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REVIEW

The Growing Role of Bariatric Surgery in the Management of Type 2 Diabetes: Evidences and Open Questions

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Abstract The use of bariatric surgery in the clinical management of type 2 diabetes has been recently endorsed in the clinical practice recommendations released by the most influential diabetologic associations. However, authoritative critic voices about the application of metabolic surgery in type 2 diabetes continue to appear in diabetologic literature. In this review, we will try therefore to understand what the reasons for this apparent dichotomy. In this paper, we revised what we believe are now clear evidences about the role of bariatric surgery in the treatment of type 2 diabetes in patients with morbid obesity: the efficacy of bariatric surgery in metabolic control, the existence of plausible weight-independent metabolic mechanisms at least in some bariatric procedure, and the importance of the early referral to surgery in patients with firm indications. However, we stressed also the lack of clear high-quality long-term data about the effects of bariatric surgery in the prevention of both macro- and microvascular hard endpoints in patients with type 2 diabetes. The accrual of these results will be critical to completely clarify the risk/benefit ratio of bariatric surgery in diabetes, as compared to current pharmacologic therapies. This may be particularly important in patients in which data on long-term efficacy are still not completed, such as in patients with lower BMI levels.

Keywords Bariatric surgery · Metabolic surgery · Type 2 diabetes

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Introduction

Since the pioneering reports of the last decade of twentieth century [1, 2], the efficacy of bariatric procedures in improving and even normalizing glucose levels in obese patients with type 2 diabetes has been confirmed by a large number of observational studies [3]. Prospective controlled observations [4, 5] and one small randomized controlled trial [6] more recently provided higher level scientific evidences about the beneficial effects of bariatric surgery on the long-term metabolic control in type 2 diabetic obese patients. The availability of these evidences ultimately convinced the most influential scientific associations in the field to introduce for the first time the use of bariatric surgery in the mainstream of the clinical management of type 2 diabetes [7]. A wider application of these recommendations in the general clinical practice now depends on several factors: availability of technical and economic

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resources, health care systems organization, and, least but not last, the willingness of diabetologists and general practitioners to ask bariatric surgeons to treat their obese patients with diabetes. How we can increase this willingness? What steps forward are needed to further convince the general medical community and health care policy makers of the usefulness of bariatric surgery in type 2 diabetes management?

In this review, we will briefly review the evidences that now we have about the effectiveness and mechanism of actions of bariatric surgery in morbid obese patients with type 2 diabetes. A more detailed discussion will be dedicated to the still open clinical questions that we consider critical in determining the complete acceptation of bariatric surgery by the diabetologic and general medical community. Finally, a brief session will be reserved to the possible use of metabolic surgery in non-morbid obese patients.

Bariatric Surgery in Morbid Obese Diabetic Patients: The Evidences

Numerous clinical studies showed the benefits of bariatric surgery on diabetes. A systematic review and meta-analysis of these studies has been recently provided by Buchwald et al. [3]. The objective of the review was to specifically determine the impact of bariatric surgery on body weight and type 2 diabetes. The dataset included 621 studies with 888 treatment arms and 135,246 patients. Meta-analysis of weight loss overall was 38.5 kg or 55.9% excess body weight loss. Overall, 78.1% of diabetic patients had complete resolution, and diabetes was improved or resolved in 86.6% of patients. Weight and diabetes parameters showed little differences in studies with less than 2 years or more than 2 years of follow-up [3]. The robustness of these estimations may be reduced by the acknowledgment that the large majority of the studies included in the review are observational retrospective not randomized studies without appropriate control groups [8]. However, the results of the few published long-term controlled trials seem to confirm this favorable picture.

