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Current Recommendations for Surgical Treatment of Diabetes

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1. Introduction

The incidence of type 2 diabetes mellitus continues to rise worldwide and it is now estimated that diabetes affects more than 382 million people worldwide [1]). In the United States, the prevalence of diabetes ranges from 5.8 to 12.9 percent [2], but one of the most bothersome finding is the continuous increase in its prevalence; both community-based Framingham Heart Study and the National Health and Nutrition Examination Survey (NHANES) reported nearly doubling in the incidence of type 2 diabetes over the past decades [3] [4]

Obesity is one of the most important clinical risk factor for diabetes. In Nurses' Health Study, there was an approximately 100-fold increased risk of incident diabetes over 14 years in individuals whose baseline BMI was $>35 \text{ kg/m}^2$ compared with those with BMI <22 [5]. While the relationship between BMI and the risk of type 2 diabetes seems to be curvilinear, there is also an additional risk brought by the weight gain. In the same study, a weight gain of 8.0 to 10.9 kg after 18 years was associated with a relative risk for diabetes of 8.0 to 10.9 kg compared with those with minimal weight gain [5].

Sustained weight loss, on the other hand, can substantially improve glycemic control in patients with type 2 diabetes, by providing a partial correction of the two major metabolic abnormalities in type 2 diabetes: insulin resistance and impaired insulin secretion. A weight reduction of only 5 to 10 percent of initial body weight in overweight individuals can have a lasting beneficial impact on serum glucose, dyslipidemia, and hypertension [6]. However, the amount of weight loss required to achieve an ideal glycemic response may depend on the initial glucose level, as shown by the UKPDS study, with higher goals needed for those with non-controlled diabetes [7].

While the benefits of weight loss for obese patients with diabetes are indubitable, there are several strategies for achieving weight loss, with physical activity and intensive lifestyle modification being important components of almost all programs. The Look AHEAD Study, the largest and longest randomized controlled trial of a behavioral intervention for weight loss in patients with diabetes, showed a mean body weight reduction of 8.5% at year one; over the next four years, a gradual regaining of weight was observed, followed by the maintenance of losses of approximately 4-5% in subsequent years [8]. This quite poor maintenance of weight loss, associated with the trial's negative finding with regard to its cardiovascular endpoints [9] sustains the need, at least in some diabetic patients, for more aggressive approaches in order to obtain substantial and durable weight loss.

2. History of bariatric surgery and its use in treating diabetes

The first report of a surgical procedure aiming for weight loss is said to be the Talmud. There it is said that Rabbi Eleazor, who was morbidly obese, underwent an operation after being given a soporific potion wherein his abdomen, or abdominal wall, was opened and a number of "baskets of fat were removed" [10]. However, the first bariatric surgery intervention performed in modern time dates back to 1953, when Varco from Minnesota University performed a bypass of small intestine in an obese patient, with bowel reconstruction by an jejunioileostomy [11]. This jejunio-ileal by-pass caused excellent and lasting weight loss but proved to be associated with extensive complications due to short bowel syndrome and bacterial overgrowth. In 1966, Edward Mason, who is considered the father of bariatric surgery, published the landmark paper on gastric bypass [12], while in 1977 Griffen and his colleagues performed the first gastric bypass with a Roux-en-Y gastrojejunostomy (RYGB). The popularity of this intervention rapidly rose, as it proved to be efficient and quite safe, with reduced request for revisional surgery. From the beginning of the 70's gastroplasty was introduced as an important bariatric procedure, firstly as a partial horizontal gastric transection, than as a vertical banded gastroplasty. The following years brought into attention other innovative techniques, such as bilio pancreatic diversion (BPD), laparoscopic adjusted gastric banding (LAGB), sleeve gastrectomy (SG) or gastric plication, designed to improve the main outcome: weight loss and metabolic improvement, but also to reduce the incidence of complications.

The Greek word "baros" means weight and the term bariatric came into use in 1965, defining a branch of medicine dealing with causes, prevention, and treatment of obesity. At the beginning, interventions performed in order to obtain weight loss were mechanistically defined as purely restrictive of food intake (e.g., vertical banded gastroplasty, laparoscopic adjustable gastric banding), restrictive/malabsorptive (e.g., gastric bypass), and primarily malabsorptive (e.g., bilio pancreatic diversion/duodenal switch). It was lately clear that these anatomical descriptions did not provide the mechanism of action and the mechanical explanation of weight loss was subsequently challenged. More than that, the consequences of these procedures go far beyond weight loss, as, in addition to solving mechanical problems of gastroesophageal reflux disease, obstructive sleep apnea, and back and joint pain, they

improve or even cure metabolic diseases (e.g., type 2 diabetes, hyperlipidemia, hypertension, polycystic ovary syndrome, nonalcoholic steatohepatitis, possibly cancer).

Metabolic surgery was defined in 1978 by Henry Buchwald and Richard Varco as “the operative manipulation of a normal organ or organ system to achieve a biological result for a potential health gain” [13]. The practice of metabolic surgery goes, however, way before this timeline; examples are the procedures of gastrectomy or vagotomy for duodenal ulcers, procedures that don’t touch the actual lesion, or splenectomy for idiopathic thrombocytopenic purpura. In the late 80’s, The Program on the Surgical Control of the Hyperlipidemias (POSCH) showed that a surgical procedure (partial ileal by-pass) could dramatically improve total cholesterol and low-density lipoprotein cholesterol levels, as well as atherosclerotic coronary heart disease mortality and recurrent nonfatal myocardial infarction as well as overall mortality, the incidence of coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, and the development of peripheral vascular disease [14].

