes, have several risk factors directly related to excess weight that may markedly worsen their overall prognosis (such as hypertension, dyslipidaemia and sleep apnoea). However, the choice of procedure is not yet based on sound data [23], although many surgeons currently favour either RYGB or the duodenal switch over LAGB in patients with T2DM for reasons discussed above [7, 15, 16, 22].

8. Perspectives

Certain types of bariatric surgical procedures have proved not only to be effective for treating obesity, but also appear to be associated with endocrine changes that, independent of weight loss, give rise to remission of T2DM [37, 51]. Observations in animals and in humans suggest that changes in the gut hormonal milieu after bypass of the distal stomach, duodenum and proximal jejunum can influence T2DM, despite the absence of significant weight loss [17, 51]. As a result, the use of bypass bariatric surgery and experimental gastrointestinal manipulations to treat T2DM is increasing among less obese patients (BMI < 35 kg/m² or even < 30 kg/m²). While BMI currently represents a significant indication for bariatric surgery (see Indications above), evidence shows that, so far, no clear cut-off BMI score accurately predicts successful surgical outcomes. Furthermore, BMI appears to have limited value in defining the risk profile in T2DM patients. For this reason, the current BMI-based criteria for bariatric surgery may not be an adequate indication for such patients [17].

There is also increasing evidence that bariatric operations may exert intrinsic antidiabetic actions beyond weight loss. Malabsorptive operations currently offer the best chances of revealing weight-independent mechanisms of diabetes resolution, but other smart manipulations of food passage may open up entirely new avenues of treatment. At present, it is speculated that surgical rerouting of nutrients triggers changes in the release of gastrointestinal-derived hormones that, in turn, ameliorate the diabetic state. The hindgut hypothesis states that surgical rerouting of nutrients to the distal part of the small intestine results in increased secretion, and concomitant glucose-lowering effects, of GLP-1, whereas the foregut hypothesis emphasizes that surgical bypass of the foregut prevents the release of hitherto unidentified nutrient-induced diabetogenic signals (? glucagon/glucagonotropic signalling) in susceptible individuals [37]. Recent animal investigations using duodenojejunal bypass, a stomach-preserving experimental model of RYGB, have shown that diabetes control is not a mere collateral effect of the treatment of obesity, but directly results from exclusion of the duodenum and proximal jejunum from the flow of nutrients. A recent report has described lean T2DM patients who experienced marked improvement of their diabetes with duodenojejunal exclusion surgery that was independent of changes in BMI, fat distribution and body composition [26]. Such a surgical approach was superior to standard care in achieving better glycaemic control, along with reduction or even interruption in insulin requirements. Also, as an alternative approach, ileal transposition may result in significant endocrine changes in the gut, particularly by promoting secretion of GLP-1, an ileal-produced hormone with a well-known role in T2DM [27]. Promising results with ileal interposition (the so-called ‘neuroendocrine break’) combined with sleeve gastrectomy were recently reported in a small series of patients with T2DM and no obesity [28, 29]. Adequate glycaemic control was obtained in > 90% of the patients and several hormonal changes were also observed, especially a marked increase in GLP-1 and GIP (glucose-dependent insulinotropic polypeptide).

Large randomized clinical trials against the best medical care should be prioritized to define the role of bariatric surgery in the management of diabetes. Experiments involving less obese or non-obese diabetic patients, or minimizing weight loss, may provide further evidence in favour of so-called metabolic surgery [18]. However, difficult as they may be to carry out, controlled clinical studies using state-of-the-art methodology (including randomization if possible) are necessary to establish the value of metabolic surgery. It would also be of interest to assess the efficacy/safety of bariatric/metabolic surgery in special populations presenting with diabetes, such as pregnant women, adolescents and individuals who are at least 65 years old [48].

9. Conclusion

Numerous studies demonstrate that bariatric surgery for obesity can lead to substantial and sustained weight loss. In addition, patients with T2DM have experienced remission of hyperglycaemia or a reduced need for medication. These effects partly explained by weight loss, but also by specific hormonal changes, especially after bypass procedures that alter the passage of food in the gut. This may explain why RYGB appears to be superior to LAGB in obese patients
with T2DM. Surgical intervention for patients with more recent diabetes onset may see higher rates of resolution than patients with longer T2DM duration because of less-advanced disease and a better insulin secretory reserve. In addition to better glucose control, dyslipidemia, hypertension and other risk factors improve more markedly in patients treated by surgery compared with those receiving the optimal medical treatment. Such pleiotropic effects may offer special benefits to those with T2DM, who are also known to present with high cardiovascular risks. Observational studies and the prospective SOS trial suggest that long-term survival is favourable for obese (diabetic) patients following bariatric surgery. This suggested disorder (surgical intervention in cases of T2DM associated with other weight-related complications may be clinically appropriate in patients for whom operative risks are acceptable, with no contraindications. Finally, new surgical procedures are currently undergoing evaluation and may be proposed in future for management of T2DM, even in the absence of severe obesity. Thus, the old paradigm of bariatric surgery may progress towards a new paradigm of “metabolic obesity”. Recognizing the need to work as a team across disciplines—in particular, endocrinologists and surgeons—is the first step towards addressing the issues and opportunities that surgery has to offer diabetes care and research.

**Conflicts of interests**

The authors have reported no conflict of interests.

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Medical follow up after bariatric surgery: nutritional and drug issues
General recommendations for the prevention and treatment of nutritional deficiencies

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Abstract
This review is an update of the long-term follow-up of nutritional and metabolic issues following bariatric surgery, and also discusses the most recent guidelines for the three most common procedures: adjustable gastric bands (AGB); sleeve gastrectomy (SG); and roux-en-Y gastric bypass (GBP). The risk of nutritional deficiencies depends on the percentage of weight loss and the type of surgical procedure performed. Purely restrictive procedures (AGB, SG), for example, can induce digestive symptoms, food intolerance or maladaptive eating behaviours due to pre- or postsurgical eating disorders. GBP also has a minor malabsorptive component. Iron deficiency is common with the three types of bariatric surgery, especially in menstruating women, and GBP is also associated with an increased risk of calcium, vitamin D and vitamin B12 deficiencies. Rare deficiencies can lead to serious complications such as encephalopathy or protein-energy malnutrition. Long-term problems such as changes in bone metabolism or neurological complications need to be carefully monitored. In addition, routine nutritional screening, recommendations for appropriate supplements and monitoring compliance are imperative, whatever the bariatric procedure. Key points are: (1) virtually routine mineral and multivitamin supplementation; (2) prevention of gallstone formation with the use of ursodeoxycholic acid during the first 6 months; and (3) regular, life-long, follow-up of all patients. Pre- and postoperative therapeutic patient education (TPE) programmes, involving a new multidisciplinary approach based on patient-centred education, may be useful for increasing patients’long-term compliance, which is often poor. The role of the general practitioner has also to be emphasized: clinical visits and follow-ups should be monitored and coordinated with the bariatric team, including the surgeon, the obesity specialist, the dietitian and mental health professionals.

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Keywords: Bariatric surgery; Guidelines; Gastric bypass; Adjustable gastric band; Vertical banded gastroplasty; Sleeve gastrectomy; Nutritional deficiency; Supplementation; Therapeutic patient education; Review

Résumé
Prise en charge médicale après chirurgie bariatrique: prescriptions diététiques, médicamenteuses et suivi. Mesures générales indispensables
Dans cette revue sont présentés les principaux problèmes nutritionnels et métaboliques que pose le suivi à long terme des patients ayant bénéficié d’une chirurgie bariatrique et discutées les recommandations récemment publiées concernant l’anneau gastrique ajustable (AGA), la gastrectomie longitudinale (GL) et le court circuit gastrique (CCG). Le risque de carence nutritionnelle dépend de l’importance de la perte de poids et du type de chirurgie; les techniques purement restrictives (AGA, GL), peuvent induire des troubles digestifs, une intolérance pour certains aliments et des comportements alimentaires mal adaptés en rapport avec des troubles du comportement alimentaire pré ou post opératoires. Le CCG entraîne de plus une malabsorption intestinale modérée. La carence en fer est fréquente dans les 3 cas et concerne particulièrement les femmes non ménopausées. Le CCG augmente le risque de carences en fer, calcium-vitamine D et vitamine B12. Certaines carences rares conduisent à des complications sérieuses comme l’encéphalopathie ou la malnutrition protéino-énergétique.

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Le risque à long terme de maladies osseuses ou de complications neurologiques doit être connu et prévenu. Quelle que soit la technique chirurgicale, la surveillance nutritionnelle, la prescription de suppléments appropriés et la surveillance de l’adhésion des patients à ces mesures s’imposent. Les trois points clefs sont (1) la prise quasi systématique de minéraux et de multivitamines; (2) la prévention de la lithiase biliaire par l’acide ursodésoxycholique pendant les 6 premiers mois; (3) le suivi à vie des patients. L’éducation thérapeutique du patient (ETP) est une nouvelle approche, par nature multidisciplinaire, centrée sur la personne. Des programmes d’ETP doivent être mis en place avant et après la chirurgie pour améliorer l’adhésion et la compliance à long terme des patients, qui est souvent médiocre. Le rôle du médecin traitant est à valoriser car c’est lui qui peut coordonner et contrôler le suivi, en collaboration avec l’équipe médicoc chirurgicale qui accomplit le chirurgien, le spécialiste de l’obésité, la diététicienne, le psychologue et le psychiatre.
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Mots clés : Chirurgie bariatrique ; recommandations ; court circuit gastrique ; anneau gastrique ajustable ; gastroplastie verticale calibre ; gastrectomie en gouttière ; carence nutritionnelle ; supplémentation ; éducation thérapeutique du patient ; revue

1. Introduction

Current bariatric surgery includes solely restrictive gastric procedures—adjustable gastric bands (AGB), vertical banded gastroplasty (VBG) and sleeve gastrectomy (SG)—and a combined procedure, the roux-en-Y gastric bypass (GBP) [1]. GBP, characterized by a restrictive component and a minor malabsorptive state, is believed to affect the hormones [such as ghrelin, glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)] that control eating behaviours and body weight [2]. Indeed, changes in gut peptide concentrations can cause a profound loss of appetite. SG also affects ghrelin secretion. This is a review of the standard of practice for long-term nutritional management, mainly in relation to the most common bariatric procedures (AGB, GBP and SG). VBG is no longer performed in France, and biliopancreatic diversion (BPD), with or without duodenal switch (DS), is a complex procedure that is reserved for very specific situations. The perioperative management of the obese patient and of any surgical complications are beyond the scope of this review.