The Swedish Obese Subjects (SOS) Study was launched in the early 1990s with the aim of to prospectively evaluate total and cause-specific 10-years mortality in a large group of morbid obese patients treated by several types of bariatric procedures [4]. A well-matched group of highly comparable morbid obese patients participating in a national obese registry and not willing to undergo surgery was used as a control group. Weight loss observed in the surgical arm of the SOS study was 23.4% of baseline body weight 2 years after surgery and 16.3% 10 years after surgery. In the same time, the control group of morbid obese patients treated by conventional medical treatment remained substantially weight stable [4]. In the first 2 years of SOS study, 72% of 342 diabetic surgically treated obese patients had a complete resolution of type 2 diabetes, while only 21% of 248 diabetic obese controls did so. The odds ratio for being free from type 2 diabetes 2 years after surgery was 8.42 (95% CI, 5.68–12.5) in the surgically treated as compared with the medically treated controls [4]. In the long-term, some of the benefits observed in the first years after surgery tend to vanish, maybe because of the slight tendency to weight regain observed in the surgical group as a whole and of the aging of the study population. Anyway, the proportion of patients with type 2 diabetes at baseline still normoglycemic without pharmacologic treatment 10 years after surgery was higher in the surgically treated group (36%) than in the control group (13%). The probability of being free from diabetes 10 years after surgery was still 3.45 (95% CI, 1.64–7.28) times higher in the surgical group [4]. The sustained weight loss observed in the surgical arm of the SOS study was not only associated to an improvement of the diabetic state, but also to the prevention of new cases of type 2 diabetes in those morbid obese patients free from the disease at baseline. Indeed, the incidence of new cases of type 2 diabetes was 1% in the surgically treated patients and 8% in the control group at 2 years (odds ratio (OR), 0.14; 95% CI, 0.08–0.24), and it was 7% and 24%, respectively, at 10 years (OR, 0.25; 95% CI, 0.17–0.38) [4]. The surgical induced weight loss seems thus to be able to prevent about 75% of new type 2 diabetes cases over a 10-years follow-up.

The results of the SOS study have been confirmed by a smaller prospective study evaluating the outcome of diabetes in 73 morbid obese patients treated by laparoscopic adjustable gastric banding and in 43 eligible morbid obese patients who refused surgery for personal reasons [5]. Form baseline to the end of the 4-year follow-up, BMI decreased from 45±0.89 to 37.7±0.71 kg/m^2 in the gastric banding group and remained steady in the non-surgical group. In patients without type 2 diabetes at baseline, the primary intervention study, 17.2% of the subjects in the control group and none of the gastric banding patients (P=0.0001) progressed to type 2 diabetes. In patients with type 2 diabetes at baseline, the secondary intervention study, type 2 diabetes remitted in 4.0% of the patients in the control group and in 45.0% of the surgically treated patients (P=0.0052) [5].

The first randomized clinical trial comparing bariatric surgery and conventional-therapy in the management of obese patients with type 2 diabetes has been published in 2008 [6]. Dixon et al. randomized 60 patients with BMI ranging from 30 to 40 kg/m^2 and recent type 2 diabetes (less than 2 years from diagnosis) to laparoscopic adjustable gastric banding or to a program of conventional therapy with a specific focus on weight loss. After a 2-year follow-up, weight loss was 21.1±10.3 kg in the surgical group and 1.5±5.4 kg in the conventional-therapy group ($P<0.001$). Remission of type 2 diabetes was achieved by 73% of the patients in the surgical group and 13% in the conventional-therapy group. Relative risk of remission for the surgical group was 5.5 (95% CI, 2.2–14.0) [6]. Efficacy of bariatric surgery was therefore supported now by high-quality research data.

The meta-analysis of Buchwald et al. [3] showed substantial differences in the efficacy of different bariatric procedures in metabolic control. Diabetes resolution was greatest for patients undergoing biliopancreatic diversion/duodenal switch (95.1% resolved), followed by gastric bypass (80.3%), gastroplasty (79.7%), and then laparoscopic adjustable gastric banding (56.7%). These differences in metabolic efficacy were paralleled by differences in weight loss efficacy. By simply putting in a simple correlation, the percentage of excess weight loss and the percentage of diabetes resolution reported by Buchwald et al. for the different procedures (Fig. 1), we may obtain a linear regression line with a R^2 of 0.949, thus implying that 95% of the variability in diabetes resolution may be explained by variations in weight loss. However, even a strong statistical association does not imply automatically a direct causal relationship: the association may be well explained by the existence of other factors having an independent effect on both metabolic control and weight loss. Potential mechanisms underlying the direct anti-diabetic impact of metabolic procedures, gastric bypass in particular, have been recently reviewed [8] and their detailed description is beyond the scopes of this paper.