Nicola Scopinaro and Walter Pories were among the first who stated the effectiveness of gastrointestinal surgery procedures in correcting or even curing type 2 diabetes; they showed normalization of blood glucose levels after biliopancreatic diversion [15] and gastric by-pass, respectively [16]. In a milestone publication entitled “*Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus*”, Pories underlined the importance of hormonal mechanisms in the process of improving or even curing type 2 diabetes mellitus, independent of weight loss. Bariatric surgery is beyond doubt metabolic surgery, as it causes dramatic improvement of type 2 diabetes and can effectively prevent progression from impaired glucose tolerance to diabetes in severely obese individuals, but it also resolves or mitigates some other important complications of obesity, such as dyslipidemia, hypertension, insulin resistance, sleep apnea [17].

3. Short description of the main bariatric surgery procedures used in diabetic patients

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 duodenal switch variant (BPD-SD), and sleeve gastrectomy (SG) [18]

The Roux-en-Y gastric bypass (Figure 1) is one of the most commonly performed bariatric procedures worldwide. It developed in the late 60’s from the observation that patients with partial gastrectomy suffer a significant and persistent weight loss. After successive changes and optimizations, it is now considered the gold-standard in bariatric surgery. The intervention has several components: in the first step, a 30 milliliters stomach pouch is created by dividing the top of the stomach from the rest of it. Next, the first portion of the small intestine is divided, and the bottom end of the divided small intestine is connected to the newly created stomach pouch. In the final step, the top portion of the divided small intestine is connected to the small intestine further down so that the stomach acids and digestive enzymes from the bypassed stomach and first portion of small intestine will eventually mix with the food [19].

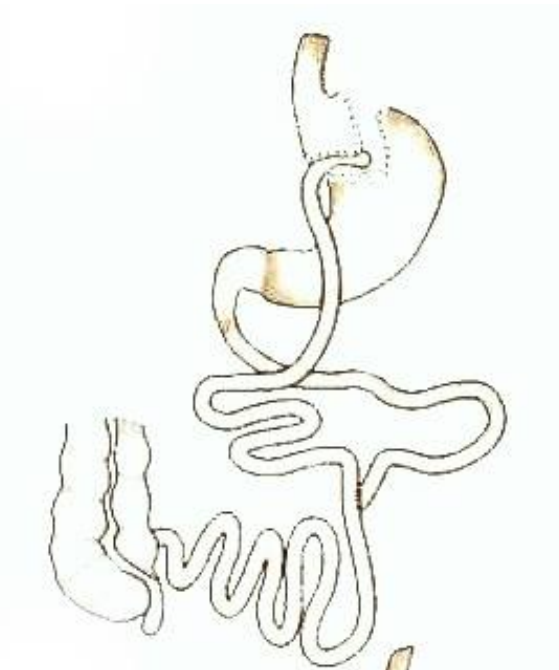


Figure 1. Roux-en-Y gastric bypass

Laparoscopic adjusted gastric banding (Figure 2) involves surgical insertion of an adjustable inflatable band that is placed around the upper part of the stomach to create a smaller stomach pouch. This slows and limits the amount of food that can be consumed at one time, but it does not decrease gastric emptying time. The size of the stomach opening can be adjusted by filling the band with sterile saline, which is injected through a port placed under the skin.



Figure 2. Laparoscopic adjusted gastric banding

Sleeve Gastrectomy (SG) is a procedure that involves removing the lateral part of the great gastric curvature, with stomach resection along the little curvature, from Hiss angle to the antrum [20] – Figure 3. The intervention was initially used as the first part of a two-stage procedure for super-obese patients ($BMI > 60\text{kg/m}^2$), who were considered poor surgical candidates and who would not tolerate a prolonged or more involved procedure. The aim of the procedure was to allow the patients an opportunity to achieve some weight loss before being converted to the more complex gastric bypass or biliopancreatic diversion with duodenal switch (BPD-DS) [21]. It was, however, rapidly proved that weight loss and metabolic benefits were significant and nowadays it is used as a definitive weight loss procedure, with the advantage of the technical simplicity and the lower risk for complications [22]. The most recent guideline of the American Society for Metabolic and Bariatric Surgery also endorsed by the American Association of Clinical Endocrinology does not include this procedure among the investigational ones but considers it consecrated [23]

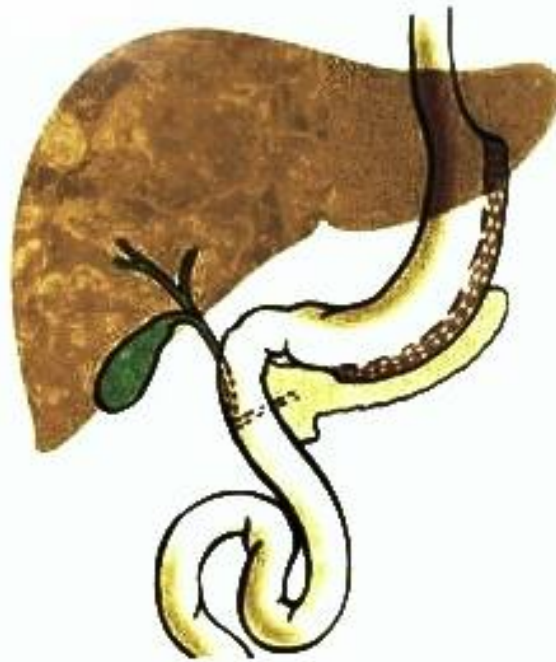


Figure 3. Sleeve gastrectomy

Biliopancreatic diversion with duodenal switch (Figure 4) is a weight loss surgery intervention that is composed of two procedures: in the first one, a smaller, tubular stomach pouch is created by removing a portion of the stomach, and afterwards, a large portion of the small intestine is bypassed. After dividing duodenum just past the outlet of the stomach, a segment of the distal small intestine is then brought up and connected to the outlet of the newly created stomach; in this way, approximately three-fourth of the small intestine is bypassed by food. The bypassed small intestine, which carries the bile and pancreatic enzymes, is reconnected to the last portion of the small intestine [19]

