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Review Article

May Surgery be the Treatment of Type 2 Diabetes?

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Abstract

Bariatric surgery has confirmed its efficacy and safety in treating patients with severe obesity. In such cases, a rapid improvement of diabetes usually occurs, which has led several authors to suggest extending this surgery to patients with diabetes with a moderate increment in weight or to subjects at risk of severe complications such as super-obese adolescents, subjects with diabetes over 55 years with impaired glycaemic equilibrium, women with diabetes or pre-diabetes before pregnancy, or subjects presenting with impaired fasting glucose. However, this raises many unresolved questions regarding the mechanisms involved in the resolution of glycaemic disorders, the risk of a recurrence of diabetes, the onset of nutritional disorders after surgery in pregnant women and older subjects, the risk of peri-operative complications and the efficacy and safety of recent endoluminal techniques. Long-term prospective and randomised studies are therefore necessary to answer questions linked to the use and extension of metabolic surgery.

Keywords: *Metabolic Surgery; New Indications; Benefits; Risks; Review*

Introduction

Metabolic surgery is a new concept that has resulted from the development of bariatric surgery which was initially reserved for the morbidly obese. The spectacular benefits that are rapidly obtained following gastric band or intestinal short-circuit surgery with respect to the co-morbidities associated with excess weight, such as diabetes, hypertension, dyslipidaemia or sleep apnoea, have aroused hopes for new therapeutic opportunities. It has appeared that reducing metabolic disorders is not solely dependent on the postoperative regression of fat mass, but is certainly linked to other pathophysiological mechanisms. This has gradually led to the possibility of treating these metabolic disorders at an earlier stage by broadening the indications for surgery to subjects affected by these pathologies in a context of less extreme obesity [1].

Among the numerous co-morbidities that accompany obesity, type 2 diabetes is indeed the leading problem because of its growing incidence, the severity of its complications and its cost to the healthcare budget. Numerous studies have confirmed the relative failure of medicinal management. In France, the ENTRED study in 2007 determined that 55% of patients with type 2 diabetes had HbA1c levels higher than 7%, and a large proportion of them developed complications [2,3]. The principal cause of this deleterious situation is poor compliance with diet and lifestyle recommendations and therapy, and the reluctance of physicians to escalate treatment which is nonetheless essential when the glycaemic control deteriorates. We shall therefore be focusing our presentation on this highly topical theme.

Several questions are thus posed: 1- What are the pathophysiological mechanisms that can explain the rapid regression of diabetes? 2- Are data available on the long-term course of glycaemic equilibrium, the onset of complications, quality of life and healthcare expenditure, by comparison with what is known about patients with diabetes who are treated with medication? How far can the surgical indications be broadened, and based on which criteria? Which advances in surgical techniques and drug therapies will determine therapeutic choices? We shall try to consider these different questions by clarifying what we already know and also looking at the numerous uncertainties that still weigh on this new therapeutic approach to diabetes.

Current state of knowledge or certainties

As early as 1992, an improvement in diabetes was confirmed by Pories in subjects treated with a gastric bypass [4]. The same observations were subsequently reported by other authors, who noted how rapidly diabetes improved or even disappeared in this setting, allowing the withdrawal of medication, and notably of insulin in insulin-dependent patients [5]. Two meta-analyses, in 2009 and 2010, reached concordant and documented conclusions regarding a large number of cases [6,7]. The benefits achieved regarding diabetes increased depending on the use of either a gastric band (GB), sleeve gastrectomy (SG), gastric bypass (GBP) or a biliopancreatic diversion (BPD), which achieved the highest percentage improvement. Diabetes was improved in 89,2% or in remission in 64,7% of patients in a recent systematic review [8]. So, bariatric surgery offered better treatment outcomes than non-chirurgical options. Incidence and remission of type 2 diabetes is not in relation to degree of obesity at baseline but to 2 year weight change in the Swedish Obese Subject study [9]. These encouraging data also concerned other co-morbidities such as hypertension, sleep apnoea or hypertriglyceridemia, while several publications confirmed an increase in life expectancy following these surgical procedures. However, most of these studies were retrospective and non-randomised, although this does not in any way detract from the importance of their message. Two randomised studies confirmed that in obese subjects with unbalanced diabetes, SG or GBP [10], or GBP or BPD [11], enabled an improvement in glycaemia that was superior to that achieved by drug therapy alone, after follow-up periods of 12 months [10] or 24 months [11]. In a nationwide observational cohort study including data 6132 patients with diabetes who had undergone bariatric surgery and 6132 control patients, the median follow-up was 3 - 5 years. The risk of fatal and no-fatal infarction was 49% lower and cardiovascular death was 59% lower in the bariatric surgery group than in the control group [12].