Assessment of the metabolic and nutritional consequences of bariatric surgery is best guided by the type of surgical procedure involved. Both AGB and VBG have minor effects on normal physiological digestive processes and, as a result, selective nutritional deficiencies are presumed to be unusual. However, caloric or nutritional restriction, maladaptive eating behaviours and digestive symptoms can lead to nutritional deficiencies. This is particularly true when weight loss is rapid and significant. On the other hand, it is well established that the anatomical changes imposed by malabsorptive surgical procedures can also increase the risk of nutrient deficiencies.

The major issues summarized here are based on the recently published French, European and US guidelines [3–6] [all recommendations (R) are shown in italics], along with the few published expert recommendations [7–14] and our own accumulated experience. However, consensus is still lacking on many critical issues, probably because the long-term nutritional outcome data are scanty. Also, there are no evidence-based guidelines for an optimal postoperative supplementation strategy.

2. Preliminary comments on perioperative nutritional management

2.1. Preoperative management

Many patients have preoperative eating disorders or nutritional deficiencies that may persist after undergoing a bariatric procedure. There is now evidence to support the need for routine assessments of the patient’s protein and micronutrient status prior to bariatric surgery [15,16]. An appropriate nutritional evaluation, including selective micronutrient measurements, is absolutely necessary for all patients before any bariatric surgical procedure [5].

2.2. Early postoperative nutritional management (< 5 days)

In general, the following guidelines are used [3–6]: (1) clear liquids usually in the morning after any bariatric surgical procedure (R46) [5]; (2) gradual progression in food consistency over the subsequent weeks and months, depending on the type of surgical procedure (R48) [5]; and (3) nutritional and meal-planning guidance provided to the patient during the postoperative hospital course (R49) [5]. In addition, consultation with the dietician who was also a member of the bariatric surgery team is absolutely necessary (R47) [5].

3. Late postoperative nutritional management (≥ 5 days)

Follow-up of the morbidly obese patient who has been surgically treated can be divided into three periods: (1) the weight-loss phase (0–18 months, with the vast majority of weight loss accomplished by around 1 year); (2) the weight-regain phase [2–6 years after surgery, according to the Swedish Obese Subjects (SOS) study [17], in which about one-third of the initial weight loss was regained within 5 years]; and (3) the weight-stability phase (6–15 years, according to the SOS study).
3.1. Postsurgical eating behaviours and weight loss

Bariatric surgery requires a considerable change in eating behaviours [3,5,18]. Gastric restriction leads to a drastic reduction in the quantity of food eaten at each meal because of the limited volume capacity of the surgically created gastric pouch (30–60 ml for GBP) [5]. This physical restriction is the major mechanism of the weight loss.

As recommended by all experts, surgically treated patients need to adhere to a plan of multiple small meals per day; they must chew their food well and drink no beverages at the same time (> 30 min apart), and they need to stop eating as soon as they feel full (R50) [3-5]. Patients should also adhere to recommendations for a healthful lifestyle, including increased consumption of fruit and vegetables, while limiting foods that are high in saturated fats and simple carbohydrates (R51) [5].

Changes in body mass index (BMI), weight loss as percent of excess body weight (EBW) and weight loss as percent of initial weight are the most common parameters for assessing weight changes after bariatric surgery [3-5]. Success can be defined as the loss of at least 50% of EBW, with a minimal follow-up duration of 3–5 years [5,19].

Either dramatic or inadequate weight loss has to be monitored. The most rapid weight loss occurs during the first 3 months postoperatively, when dietary intake is highly restricted [3, 5], and the peak weight loss is achieved at 12–18 months following the procedure. After AGB, changes in weight are less rapid and a weight loss of 1.13 kg/week is advisable [5].

Inadequate weight loss after bariatric surgery (phase 1) may be observed after any procedure, but is especially commonly seen after AGB and VBG. This may be due to a poorly adjusted laparoscopic adjustable gastric band (LAGB) or loss of integrity of the gastric pouch (AGB, GBP, SG) [5]. More frequently, it is the result of the development of maladaptive eating behaviours: increased calorie intake; increased consumption of calorie-dense foods (sweets and ice cream); and grazing (continual eating of small amounts of food throughout the day), often associated with psychological disorders [3,5,7,8]. Clinical assessment then involves: (1) evaluation of current eating behaviour; (2) psychological evaluation; and (3) if indicated, imaging studies of the upper gastrointestinal tract (R79) [5].

Long-term weight maintenance (phases 2 and 3) is better with GBP than that reported with purely restrictive gastric procedures although, as already mentioned, weight regain is also observed 2–5 years after GBP [5,17]. For many patients, calorie intakes increase gradually over time. In the SOS study [20], self-reported intakes decreased within the first 6 months after surgery from about 2900 kcal/d to 1500 kcal/d, but then increased to around 2000 kcal/d over the next 6 years. Other factors may also be involved, such as a decrease in the frequency of ‘dumping’ (rapid gastric emptying) symptoms, resolution of food intolerances and a return to preoperative disordered eating [5].

3.2. Gastrointestinal symptoms

During the first few months of bariatric surgery, episodes of regurgitation—typically without nausea or true vomiting—are common when food is consumed in large volumes, or too quickly or without being thoroughly chewed [5].

3.2.1. Chronic vomiting

One- to two-thirds of patients report postoperative vomiting [3,5,8], especially during the first 6 months of surgery. Vomiting occurs in response to feelings of fullness, or to food lodged in the gastric pouch or upper digestive tract (‘plugging’). Frequent vomiting that persists for more than 6 months suggests: (1) obstruction, requiring evaluation with a gastrointestinal contrast study or endoscopic procedure; or (2) reflux, inflammation, stomal ulceration or stenosis, necessitating endoscopy [5]. Regurgitation or vomiting that occurs after an LAGB procedure can be managed with appropriate band adjustments and nutritional advice [3–5].

3.2.2. Diarrhoea

Diarrhoea is uncommon after bariatric surgery but, if it persists, an evaluation should be initiated (R132) [5].

3.3. General symptoms

Cold intolerance, hair loss and fatigue are common complaints, but tend to diminish as weight loss stabilizes [3,5].

3.4. Gastric bypass-specific problems

3.4.1. Dumping syndrome

Dumping syndrome—beginning 30–60 min after eating—is common, occurring in about 70% of patients who have undergone GBP [5], but often only transiently during the first postoperative year.

Calorie-dense liquids or foods (foods high in sugar, including ice cream and pastries) that bypass much of the stomach undigested will cause hyperosmolarity of the intestinal contents. Such an osmotic overload draws fluid into the intestinal lumen, with subsequent intestinal distention, fluid sequestration, decreased intravascular volume and hypotension. As has been recently suggested, the release of gut peptides may also be involved [5].

Symptoms (abdominal pain and cramping, nausea, light-headedness, flushing, tachycardia, sweating and even syncope) lead to extremely uncomfortable feelings and immense fatigue [3,5]. Diarrhoea is infrequent, as there is usually sufficient distal bowel to absorb food [8].
For many patients, these adverse events encourage them to make more appropriate food choices. For others, however, dumping symptoms are persistent and aversive. In such cases, nutritional manipulations are useful, including: (1) avoiding simple sugars, and increasing intakes of dietary fibre and complex carbohydrates; (2) avoiding ingestion of liquids within 30 min of a solid-food meal; and (3) eating small, frequent meals [5].

In some departments, it is possible to measure body composition using dual-energy X-ray absorptiometry (DEXA), which may also be useful for characterizing the risk factors for changes in fat-free mass.

4. Psychological and quality-of-life outcomes

Health-related quality-of-life (HRQL) measures, including psychosocial functioning, perceived health, mood, anxiety, mobility, self-image and other obesity-specific problems, are improved in the majority of patients following anti-obesity surgery [3, 5]. However, changes in HRQL after surgical treatment followed phases of weight loss, weight regain and weight stability, as demonstrated by the SOS study [17]. Indeed, the long-term effects of bariatric surgery on HRQL are attenuated by significant weight regain in large numbers of patients [17]. For this reason, it is recommended to assess HRQL in clinical practice [3].

4.3. Drug management

4.3.1. Prevention of gallstone formation

An increased risk of gallstone formation has been associated with obesity and with episodes of significant weight loss, and is a major problem with bariatric surgery. Gallstones and sludge formation have been reported in 30% of patients 6 months after GBP, but also with the other procedures (AGB, SG, BPD) [5,27–29]. Rapid weight loss (about 25% of initial weight) is the most important risk factor for the development of gallstones [5,29]. The effect of ursodeoxycholic acid therapy on gallstone formation has been clearly demonstrated in surgically treated patients [5,30]. Oral administration of ursodeoxycholic acid (Ursolvan® 200 mg three times a day, or Delursan® 250 mg twice a day) for at least 6 months postoperatively may be considered in patients not undergoing a prophylactic cholecystectomy (R145) [3,5].

4.3.2. Concomitant drug treatment

There is clear consensus in the management of preexisting medical conditions to make adjustments to concomitant drug treatment [3–5,31].

• In those patients without complete resolution of their T2DM, hyperlipidaemia or hypertension, continued surveillance and management should be guided by currently accepted practice guidelines for those conditions (R82) [5].

• In those patients in whom T2DM, hyperlipidaemia and hypertension have resolved, continued surveillance should be guided by recommended screening guidelines for the specific age group (R83) [5].
Diuretics induce magnesium, potassium and thiamine loss through the urine, and may increase vitamin and mineral requirements [12,14]. Diuretic treatments may also be responsible for dehydration, hypotension and loss of electrolytes [12].

Non-steroidal anti-inflammatory drugs (NSAIDs) should be used with extreme caution due to their potential to cause anastomotic ulcers [8].