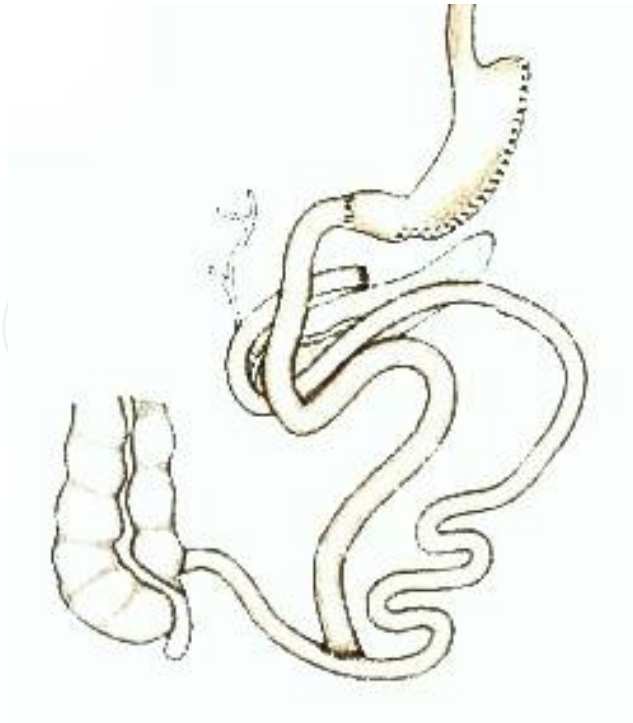


Figure 4. Biliopancreatic diversion with duodenal switch

4. Mechanisms involved in diabetes control or remission

It is very clear that weight loss has a profound impact on diabetes control and much of the effects of bariatric surgery on glucose homeostasis were attributed to its impact on weight. However, several investigators demonstrated the very rapidly normalisation in glucose metabolism (in a few days), way before the weight loss becomes significant [24]. This suggests that diabetes remission may be due to mechanisms involving the surgical technique, aside from weight loss. The most common hypothesis are:

4.1. Caloric restriction hypothesis

It is well-known that very low calories diets may significantly and early improve glycemic control in diabetes patients [25], as caloric restriction can improve hyperglycemia through regulation of hepatic glucose production [26]. Considering the level of caloric absorption from the intestinal tract, all bariatric procedures are restrictive; caloric intake can be restricted by the inhibition of eating, as in AGB, SG or RYGB, or by the insufficient intestinal surface, as in BPD or other so-called “malabsorbative” procedures.

In a recent study, Jackness et al compared the effect of a very low-calorie diet (VLCD) (500 kcal/day) and RYGB on β -cell function in type 2 diabetic patients during the first 3 weeks after intervention and reported similar degrees of weight loss and no significant differences in β -cell function between the groups [27]. Similar results were presented by Plourde et al in a study

regarding the improvement of insulin sensitivity and β -cell function following bilio-pancreatic diversion with duodenal switch (BPD-DS) [28]. Both groups concluded that caloric restriction was primarily responsible for the early effects of bariatric surgery procedures on glucose metabolism. However, this theory doesn't explain the long term differences in efficiency between the different bariatric procedures, despite the similar caloric restriction.

4.2. The neural networks hypothesis

The intestinal tract has important parasympathetic and sympathetic innervations. Vagally mediated reflexes are critical to the control, regulation and organization of appropriate GI functions, including hunger, appetite and satiety. Several studies have demonstrated that the behavior, activity and responsiveness of vagal afferents are altered by diet and obesity [29]. As shown by Browning et al [30], RYGB reversed some of the alteration of dorsal motor nucleus of the vagus neurons induced by high fat diet and improved vagal neuronal health in the brain. Sympathetic gut innervation, on the other hand, is involved in glucose production and release, inhibition of peristalsis and inhibition of gastrointestinal enzyme secretion. Weight loss induced by bariatric surgery may trigger profound sympathoinhibitory effects [31]

4.3. The hindgut hypothesis

This is probably the most accepted hypothesis that focuses on the expedited delivery of nutrients to the ileum after most of the bariatric procedures, which results in the accentuated production of peptides produced by L cells in the distal small intestine, including glucagon-like peptide (GLP)-1, peptide YY (PYY), and oxyntomodulin [32]. GLP-1 and PYY are both secreted by the L cells located in the distal gastrointestinal tract in response to nutrient ingestion and elicit almost the same metabolic responses. Together with GIP, they are responsible for the incretin effect, which consists in the greater insulin response after oral ingestion of glucose as compared with the insulin response after intravenous infusion of glucose when plasma glucose concentrations are the same [33].

It was shown that GLP-1 amplifies important steps in insulin synthesis and transcription, stimulates beta cell proliferation, reduces appetite and gastrointestinal motility [34]. It has been shown that GLP-1 is reduced in patients with type 2 diabetes and this have resulted in the development of two drug classes currently approved for the treatment of T2DM: the long-acting analogues of GLP-1, and the inhibitors of dipeptidyl peptidase 4 (the enzyme responsible for the rapid degradation of GLP-1) [33]. After RYGB, postprandial secretion of GLP-1 increases approximately 20 times [32]; this effect has been demonstrated as early as one week after surgery and persists for at least 10 years thereafter [35]. The improvement in incretin levels is not dependent on weight loss and, in diabetic patients, it has been paralleled by improved glucose tolerance [33]. An increased of postprandial GLP-1 levels has also been reported following gastric sleeve, apparently comparable to that obtained after RYGB, in the short and in the long term [36]. However, several recent studies suggest that the dramatic increase in GLP-1 secretion observed in the long term after RYGB surgery contributes to improved beta-cell function but does not appear to be the key determinant for the resolution of T2DM following this type of surgery [36]. Likewise, data from a rodent model have shown

that blocking the action of GLP-1 does not influence the dramatic improvement in glucose tolerance observed after sleeve gastrectomy and therefore that GLP-1 receptor activity is not necessary for the beneficial metabolic effects of SG [37].