These favourable results encouraged several authors to broaden the applications of surgery beyond the indications recognised by the French National Health Authority (HAS) which restricts them to subjects with a BMI > 40 or > 35 when at least one co-morbidity is present, the prime objective being the treatment of morbid obesity.

In contradiction to these rules, the management of moderately obese (BMI < 35) or non-obese (BMI < 30) subjects was recently proposed. The initial results were the subject of a recent meta-analysis which confirmed that the effectiveness of surgical techniques on the course of diabetes was similar to that achieved in severely obese patients [13].

The complications of surgery are well-documented. Postoperative mortality rates remain low but are not negligible following biliopancreatic diversions, at about 1% [14]. On the other hand, incidents or accidents have been reported with varying frequency depending on the technique employed and the experience of the surgeon. Gastric band (GB) surgery causes the lowest mortality rate (0.05%) but quite a high level of complications (11.3%) requiring regular surveillance; more serious accidents may be observed after sleeve gastrectomy (SG), or gastric bypass (GBP) (23.6%), and particularly following biliopancreatic diversion (BPD). All procedures taken together, the global risk reaches 5% [14].

It should be pointed out that the incidence of complications increases in line with the efficacy of surgical techniques. Modifications have been proposed in order to reduce the problems linked to complex anastomoses, such as the mini-gastric bypass, while laparoscopy has markedly reduced surgical shock and improved patient comfort. The life-long follow-up of operated patients is essential, combined with dietetic education and permanent monitoring by a clinical psychologist. It is essential to compensate for vitamin and micronutrient deficiencies and prevent dumping syndrome and functional hypoglycaemia through an appropriate diet.

The uncertainties

Which mechanisms can explain an improvement in glycaemic control?

Knowledge of these mechanisms is important as it may open the way to new surgical techniques or pharmacological advances. However, many uncertainties still weigh on our understanding of the roles played by the numerous factors which contribute to a regression of diabetes.

A reduction in body weight and calorie restriction is considered to be determining factors in improving the glycaemic control. In favour of this hypothesis, it should be noted that an excess fat mass is closely linked to the presence of type 2 diabetes, and that weight loss achieved through simple dietary and lifestyle measures improves glycaemic equilibrium [15]. However, it has been suggested that there is no chronological correlation between a - sometimes very rapid - regression of diabetes and weight loss that may occur more slowly [16,17]. These facts have led to a search for mechanisms other than a restricted calorie intake to explain rapid and spectacular improvements in the glycaemic control. Several pathophysiological hypotheses have been advanced, some of which are still speculative.

The hormonal hypothesis concerns several mechanisms:

- A reduction in the secretion of ghrelin (an orexigenic hormone) by gastric restriction procedures could explain a lower appetite and greater weight loss. This hypothesis, put forward by Cummings [18], remains controversial.
- The levels of three anorexigenic hormones: GLP1, YY peptide, and oxyntomodulin [19-21] rise after RYGBP, which may explain the reduction in calorie intake. The effects of different hormones including gastrin, cholecystokinin, GIP, insulin, glucagon and somatostatin are unclear but may play an important role [22]. The more rapid contact between foods and the distal intestine, where these hormones are produced, may explain their elevation after surgical procedures which shorten intestinal transit.
- Postprandial insulin secretion rises rapidly after GBP in patients with type 2 diabetes [21] and independently of weight loss [23]. Some authors have suggested the intervention of GLP1, others a reflex arc from the jejunum via the central nervous system [24], and others the effect of excluding the duodenum which may secrete substances endowed with an anti-incretin effect [25]. The function of beta cells improves after GBP. Several mechanisms have been proposed to explain this phenomenon. The regression of hyperglycaemia and hypertriglyceridemia that is induced by all bariatric surgery techniques certainly contributes to reducing glucotoxicity and lipotoxicity affecting Langerhans beta cells [26]. Development of the beta cell mass through proliferation, or a reduction in apoptosis, have also been suggested, based on rare observations of severe hypoglycaemia occurring after GBP [25] and on studies in animals [27]. However, this hypothesis still needs to be confirmed in humans, where it has been doubted by some authors [28].
- Tissue sensitivity to insulin increases after all types of bariatric surgery, in parallel with a loss of weight and fat mass. The muscle and liver are the principal beneficiaries [29]. Hepatic steatosis may regress after GBP, being linked to an improvement in insulin resistance [30,31]. Lipids stored in the muscles and liver appear to be a determining factor in insulin resistance. Fatty acids may favour the production of ceramides, thus reducing insulin sensitivity.

Modifications to the intestinal flora in a context of obesity is a new approach, based on numerous experimental studies. A family of bacteria, the *Fermicutes*, is preponderant in obese subjects, to the detriment of another family, the Bacteroidetes [32]. Because of their enzymatic equipment the *Fermicutes* enable an increased capacity for absorption in the digestive tract. GBP modifies the intestinal flora but it seems premature to hold this responsible for improving the metabolic equilibrium because of the numerous unknowns that weigh upon the true effects of different microbial families on metabolic equilibrium. Postoperative modifications to the intestinal microbiota may also explain the regression of low-grade inflammatory symptoms attached to a poorly equilibrated intestinal flora in obese subjects [33].

Intestinal neoglucogenesis is another mechanism that has been suggested to explain the rapid improvement in carbohydrate metabolism. During an experimental study in rats, Troy., *et al*. showed that GBP caused an enrichment of portal blood in glucose of gut origin [34] thanks to the activation of glucose 6 phosphatase [35]. A portal "sensor" sensitive to elevated glucose levels in blood entering the portal vein circulation sends the brain a signal, and in return this causes a reduction in hepatic glucose production, an increase in insulin sensitivity, and a reduction in food intake. These phenomena are solely dependent on GBP, because GB does not have the same effects.

The very rapid improvement in carbohydrate metabolism induced by GBP may therefore depend on several factors whose type and respective importance are still poorly understood. At a later stage, weight loss and a reduction in calorie intake will add to these initial mechanisms to sustain the initial benefit.

Are the benefits on weight and metabolism sustainable?

Few studies, most of them retrospective, have been able to answer this question. Sjöstrom., *et al*. [36] reported on the retrospective follow-up of 4,047 subjects who were observed two years after bariatric surgery, and 1,703 ten years after. These subjects were compared with a control group. The majority had benefited from a gastric band or vertical gastroplasty, the remainder from a gastric bypass (RYGB). Their weight had fallen by 23.4% at 2 years and by 16.1% at 10 years, versus increases of 0.1% and 1.6% in the control group. It should be noted that the best results were obtained with GBP. The incidences of diabetes, hypertriglyceridemia and hyperuricemia were significantly lower among operated subjects than among the controls. The same applied to the rates of recovery from diabetes and other risk factors, such as hypertension, hypertriglyceridemia and low HDL cholesterol levels, although the differences had diminished at 10 years.

In a retrospective study, Kim., *et al.* [37] reported on the follow-up of 219 obese and patients with diabetes who underwent laparoscopic surgery using the RYGB technique. The results at one year confirmed a significant lowering of HbA1c levels from 7.6% to 6.1%, in parallel with the reduction in the BMI (50.4 versus 34.4). At 2 years, 71.1% of subjects had discontinued any treatment for diabetes. These results were sustained at 4 years, although a large number of patients had been lost to follow-up by this stage (32%). The chances of a resolution of type 2 diabetes were reduced as a function of age, the duration of diabetes and previous insulin therapy. Nine per cent of patients experienced a worsening in their glycaemic equilibrium. The determining factor appeared to be a resumption of weight gain.