Briefly, the existence of procedure-related factors that are able to have a weight loss-independent effect on the control of diabetes is supported by at least three lines of evidence [9]:

1. Glycemic control often occurs within days after gastric bypass, long before significant weight loss was achieved [1, 10, 11].
2. Glucose control improves more after gastric bypass than with equivalent weight loss obtained by dietary intervention [12] or pure restrictive bariatric procedures [13, 14].
3. The occurrence of cases of hyperinsulinemic hypoglycemia related to pancreatic islets hyperplasia or nesidioblastosis long term after gastric bypass [15], but not after pure restrictive surgery.

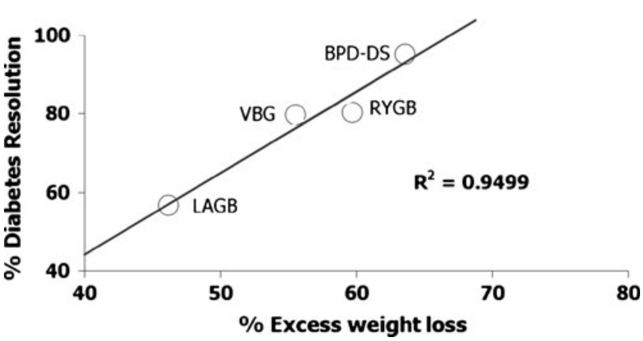

Fig. 1 Linear regression analysis between percentage of excess weight loss and the percentage of diabetes resolution after bariatric surgery. The data reported in the meta-analysis of Buchwald et al. [3] are used. *LAGB* laparoscopic gastric banding, *VBG* vertical banded gastroplasty, *RYGB* gastric bypass, *BPD-DS* biliopancreatic diversion/duodenal switch

Several plausible hypotheses have been articulated to explain the weight-independent effects of metabolic procedures [9]. The two most popular ones were both related to changes in the secretion of intestinal peptides involved in glucose homeostasis and energy balance regulation [16]. The "hindgut" or "lower intestinal" hypothesis holds that diabetes control results from the expedited delivery of nutrients to the distal intestine, enhancing the secretion of physiologic mediators able to improve glucose metabolism. Potential candidates are glucagon-like peptide 1 and peptide YY. Both of these hormones have been found to be substantially and durably increased after gastric bypass, but not after gastric banding [14]. According to the "foregut" or "higher intestinal" hypothesis, the effect of selected bariatric procedures on glucose metabolism depends on the exclusion of the duodenum and proximal jejunum from the transit of nutrients, possibly preventing the secretion of some yet unknown molecule promoting glucose intolerance [16]. Besides "hindgut" and "foregut" hypotheses, several other intestinal mechanisms may play a role: suppression of ghrelin secretion [17], alterations of intestinal nutrient sensing [9], and perturbations of gut microbiota [18]. Furthermore, plausible explanations may be found also out of gastrointestinal tract: in biliopancreatic diversion, the malabsorption of fat is typically associated to a highly significant reduction of the plasma triglycerides levels both in the fasting and in the post-prandial states [19]. Reduction in lipid overload has been found to be associated to a reduced fat deposition in skeletal muscle. Intra-myocellular fat deposition is associated to a reduced glucose uptake and utilization, a clear metabolic marker of insulin-resistance. Indeed, in patients treated with biliopancreatic diversion the improvement of insulin sensitivity after surgery was more strictly associated to the reduction of the muscle lipid content than to the fat mass loss [19]. In summary, several hypotheses remain in the field and probably others will appear in the future. Neither of them is mutually exclusive and probably they may have a different importance in different clinical situations or after different surgical techniques.