4.4. The foregut hypothesis

This theory suggests that the bypass of the duodenum and proximal jejunum after RYGB, or the lack of food exposure to these areas of the small intestine, might determine the decrease in secretion of an unknown duodenal factor (an antiincretin) influencing glucose homeostasis. The anti-incretin hypothesis, embraced by Rubino [38], postulates that, in addition to the well-known incretin effect, nutrient passage in the bowel can also cause activation of negative feedback mechanisms (anti-incretins) to balance the effects of incretins and other postprandial glucose-lowering mechanisms. Supporters of this theory suggest the physiologic necessity of these control mechanisms to prevent the risk for postprandial hyperinsulinemic hypoglycemia and uncontrolled beta cell proliferation induced by incretins. Excess of anti-incretin signals, perhaps stimulated by macronutrient composition or chemical additives of modern diets, might cause insulin resistance, reduced insulin secretion, and beta cell depletion, leading to type 2 diabetes [38]. On the other hand, bariatric surgery, by resecting or excluding parts of the small bowel from nutrients transit, changes the incretins/anti-incretins balance; this might explain the improvement or even the cure of type 2 diabetes, but also the postprandial hyperinsulinemic hypoglycaemia that can complicate RYGB [39]

4.5. Other theories

4.5.1. Bile acids hypothesis

Among the changes to intestinal physiology that occur after bariatric surgery is the altered enterohepatic circulation of bile acids. Bile acids are now recognized to be involved in the regulation of various metabolic processes including lipids, glucose, and energy homeostasis. Their binding to a nuclear receptor (farsenoid-X-receptor or FXR) produces alterations in hepatic glucose production and intestinal glucose absorption influences on peripheral insulin sensitivity and incretin effects [40]. After RYGB, fasting and postprandial serum concentrations of bile acids increase. Gerhard et al reported that patients with postoperative remission of diabetes after RYGB showed larger increases in fasting bile acids than did patients who did not achieve diabetes remission or who did not have diabetes preoperatively [41]. A recent study published by Karen Ryan and colleagues from the University of Cincinnati showed that VSG is associated with increased circulating bile acids and that, in the absence of FXR, the ability of VSG to reduce body weight and improve glucose tolerance is substantially reduced. These results point to bile acids and FXR signaling as an important molecular underpinning for the beneficial effects of bariatric surgery [42].

4.5.2. Gut microbiota hypothesis

The gut microbiota is recognized to have an important role in energy storage and the subsequent development of obesity. It is well-known that obese individuals have an increased ratio

of Firmicutes to Bacteroidetes bacteria and decreased bacterial diversity compared with lean controls—differences that disappear in response to weight loss, whether surgical or dietary intervention [43]. Recent studies proved the change in gut flora after RYGB; in addition to the standard decrease in the Firmicutes to Bacteroidetes ratio that accompanies weight loss, a major finding from microbial sequencing analyses after RYGB is the comparative overabundance of the phylum Proteobacteria in the distal gut microbiome [44]. In a murine bariatric model changes in gut microbiota were similar to those seen in humans after RYGB, and transfer of the surgically altered microbial species to non-operated, germ-free mice resulted in weight loss; this suggests that changes in gut microbiota might contribute to the beneficial effect of RYGB [45].

5. Trials proving the efficacy of bariatric surgery in diabetes control

Obesity and type 2 diabetes mellitus are both major health problems due to growing incidence and increasing costs of care [46]. Type 2 diabetes mellitus closely follow incidence and prevalence of obesity and the evolution of the disease is marked by several complications such as retinopathy and blindness, neuropathy and lower limb amputations, end stage renal disease, myocardial infarction and stroke if the disease is not well controlled. Despite of tremendous progressions which have been made in type 2 diabetes mellitus treatment, more than fifty percent of patients do not reach their glycemic control targets [47].

There are a number of **observational trials** and published meta-analyses that demonstrate consistent improvement of type 2 diabetes after metabolic surgery. In an observational controlled study from Norway, morbidly obese patients with mean BMI 45.1 kg/m² were treated with either Roux-en-Y gastric bypass or intensive medical therapy. At one year weight loss was 30% in surgery group compared with 8% in lifestyle group and diabetes remission rate was 70% versus 33%. [48]

A meta-analysis of studies on type 2 diabetes obese patients who underwent different types of bariatric procedures showed at baseline the mean age 40.2 years, body mass index was 47.9 kg/m², 80% were female, weight loss overall was 38.5 kg or 55.9% excess body weight loss and an overall rate of remission of diabetes of 78%. [49] Remission of diabetes occurred in half of patients who underwent laparoscopic adjustable gastric bypass, 80% of patients who underwent Roux-en-Y gastric bypass, and 95% of those who underwent biliopancreatic diversion. [49]

The key results from the Swedish Obese Subjects (SOS) study have been published in a review. This is a long term, prospective, controlled trial on 2010 obese subjects who underwent metabolic surgery (13% gastric bypass, 19% banding and 68% vertical banded gastroplasty) and 2037 matched obese control subjects receiving usual care. [50] The diabetes remission rate was increased several fold at 2 years (adjusted OR=8.42) and 10 years (adjusted OR=3.45). After 2 years of follow-up, 72% of SOS patients with type 2 diabetes mellitus at baseline were in remission in the surgery group. But amongst patients who underwent surgery with remission of diabetes at 2 years, 50% had relapsed after 10 years. [50]