For a mean period of nine years, Kenneth., *et al.* [38] followed 154 super-obese and patients with diabetes who had undergone RYGBP, comparing them with a control group of 78 comparable subjects who were initially receiving medication for their diabetes. The percentage of subjects who required medication for their diabetes rose from 56.4% to 87.5% in the control group, while it fell from 31.8% to 8.6% among those who had undergone surgery. The mortality rate was found to be significantly different between the two groups, at 28% in the control group versus 9% in the operated group.

Schauer., *et al*. evaluated the evolution over a four-year period of body weight, diabetes and its co-morbidities in 1,160 obese patients who undergone GBP. 240 were patient with diabetes or pre-diabetes. 83% of the patients with diabetes achieved a complete remission and 17% an improvement, with a significant reduction in their medications for diabetes. Favourable prognostic factors were the short duration of diabetes, its benignity and the degree of weight loss following surgery. Insulin therapy prior to surgery was an unfavourable factor. Weight loss was more marked among people without diabetes. These authors also noted neuropathic improvements in 50% of these patients, and in erectile dysfunction in 18% of them.

Two prospective, randomised studies [10,11] recently confirmed the superiority of surgery over a control group with respect to weight loss and diabetes remission rates. However, the duration of observation (of one and two years, respectively) was insufficient to evaluate the risk of a relapse. No long-term prospective study has yet confirmed the benefits of surgery over standard management with respect to the complications of diabetes (retinal, renal, coronary and arterial disease).

The stability of glycaemic remission is controversial. Two recent articles have reported a re-emergence of diabetes in a high percentage of cases. Caiazzo., *et al*. [39] studied the outcomes of 23 patients presenting with type 2 diabetes and 53 with glucose intolerance, with a mean BMI higher than 45. Adjustable gastric band was used under laparoscopic surgery. Postoperative controls were performed after varying periods, the last at 60 months. A significant improvement in HbA1c levels was observed in 13 patients with diabetes, but 73% remained patients with diabetes at 5 years, and 41% did not achieve the 7% threshold for HbA1c. Unfavourable factors included more advanced age, a longer duration of diabetes prior to surgery, high fasting blood sugar levels and preoperative insulin therapy. In subjects presenting with glucose intolerance, 67% achieved a normal glycaemic control at 5 years and 4% progressed towards a diabetic state. The long-term benefits obtained with adjustable band in a context of glucose intolerance could be compared with the results of dietary and lifestyle measures alone, which have proven their efficacy.

M DiGiorgi., *et al*. [40] followed 42 super-obese with diabetes who had been treated with RYGBP for an average period of five years. Sixty-four percent had achieved a complete remission of their diabetes at 6 months, and 36% had improved. The rate of re-emergence of diabetes was 26%, and that of a worsening among those initially improved was 20%. A fall in body weight was observed in both groups. Operated subjects were less severely overweight prior to surgery and experienced less weight loss after RYGBP. This study was particularly interesting as it highlighted the reversible nature of the benefits achieved with RYGBP, which is considered to be one of the best performing procedures. It confirmed the need for further studies involving the long-term follow-up of patients, and including a discriminant analysis of prognostic criteria for efficacy. A recent review shows that type 2 diabetes can reappear especially in the following years in patients with advanced age, female sex, longer duration of diabetes, use of insulin before surgery and weight regain [41]. Baseline HbA1c and waist circumference predict improved glycemic control [42]. However even though weight loss-independent effects are important for short-term diabetes remission, the results of the Swedish Obese Subjects study suggest that degree of weight loss is more important for long-term reductions in fasting insulin and glucose than choice of bariatric surgery procedure [43].

What are the advantages and risks of the different surgical techniques? What advances can be anticipated?

It is necessary to make a distinction between reversible techniques such as a gastric band, and those of an irreversible type involving a reduction in stomach size such as sleeve gastrectomy (SG), a reduction in stomach size associated with duodenal exclusion by anastomosis of the gastric pouch with the jejenum, and biliopancreatic diversion procedures which are performed less frequently in France because of their effects on nutritional status. The respective efficacy of these different methods is proportional to their secondary complications. Various developments have been proposed to simplify the surgical procedures and limit peri-operative and postoperative complications. The generalisation of laparoscopy has been a definite advance with respect to surgical risks in particularly vulnerable subjects.