Even by using the most metabolically effective procedure, still some diabetic patients remain to not achieve diabetes remission or improvement after surgery. Several factors have been proposed as positive or negative predictors of diabetes remission, but the more consistent one was diabetes duration. A shorter history of diabetes has been found to be associated to a greater chance of diabetes remission after any type of bariatric procedure [20, 21]. This latter observation may be expected, given that progressive deterioration of β-cell function driven the progression from glucose intolerance to overt hyperglycemia. If the bariatric procedure is performed before irreversible β-cell failure has occurred, then a higher likelihood of long-term remission may be expected. The importance of considering bariatric surgery early in the course of the disease in morbid obese patients with type 2 diabetes has been recently endorsed in a recent position statement on bariatric surgical and procedural interventions in the treatment of obese patients with type 2 diabetes from the International Diabetes Federation Taskforce on Epidemiology and Prevention [22].

Open Question About the Use of Bariatric Surgery in Morbid Obese Diabetic Patients

In the first part of this manuscript, we revised what we believe are now clear evidences about the role of bariatric surgery in the treatment of type 2 diabetes in patients with morbid obesity: the efficacy of bariatric surgery in metabolic control, the existence of plausible weight-independent metabolic mechanisms at least in some bariatric procedure, and the importance of the early referral to surgery in patients with firm indications. However, authoritative critic voices about the application of metabolic surgery in type 2 diabetes continue to appear in diabetologic literature [23, 24]. In this second paper of our review, we will try therefore to understand what the reasons for this apparent dichotomy.

Bariatric literature usually presents results in terms of rate of diabetes cure or remission, usually defined as the normalization of glucose levels in the absence of active anti-diabetic therapy [3]. This definition has been recently endorsed by a consensus group comprising experts in pediatric and adult endocrinology, diabetes education, transplantation, metabolism, and bariatric/metabolic surgery [25]. In analogy to the oncologic literature, where cure is defined as complete remission of cancer of sufficient duration that the future risk of recurrence is felt to be very low, experts agreed that it may make sense, on a practical ground, to consider prolonged (arbitrarily 5 years) remission of diabetes essentially equivalent to cure. Since the definition of complete diabetes remission required the absence of active pharmacologic therapy, prolonged remission may not be achieved by pharmacology therapy itself [25]. On the other hand, diabetologists and the medical community are used to compare anti-diabetic therapy in terms of metabolic control: how many patients reach therapeutic target with a specific treatment? For how many months I may be able to maintain my patients in metabolic control by using a specific drug or combination of several drugs? It may be difficult to compare these two very different outcomes. In practical terms, it is better for my patient to be in metabolic control for some years by taking three or four pills per day or it is better to be in complete remission without any anti-diabetic drugs, but facing the risks and side effects of a given bariatric procedure? An evidence-based answer probably relies on the appreciation of the number of hard diabetes-related endpoints that may be prevented by each of the two strategies (macro and micro-vascular complications and deaths). However, we lack at this moment comparable data on this crucial point.