5. Nutritional deficiencies: metabolic and nutritional surveillance

Which vitamins and/or minerals should be measured for which bariatric procedures, and which supplements should be given? It should be emphasized that the frequency of and recommended nutritional surveillance, as well as vitamin and mineral supplementation, remain empirical for surgically treated patients [5,7–13]. Such schedules have not been precisely delineated in the French guidelines [3], most likely because of the lack of evidence-based data. Moreover, such a schedule would be difficult to determine as the results so far are equivocal, given the wide range of definitions of deficiency, supplement protocols, duration of the studies and types of surgical procedures.

The main pathophysiological mechanisms are presented in Table 1, and guidelines are presented in Table 2. As for the most important recommendations, the main principles are clear in all guidelines. *Routine metabolic and nutritional monitoring is recommended following all bariatric surgical procedures (US R85)* [5]. In addition, all patients who have undergone bariatric procedures require regular life-long, qualified surveillance [4].

Table 1

<table>
<thead>
<tr>
<th>Deficiency or complication</th>
<th>Prevalence (or risk)</th>
<th>Causal factors or circumstances</th>
<th>Complications or consequences</th>
<th>Laboratory test* or other investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vomiting</strong></td>
<td>G: ++</td>
<td>Stuck food (G: ++), anastomotic stenosis (G: BP)</td>
<td>Hypokalaemia, dehydration, renal failure</td>
<td>Electrolytes, haematocrit (CBC)</td>
</tr>
<tr>
<td><strong>Iron</strong></td>
<td>G: +, S: +</td>
<td>Menstruating women, meat intake</td>
<td>Microcytosis, anaemia, fatigue, brittle nails</td>
<td>4% transferrin saturation (iron) CBC (haemoglobin), ferritin &lt; 20 mg/L (transferin soluble receptor)</td>
</tr>
<tr>
<td><strong>Vitamin B12</strong></td>
<td>G: +, S: + (? )</td>
<td>Meat and dairy intakes, malabsorptive procedure (G: BP), extreme weight loss (i.e. low food intake)</td>
<td>Macrocytosis, anaemia, neuropathy</td>
<td>Vitamin B12, MMA (optional), holotranscobalamin II (optional), homocysteine (optional)</td>
</tr>
<tr>
<td><strong>Calcium, vitamin D</strong></td>
<td>G: – or ±, S: ++</td>
<td>Intake of calcium-rich foods, malabsorption of calcium and vitamin D</td>
<td>Osteomalacia, osteoporosis, fractures</td>
<td>1,25(OH)2D, PTH, alkaline phosphatase, icalcaemia: rare, DEXA (I bone density)</td>
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<tr>
<td><strong>Vitamin B9</strong> (folate)</td>
<td>G: ±, S: ± (? )</td>
<td>Low intake, low compliance with supplements</td>
<td>Macrocytosis, anaemia, pregnant women: fetal neural-tube defects</td>
<td>Folate, IRBC folate, homocysteine (optional)</td>
</tr>
<tr>
<td><strong>Proteins</strong></td>
<td>G: –, S: ± (? )</td>
<td>Low protein (and energy) intakes, intercurrent illness, extreme weight loss (i.e. low food intake)</td>
<td>Oedema</td>
<td>Albumin, prealbumin, DEXA (1 fat-free mass)</td>
</tr>
<tr>
<td><strong>Vitamin B1</strong> (thiamine)</td>
<td>G: ±, S: ± (? )</td>
<td>Recurrent vomiting (G:), glucose intravenous infusion with no vitamin B1 supplementation</td>
<td>Neuropathy, Gayet–Wernicke encephalopathy</td>
<td>Thiamine</td>
</tr>
<tr>
<td><strong>Zinc, selenium</strong></td>
<td>G: – or ±, S: ±</td>
<td>Low intake, severe weight loss (i.e. low food intake)</td>
<td>Hair loss (? zinc), selenium: no symptoms</td>
<td>Zinc RBC, +selenium</td>
</tr>
<tr>
<td><strong>Other vitamins (A, E, K)</strong></td>
<td>G: –, S: ± (? )</td>
<td>Malabsorptive procedure (G: BP), extreme weight loss (i.e. low food intake)</td>
<td>Vitamin A: night blindness, vitamin E: oxidative stress, vitamin K: bleeding disorder</td>
<td>Vitamin A, vitamin E, vitamin K1 + INR</td>
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</tbody>
</table>

*Based on plasma concentrations; 
- very rare; e: rare; v: very frequent; (?): no data available; 
AGB: adjustable gastric bands; GBP: gastric bypass; SG: sleeve gastrectomy; CBC: complete blood cell count, DEXA: dual-energy X-ray absorptiometry; INR: international normalized ratio; MMA: methylmalonic acid; PTH: parathyroid hormone; RBC: red blood cells; All data are adapted from references 3–6, 8, 11, 12 
VBG: vertical banded gastropasty
The present authors' protocol is summarized in Table 3. Follow-up nutritional and metabolic visits need to be stratified by type of surgical procedure and presence of complications or co-morbidities [3–6]. These consultations have to be performed by a physician with expertise in nutritional and metabolic medicine [5]. Intestinal adaptation occurs after 1–3 years, so weight loss and metabolic or nutritional derangements should eventually be stabilized [5]—but only if the patient makes healthy food choices.

5.1. Vomiting consequences (AGB and VBG)

5.1.1. Dehydration

After gastric restriction, many patients have difficulties with drinking water separately from meals, and it is not easy to hold much fluid when the gastric pouch is small. Consequently, dehydration is a common problem. Patients need to learn how to sip fluids and not take large gulps [8].

5.1.2. Hypokaliemia

Control of kaliemia is necessary if vomiting is frequent or prolonged [3,5,12].

5.1.3. Thiamine deficiency and Gayet–Wernicke syndrome (see below)

Thiamine deficiency is mainly due to vomiting and the administration of intravenous glucose with no parenteral supplementation with thiamine [3,5,7].

5.2. Protein depletion and protein-energy malnutrition

Intolerance of protein-rich foods is common, especially in the form of meat products, within the year after bariatric surgery. For this reason, many patients fail to meet the recommended daily intake of protein, and limit their intake to less...
than 50% of the recommended amount [5]. Protein depletion is rarely isolated, as energy intake is often extremely low in such cases [8], leading to a state of protein-energy malnutrition.

Protein intake should average 60–120 g/d (R52) [5]. Regular assessment of protein intake should be performed periodically (R90) [5], and protein supplements have to be proposed if protein intake remains < 60 g daily (R91) [5]. Nevertheless, protein malnutrition is rare in morbidly obese surgically treated patients whatever the procedure (AGB, GBP, SG) [12,32], and the standard GBP is not associated with severe protein malnutrition [32], a condition characterized by oedema, loss of muscle mass and frank hypoalbuminaemia.

Parenteral nutrition should be considered for patients with severe protein malnutrition who are not responsive to oral protein supplementation (R92) [5], and prompt hospital admission for initiation of nutritional support is necessary (R158) [5].

At our centre, artificial enteral nutrition (using nasogastric delivery) is used, if possible, based on the same considerations that guide treatment decisions for severely malnourished patients: the potential benefits and risks compared with parenteral nutrition.

5.3. Iron

Surgically treated patients are at high risk of developing iron deficiency [3–6, 9]; this is true for both the restrictive and malabsorptive procedures. In fact, iron stores continuously decline after GBP surgery [8]. Iron status should be monitored in all bariatric surgery patients and then appropriately treated as in any medical or surgical patient (R109) [5]. After GBP, iron supplementation could be provided routinely and systematically to menstruating women, or when ferritin levels or siderophilin saturations are low.

Calcemia + 25OH D GBP GBP GBP GBP GBP GBP

Intact PTH GBP GBP GBP GBP GBP GBP

DRE, bone density GBP GBP GBP GBP GBP GBP

Albumin (prealbumin) AGB AGB AGB AGB AGB AGB

Table 3 Follow-up and laboratory tests after AGB, GBP and SG*

<table>
<thead>
<tr>
<th></th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
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<td>Chemistry panel: CBC</td>
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<td>Iron (% transferrin saturation), ferritin</td>
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<td>Vitamin B12 (± MMA)</td>
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<td>RBC, folate</td>
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<td>Calceamia + 25OH D</td>
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<td>DRE, bone density</td>
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</table>

*Data adapted from references 3–6, 8, 11, 12; intensive clinical follow-up is recommended after AGB during the first year at month 1, 2, 3, 4, 6, 8, 10 and 12 (if necessary) [6];
* For patients non-compliant with oral multivitamin supplementation during weight-loss phase or according to clinical symptoms; † if deficiency is suspected;
CBC: complete blood cell count; DEXA: dual-energy X-ray absorptiometry; MMA: methylmalonic acid; PTH: parathyroid hormone; RBC: red blood cells.
From a practical point of view, patients need to take iron supplementation and other supplements at different times, as iron interferes with the absorption of calcium, magnesium and zinc [12].

5.4. Vitamin B12

Vitamin B12 deficiency is a common consequence of GBP [7]. GBP produces changes in vitamin B12 physiology, but the risk of B12 deficiency may also be increased by restrictive surgery if patients have a low intake of meat or dairy products. The consequences are serious: there is a risk of irreversible neuropathy if the deficiency is maintained over a long period of time. Fortunately, the body storage of vitamin B12 is substantial, and deficiencies are usually described after 1 or more years following bariatric surgery. However, SG may theoretically be the cause of an intrinsic factor deficit for anatomical reasons, although long-term data are lacking.

Evaluation for vitamin B12 deficiency is recommended in all bariatric surgery patients (R113) [5]. It should be done annually in patients who have undergone GBP (R116) [5]. After GBP, oral supplementation with crystalline vitamin B12 at a dosage of ≥ 350 μg daily may be used to maintain vitamin B12 levels (R114) [5]. Parenteral supplementation with either 1000 μg of vitamin B12 monthly or 1000–3000 μg every 6–12 months is necessary if vitamin B12 sufficiency cannot be maintained by means of oral supplementation (R115) [5].

5.5. Vitamin B9 (folate)

Folic acid supplementation (400 μg/d) is provided as part of a routine multivitamin preparation (R117) [5]. However, there is no need for specific supplementation, as folate deficiency is uncommon except for patients who do not eat vegetables.

Folic acid supplementation should be provided in all women of childbearing age because of the risk of fetal neural-tube defects with folic acid deficiency (R118) [5].