The outcomes of bariatric surgery are analyzed in a retrospective case-matched study comparing medical treatment, duodenal switch, and laparoscopic adjustable gastric band to Roux-en-Y gastric bypass for treatment of obese type 2 diabetes. [51] At one year of follow-up the Roux-en-Y gastric bypass produced greater weight loss, A1c improvement, and higher diabetes medication score reduction than medical therapy and laparoscopic adjustable gastric bypass but duodenal switch produced greater reduction in A1c and diabetic medication score than Roux-en-Y gastric bypass. [51]

Recently more and more evidences come from **randomized controlled trials**. These studies are difficult to be compared because of different inclusions criteria regarding the mean age, duration of diabetes, mean BMI and different primary endpoints and also lack of homogenous definition of diabetes remission. The first randomized controlled trial conducted on a small group compared conventional diabetes therapy consisting on weight loss by lifestyle changes versus laparoscopic adjustable gastric banding associated to diet on 60 obese patients (BMI >30 and <40) with recently diagnosed type 2 diabetes [52]. After two years of follow-up, remission of type 2 diabetes defined by fasting glucose level <126 mg/dl and glycated hemoglobin value <6.2% without glycemic therapy, was achieved by 73% in surgical group and by 13% in the conventional group. [52] As the authors recognized, this study has several limitations: relatively small number of patients, limited time of follow-up thus the results cannot be extrapolated for a longer period, lack of hard end points such as mortality and cardiovascular events [52].

A higher number of patients, 150 were included in Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently trial (STAMPEDE trial) and were randomly assigned to intensive medical therapy alone or intensive medical therapy plus either Roux-en-Y gastric bypass or sleeve gastrectomy. [53] These patients had a longer duration of diabetes, >8 years and mean BMI was 36 and glycated hemoglobin at baseline range from 8.9% to 9.5%. At 12 months of follow-up the target glycated hemoglobin level <6% was achieved by 12% in the intensive medical therapy alone group versus 42% in the gastric-bypass group and 37% in the sleeve-gastrectomy group, without significant differences between surgical groups. [53] Glycated hemoglobin and fasting plasma glucose improved significantly faster and at a great magnitude at three months in surgical groups compared with medical therapy group with a lower use of antidiabetic agents and this improvement was sustained over the entire follow-up period. [53] Type 2 diabetes mellitus control was significantly improved after both bariatric surgery procedures with a reduction of glycated hemoglobin by 2.9 percentage points. The average number of diabetes medications per patient per day increased in intensive medical therapy from 2.8 at baseline to 3 at one year and decreased in surgical groups from 2.6 (Roux-en-Y bypass group) and 2.4 (Sleeve gastrectomy group) to 0.3 and 0.9 respectively. [53] Insulin treatment at 12 months of follow-up was more prevalent among patients on intensive medical therapy group 38% versus gastric by-pass group 4% and sleeve-gastrectomy group 8%. [53] Not only glycemic control was improved secondly bariatric surgery but also HOMA-IR index, CRP level, lipid profile, with significantly decreased of triglycerides and increased of high-density lipoprotein (HDL) cholesterol. The main limitation of this study, short duration of follow-up is overcome by another study with a follow-up period of two years, performed on

60 obese (BMI over 35), type 2 diabetic patients randomized on medical therapy, laparoscopic gastric bypass and biliopancreatic diversion. [54] In this study remission of diabetes was defined by fasting plasma glucose level of less than 100 mg/dl (5.6 mmol/l) and glycated hemoglobin level of less than 6.5% for at least one year without antidiabetic agents. At two years of follow-up the remission of diabetes occurred in 75% of patients in gastric bypass group, 95% of patients in biliopancreatic diversion group and none of patients in medical therapy group. [54] The relative risk of diabetes remission was 7.5 in the gastric-bypass group and 9.5 in the biliopancreatic-diversion group as compared with the medical-therapy group. [54] The average time to the normalization of fasting glucose and glycated hemoglobin was 10 months for gastric bypass versus 4 months for biliopancreatic diversion, differences being significant. [54] Biliopancreatic diversion and gastric bypass are much more effective in controlling glycemia in type 2 obese diabetes patients than medical therapy. [54] The Diabetes Surgery Study compared Roux-en-Y gastric bypass versus medical therapy in achieving a composite endpoint consisting in cardiovascular risk factors, glycated hemoglobin under 7%, LDL cholesterol under 100 mg/dl and systolic blood pressure under 130 mg/dl. [55] At 12 months, 19% in the medical group and 49% in the gastric bypass group achieved the primary composite endpoint. [55]

Glycated hemoglobin was significantly improved at follow-up visit in all groups who underwent a surgical procedure compared with medical group. In the Diabetes Surgery Study the mean A1c at 1 year after gastric bypass was 6.3%, in the Schauer et al study A1c was 6.4% after Roux-en-Y gastric bypass and in the Mingrone et al study A1c was 6.3% after laparoscopic gastric bypass or biopancreatic diversion. [53-55]

Very recently a systematic review and meta-analysis focused on medium term outcomes (five years) after banded Roux-en-Y gastric bypass showed that diabetes remission occurred in 82.2%. [56]

5.1. Lipid profile

Total cholesterol, LDL cholesterol and triglycerides were significantly lower in patients undergoing biliopancreatic diversion than among those receiving medical therapy but there were no significant differences between medical therapy and gastric bypass. [54] The mean LDL cholesterol at follow-up was 83 mg/dl among patients who underwent gastric bypass versus 89 mg/dl in medical therapy groups. [54, 55] But triglycerides were significantly lower after one year in gastric bypass group versus medical group. [55] HDL cholesterol increased significantly in all three groups (medical therapy, gastric bypass and biliopancreatic diversion) but much more among patients undergoing gastric bypass. [54, 55]