The mini-gastric bypass (MGP) proposed by Ruledge [44] involves making a longer and narrower gastric pouch than that obtained using the Roux-en-Y bypass (RYBP), anastomosed to a jejunal loop via the small gut. This procedure has the advantage of involving only one anastomosis, thus reducing the risk of fistulas which are a major complication of RYBP. A prospective, randomised study confirmed a lower rate of postoperative complications following MGP when compared to RYBP, but the outcomes were comparable at 1 and 2 years; weight loss was identical in the two groups. Despite the advantages of its shorter procedure and lower risk of fistulas, this technique has been the subject of controversy because of the risk of biliary reflux (causing gastritis), gastroesophageal reflux and cancer of the lower oesophagus.

Endoscopic techniques are currently being tested; some of them modify the gastric cavity while others have an impact on the duodenum. It is much too early to assess their potential contribution to the management of type 2 diabetes. The same applies to gastric electrical stimulation techniques.

Uncertainties regarding new indications for metabolic surgery

The current indications retained in France by the National Health Authority (HAS) are restricted to obesity with a BMI > 40 or > 35 and the existence of an associated co-morbidity [45].

New indications

The favourable results achieved with bariatric surgery on the course of diabetes have led some authors to propose a broadening of surgical indications to situations where diabetes appears to be a major risk factor independently of the degree of obesity. This option could logically concern patients with diabetes who are poorly-equilibrated despite satisfactory compliance with dietary and lifestyle measures and appropriate medicinal management. The association of other cardiovascular risk factors and dyslipidaemia would constitute a further argument in favour of recourse to metabolic surgery, independently of the degree of obesity. However, these perspectives should be tempered by the weaker efficacy of surgery when diabetes is long-standing, is treated with numerous medications and is insulin-dependent, and if the subject is older. Furthermore, less satisfactory results regarding the glycaemic control have been reported in subjects who have less weight to lose.

Taken to its extreme, should we propose an irreversible and high-risk surgical procedure to patients who are moderately overweight, with diabetes that is recent, uncomplicated but poorly equilibrated because of poor compliance with dietary and lifestyle measures, the argument being the probable onset of complications linked to this glycaemic control? This decision is difficult and can only be taken on an individual basis after account has been taken of all elements in the patient's file, in the context of multidisciplinary consultations. In the event of a serious accident – which always remains possible – those responsible would be exposed to legal consequences motivated by non-compliance with the guidelines laid down by the HAS.

To enhance this discussion, it might be useful to recall experiences in other countries that lie outside the traditional regulatory framework applicable to bariatric surgery in France. These concern the highly specific cases of adolescents, preparation for pregnancy, patients with diabetes who are simply overweight and subjects with pre-diabetes.

Adolescents are increasingly becoming victims of obesity and the onset of type 2 diabetes. Medicine management often fails, thus raising the prospective of severe complications. A few Australian and American teams have published their experiences in this area [46,47], but the scarcity of prospective studies with long-term follow-up should encourage us to be cautious regarding this indication, which can only be considered on a case-by-case basis.

Subjects aged over 55 years constitute the largest contingent of patients with type 2 diabetes with a high risk of complications linked to late management and diabetes that is frequently poorly equilibrated. The data relative to bariatric surgery in this age group are scarce, as the co-morbidities associated with diabetes increase the surgical risk. Gastric band procedures do not cause more complications than in younger subjects, unlike GBP. A few studies have confirmed the benefits of GB or GBP with respect to weight loss, quality of life and co-morbidities, except for hypertension and osteoarthritis, with a reduction in the need for medications. At 5 years, the prevalence of diabetes was seen to fall from 49% to 19% in a study by Suggerman [48]. Gastric bypass and sleeve gastrectomy achieved good weight loss and resolution of comorbidities [49]. The studies we refer to were of a short-term type and contained little information regarding the benefits with respect to mortality and the risks of protein malnutrition and nutritional deficiencies which could worsen any concomitant infectious or oncological conditions which are more common in elderly subjects.