5.6. Vitamin D and calcium

At present, there are no conclusive data regarding the association of altered calcium and vitamin D homeostasis with AGB surgery [5]. However, calcium deficiency and metabolic bone disease can occur in patients who have undergone GBP [5]. Calcium absorption is especially reduced due to the loss of acid action. Also, it needs to be emphasized that rapid and extreme weight loss is associated with bone loss, even in the presence of normal vitamin D and parathyroid hormone (PTH) levels [5].

An increase in serum intact PTH is indicative of a negative calcium balance or vitamin D deficiency, or both. Secondary hyperparathyroidism, which is commonly seen after GBP (30–40%), promotes bone loss while increasing the risks of osteopenia and osteoporosis [5]. Elevated levels of bone-specific alkaline phosphatase and osteocalcin levels, indicative of increased osteoblastic activity and bone formation, are often the initial abnormalities [5].

Vitamin D supplementation can be provided by ergocalciferol or cholecalciferol (Table 2), and parenteral vitamin D supplementation can also be used. Calcitriol [1,25-(OH)2D] therapy is generally unnecessary, and can increase the risk of hypercalcaemia and hyperphosphataemia [5].

5.7. Vitamin B1

The prevalence of vitamin B1 deficiency is low, but the consequences can be serious [3–5]. Irreversible polyneuropathy and Gayet– Wernicke encephalopathy (ocular disorders with nystagmus, ataxia, and mental disturbances and confusion) have been described [33–41]. High glucose intakes (dietary or glucose intravenous infusion) may precipitate a deficiency in patients who have low vitamin B1 reserves [5,7–12].

The following US guidelines [5] are clear and specific:
- All bariatric surgery patients should be provided with an oral multivitamin supplement that contains thiamine (R124);
- Routine screening for thiamine deficiency or additional empirical thiamine treatment (or both) is not recommended in bariatric surgery patients who are already routinely receiving a multivitamin supplement that contains thiamine (R125);
- Patients with protracted vomiting should be screened for thiamine deficiency (R126);
- In patients with persistent vomiting after any bariatric procedure, aggressive supplementation with thiamine is imperative; intravenously administered glucose should be provided judiciously in this situation because it can aggravate thiamine deficiency (R127);
- In patients presenting with neurological symptoms suggestive of thiamine deficiency (that is, Wernicke encephalopathy and peripheral neuropathy), aggressive parenteral supplementation with thiamine (100 mg/d) should be administered for 7–14 days (R128);
- Subsequent oral thiamine supplementation (100 mg/d) should be continued until neurological symptoms resolve (R129).

The optimal dose and duration of thiamine treatment for prophylaxis or treatment of Gayet–Wernicke encephalopathy remain controversial [42].

5.8. Selenium

Few clinical studies have been published of selenium deficiency after the usual bariatric procedures [9, 43]. In our experience, around 25% of patients have low selenium
plasma concentrations, but no clinical symptoms. In addition, there are insufficient data to support routine screening for selenium deficiency or empirical selenium supplementation in patients who have undergone a bariatric surgical procedure (R120) [5].

5.9. Zinc

Low zinc concentrations have been described following gastroplasty due to reduced dietary zinc intake [3,5,9,12]. Hair loss is often considered a consequence of zinc deficiency, although evidence is lacking [8]. One study reported resolution of alopecia using high-dose zinc sulphate in patients who had undergone VBG [44]. However, hair loss may also be associated with the ‘stress of weight loss’ [8], or linked to protein or iron deficiencies [12].

5.10. Vitamins A, E and K

Deficiencies in vitamins A, E and K are evidently extremely rare after standard GBP [3,5,12,13].

6. Severe long-term nutritional complications

6.1. Osteoporosis

The impact of obesity surgery on bone metabolism has been reviewed by Wucher et al. [45]. Bone loss frequently occurs after bariatric surgery and particularly after GBP. Early bone loss due to bone resorption has been described, as suggested by an increase in bone markers. The mechanisms may involve adipokines such as leptin and adiponectin [45].

As long-term studies of the risk of osteoporosis are lacking [3,5,7,9], it is difficult to view the future with confidence for young women who do not like dairy products and/or are not compliant with calcium or vitamin D supplementation. Significant changes in bone mass could be problematical 20 to 40 years later. On the other hand, postmenopausal women with other risk factors for osteoporosis are at high risk of decreased bone mass after bariatric surgery [5,7,8]. For this reason, regular DEXA assessments of bone density (Table 3) should be scheduled for patients who are at high risk of osteoporosis.

6.2. Neurological complications

A wide spectrum of serious neurological conditions can occur after bariatric surgery (GBP, VBG and AGB) [33–35], and most often manifest as encephalopathy, myelopathy, optic neuropathy, polyradiculoneuropathy and polyneuropathy [34]. Encephalopathy and polyradiculoneuropathy are acute, and early complications are associated with rapid weight loss [34]. Myelopathy is a late severe complication that has been observed around a decade after surgery [34]. A retrospective study [33] revealed three clinical patterns of peripheral neuropathy after bariatric surgery: sensory-predominant polyneuropathy; mononeuropathy; and radiculoplexus neuropathy. Their pathogenesis is still a subject of debate, but malnutrition, inflammation and altered immunity may be involved [33,34]. The role of vitamin B1 has been already emphasized in Gayet–Wernicke encephalopathy, and, in general, these patients have multiple nutritional deficiencies (such as vitamin B12 and copper) [3,5,33,34].

A newly described syndrome—‘acute postgastric reduction surgery neuropathy’—is characterized by vomiting, weakness, hyporeflexia, pain, numbness, incontinence, visual loss, hearing loss, attention loss, memory loss, nystagmus and severe proximal symmetrical weakness in the lower extremities [5]. The underlying cause is thought to be insufficient thiamine in addition to other nutritional deficiencies [5].

6.3. Multifactorial nutritional anaemia

Nutritional anaemias resulting from malabsorptive bariatric surgical procedures can also involve deficiencies in protein, copper and selenium, requiring evaluation of these nutrients when routine screening for iron, vitamin B12 and folic acid deficiencies is negative (R119) [5].

6.4. Cardiovascular diseases

Hyperhomocysteinaemia, an independent risk factor for coronary artery disease, has been associated with folate and vitamin B12 deficiencies in bariatric surgery patients [46]. An increase in homocysteine levels was observed in two-thirds of gastroplasty-treated patients in the Lyon study [46], with clear-cut hyperhomocysteinaemia (> 15 micromol/L) in 32%. Changes in homocysteine concentrations were significantly correlated with weight loss and with decreases in plasma folate concentrations. Although the long-term SOS study [47] results indicated a decrease in the risk of cardiovascular mortality, the debate is still open for vulnerable groups at risk of nutritional deficiency, especially patients who are non-compliant with folate supplementation.

7. High-risk groups or situations

7.1. Pregnant women

Pregnancy is not recommended in the 12–18 months after surgery, as various deficiencies of vitamins and micronutrients could play a role in causing fetal malformations or complications. Assessing nutritional status and the supplements to be prescribed have been reported by Poitou et al. [12]. Iron, vitamin D/calcium and folate are the three priorities in terms
of nutritional deficiencies that require careful monitoring (before conception, if possible) [12]. It is also important to look out for overdoses, especially of vitamin A. In addition, a contraceptive strategy may be proposed if necessary.

7.2. Adolescents

Bariatric surgery is being more and more discussed for ‘super-obese’ adolescents. However, the consequences on adolescent growth and development are yet to be carefully evaluated for the long term [7]. Moreover, it is well known that compliance with multivitamin supplements is often low among patients in this age category.

7.3. Eating disorders

The impact of pathological eating and, especially, binge-eating disorder (BED) on postsurgical outcomes is of particular interest for several reasons [18, 48]: (1) the prevalence of BED is high among the massively obese patients who seek surgical treatment (10–50% or more); (2) uncontrolled eating has deleterious effects on weight management after surgery; and (3) the frequency of psychiatric co-morbidities in this subgroup of obese patients is high. However, studies that have examined the impact of BED on postsurgical outcomes have, so far, yielded equivocal results [18, 48].

As highlighted by Marcus et al. [18], binge eating that starts or reemerges after surgery is associated with less weight loss and with weight regain. One difficulty in assessing BED according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM IV) definition is that the loss of control over eating is usually more subjective than objective. From an anatomical point of view, binge eating is difficult with the small gastric pouch, but BED can lead to stretching of the pouch or of the gastrojejunal anastomosis, which is a severe complication.

In our experience, some individuals with BED resume objective binge eating in the short term, during the weight-loss phase, but its reemergence in the maintenance period (phase 2) leads to weight regain. However, the de novo appearance of disordered eating—the so-called ‘post-surgical eating-avoidance disorder’—has been described by Segal et al. [49], and is characterized by a number of features, including very rapid weight loss, excessive reduction of food intake, the use of a purgative strategy and body-image dissatisfaction or distortion.

7.4. Concomitant illness and major aggression

Major trauma, aggression, fever or any severe concomitant illness (such as infectious disease or heart failure) can accelerate the clinical manifestations of nutritional deficiencies because of the increased energy, protein, vitamin or mineral requirements brought about by such events [3, 5]. This suggests that all surgically treated obese patients should be considered as potentially severely malnourished patients.

Parenteral nutrition (PN) should be considered in high-risk patients, such as critically ill patients unable to tolerate sufficient enteral nutrition for > 5–7 days or non-critically ill patients unable to tolerate sufficient enteral nutrition for > 7–10 days (R56) [5]. However, as already stated, in our experience, artificial enteral nutrition and hydration often constitute a better solution.

7.5. Depression and risk of suicide

Mood disorders appear to be the most common psychiatric co-morbidity in this patient population. The impact of depression or other psychiatric disorders on postsurgical outcomes remains unclear, given the lack of specific data [3, 5, 18]. Marcus et al. [18] recently reported that a lifetime history of mood or anxiety disorder was associated with poorer short-term weight loss at 6 months after GBP. However, the SOS study [17] found a substantial positive long-term effect of weight reduction on depression symptoms that was at least partly dependent on weight loss.

However, negative psychological responses to bariatric surgery have been reported in a significant minority of patients, and any improvements in psychosocial status have been lost 2–3 years after surgery [5]. The reasons for this remain unclear and require further investigation. Also, some published reports show an increased risk of suicide after bariatric surgery [50, 51] and, again, further specific studies are needed to explore this important issue.