5.2. Blood pressure

Systolic and diastolic blood pressures were significantly improved by gastric bypass and biliopancreatic diversion. [54, 55] No improvement of systolic and diastolic blood pressures was found in another study after Roux-en-Y gastric bypass or sleeve gastrectomy. [53]

Almost all studies showed that all metabolic improvements in the lifestyle-medical group were realized in the first 6 months of follow-up with subsequent decrease of the benefits by 12 months. In contrast improvement continues to increase in the bariatric surgery groups throughout the entire period of follow-up. [52-55]

The most recently published meta-analysis on observational and randomized clinical trial included 6131 patients: 3076 underwent bariatric surgery and 3055 underwent conventional therapy. [57] The mean age of patients included in this meta-analytic research was 47.8 years, ranging from 35.8 to 62.0 years. In the observational studies, the mean A1c in surgery groups was 7.6% versus 7.2% in conventional groups and at follow-up the mean A1c was 6.1% in surgery group versus 7% in conventional group. In the randomized trials, the mean A1c in surgery group was 8.9% versus 8.7% in conventional group and at follow-up the mean A1c was 6.1% in surgery group versus 7.6% in conventional group. In this meta-analysis the remission rate of type 2 diabetes ranged from 38% to 100% in surgery group versus 0% to 46.7% in conventional group. The odds of bariatric surgery patients reaching T2DM remission ranged from 9.8 to 15.8 times the odds of patients treated with conventional therapy. [57]

5.3. Safety and adverse events

The 30-day mortality associated with bariatric surgery is low, estimated at 0.1-0.3%, a rate similar to that for laparoscopic cholecystectomy. [58]

Biliopancreatic diversion and gastric by-pass are relatively safe and adverse events were rare including: incisional hernia, intestinal occlusion. [54, 55] Postoperative complications after gastric bypass consist on anastomotic and staple-line leaks (3.1%), wound infection (2.3%), pulmonary events (2.2%) and wound hematoma (1.7%) and late surgical complications consist on stricture, bleeding anastomotic ulcer, gastritis proximal pouch and small bowel obstruction but no mortality. [55, 59] Rare but often severe hypoglycemia from insulin hypersecretion could occur. [60] Patients in the gastric bypass group experienced 50% more serious and 55% more nonserious adverse events than did those in the lifestyle-medical group. [55] The most serious complication, anastomotic leakage, has decreased in incidence from 5% to 0.8%. [61, 62] A study performed by the US Agency for Healthcare Research and Quality reported a 21% decline in complications after bariatric surgery between 2002 and 2006. [63] The prevalence of postsurgical infections decreased by 58% and abdominal hernias, staple leakage, respiratory failure and pneumonia rates decreased by 29-50%.

Nutritional deficiencies such as: iron-deficiency anemia, hypoalbuminemia, vitamin B deficiency, vitamin D deficiency, osteopenia were more frequent in patients who underwent Roux-en-Y gastric bypass or biliopancreatic diversion despite monitoring of laboratory values and prescription of nutritional supplements. [54, 55, 60]

Some patients and surgery procedures factors related to higher risk have been identified until now. Patients' factors are: older age, increasing BMI, male gender, hypertension, obstructive sleep apnoea, high risk of pulmonary thromboembolism, limited physical mobility. Surgery procedures factors are: surgeon inexperience, low volume centre or surgeon performing surgery occasionally, morbidity and mortality increase with the complexity of the procedure,

open compared with laparoscopic procedures, revisional surgery. [60, 64, 65] The presence of type 2 diabetes has not been found to be associated with increased risk for bariatric surgery.

5.4. Conclusions

Up to date, all randomized controlled studies proving effects of bariatric surgery among obese type 2 diabetic subjects have been short-term and have been conducted on relatively small number of patients. Until now only the Swedish Obese Subjects (SOS) study provides evidence of cardiovascular benefits and prolonged improvement in glycemia but this is a non randomized trial. [66, 67] Larger multicenter randomized controlled studies will be required in order to confirm these results. Furthermore is mandatory that studies designed for cardiovascular safety to be performed. More studies are needed especially studies that may provide a better prediction and duration of the remission of diabetes and long-term complications. The success of different bariatric surgery procedures suggests that they should not be seen as a last treatment. Such procedures have to be taken into account earlier in the treatment of type 2 diabetes obese patients.

6. Factors predicting the outcome of surgery in diabetic patients

Most obese type 2 diabetes subjects who underwent bariatric surgery show an important improvement of metabolic features but not every patient has diabetes remission after surgery, suggesting that some clinical characteristics could predict which patient is best suitable for a particular metabolic surgery procedure. Furthermore it is important to identify patients who will not respond to metabolic surgery, so that these patients not to be exposed to an unnecessary surgical procedure that could be without clear benefits. Clinical studies showed that the main factors that contribute to the control of diabetes and eventually to the remission of the diseases are as follows:

- a. **Age:** A younger age at the moment of bariatric surgery increased the chance of diabetes remission. [68] In a study on 154 Chinese patients who underwent gastric bypass, younger age was associated with remission of diabetes at 12 months [69]. However, in other studies age was not a predictor of diabetes remission one year after Roux-en-Y gastric bypass or sleeve gastrectomy [53], or at two years of follow-up after gastric by-pass and biliopancreatic diversion. [54]
- b. **Diabetes duration:** As an estimation of diabetes severity, the longer the duration, the lower the chances of remission [70]. An analysis of 161 patients showed that duration of diabetes below 4 years was a predictive factor of diseases remission [71]. The duration of diabetes strongly and independently influenced remission at 1 year after gastric bypass [69]. On the other hand at two years of follow-up after gastric by-pass and biliopancreatic diversion diabetes duration was not a predictor of diabetes remission [54].
- c. **Insulin treatment** Frequently insulin treatment is used in type 2 diabetes as ad on therapy after oral antidiabetic agents have failed because of the progressive nature of the disease

characterized by continuous decrease of beta cell function. Absence of insulin treatment was a predictive factor for remission of diabetes after bariatric surgery. [68, 71] The insulin use was associated with lower remission rates compared with oral medication (13.5 versus 53.8%). [72]

- d. **Weight loss.** The amount of weight loss seems to be of major importance in the improvement of glucose control after laparoscopic adjustable gastric banding. [52] Also percentage weight loss at 1 year over 25% independently influenced remission of diabetes after gastric bypass. [69] But no correlation between normalization of fasting glucose levels and weight loss after gastric bypass and biliopancreatic diversion was observed in another study. [54] Weight changes after these former surgical procedures were not significant predictors of diabetes remission at 2 years or of normalization of glycosylated hemoglobin. [54] But in the Diabetes Surgery Study weight loss explains most of the benefit on glycemic control of gastric bypass. [55] A baseline BMI under 50 kg/m² and a one year BMI under 35 kg/m² were predictive factors for diabetes remission whatever the procedures. [71]
- e. **Initial level of C peptide:** Fasting C-peptide concentration is correlated with beta cell mass and insulin secretion. Very low C-peptide levels could be useful in identifying type 1 diabetes and latent autoimmune diabetes in adults that could have as comorbidity obesity. C-peptide levels are increased as response to insulin resistance in obese type 2 diabetes subjects and are correlated with BMI but decreased with duration of diabetes. [69] A high level of C-peptide before metabolic surgery increased the chance of a good outcome. The cut-off value of C-peptide ≥ 2.9 ng/ml at baseline predicts the remission of diabetes after gastric bypass. [69] Also in another study the diabetes remission rates strongly correlate with the level of C-peptide: 55.3% for those with preoperative C-peptide <3 ng/ml, 82% for C-peptide 3-6 ng/ml, and 90.3% for C-peptide >6 ng/ml. [73] Another study showed that 90% of type 2 diabetes patients with preoperative fasting C-peptide levels over 1 nmol/l had mean A1c <6.5% after Roux-en-Y gastric bypass and 74% had complete resolution of diabetes. But none of the patients with fasting C-peptide level less than 1 nmol/l before surgery experienced diabetes remission. The authors of this study recommend fasting C-peptide levels to be measured in order to a better prediction of diabetes remission after surgery. [74]
- f. **Type of surgical procedures** Preoperative data of patients could be of greater importance in the resolution of diabetes than the choice of bariatric surgery procedures. 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 biliopancreatic diversion. [75] Weight loss and diabetes resolution were greatest for patients undergoing biliopancreatic diversion/duodenal switch, followed by gastric bypass, and least for banding procedures. [49]

The combination of these factors has an increased power in prediction of the outcomes. If a score of 1 is assigned to duration of diabetes <4 years, percentage weight loss at 1 year >25%, and C-peptide ≥ 2.9 ng/ml at baseline, a cumulative score of 2 or 3 was associated with a remission rate of 92%, and a score of 0 or 1 was associated with a remission rate of 27%. [69]

In a retrospective cohort study on 690 patients was developed a score, DiaRem, to predict probability of diabetes remission within five years after Roux-en-Y gastric bypass surgery. Four preoperative clinical variables were identifying of importance in this score: insulin use (no use 0, use of insulin 10 points), age (<40 years 0, 40-49 years 1 point, 50-59 years 2 points, >60 years 3 points), glycated hemoglobin (<6.5% 0, 6.5-6.9% 2 points, 7-8.9% 4 points, >9% 6 points), and type of antidiabetic drugs (no sulfonylureas or insulin-sensitising agents other than metformin 0, sulfonylureas and insulin-sensitising agents other than metformin 3 points). [68] The DiaRem score ranges from 0 to 22. [68] 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 ADA definition. [68]

7. Actual guidelines for surgical treatment in diabetic patients

Obesity and type 2 diabetes mellitus are chronic, multifactorial and complex disorders with serious outcomes on health and requires multidisciplinary approach in order to improve prognostic.

Several international society have launched their guidelines, position statement and recommendations on type 2 diabetes mellitus and metabolic surgery based on growing evidences form observational, randomized controlled studies and metaanalysis. [60, 76-79] These guidelines and position statement are needed because the global prevalence of type 2 diabetes is rising dramatically as a consequence of obesity epidemic and environmental changes including high calorie food abundance and lack of physical activity. Type 2 diabetes and obesity are associated with premature morbidity and mortality and are major public health threats of the 21st century. There is increasing evidence that prognostic of patients with type 2 diabetes mellitus and obesity is dramatically improved by bariatric surgery that produces important weight loss, substantially decreases of glycated hemoglobin, improvement of lipid profile and reduces the cardiovascular risk and it even can produces remission of diabetes. [60] Bariatric surgery for severe obesity associated with diabetes mellitus is cost-effective. [60]

8. Indications for bariatric surgery in adults with type 2 diabetes mellitus

Bariatric surgery is clearly indicated in type 2 diabetes mellitus patients with BMI >35kg/m² (evidence level A) especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. In these patients surgery can contribute to beta cell function improvement and diabetes remission. For patients with type 2 diabetes mellitus and BMI ranged between 30 and 35 kg/m² surgery may be considered on an individual basis (evidence level A, B, C and D). [77] In patients with type 2 diabetes and BMI >30 kg/m² and <35 kg/m², bariatric surgery may be considered if HbA1c >7.5% despite fully optimized conventional therapy, especially weight is increasing, or other weight responsive co-morbid-

ities not achieving targets on conventional therapies (blood pressure, dyslipidaemia, and obstructive sleep apnea). [60] There are insufficient data to generally recommend surgery in patients with BMI under 35 kg/m² outside of a research protocol. [76] Table 1 summarized indications of bariatric surgery in type 2 diabetes mellitus according different international organizations.

