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METABOLIC SURGERY FOR DIABETES MELLITUS BETWEEN BENEFITS AND RISKS

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Abstract

The incidence of type 2 diabetes is continuously growing worldwide, with enormous costs for individuals as well as for society. In the last decades, bariatric surgery has emerged as a possible solution for ameliorating metabolic control or even obtaining diabetes remission. Observational trials and metaanalyses demonstrate consistent improvement of type 2 diabetes following various bariatric procedures, but they are generally uncontrolled or they use historic controls as comparators. In recent years, several randomized trials studying the effectiveness of bariatric surgery in type 2 diabetes have been conducted and they all show substantial benefits, with the observation that the majority are short-term trials. With the increased popularity of diabetes surgery, concerns about its immediate and long-time safety have also grown. The most frequent peri-operative are ulcers or stenosis, obstruction, venous thrombosis, pulmonary embolism and other pulmonary complications, with a mortality of less than 1%. Gastro-intestinal diseases, nutritional deficiencies and psychiatric disorders are the most important long-term problems to be addressed. The uncertainty regarding the long-term effects of bariatric surgery, together with its potential for morbidity and mortality, underline the necessity of large, long-term, randomized clinical trials comparing the best medical therapy with bariatric surgery in patients with type 2 diabetes.

Key words: bariatric surgery, type 2 diabetes, diabetes remission, nutritional problems.

INTRODUCTION

The incidence of type 2 diabetes mellitus continues to rise worldwide and it is now estimated that diabetes affects about one in twelve people worldwide (1), with enormous costs for individuals as well as for society. According to International Diabetes Federation, diabetes caused 4.9 million deaths in 2014, meaning that every 7 seconds a person dies from diabetes. The most bothersome finding is the continuous increase in diabetes prevalence in almost every country; in the recently reported data from National Health and Nutrition Examination Survey (NHANES), the incidence of type 2 diabetes nearly doubled over the past decades (2). In Romania, data from PREDATORR study show a diabetes prevalence of 11.6% among adults (unpublished data).

The current type 2 diabetes mellitus treatment strategy is to control blood glucose levels and also to address other metabolic aspects associated with diabetes, including dyslipidemia and hypertension, as this approach was shown to reduce associated risks and complications (3). However, NHANES data showed that, despite the substantial improvements seen in the last years, less than 20% of patients with diabetes are able to reach the optimal targets for HbA1c, blood pressure and LDL-cholesterol with conventional therapy (2, 4).

Obesity is the single best predictor of type 2 diabetes, as almost 90% of type 2 diabetic patients are overweight or obese (5). Studies have shown that weight loss can substantially improve glycemic control in patients with type 2 diabetes (6), and a weight reduction of only 5 to 10 percent of initial body weight can have a lasting beneficial impact on serum glucose, dyslipidemia, and hypertension (7). On the other hand, important weight loss is difficult to maintain and might not associate with improvement in cardiovascular complications, as it was clearly shown in the Look AHEAD Study, the largest randomized controlled trial of a behavioral intervention for weight loss in patients with diabetes (8). If we add the fact that, over time, the effectiveness of medical treatment regimens for type 2 diabetes commonly declines (9), it is clear the need, at least in some diabetic patients, for more aggressive approaches in order to obtain substantial and durable results.

Bariatric surgical procedures result in significant reductions in body weight and have consequently been

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shown to have important clinical benefits in severely obese patients, including significant improvements in glycemic control in type 2 diabetes patients (10).

However, it was repeatedly demonstrated that glycemic control was improved and even normalized within weeks of the surgery, before major weight loss occurs, suggesting that other factors than weight loss are major contributors to the beneficial effects of the surgery on glycemic improvement. This has raised the issue of bariatric surgery as a primary therapy for type 2 diabetes, as it was suggested even back to 1994 by Walter Pories in a milestone publication entitled "Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus" (11) was reinforced 8 years later by Francesco Rubino (12). After the Diabetes Surgery Summit from Rome, in 2007, the concept of "metabolic surgery" has rapidly emerged to indicate a broader surgical approach aimed at treating diabetes and obesity.

Currently accepted bariatric procedures for the treatment of type 2 diabetic patients are Roux-en-Y gastric by-pass (RYGB), laparoscopic adjusted gastric banding (LAGB), bilio-pancreatic diversion (BPD) and sleeve gastrectomy (SG) (13).

This review summarizes the most recent data regarding the benefits of metabolic surgery regarding type 2 diabetes prevention, glycemic control, and remission, but also analyses the most frequent nutritional and long term side effects of these procedures.