7.6. Addictive behaviours

The prevalence of ‘addictive’behaviours, such as alcohol abuse, gambling, addiction to medications, compulsive shopping and driven sexual behaviours, may be increased in the morbidly obese population, and may also be a problem for bariatric surgery patients[18]. Indeed, in our experience, BED resolves in some patients, but a new addictive behaviour then emerges. This suggests that there is probably a relationship between substance abuse and eating problems. It may be prudent to monitor patients’ alcohol use following bariatric surgery, as has been recommended by Marcus et al. [18].

8. Specific management and frequency of follow-up visits by surgical procedure

The frequency of follow-up visits should be modified according to the patients’ weight loss over time, occurrence of clinical symptoms or complications and type of procedure performed [3–6]. Closer clinical follow-up is more necessary after AGB than after GBP, whereas the reverse is true for perioperative nutritional evaluations [3–6].
8.1. Adjustable gastric bands

All experts agree that regular consultations for advice and adjustments are critical for achieving good weight loss, at least during the first postoperative year [3–6]. At that time, follow-ups should take place at least every 3 months, starting 2–4 weeks postoperatively until a clinically satisfactory rate of weight loss is achieved, and with repeated band fills if necessary. Thereafter, follow-up should be at intervals of no greater than 1 year for as long as the device has not been reverted or removed [3–5].

Appropriate AGB adjustments should be performed according to the individual patient’s weight loss and the type of the implant as a medical/clinical decision, by trained medical or paramedical staff with adequate experience (such as a surgeon, medical physician, nurse practitioner or dedicated radiologist) [4].

Metabolic and nutritional statuses, including vitamin and micronutrient blood levels, should be regularly monitored to prevent nutritional deficiencies and to allow appropriate supplementation [4,5]. Vitamin and micronutrient supplements should compensate for their possible reduced dietary intakes [3–6].

8.2. Non-adjustable gastric bands and other purely restrictive operations

For these procedures, the recommendations are similar to those for AGB except that band adjustments are not required [4,5]. There are no specific published nutritional guidelines for SG, although a decrease in ferritin plasma concentrations has been reported by Toh et al. [16] in a small group of SG-treated patients.

8.3. Gastric bypass procedures

With GBP, the clinical follow-up is often easier than with solely restrictive procedures, as digestive symptoms (regurgitation, vomiting, plugging) are uncommon [3–5]. Weight loss is also usually more rapid, making the clinical follow-up protocol less restrictive [3–6].

Nevertheless, routine laboratory surveillance for nutritional deficiencies is recommended after GBP (Table 3), even in the absence of calorie or nutrient restriction, vomiting or diarrhoea. European guidelines [4] recommend the following protocol: checkup after 1 month, then follow-up at a minimum of every 3 months during the first year, every 6 months during the second year and annually thereafter.

Daily supplementation with a multivitamin– mineral preparation (1 or 2 tablets) is often inadequate, so additional iron and vitamin B12 supplements are usual after GBP [5]. If necessary, iron and calcium plus vitamin D may also be given for a few months or even continuously [3–5].

As recently demonstrated by Gasteyger et al. [52], nutritional deficiencies after GBP are commonly seen and cannot be prevented by standard multivitamin supplementation. Almost all patients required one or more nutritional supplements 2 years after surgery. This study also suggests that the prevalence—and probably the severity—of nutritional deficiencies will increase over time, at least during the first few years after GBP.

9. Multidisciplinary team

The pre- and postoperative management of bariatric surgery patients is clearly multidisciplinary [3–6]. The treating physician (in our experience, the nutritionist, who, in France, is a physician) and surgeon are responsible for the treatment of co-morbidities before the operation and for the follow-up after the operation [4]. Complementary follow-up pathways (surgical and medical) should be provided to all patients [4]. The surgeon is responsible for all possible short- and long-term events directly related to the operation. The medical physician is responsible for the long-term post-surgery follow-up, and management of obesity and obesity-related diseases and operation-related non-surgical consequences [4].

The US guidelines define the primary team as comprising the bariatric surgeon, the obesity specialist and the dietitian [5]. Yet, as general practitioners (GPs) or family physicians play a pivotal role in many health-service systems [3], it is crucial that GPs find their true place in both the pre- and postoperative management of these patients.

In addition, the intervention of mental-health professionals should be facilitated to help patients adjust to the psychosocial changes they will experience postoperatively. Regardless of the bariatric procedure, psychiatric counselling can benefit all bariatric surgery patients [5]. This is especially true when eating disorders or psychiatric co-morbidities are present [3].

10. Therapeutic patient education and patient responsibility

Behavioural treatments, generally considered a necessary component of any adequate obesity-treatment programme, are paradoxically rarely proposed after bariatric surgery. According to the guidelines, it is recognized that: (1) the patient takes lifelong responsibility for adhering to the follow-up rules [4]; and (2) treatment outcome is significantly dependent, among other factors, on patients' compliance with long-term follow-up [4]. All patients should be encouraged to participate in ongoing support groups after discharge from the hospital (R87) [5].

10.1. Adherence to nutritional treatment

As it is well known that the compliance rate with nutritional treatment is dramatically low [3–5], it is appropriate that
compliance be regularly assessed and encouraged during the postoperative follow-up. However, taking several pills every day is a problem for many patients, and the cost of treatment is probably a major barrier to adequate compliance. Gasteiger et al. [52] calculated that, at 2 years after GBP, a patient in Switzerland will have spent, on average, $35 a month for nutritional supplements alone. In addition, the costs related to extensive biological nutritional assessments are also high, averaging $360 per patient per sample at the Lausanne center, or $2100 for the six blood samples obtained during the entire follow-up period [52].

10.2. Therapeutic patient education by a multidisciplinary team

It is clear that disordered eating patterns, psychological difficulties and coping problems are present in many surgically treated patients, and that they are a cause of weight regain. Indeed, the conclusions of the SOS study [17] should be taken into account in clinical practice: “Difficulties among surgical patients to control and maintain weight loss over time should not be ignored. Many surgical patients may benefit from behavioural support programmes, and future research should systematically study whether the long-term efficacy of bariatric surgery may be further enhanced by implementing lifestyle-modification techniques in the postoperative management of patients’” [17].

It is now well established that education enables the patient to acquire greater knowledge and understanding of obesity and energy balance, self-management skills and psychosocial competencies. This approach is called ‘therapeutic patient education’ (TPE). The healthcare teams in charge of the education of surgically treated patients are increasingly focusing on education (patient-centred education), and not only on weight loss and eating behaviours. One major objective is to overcome the constraints that are derived from all sorts of barriers (psychosocial, cultural, ethnic, geographical) to TPE.

In fact, TPE could be a part of the patient’s preoperative management, as it is crucial to determine a person’s readiness to change behaviour before bariatric surgery. For example, emotional eating could be taken into account before any weight regain occurs 2–3 years after the surgical treatment. Emotional distress—especially depression and anxiety—interferes with self-management. As many obese patients take an ‘all-or-nothing’ approach to their eating behaviours, it may be that any antiobesity surgery would be unsuccessful. This suggests that the best approach may be to have, before surgery, well-informed patients who have received support and guidance from trained healthcare professionals working within a healthcare system that is able to respond to patients’ needs. In addition, from a practical point of view, nutrition and meal-planning guidance should be provided to the patient and family before bariatric surgery (R49) [5].

11. Conclusion

Severe obesity is a serious chronic clinical condition that requires the application of long-term strategies for its effective management and prevention. Bariatric surgery has a major impact on obesity-related co-morbidity [52], and decreased mortality rates in surgically treated obese patients are now relatively well documented [47,53,54]. Yet, bariatric surgery is not a ‘magic bullet’. Intensive preoperative nutritional and psychosocial counselling is believed to be important not only in the immediate postoperative period, but also in the long-term patient follow-up. It can promote greater adherence to diet, and improve weight loss and psychosocial functioning.

Furthermore, as follow-up should be considered lifelong, it is essential to involve the patient’s GP in the long-term postoperative management. Surprisingly, little is known of the factors that can facilitate and disrupt weight maintenance after surgical weight-loss treatment, and little scientific attention has been paid to ensure its long-term success [17].

As the incidence of nutritional deficiencies is known to be related to the magnitude of weight loss, attention should be focused on those patients who achieve extreme weight losses even with purely restrictive procedures (AGB). However, any deficiencies can easily be avoided by an adequate strategy of nutritional supplementation, which is important as serious complications related to the development of nutritional deficiencies have been described, including neurological dysfunction due to multivitamin deficiency, and osteoporosis because of calcium and vitamin D deficiencies. Moreover, an important question yet to be answered is: What happens in the long run?

Clinical guidelines have been developed and recently published, and it is now time to put them into practice and to verify that established standards of postoperative management of bariatric surgical patients are applied in real life.

Conflicts of interests

The authors have reported no conflict of interests.

References


Medical management of diabetes after bariatric surgery

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Abstract

Several studies indicate that bariatric surgery frequently leads to resolution or improvement of type 2 diabetes in overweight patients. However, the medical postoperative management requires lifelong counselling, monitoring and nutrient supplements in patients in remission as well as in patients who continue to be diabetic. The aim of such management is to avoid nutritional deficiencies, and to delay diabetes relapse by optimizing the control of risk factors. To this end, diet and pharmacological prescriptions, including vitamin and mineral supplements, are indispensable, despite the fact that specific recommendations, until now, have been lacking for these particular patients.

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Keywords: Bariatric surgery; Diabetes; Nutritional deficiency; Medical management; Review

1. Introduction

Patients with type 2 diabetes (DT2) are often able to achieve remission of their hyperglycaemia or reduce their required medication following bariatric surgery. In a recent systematic review and meta-analysis [1], 78.1% of diabetic patients showed complete disease resolution and, in 86.6% of cases, the diabetes was either improved or resolved. Fasting glucose levels, insulinaemia and haemoglobin A1c (HbA1c) levels can also decline significantly after bariatric surgery. Also, these favourable responses were maintained for 2 years or more, and were more frequent and pronounced in patients with early diabetes onset, and whose surgical procedures were associated with greater percentages of weight loss such as the roux-en-Y gastric bypass (RYBP). A randomized controlled trial comparing the laparoscopic band with optimized medical
approaches in patients with DT2 clearly demonstrated that surgically treated patients had a 5.5 relative risk of remission (P < 0.001) [2]. Today, the available data convincingly suggest that early surgical intervention for overweight DT2 patients may be clinically appropriate in those for whom operative risks are acceptable. This means that, in the near future, the indications for bariatric surgery are set to drastically increase in overweight [body mass index (BMI) > 30 kg/m²] DT2 patients. However, before this happens, it is important to be better able to assess the risks associated with bariatric surgery in order to design the optimal postoperative, long-term, medical management and lifestyle modifications required in this particular category of patients.