9. Indications for bariatric surgery in adolescents

Surgery should be considered if adolescents had BMI >40 kg/m², or >35 kg/m² with severe comorbidities, including type 2 diabetes mellitus, aged >15 years, with Tanner pubertal stage 4 or 5 and skeletal maturity, and could provide informed consent and patients have failed a lifestyle and pharmacotherapy for six months [80]. International Diabetes Federation position statement advised that only two procedures Roux-en-Y gastric bypass and laparoscopic adjustable gastric banding are currently conventional bariatric surgical procedures for adolescents [60].

	Type 2 diabetes mellitus and BMI >35kg/m ²	Type 2 diabetes mellitus and BMI >30, <35 kg/m ²	Type 2 diabetes mellitus and BMI <30 kg/m ²
IDF 2011 [60]	Yes	May be considered on individual basis	Research only
ADA 2014 [76]	Yes	May be considered on individual basis	Research only
AACE 2013 [79]	Yes	May be considered on individual basis	Research only
EASO/IFSO EC 2013 [77]	Yes	May be considered on individual basis	Research only
AHA/ACC/TOS 2013 [78]	Yes	No recommendation for or against	

Table 1. Current recommendations for surgical treatment in type 2 diabetes

Contraindications for bariatric surgery in the treatment of type 2 diabetes mellitus are: secondary diabetes, pancreatic autoantibodies (anti glutamic acid decarboxylase, islet cells antibodies) positivity, C-peptide < 1ng/ml or unresponsive to mixed meal challenge.

Which surgical procedures are indicated for obese type 2 diabetes patients? Nowadays there is no evidence in favor of any particular procedure but the impact on weight loss, lipid profile, glycated hemoglobin and diabetes remission is increasing according to the surgical procedures as follows: adjustable gastric banding, sleeve gastrectomy, Roux-en-Y gastric bypass, biliopancreatic diversion with duodenal switch, biliopancreatic diversion. A laparoscopic technique should be considered as the preferable approach to the operation. Some pre-operative

factors specific to type 2 diabetes mellitus could influence the choice of surgical procedures: duration of diabetes, pre-operative level of glycated hemoglobin, number of antidiabetic drugs used, and fasting C-peptide levels. [60, 77]

The assessment of bariatric surgery outcomes in type 2 diabetes and factors indicating the beneficial effects of bariatric surgery in diabetes: There is not an international consensus regarding definition of success of bariatric surgery in diabetes mellitus.

Partial remission of diabetes is characterized by: HbA1c >6% but <6.5%, fasting plasma glucose 100-125 mg/dl, at least 1 year duration, no active pharmacological therapy or ongoing procedures. Complete remission of diabetes is characterized by: HbA1c <6%, fasting plasma glucose <100 mg/dl, at least 1 year duration, no active pharmacological therapy or ongoing procedures. Prolonged remission is characterized by complete remission of at least 5 years duration. [60, 76, 77]

According IDF optimization of the metabolic state may be defined as: HbA1c \leq 42 mmol/mol (6%); no hypoglycaemia; total cholesterol < 4mmol/l; LDL cholesterol <2 mmol/l; triglycerides <2.2mmol/l; blood pressure < 135/85 mmHg; >15% weight loss; with reduced medication from the pre-operated state or without other medications. A substantial improvement in the metabolic state may be defined as: lowering of HbA1c by >20%; LDL cholesterol <2.3 mmol/l; blood pressure <135/85 mmHg with reduced medication from the pre-operated state. [60]

Adverse events: The morbidity and mortality associated with bariatric surgery is generally low and similar to that of well-accepted procedures such as elective gall bladder or gallstone surgery. [60] There are patients and surgical procedures factors that can modify the risk of operation. The surgical complexity and potential surgical risks of procedures decrease in following order: biliopancreatic diversion, biliopancreatic diversion with duodenal switch, Roux-en-Y gastric bypass, laparoscopic sleeve gastrectomy, adjustable gastric bypass. [77]

Follow-up should be provided to all patients who underwent bariatric surgery in interdisciplinary (medical and surgery) joint clinics. Generally the follow-up starts at 1 month after surgery and after that every 3 months in the first year, every 6 months for the second year and annually thereafter. Patients with type 2 diabetes who underwent to metabolic surgery need lifelong nutritional support and medical monitoring. The nutritional support consists in: adequate protein intake (minimum advised protein intake of approximately 90 g/day after biliopancreatic diversion) in order to prevent excessive lean body mass loss, avoidance of ingestion of concentrated sweets to prevent dumping syndrome, vitamin and other micronutrients supplementations according to the type of surgical procedures. Medication for diabetes and insulin should be adjusted immediately after surgery in order to decrease the risk of hypoglycaemia. After biliopancreatic diversion procedure, proton pump inhibitors/histamine 2 receptor antagonists for the entire first post-operative year are recommended. [60, 77, 78]

It is necessary to perform more research (larger, well-designed, randomized control trial with longer-term follow-up) in order to bring up evidence for guidelines in the following areas: which type 2 diabetes patients are most likely to benefit from and least likely to have adverse events of bariatric surgery and which surgical procedures are best fitted to different populations.

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