1. The effects of metabolic surgery on type 2 diabetes prevention

The possible effect of bariatric surgery on type 2 diabetes prevention is of particular importance as it was shown that 3% of severely obese individuals develop diabetes every year (14) and it is estimated that in the following 20 years, more than 200 million people will develop diabetes (1). Data regarding this subject are quite scarce, as there are no randomized control studies and only two major cohort studies (14, 15) in which the development of diabetes after bariatric surgery was assessed.

The Swedish Obese Subjects (SOS) study is the most extensive ongoing long-term, prospective, controlled trial to provide information on the effects of bariatric surgery on weight loss, mortality and other endpoints. A subanalysis of 1,658 participants who underwent surgery and 1,771 obese matched controls with no diabetes at the baseline showed a reduction of 78 % in the incidence of type 2 diabetes over a median follow-up period of 10 years after surgery (14), with an even higher effect on patients with impaired fasting glucose at baseline (87%). It should be noted that the preoperative BMI did not predict the effect of surgery on the incidence of type 2 diabetes. These results were confirmed in a recently published populational study including obese non-diabetics selected from the participants in the Clinical Practice Research Datalink (CPRD), a database including more than 5 million individuals from Great Britain. 2167 patients who had undergone bariatric surgery were matched with 2167 controls and were followed up for a maximum period of 7 years (15). The results showed a reduction of 80% in the incidence of type 2 diabetes mellitus in the surgical group.

It is noteworthy that both studies showed a reduction in diabetes incidence that was almost two times higher than the best results of non-surgical therapies (16), such as Diabetes Prevention Program(17) or China Da Qing Diabetes Prevention Study (18). However, individual risk related to surgical interventions should be evaluated in every patient and, on the other hand, only randomized controlled trials will be able to determine which intervention has the best risk - benefit ratio.

2. The influence of metabolic surgery on metabolic control in type 2 diabetes

Observational and cohort studies

The spectacular effects of metabolic surgery on glycaemic control have brought the concept of diabetes "remission" or "cure" in focus, as a possible outcome. In 2009, an ADA consensus group defined "remission" as achieving glycaemia below the diabetic range in the absence of active pharmacologic or surgical therapy. Partial remission is sub-diabetic hyperglycemia (A1C < 6.5%, fasting glucose 100–125 mg/dL) of at least 1 year's duration while complete remission is a return to "normal" measures of glucose metabolism (HbA1C in the normal range, fasting glucose < 100 mg/dL) of at least 1 year's duration in the absence of active pharmacologic therapy or ongoing procedures (19).

The impressive link between bariatric surgery and type 2 diabetes resolution was firstly reported almost 20 years ago (11) and subsequently, a series of observational trials and meta-analysis demonstrated substantial improvement of diabetes after this kind of surgery (20-22). A meta-analysis by Buchwald *et al.* that included 621 studies with 135,246 patients reported an overall remission rate of 78% among diabetic patients undergoing bariatric surgery (21). All these data supporting surgical treatment of diabetes has led the International Diabetes Federation (23) and ADA (3) to recognize bariatric surgery as an effective treatment option for obese patients with T2DM. However, it should be emphasized that these studies are not randomized and the vast majority have short or medium term follow-up (usually up to two years).

In one of the very few studies with at least 5 years of follow-up, Brethauer *et al.* assessed clinical outcomes of 217 patients with type 2 diabetes mellitus who underwent bariatric surgery (24). The mean excess weight loss of 55 % was associated with a reduction in the mean HbA1c level from 7.5 to 6.5%. The long-term complete remission rate was 24 % and the recurrence of diabetes after initial remission was observed in 19 % of patients. SOS study data regarding the long-term diabetes outcome were recently published (25) showing that, after 15 years of follow-up, diabetes remission rate was 30.4% for bariatric surgery patients, compared with 6.5% in controls. Relapse from remission, defined as the proportion of patients who fulfilled diabetes criteria at the 15-year follow-up among those who were in remission at year 2, reached 60%. In a meta-analysis including all cohort studies with more than 2 years follow-up, Yu *et al.* showed a mean change in HbA1c levels of -1.8% (95%CI:, -2.4 to -1.3), complete or partial remission in 64.7% of patients and diabetes recurrences rate between 20.6% (at 3 years follow-up) and 43.3% (at 8.6 years follow-up) (26).