2. Benefits of bariatric surgery in diabetes: the postoperative period

More than a decade ago, it was shown that DT2 patients had fewer disease complications and longer lives following bariatric-surgery-induced diabetes resolution [3]. Surgery is not only followed by a significant resolution or improvement of diabetes, but also leads to a significant benefit in mortality [4] with, for example, lower disease-specific death rates for diabetes (~92%) and coronary artery disease (~59%) [5]. In general, bariatric surgery is particularly useful for the management of factors responsible for the high risk of cardiovascular disease. However, it would be unwise to consider DT2 patients whose diabetes was resolved after surgery as if they were the same as non-diabetic patients. The pathophysiology of DT2 suggests that these patients should continue to be treated as potential diabetics with residual risk, despite improvements in the main measurable risk factors such as blood pressure, serum lipid concentrations, insulin resistance and serum markers of inflammation. Indeed, these patients remain at risk of diabetes in the future, and the resolution of their diabetes and related risks are not necessarily definitive. However, it may also be postulated that, as in non-diabetic subjects, persistent weight loss, a healthy diet and increased physical activity will remain the cornerstones of a programme to prevent or delay the recurrence of diabetes and its complications.

3. The dietary challenge: maintaining weight loss and avoiding nutrient deficiency

Bariatric surgery is certainly the most effective tool in the management of obesity and diabetes so far, but it also presents a difficult dietary-management challenge. The role of the clinician is to carefully monitor and support their patients during the long-term changes they will have to make in eating and activity behaviours, while also aiming to both optimize the results of surgery and prevent any nutritional complications related to the procedure. Given this context, the long-term maintenance of the weight loss and the subsequent metabolic benefits is more challenging than the initial weight reduction.

Although the diet then becomes of major importance, until now, precise guidelines have been lacking [6]. Bariatric surgery—and especially RYGP, which is the procedure most frequently associated with resolution of diabetes—results in considerable changes and alterations in the digestive process. This results in a non-negligible risk of iatrogenic pathological syndromes such as functional complications (vomiting, dumping syndrome and diarrhoea), metabolic disorders (hypoglycaemia due to pancreatic cell hyperplasia) and nutritional dysfunction (due to an imbalance between digestive secretions, such as acids, enzymes and hormones, and nutrients). Moreover, bariatric surgery is frequently associated to selective food intolerance and more-or-less voluntary dietary restrictions that have consequences that may be more serious in DT2 patients [7].

Few data are available on the specific consequences of RYGB on meal digestion and absorption in diabetic patients. The absorption of carbohydrates starts early in the duodenum, but is limited in the foregut because of the reduced absorptive surface, and the shorter interaction time between polysaccharides and pancreatic enzymes. The resulting large amounts in fructose and polyols lead to diarrhea. As for lipids, reductions in hydrolysis and micella formation are associated with a decrease in lipid and liposoluble-vitamin absorption. Also, the frequent distaste for meat reported after these surgical procedures [8] leads to a decrease in enzyme secretions, while the reduced intestinal absorptive surface due to exclusion of the duodenum may result in protein deficiency. Nevertheless, such a risk—more often seen with biliopancreatic-diversion procedures—is limited with RYGP.

Micronutrient deficiencies have been widely described after bariatric surgery [9–12], and is of particular importance in diabetes because such deficiencies in micronutrients and microconstituents such as polyphenols are linked with the prevention of oxidative stress. Mitochondrial production of reactive oxygen species (ROS) due to up-regulated glucose oxidation is thought to play a crucial unifying role in the pathogenesis of long-term diabetic complications [13]. An overproduction of ROS contributes to the reduction of glucose-stimulated insulin secretion and to beta-cell apoptosis. ROS also induce a relative increase in levels of oxidized LDL (low-density lipoprotein)-cholesterol particles, which contribute to the patient’s risk of developing cardiovascular disease. The ideal diet needs to protect against oxidative stress. The consumption of five or more servings of fruits and vegetables every day, together with reductions in BMI score, are recommended to reduce cardiovascular disease risk through the beneficial combination of micronutrients, antioxidants, phytochemicals and fibre from these foods, which is often limited after surgery [8]. Nevertheless, although surgical procedures have the advantage of reducing chronic hyperglycaemia and intake of excess high-calorie foods responsible for the production of extracellular ROS (eROS), they also have the disadvantage of leading to deficiencies in the micronutrients and microconstituents involved in antioxidant processes.
The most common micronutrient deficiencies of concern are of vitamins B12 and D, iron and calcium. Other micronutrient deficiencies that can lead to serious complications include thiamine, folates and fat-soluble vitamins. Also, some deficiencies may be of particular concern in diabetics. The accumulated evidence, for example, suggests that low vitamin D levels are associated with impaired glucose metabolism and an increased risk of DT2 [14].

Furthermore, diabetes is associated with alterations in the metabolism of copper, zinc and magnesium, the absorption of which may be profoundly altered after gastric bypass surgery. Copper, for example, is an essential cofactor in many enzymatic reactions in several systems, including those of oxygen radical scavengers and mitochondrial respiration, and may be deficient following bariatric surgery [15,16]. It is postulated that other trace elements more directly involved in islet β-cell function and insulin sensitivity, such as chromium, may also be deficient after such surgery.

4. Long-term postoperative diet

Diet is a major part of the postoperative management strategy in DT2 patients after bariatric surgery. It has important additional health effects, as it can improve the tolerability of the surgical procedure, as well as contribute to the resolution of DT2 in the long term and the control of other risks factors of cardiovascular disease. Further studies, however, are required to define the most appropriate diet for DT2 patients treated by bariatric surgery.

4.1. Patients that are still diabetic

Counselling, monitoring, and nutrient and mineral supplementation are essential for the prevention of nutritional and metabolic complications after bariatric surgery, including in diabetic patients. However, patients who remain diabetic have a greater need for specific dietary advice to help them achieve good glycaemic control based on eating healthy foods with a low glycaemic load and low in saturated fats. A diet that is rich in unsaturated fats and simple carbohydrates with a low glycaemic index, and relatively rich in protein from lean sources and from a wide variety of foods, has proved to be best suited for the management of diabetes.

4.2. Patients in remission

As for patients whose DT2 was resolved after bariatric surgery, there is no good reason to believe that another diet should be prescribed, as diet is the best means, along with physical activity, of preventing diabetes and its cardiovascular complications. Nevertheless, in practice, some alterations in the diet are often necessary to counteract food intolerance and to minimize the mechanical complications associated with the surgical procedure. Judicious monitoring with periodic dietary screening can limit excessive food exclusions, such as meat, to avoid the risk of protein deficiency, and cooked mixed vegetables and fruit may be easier to tolerate than eating them raw. In general, and particularly in cases of the dumping syndrome, limiting the ingestion of simple sugars is necessary. Also, having frequent small meals that include proteins and fibre is useful [17].

As micronutrient deficiencies are commonplace following obesity surgery, it is justified to routinely prescribe an oral multivitamin supplement to ensure that patients receive all of the recommended daily allowances. However, it has been demonstrated that such supplementation does not always prevent deficiencies or cover all mineral needs. For this reason, it may be better to prescribe additional calcium, vitamin D, vitamin B12 and iron as supplements as well.

5. Pharmacological management

There is no place for antidiabetic oral agents in patients whose diabetes has been resolved by surgery. However, the benefits of protective agents against cardiovascular risk such as aspirin, statins or fibrates need to be discussed with each patient on an individual basis. Also, in those who are still diabetic, the dosages of their antidiabetic medications—whether insulin or oral—often need to be decreased. In theory, it is more important to maintain insulin sensitivity rather than resort to insulin-secreting agents to avoid the possible risk of nesidioblastosis seen in the milder forms of diabetes.

However, so far, there has been no controlled trial of the optimal type of supplements and dosages to be prescribed after RYGB. A multivitamin supplement is recommended and should eventually be adapted to any specific deficiencies that arise [20], while particular care needs to be taken concerning vitamin D, iron, vitamin B12 and folic acid. A formula adapted to French requirements has been well described by Poitou-Bennert et al. [10].

6. Prevention of postprandial hyperinsulinaemic hypoglycaemia

Symptoms such as palpitations, tremor, sweating and hunger similar to those experienced with late dumping syndrome, or more severe symptoms such as confusion or loss of consciousness, may occur postprandially. These complications, which are mostly observed 1 or 2 years after RNYB, are due to hyperinsulinaemic hypoglycaemia that is related to diffuse islet hyperplasia, with a large number of islet cells and no evidence of insulinoma, and probably secondary to elevated GLP-1 (glucagon-like peptide 1) levels. Although this complication appears to
be less common in patients with preexisting diabetes, its prevention by diet is of particular interest. Indeed, small meals low in carbohydrates (and also with a low glycaemic index), and higher in protein and in unsaturated fats, may prevent it [18,19].

7. Conclusion

Surgical intervention for overweight DT2 patients may be pertinent for those in whom the operative risks are acceptable. However, lifelong dietary counselling and monitoring, and nutritional supplementation, are required for the treatment and prevention of nutritional complications, and for the prevention of diabetes relapse. Also, pharmacological treatments need to be discussed according to the particular risk factors and metabolic situation present in each given patient.

Conflicts of interests

The authors have reported no conflict of interests.