Bariatric surgeons usually focused the presentation of their results in patients with type 2 diabetes on normalization of glucose levels, without a specific attention to other cardiovascular risk factors and rates of macro and micro-vascular events [3]. Classic data from the UK Prospective Diabetes Study (UKPDS) demonstrated that the rates of both cardiovascular events (myocardial infarctions) and micro-vascular complications (diabetic retinopathy and nephropathy) are directly related to glycemic control (glycated hemoglobin or HbA1c levels) [26]. However, the strength of the association is not equal for the two groups of diabetes-related outcomes. By classifying patients according to their exposure to increasingly higher glycemic levels, UKPDS investigators calculated that a 1% reduction in HbA1c levels should be associated to a 37% decrease in the incidence of micro-vascular endpoints and to only a 14% decrease in the incidence of fatal and non-fatal myocardial infarction [26]. This estimation was confirmed by the results of the UKPDS prospective randomized trial [27]. Over a 10-year follow-up, patients in the intensive blood glucose control group (HbA1c levels 7.0%) as compared to patients in the conventional treatment group (HbA1c levels 7.9%) had a significant 25% risk reduction in micro-vascular endpoints (RR, 0.75; 95% CI, 0.60–0.93) and a non-significant 16% risk reduction in myocardial infarction (RR, 0.84; 95% CI, 0.71–1.00)[27]; an additional 10-years follow-up was needed in order to reach statistical significance in the risk reduction for myocardial infarction [28]. A recent meta-analysis of five randomized clinical trials aimed at the assessment of the efficacy of lowering blood glucose [28–32] confirmed a significant but moderate effect of intensive glucose control on myocardial infarction rate (overall odds ratio, 0.849; 95% CI, 0.778–0.926) [33]. On the other hand, one small randomized trial tested the efficacy of a broader, targeted, intensified, multi-factorial intervention in patients with type 2 diabetes [34]. In the Steno-2 trial, 160 patients were randomly assigned to receive either conventional treatment in accordance with standard guidelines or intensive treatment, with a multi-factorial stepwise implementation of behavior modification and pharmacologic therapy that targeted at the same time hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of cardiovascular disease with aspirin. The decline in glycosylated hemoglobin values, systolic and diastolic blood pressure, serum cholesterol and triglyceride levels, and urinary albumin excretion rate were all significantly greater in the intensive-therapy group than in the conventional-therapy group. At the end of a 4-year follow-up, patients receiving intensive therapy had an impressive 50% reduction in cardiovascular events (OR, 0.47; 95% CI, 0.24–0.73), along with large reduction in the rates of nephropathy (OR, 0.39; 95% CI, 0.17–0.87), retinopathy (OR, 0.42; 95% CI, 0.21–0.86), and autonomic neuropathy (OR, 0.37; 95% CI, 0.18–0.79) [34]. A reduction in total mortality (OR, 0.54; 95% CI, 0.32–0.89) and mortality from cardiovascular causes (OR, 0.43; 95% CI, 0.19–0.94) was observed after a prolonged follow-up period [35]. Sustained weight loss produced by bariatric surgery in patients with type 2 diabetes may probably induce an improvement in cardiovascular risk factors well beyond pure glycemic control and therefore may enable a reduction of micro- and particularly macro-vascular endpoints more similar to those achieved by multi-factorial intervention than by simple intensive glucose control. However, reduction of global cardiovascular risk was seldom appreciable in bariatric reports and no data about the reduction of micro- and macro-vascular events after bariatric procedures in patients with type 2 diabetes are as yet available.

Intensive glycemic control is not without risks. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients in the intensive control group achieved and maintained a 6.4% HbA1c levels whereas patients in the standard therapy group had a mean 7.5% HbA1c level [29]. Intensive glucose control was associated with a small reduction in non-fatal myocardial infarction rates (OR, 0.76; 95% CI, 0.62–0.92). However, both deaths for any cause (OR, 1.22; 95% CI, 1.01–1.46) and cardiovascular deaths (OR, 1.35; 95% CI, 1.04–1.76) were more frequent in the intensive control group than in the standard therapy group [29]. A recent retrospective analysis of a large cohort of type 2 diabetics confirmed the existence of a U-shaped association between HbA1c levels and total mortality [36]. Both in patients treated with oral hypoglycemic agents and in insulin-treated patients, the lowest mortality risk was observed in patients with 7.5% HbA1c levels, and increase mortality rates were observed both at higher than lower HbA1c values [36]. The increase in total mortality observed in the ACCORD trial has been related to the higher frequency of severe episodes of hypoglycemia observed in the intensive control group [33]. Hypoglycemia seldom represents a problem after some of the bariatric procedures [15] and we do not intend to suggest that hypoglycemic events after surgery may per se reduce substantially the benefits of bariatric surgery in patients with type 2 diabetes. However, the key message coming from the ACCORD study was that, beyond certain limits, the benefits of tight metabolic control on cardiovascular risk are so small that they may be overcome by unexpected and also unrelated side effects. This message should be taken into account when we propose the use of bariatric surgery in patients with type 2 diabetes, particularly in patients with not so bad glucose control and at a lower BMI level. Are we sure that the benefits will not be overcome by the side effects induced by the procedures? Still again, more data about hard endpoints are needed.