Randomized control studies

The only valid estimate of the value of metabolic surgery in type 2 diabetes is to compare health outcomes from metabolic surgery with those of the best medical and nutritional therapy in long-term, randomized controlled clinical trials. Up to now, there are 4 such clinical trials, comparing bariatric surgery procedures with medical and lifestyle intervention for patients with type 2 diabetes (27). An analysis of the results from these randomized studies shows that the percentage of patients in remission ranged from 38 to 75 % at the end of follow-up (28).

In STAMPEDE, the randomized study with the longest follow-up (3 years), there was a higher HbA1c reduction in the surgical group (-2.5%) than in the medical therapy group (-0.6%), which paralleled the greater reduction in weight (29). At 3 years, 5% of the medical therapy group, 38% of the gastric bypass group and 24% of the gastric sleeve group reached HbA1c levels of 6.0% or less. Quality of life questionnaires showed significantly better results in the two surgical groups than in medical therapy group. Diabetes Surgery Study is a prospective randomized study conducted in four academic hospitals from US and Taiwan, which included 120 participants with type 2 diabetes with HbA1c level of at least 8.0% and BMI between 30.0 and 39.9 kg/m^2 (30). All 120 patients received the intensive lifestyle-medical management protocol and 60 were randomly assigned to undergo RYGB. After 12 months, 49% of patients in the RYGB group and 19% in the lifestyle-medical management group achieved the composite goal, that is, HbA1c less than 7.0%, low-density lipoprotein cholesterol less than 100 mg/dL, and systolic blood pressure less than 130 mm Hg. This study is important because it included patients with BMI < 35 kg/m^2, proving that RYGB might be an important option in diabetes persons who are not morbidly obese.

It is clear that available data from these randomized controlled trials suggest that surgery procedures are superior to medical intervention for the control of hyperglycemia, at least in the first 2-3 years (26). The following years will probably bring more data regarding the long term effect and sustainability of these results, as well as the impact on diabetes complications and mortality.

Predictors of type 2 diabetes remission

The majority of obese subjects with type 2 diabetes who underwent bariatric surgery show an improvement of metabolic features but diabetes remission is reported only in a limited number of cases. This suggests the importance of identifying clinical and biological parameters associated with the best diabetes outcome. Clinical studies showed that the most important factors that contribute to the successful remission of diabetes following bariatric surgery are:

a. Diabetes duration – as an estimation of diabetes severity, the longer the duration, the lower the chances of remission (31).

b. Insulin treatment – associated with lower remission rates compared with oral medication (13.5 *versus* 53.8%) (32). Insulin therapy is a marker of an increased diabetes severity, a poorer control in the context of a markedly affected beta cell function.

c. Weight loss – Recently, Dixon *et al.* showed that a loss of minimum 50% of the excess weight (or 30% of the initial weight) is needed for significant amelioration or even remission of diabetes (33). However, another analysis of the currently available data suggests that weight loss may contribute only slightly to late diabetes remission and not at all to early diabetes remission (34). Weight regain, on the other hand, may be a more important factor for diabetes relapse.

d. Initial level of C peptide – is a surrogate marker of beta cell mass and insulin secretion. Preoperative fasting C-peptide levels correlate strongly with remission of T2D following bariatric surgery (35).

e. Type of surgical procedure – there are several studies that analysed the efficiency of different types of surgical procedures, reporting remission rates of 7 -70% for gastric banding, 38-98% for gastric by-pass, 33-85% for sleeve gastrectomy and 52-100% for BPD (36).

There are several algorithms designed to predict the outcome of bariatric surgery and the chances of remission. Very recently, a novel scoring system, DiaRem, was designed, based on a retrospective study of 690 patients with diabetes, and four preoperative clinical variables were identified in the final scoring model: insulin use, age, HbA1c, and type of antidiabetic drugs used (34). The DiaRem score ranges from 0 to 22. The study showed that 88% of patients who scored 0-2, 64% of those who scored 3-7, 23% of those who scored 8-12, 11% of those who scored 13-17, and 2% of those who scored 18-22 achieved remission (partial or complete) according to ADA definition.

Potential risks of bariatric surgery

Bariatric procedures are probably the most effective modality of obtaining a consistent diabetes control and even diabetes remission. However, concern about the safety of bariatric surgery has grown with its increasing popularity. Surgical treatment of obesity and diabetes carries a risk for considerable morbidity and potential mortality.