References

Bariatric surgery for diabetes treatment: why should we go rapidly to surgery

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Abstract

Surgical treatment of morbid obesity has been shown to be efficient for long-term weight loss and to improve obesity-related complications. The improvement of type 2 diabetes (T2DM) is dependent of the type of surgery, and is more frequent with gastric bypass than with gastric band. Normalization of glucose metabolism is rapid, often occurring before weight loss, and shown to be related to both a decrease in insulin resistance and an increase in insulin secretion. Some factors limiting the efficiency of gastric bypass on T2DM is the duration of diabetes and the residual beta-cell mass. However, a decrease in diabetes-related death has been found in a large series of surgical cases. These data constitute a good argument for proposing surgery in T2DM obese patients as soon as possible. Nevertheless, whether or not this suggests changing the usual indications for bariatric surgery on T2DM patients, such as a body mass index (BMI) score of < 35 kg/m², remains controversial.

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Keywords: Bariatric surgery; Gastric bypass; Type 2 diabetes mellitus; GLP-1; Review

Résumé

Chirurgie bariatrique pour traiter le diabète: pourquoi devrions-nous envisager le recours rapide à la chirurgie ?

La chirurgie de l’obésité morbide a fait la preuve de son efficacité sur la perte de poids à long terme et la réduction des complications induites par l’obésité. L’amélioration du diabète de type 2 dépend du type de chirurgie et est plus fréquente avec le bypass gastrique qu’avec l’anneau gastrique. La normalisation de l’équilibre glyémique est rapide et survient souvent avant la perte de poids. Cette amélioration est due à une réduction de l’insulinorésistance et à une amélioration de l’insulinosécrétion. La limite à l’efficacité sur le diabète du bypass gastrique est l’ancienneté du diabète et l’insulinosécrétion résiduelle. Une diminution de la mortalité liée au diabète a été montrée dans de larges séries de chirurgie bariatrique. Tout ceci plaide en faveur d’un recours rapide à la chirurgie chez les obèses diabétiques. Cependant un changement des recommandations en faveur d’un élargissement des indications à un indice de masse corporelle inférieur à 35 en cas de diabète demeure très discuté.

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Mots clés : Chirurgie bariatrique ; Bypass gastrique ; Diabète de type 2 GLP-1 ; Revue générale

Obesity is a chronic disease that is more and more being associated with complications such as type 2 diabetes (T2D), hypertension, cardiopulmonary failure, asthma, polycystic ovary disease syndrome and cancer. It also comes with a heavy burden of psychosocial consequences. In addition, there is usually a general resistance of obesity to conventional treatments that rely mostly on lifestyle changes, and only few drug treatments are available. Epidemiological data have

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shown that obesity is largely found in populations living in poorer socioeconomic conditions. This suggests that these are individuals who are likely to find it particularly difficult to change their lifestyles, as following a healthier balanced diet, joining a fitness club or a weight-watcher group, or hiring a personal trainer or dietician. All come with a cost that most obese people cannot afford.

However, surgery proved efficiency on obesity and its complications, and the cost is reimbursed. Also, of all the complications of obesity, T2D appears to be the one most affected by the surgical procedure. Whereas the decrease in other complications can be directly linked to the surgery-induced weight loss, procedures such as the gastric bypass (GBP) appear to have a specific effect on T2D through actions not only on insulin resistance, but on insulin secretion as well.

In a series of 165 patients with T2D and 165 with impaired glucose tolerance (IGT), Pories [1] reported a long-lasting resolution of T2D, with normalization of HbA1c levels in 83% of the diabetics and 99% of the IGT patients at 1 year after GBP surgery. A meta-analysis of 136 reports on bariatric surgery-involving more than 22,000 individuals-confirmed a T2D remission rate of 84% after GBP [2]. In fact, the effect on T2D was so rapid and intense that their diabetic treatments had to be immediately reduced, and many of the patients were discharged with no further requirement for antidiabetic medications.

Two other major series have shown a decrease in mortality rates after bariatric surgery [3, 4]. Adams et al. [4] described a 92% decrease in diabetes-related deaths following GBP, while Macdonald et al. [5] showed that, in diabetics, mortality was reduced from 4.5% to 1% per year, based on a control-comparison group.

In the Swedish Obese Subjects (SOS) study, a multicentre trial of bariatric surgery vs medical care for obesity, it was found that, after 10 years, the risk of developing T2D was three times lower in patients who had received GBP surgery [6]. However, patients who had undergone the surgery, but who remained diabetic afterwards, had longer duration of the disease, suggesting that they lacked sufficient residual beta cells to recover normal glucose regulation [7].

This is the strongest argument for not waiting too long before proposing bariatric surgery in such patients. The natural evolution of T2D is towards persistent insulin resistance in association with decreased insulin secretion. Yet, the specific mechanisms behind the effects of GBP on T2D are still a subject of debate [8]. It is clear that insulin resistance, a major component of T2D, is improved by weight loss. However, the difference in T2D improvement between GBP and gastric bands—with 84% compared with only 48%, respectively, of cases going into remission [2]—clearly shows that weight loss is not the only factor involved in diabetes remission after GBP surgery. Indeed, an improvement in insulin secretion has been observed after GBP due to changes in incretin levels, especially glucagon-like peptide-1 (GLP-1) [9]. This ‘magical’ effect of GBP nevertheless requires the presence of sufficient residual beta cells.

Ultimately, the important question is whether or not bariatric surgery should continue to be reserved only for those patients who fill the classical indications—namely, a body mass index (BMI) score > 40 kg/m², or > 35 kg/m² if associated with significant co-morbid conditions—or to expand the indications, given the effects on T2D patients. Trials conducted in individuals with BMI scores < 35 kg/m² have reported similar, or even greater, remission rates than those seen in more obese subjects [10]. However, before reaching at the conclusion that bariatric surgery is the best treatment for T2D, it may be advisable to first concentrate our efforts towards understanding the mechanisms involved in bariatric surgery to find clues to help in the development of novel pharmacological treatments that might serve as an alternative option to surgery.

Conflicts of interests

The authors have reported no conflict of interests.

References

Bariatric surgery in patients with late-stage type 2 diabetes: expected beneficial effects on risk ratio and outcomes

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Abstract

Aim. The objective of this review was to assess the safety and efficacy of bariatric surgery in patients with severe obesity and late-stage type 2 diabetes (T2D).

Methods. A review of the literature looked for reported data on outcomes of bariatric surgery when performed in patients with T2D treated by oral medications or insulin. Recent updates in our understanding of the effects of bariatric surgery on glucose homeostasis were also examined.

Results. Data on the outcomes of bariatric surgery in advanced T2D are scarce. Having either T2D for more than 10 years or more advanced forms of the disease, according to antidiabetic therapy, is associated with less weight loss after bariatric surgery. Improvement of diabetes control is also less than seen in earlier forms of T2D, and resolution of the disease is less likely to occur. However, a reduction in oral medications or insulin doses has been documented. Residual beta-cell function is suggested to be a possible determining factor for therapeutic changes or cessation, while reductions in both weight-related and non-weight-related insulin resistance can be expected. Beneficial effects on co-morbidities and overall mortality due to the excess weight loss may also be seen.

Conclusion. Bariatric surgery in patients with severe obesity and late-stage T2D is currently justified by the expected benefits due to the excess weight loss. However, specific studies are needed to better assess the effects of such surgery on glucose control and the associated outcomes.

Keywords: Type 2 diabetes; Obesity; Bariatric surgery; Review
1. Introduction

Obesity is a major independent risk factor for the development of type 2 diabetes. As a consequence, the currently increasing prevalence of obesity is associated with a growing incidence of the disease [1]. In particular, in the United States, 50% of type 2 diabetic patients are obese and 9% are morbidly obese, with a body mass index (BMI) > 40 kg/m² [2]. While type 2 diabetes is a progressive disorder driven by the gradually growing impairment of islet beta-cell function, obesity contributes to the failure of antidiabetic therapy to control glucose. More specifically, the accumulation of fat in visceral adipose tissue, as well as in skeletal muscle and the liver, is closely correlated to insulin resistance [3–5]. Hence, the increased insulin needs to maintain glucose control cannot be fulfilled in diabetic patients who present with defective beta-cell function. Moreover, difficulties in diabetes control are combined with other major morbidity factors—such as hyperlipidaemia, high blood pressure, prothrombotic conditions and obstructive sleep apnoea—which are often seen in severely obese patients, resulting in an overall increased risk of mortality [6].

The development of bariatric surgery over the past decade has led to dramatic improvements in the management of severe obesity. While lifestyle modifications and pharmacological interventions show limited and barely sustained reductions in body weight, weight was lowered after bariatric surgery by 14–25% after 10 years in the prospective Swedish Obese Subjects (SOS) study [7], and excess weight reduced by 61.2% in a 2004 meta-analysis by Buchwald et al. [8]. Various surgical techniques of bariatric surgery have been developed, based on: a purely restrictive concept, such as laparoscopic adjustable gastric bands (LAGB) and vertical banded gastroplasty (VBG); a mostly malabsorptive, concept such as roux-en Y gastric bypass (RYGBP) and sleeve gastrectomy (SG); and a mostly malabsorptive concept such as biliopancreatic diversion (BPD) [9]. Surgical interventions including a malabsorptive component have shown the greatest benefits in terms of excess weight loss and long-term weight reduction [9]. In addition, type 2 diabetes has been resolved in 76.8%, or resolved or improved in 86% of patients, by bariatric surgery [8]. Interestingly, hyperlipidaemia was also improved in more than 70% of patients, high blood pressure was resolved in 61.7%, or resolved or improved in 78.5%, while obstructive sleep apnoea was resolved in 85.7% [8].

These impressive outcomes of bariatric surgery in patients with morbid obesity suggest that such surgery may be an optimal solution for severely obese patients with type 2 diabetes. Schauer et al. [10], looking specifically at the effects of RYGBP on type 2 diabetes, reported that patients with the shortest duration (< 5 years) of diabetes, its mildest form (diet-controlled) and the greatest weight loss after surgery were those most likely to achieve complete resolution of their diabetes. The team also observed that diabetic patients had an overall lower excess weight loss than non-diabetic patients, as did Dixon et al. [11], who investigated the use of LAGB. Moreover, Schauer et al. pointed out that patients with the more severe forms of type 2 diabetes showed significantly less weight loss than those who had milder forms [10]. Based on these observations, the present report is focused on the outcomes of bariatric surgery in patients with more advanced forms of type 2 diabetes to answer the question: is bariatric surgery in this patient population safe, efficient, helpful and cost-effective?