Does metabolic surgery have a role to play in preventing the complications of pregnancy in women with diabetes?

Several studies have confirmed the risk of obstetric and foetal complications in obese women. Evidence has been provided of the benefits achieved by bariatric surgery – mainly GBP – in terms of reducing these risks to both the mother and infant [50]; the incidences of gestational diabetes, caesarean sections, prematurity or retarded growth were significantly reduced when compared with pregnancies in obese women who had not undergone surgery. Bariatric surgery can improve the weight and metabolic prognosis of children born to mothers who have previously undergone such a procedure, when compared with any siblings born before the surgical procedure. It is probable that the weight loss associated with different hormonal modifications limits the role of the epigenetic factors implicated in the trans generational transmission of obesity and diabetes.

These prospective should be tempered by complications which could affect the surgical outcome following GBP. The most serious is an occlusion due to an internal hernia. Digestive disorders are common and it is sometimes difficult to determine their cause. Nutritional deficiencies are numerous; the most worrying is a folate deficiency involving a risk of neural tube closure defect. Iron deficiency occurs in half of women who have undergone GBP surgery. Exclusive breast feeding may cause a vitamin B12 deficiency. It is currently recommended by the HAS to avoid pregnancy following bariatric surgery until the weight has stabilised after a 12 to 18 month observation period. In no case should surgery be performed during pregnancy. Very strict nutritional follow-up is essential during pregnancy and after delivery, in order to prevent any vitamin and micronutrient deficiencies.

Can surgery be used in patients whose BMI is lower than 35 Kg/m^2?

A review by Fried [13] focused on 16 studies involving a total of 343 subjects (66% of women), 50% of whom had a BMI < 30. Six of them had been followed for more than two years. The mortality rate was 0.29%; 4% to 10% of the subjects experienced early complications. The mean reduction in HbA1c levels was 2.9%, and 80% of the patients no longer required any medication for diabetes.

Can metabolic surgery be proposed to subjects with pre-diabetes who do not present with massive obesity (BMI < 35) when they do not comply appropriately with the dietary and lifestyle measures recommended under these circumstances?

A very few studies [39] have reported on a reduction in the incidence of diabetes, but the duration of follow-up was insufficient and the lack of comparison with a randomised control group did not enable any conclusions to be drawn.

Can metabolic surgery be proposed in obese patients with Type 1 diabetes. Recents review showed that bariatric surgery is associated with a average reduction in insulin requirement (-48,95 units), HbA1c (-0,933%) and BMI (-11,04 k/m^2) [51].

Finally, bariatric surgery induced the disappearance of NASH from nearly 85% of patients in a study including one hundred and nine morbidly obese patients after 1 year of follow-up. So, this surgery could be a therapeutic option for appropriate morbidly obese or patients with diabetes with NASH who do not respond to lifestyle modifications [52].

Conclusion

Bariatric surgery can procure unquestionable benefits in extreme situations where the severity of obesity has become life-threatening. The rapidly favourable outcome regarding co-morbidities, and most particularly with respect to the type 2 diabetes which is often concomitant, raises questions about the possibility of extending these procedures to patients with diabetes who present with less excess weight, or new situations that are not covered by the HAS guidelines. The results of several studies have pleaded in favour of this approach. However, their conclusions should be considered with caution because most of them were not prospective or randomised, and lacked sufficient follow-up. Numerous uncertainties remain concerning the mechanisms involved in rapid improvements to the glycaemic equilibrium, the long-term stability of the benefits obtained, the risks secondary to different complications, quality of life and advances concerning social and professional integration. Furthermore, patients with diabetes who are poorly equilibrated using standard therapies are those who are likely to have recourse to metabolic surgery, but also those in whom the results of this surgery are the least favourable. One important unknown persists regarding the future criteria for the selection of patients for surgery in the context of new indications. It is now important to implement prospective, randomised studies in order to clarify the new perspectives for metabolic surgery.

Conflict of Interest

"The author declare that there is no conflict of interest regarding the publication of this paper".

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