Early complications that occur ≤ 30 days after bariatric surgery are generally low and vary with the type of the procedure and the experience of the surgical team. The most common are marginal ulcers or stenosis at the anastomosis site, stomal and small bowel obstruction, venous thrombosis, pulmonary embolism and other pulmonary complications. Regarding mortality, the rate is generally way beyond 1% (37), with higher rates for patients undergoing more complex operative procedures, in males, as well as those with a BMI ≥50 kg/m^2, older age, and medical comorbidities (38). This rate compares favorably with the hospital mortality of other frequently performed major surgical procedures, including hip replacement (0.3 percent), abdominal aneurysm repair (3.9 percent), craniotomy (10.7 percent), esophageal resection (9.1 percent), and pancreatic resection (8.3 percent) (39).

Late complications of bariatric surgery include gastro-intestinal and hepatobiliary diseases, nutritional deficiencies and psychiatric problems.

a. Gastrointestinal and hepatobiliary complications.

Dumping syndrome is characterized by vasomotor and gastrointestinal symptoms attributed to rapid gastric emptying or rapid exposure of the small intestine to nutrients. Clinical symptoms are typically triggered by meal ingestion and are subdivided into "early" (abdominal pain, diarrhea, bloating, flushing, palpitations, and hypotension) and "late" dumping symptoms (signs of hypoglycemia: sweating, hunger, weakness, confusion, tremor, syncope). After bariatric surgery, dumping syndrome has mainly been reported in patients who underwent operation.

Roux-en-Y gastric bypass (up to 40%) and other interventions involving partial gastrectomy(40). Initial therapy consists in dietary measures: smaller and frequent meals, avoiding rapidly absorbed sugars and lactose, use of viscous food additives like pectin, guar gum to delay gastric emptying; if the symptoms persist, somatostatin analogues may be considered (41).

Gastro-esophageal reflux is a frequent finding in obesity(42) and most studies show an improvement of the symptoms after bariatric surgery. However, particular procedures such as gastric banding or sleeve gastrectomy may be associated with new-onset reflux symptoms, explained mainly by the decreased gastric compliance (43).

Cholelithiasis. Both severe obesity and rapid weight loss are factors independently associated with the development of cholelithiasis. Cholelithiasis develops in almost 40 percent of patients within six months of RYGB, and up to 41 percent of these patients become symptomatic (44). In the SOS study, during the first 2 postoperative years, the incidence of cholelithiasis was 4% in operated men compared with 1.2% among male controls and there was also a significant difference in the incidence of cholecystitis (2.5% *versus* 0.7%) and cholecystectomy (3.4% *versus* 0.7%). In women, no statistically significant differences were found between the surgery group and controls (45).

b. Nutritional deficiencies

Bariatric surgical procedures have been associated with a number of nutritional deficiencies, but their prevalence depends on the type of surgery. Laparoscopic gastric banding and sleeve gastrectomy, which are rather restrictive than malabsorptive procedures, are less frequently associated with deficiencies; the Roux-en-Y gastric bypass, on the other hand, may result in fat, protein and vitamins malabsorption. Other important factors are persisting preoperative deficiencies, reduced overall nutrient intake in the (early) postoperative phase, post-operative vomiting, modified eating behaviour and non-compliance to dietary and supplement recommendations.

Protein deficiency (serum albumin < 3.5 mg/dL) accompanied by a severe reduction in lean tissue mass occurs in up to 13% of severely obese patients 2 years after RYGB (46) and has been demonstrated to increase both mortality and annual hospitalization rate (47). Hair loss is one of the early clinical symptoms, while the presence of oedema suggests a severe deficit. Current consensus guidelines recommend an average protein intake of 60-120 g after RYGB, 60-80 g after sleeve gastrectomy and 90 g after BPD, and also a program of regular resistance training and aerobic exercise that would significantly improve the preservation of lean body mass (48).

Minerals and micronutrients. The most frequent deficiencies involve vitamin B1 (up to 30%, with potentially irreversible neurological manifestations), B12 (19-35%), iron (17-45%), zinc (12-91%), calcium and vitamin D (47).

In case of malabsorptive procedures (RYGB, BPD), a panel of blood tests can be assessed preoperatively and at 6 month intervals in the first 2 years, and may include blood cell count, triglycerides, cholesterol, albumin, alkaline phosphatase, calcium, phosphorus, magnesium, zinc, iron, ferritin, prothrombin time, serum vitamin A, immunoglobulins, parathyroid hormone, serum vitamin D, folic acid, vitamin B12 (41). It is recommended for all patients who underwent malabsorptive surgical interventions to take multi-vitamin supplements that contain at least double the daily recommended dose, as well as 18 mg of elemental iron and 400 mg of folic acid, vitamin A, copper and zinc (49).