2. Safety of bariatric surgery in patients with late-stage type 2 diabetes

Various risk factors have been identified in association with bariatric surgery, with differences according to the technique involved [12]. The laparoscopic approach can shorten the time required before returning to work, and reduces wound and pulmonary complications [13]. Also, having the operation performed by an experienced surgeon at a centre with a high volume of bariatric interventions is the best protection against complications [14, 15], as these two factors have been shown to decrease the mortality and morbidity related to surgery, and has led to the idea of recognized ‘bariatric surgery centres of excellence’in the United States, based on threshold numbers of 50 annual cases per surgeon and 125 annual cases per hospital [6]. In such institutions, complications in patients aged > 65 vs < 65 years have been equalized [14]. However, a high body mass can be a risk factor due to the feasibility of the operation in such patients and the greater likelihood of associated morbidities [15]. Diabetes, chronic obstructive pulmonary disease, sleep apnoea and hypertension have also been identified as factors that can increase complication rates [15, 16]. Detailed programming of the surgery is, therefore, of the utmost importance. In the series reported by Schauer et al. [10], the length of hospital postsurgical stay did not significantly differ according to diabetes severity. In addition, the selection of patients based on their commitment to lifestyle changes following surgery, as explained by preoperative education, is another determinant of success [17].

This suggests that the risk– benefit ratio for bariatric surgery in patients with advanced forms of diabetes can be viewed as optimal under the following conditions: appropriate patient selection based on a multidisciplinary assessment of their commitment to compliance with educational measures, and their associated diabetes- and non-diabetes-related morbidities; and having the operation performed by a trained surgeon in an experienced centre to ensure that the specific risks associated with patients’ health conditions are thoroughly reviewed and considered in the programming of the operation, and in the immediate follow-up.

3. Efficacy of bariatric surgery in patients with late-stage type 2 diabetes

The landmark report by Schauer et al. [10] offers a valuable picture of what may be expected from RYGB in type 2 diabetic patients at various stages of the disease. In the 5-year follow-up study, data from 191 patients were assessed,
including 93 (65%) treated by oral antidiabetic agents (OADs) and 52 (27%) treated by insulin. Excess weight loss was significantly lower ($P = 0.01$) in patients using OADs or insulin vs those with impaired fasting glucose (IFG) and on a diet only; 57% and 59% vs 73% and 65%, respectively. Also, postoperative glycated haemoglobin ($\text{HbA}_{1\text{c}}$) levels in patients using insulin were significantly higher than in patients with IFG: 6% vs 5%, respectively ($P < 0.001$). Among insulin users before surgery, 79% were able to stop daily insulin after the operation whereas, in patients who still required insulin after surgery, insulin doses were reduced from 146 units/d to 45 units/d ($P = 0.019$). In addition, only 27% of patients using OADs and insulin before the operation still needed OADs afterwards whereas, among patients treated by OADs only before surgery, 87% were able to stop afterwards, while the number of medications used was reduced from 2.1 to 1.1 agents per patient ($P = 0.003$). Immediate cessation of OADs or insulin after surgery was possible in 30% of patients after the surgical treatment, and occurred significantly more often in patients with diabetes durations < 10 years and in those treated by OADs rather than insulin. Full resolution of diabetes throughout the whole study was also significantly less likely to happen in patients with a history of diabetes > 10 years and in those with more severe forms of the disease, according to treatment. Diabetes resolution was positively associated with the amount of excess weight lost and the degree of glucose control before surgery.

Interestingly, more cases were characterized by resolution and improvement of associated morbidities than by no change and worsening of such co-morbidities. This included hypertension (36% and 53% vs 9% and 2%, respectively), hypercholesterolaemia (37% and 41% vs 3% and 1%, respectively) and obstructive sleep apnoea (33% and 47% vs 10% and 1%, respectively). In addition, diabetic neuropathy, present in 25% of cases, showed symptomatic improvement in 50% of cases after surgery, and diabetic erectile dysfunction improved in 18% of the preoperatively affected male patients.

A recently published meta-analysis specifically focused on the outcomes of bariatric surgery in type 2 diabetic patients [18]. In these patients, available follow-up data showed an overall 64.4% of excess body weight loss, with resolution of diabetes in 78.1% of cases, and diabetes improved or resolved in 86% of cases. BPD with duodenal switch brought about the highest rate of diabetes resolution in 95.1%, followed by RYBP in 80.3%, SG in 79.7% and LAGB in 56.7%. $\text{HbA}_{1\text{c}}$ and plasma insulin levels were also significantly decreased after surgery, while changes in BMI had a significant impact on diabetes resolution. However, no specific information was reported according to diabetes history or severity.

Long-term results have been reported by MacDonald et al. [19] in a study that retrospectively compared the 9-year outcomes of 154 diabetic patients who underwent RYBP with those of 78 control diabetic patients who did not undergo surgery. While the percentage of control patients who used either OADs or insulin rose from 56.4% to 87.5% from the initial to the last contact, the surgically treated patients using antidiabetic therapy fell from 31.8% to 8.6%. Furthermore, the mortality rates in the control and interventional groups were 28% and 9%, respectively. The main benefit of surgery on mortality rate was explained by fewer cardiovascular deaths.

4. Mechanisms of diabetes improvement after bariatric surgery: application to late-stage type 2 diabetes

Resolution of diabetes or improvement in glucose control following bariatric surgery must be considered after various time intervals. In most cases, a dramatic improvement in glucose levels has been observed immediately following surgery—before any major weight loss—but in a context of sudden calorie restriction [20]. Persistent cases of diabetes after this initial period gradually improve in parallel with weight loss. It is worth noting that patients who undergo malabsorptive surgical interventions improve sooner and maintain glucose control for longer than do patients treated by restrictive procedures [9].

Calorie restriction following surgery is probably involved in the rapid decrease in glucose values during the early postoperative days or weeks due to increased insulin action [21]. Very low-calorie diets (VLCD) show similar, rapid improvements in glucose control within days in obese type 2 diabetic patients [22] and, in addition to glucose decreases, plasma insulin levels are also lowered [23]. The rapid improvement in insulin sensitivity appears to be independent of weight loss [9]. Recent experiments in animals have shown that duodenal exclusion from food exposure results in dramatic improvements in insulin sensitivity [24]. Intestinal gluconeogenesis is thought to be the mechanism behind this phenomenon [25]. Glucose produced in the intestine drains into the portal system, where neural connections to the brain result in improved hepatic sensitivity to insulin. Duodenal exclusion is used in RYBP, and may explain the rapid improvement in glucose levels due to increased insulin sensitivity independent of weight loss following this surgical intervention [25].

Improved dynamics of beta-cell insulin responses to glucose have also been identified as a potential mechanism behind the early improvement of glucose tolerance after bariatric surgery [26]. Compared with patients following a VLCD who achieved similar weight losses, patients who underwent RYBP have increased secretion of insulin, C-peptide, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) after oral glucose challenge [27].

In addition, decreased ghrelin secretion after RYBP may also play a role in improving glucose levels by suppressing its hormonal effects on insulin resistance [28].

In the longer term, the enhanced insulin sensitivity associated with weight loss appears to be a key mechanism in the improvement of glucose metabolism following bariatric surgery [9]. Experimental studies have shown that a 30% reduction in BMI is predictive of a 50% increase in insulin sensitivity. As malabsorptive surgical interventions lead to greater and more
sustained weight reductions, further improvement in insulin sensitivity can be expected from such procedures compared with purely restrictive ones. Data on changes in glucose homeostasis in patients with advanced stages of type 2 diabetes are scanty and, therefore, prohibit a clear understanding of the effects of bariatric surgery in such patients. Given the gradual loss of beta-cell function associated with longstanding type 2 diabetes, however, improvements of glucose control after bariatric surgery may be expected as a result of reduced insulin resistance in both the short and long terms [9]. Also, depending on the remaining insulin secretion capacity, residual beta-cell function may be sufficient to overcome the reduced insulin resistance, allowing the withdrawal of exogenous insulin administration. Improved secretion of incretins after RYBP may also help to boost insulin secretion. However, patients with poor residual insulin-secretion capacity can only expect a reduction in their insulin needs and, thus, will have to continue their daily insulin doses.

5. General expectations from bariatric surgery in patients with late-stage type 2 diabetes

As resolution of longstanding type 2 diabetes can hardly be expected from obesity surgery, a more general view is needed to assess its potential value in such patients. Recent interventional trials have shown that improvement of diabetes control in late-stage type 2 diabetes may be at risk in terms of mortality and lack of efficacy in reducing cardiovascular events [29]. This suggests that optimal control of associated cardiovascular risk factors may be of major importance. In that case, the benefits of bariatric surgery in advanced type 2 diabetes may rely more on improvements in blood pressure and lipid control, and on the reduction of specific prothrombotic risk factors associated with visceral obesity [6]. Resolution or improvement of obstructive sleep apnoea may also contribute to a better prognosis in these patients. Long-term reductions of the incidence of myocardial infarction by 43% and of overall mortality by 31% have been reported after 15 years in patients who underwent obesity surgery in the SOS study [7]. Interestingly, the diabetic patients also achieved the most benefit related to the endpoints of that study.

However, due to insufficient data, cost-effectiveness analyses of surgically induced weight loss have not been performed in those with advanced type 2 diabetes. Nevertheless, savings in healthcare costs and those generated through health benefits have been demonstrated in patients with earlier stages of diabetes associated with severe obesity [30].

6. Conclusion

The outcomes of bariatric surgery in patients with late-stage type 2 diabetes have so far been poorly assessed. However, optimal safety with such surgery is likely when it is programmed and performed in specialized centres by experienced surgeons, in light of the frequent co-morbidities and associated diabetic complications. Speedy and sustained improvements in glucose control may be expected due to the reduction of both weight-related and non-weight-related insulin resistance, whereas diabetes resolution is unlikely and insulin cessation will depend on the patient’s residual beta-cell function. Furthermore, significant, albeit mainly speculative, improvements may be expected in the overall life prognosis through beneficial effects on co-morbidities and risk factors associated with excess visceral fat. However, specific studies are needed in this population to confirm the expected benefits of bariatric surgery.

Conflicts of interests

The authors have reported no conflict of interests.

References