Calcium, vitamin D and the effect on bone metabolism

Bariatric surgery procedures are associated with some deleterious effects on the bone and mineral metabolism, including vitamin D deficiency, hyperparathyroidism, and bone loss. Pre-existing alterations in calcium homeostasis are common in severely obese patients, with vitamin D insufficiency reported in up to 90% of bariatric patients (50). After BPD and RYGB, active absorption of calcium, which predominantly happens in the duodenum and jejunum, is impaired and absorption of vitamin D is delayed. Additionally, after sleeve gastrectomy and RYGB, gastric acid production is reduced, which might affect calcium absorption (51). The consequence of these is a substantial rise in parathyroid hormone concentrations, documented by many studies (52), which has deleterious consequences especially on cortical bone. All these changes, together with the primordial mechanism of mechanical unloading induced by the drastic weight loss, which induces compensatory increases in localized bone remodelling, explains the bone loss associated with bariatric surgery.

There are numerous studies showing a decrease in bone mineral density after bariatric surgery. A recent meta-analysis showed a consistent decrease in bone mineral density in the hip and in the spine, especially after malabsorptive and combined bariatric procedures, one year after surgery (53). In addition to decreased mineral density and increased bone turnover, bariatric surgery is associated with changes in bone quality and microarchitecture. In a prospective study of 22 women who underwent RYGB, VSG, and LAGB, with high resolution peripheral QCT, a decrease of cortical area, density, thickness, and total density at the tibia were recorded 1 year after surgery. Decreases in cortical bone were predicted by the increase in parathyroid hormone (52).

If the effect of bariatric surgery on bone mineral density has been proven beyond doubt, very few data are available for the risk of fracture after bariatric surgery. A retrospective study from the UK found no significantly increased risk of fracture in 2079 bariatric surgery patients compared with 10 442 matched controls, after a mean follow-up of only 2.2 years (54). On the other hand, a historical cohort study (median follow-up 7.7 years) compared fracture incidence in 258 patients who underwent bariatric surgery, mainly RYGB, with expected incidence in a community-based population and showed an important increased risk for all fractures in bariatric patients (55). It should be mentioned that no prospective fracture data exist.

The updated clinical practice guidelines for the perioperative support of bariatric patients undergoing surgery recommend measuring 25 (OH)vitamin D in all patients before surgery and ensuring a daily intake of 1200-1500 mg of calcium citrate (from diet or supplements) and 3000 UI vitamin D (48). Evaluation of bone mineral density should be performed at 2 years after the surgery in all patients, and also before surgery in patients with RYGB and BPD.

c. Psychiatric problems

Morbidly obese patients have important psychiatric problems and around 40% of all bariatric surgery patients have at least one psychiatric diagnosis, of which depression, anxiety and eating disorders are the three commonest disorders (56). There are data showing improvement in psychopathology after bariatric surgery and even a tendency of improved cognitive function (57). On the other hand, suicide risk remains high and warrants long-term supervision. In a 10-year follow-up study, bariatric surgery patients as a group had excessive suicides compared with their age and sex-matched counterparts (58), and this finding was confirmed by a subsequent metaanalysis (59).

Alcohol abuse and alcohol related issues ar other important problems in bariatric patients. In the SOS study, both gastric by-pass and gastric banding groups had increased risk of alcohol abuse diagnoses, alcohol consumption at least at the WHO medium risk level, and alcohol problems (60). Male sex and baseline smoking and alcohol consumption increased the likelihood of postoperative alcohol abuse diagnosis. A number of studies report that, after bariatric surgery, some patients stop overeating and instead acquire new compulsive disorders such as alcoholism, gambling or other addictions like compulsive shopping; it was suggested that patients adopt a new addictive habit as an exchange for their compulsive eating problem (addiction transfer) (61). All these underline the importance of a psychological assessment before bariatric surgery and on a regular basis in the postoperative follow-up.

In conclusion, bariatric surgery results in significant improvements in glycemic control in patients with type 2 diabetes and sometimes even induces more or less permanent remission. Considering the significant surgical, nutritional and psychologic complications associated with bariatric surgery, it is imperative that large, long-term, randomized clinical trials comparing the best medical therapy with bariatric surgery be conducted in patients with type 2 diabetes as they are necessary to make appropriate benefit–risk calculations for bariatric surgery as a primary therapy for type 2 diabetes.

Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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