Bariatric Surgery in Non-Morbid Obese Diabetic Patients: The First Steps

The recognition that several bariatric procedures may exert some weight loss-independent metabolic effects suggests that metabolic surgery may be beneficial also in diabetic patients with less severe degree of obesity, or even in simply overweight type 2 diabetics. This new frontier of metabolic surgery includes the application of conventional bariatric procedures to patients with lower BMI levels (BMI 30–35 or 25–30 kg/m^2) and the introduction of new procedures, like ileal interposition and duodenal–jejunum exclusion, designed with the specific aim of having metabolic effects irrespective of causing massive weight loss.

The results of metabolic surgery in patients with type 2 diabetes and BMI <35 kg/m^2 has been recently reviewed [37]. The dataset included 16 studies and 343 patients with type 2 diabetes treated with restrictive (three studies), malabsorptive/restrictive (five studies), and primarily malabsorptive procedures (eight studies). In the whole sample, 85.3% of patients experienced diabetes resolution, defined as the number of patients not taking any anti-diabetic medications, in a relatively short follow-up (mean follow-up 23 months, range 6–216 months). Similarly to what was observed in morbid obese patients, the rate of diabetes resolution was graded according to the type of procedure (72.2% in restrictive, 97.7 in malabsorptive/restrictive, and 72.9 in malabsorptive procedures). When patients were divided according to baseline BMI levels in obese (BMI 30–35 kg/m^2) and overweight (BMI 25–30 kg/m^2) groups, a tendency to a lower effect of metabolic surgery at lower

BMI levels was observed. Rates of remission were 89.1% in the obese group and 81.8% in the overweight group [37]. This tendency has been recently confirmed by Scopinaro et al. [38] in a prospective study conducted with DBP in 15 obese (BMI 30–35 kg/m^2) and 15 overweight (BMI 25–30 kg/m^2) patients. The lower efficacy of metabolic surgery in patients with lower BMI has been attributed to the presence of a more advanced, severe, and less responsive disease [38] or to the unrecognized inclusion of patients with late onset type 1 diabetes (LADA) [37].

In summary, the results of metabolic surgery published so far seem to be promising in non-morbid obese patients and less brilliant in overweight patients with type 2 diabetes. Any definitive conclusion is tempered by the fact that we still have very few studies conducted in small numbers of patients and sometimes in patients with peculiar ethnic backgrounds (Chinese and Indian patients in particular) [37]. Moreover, the general considerations about long-term risk/benefit ratio that we exposed for morbid obese patients are obviously applicable, and even reinforced, in patients with lower BMI levels. In this particular group of patients, an additional problem may be represented by the excessive and harmful weight loss that may be produced by the application of some of the bariatric procedures in patients with less severe obesity.

In the 2009 Standards of medical care in diabetes, experts from the American Diabetes Association concluded that although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m^2, current evidence was insufficient to generally recommend surgery in patients with BMI<35 kg/m^2 outside of a research protocol [7]. An initial opening to a wider application of bariatric surgery at lower BMI levels has been recently endorsed by the International Diabetes Federation Taskforce on Epidemiology and Prevention [22]. Position statement from IDF suggests that patients with 30–35 kg/m^2 and type 2 diabetes may be conditionally considered eligible for surgery in case of HbA1c levels>7.5 despite fully optimized conventional-therapy, especially if weight is increasing, or other weight responsive co-morbidities not achieving targets on conventional therapies (for example blood pressure, dyslipidemia, and obstructive sleep apnoea) [22]. The sue of metabolic surgery in simply overweight patients remains in our opinion purely experimental and should be performed only in an adequately designed trial under strict institutional monitoring.

Conclusion

In conclusion, bariatric surgery has been accepted as a reasonable option for the treatment of patients with type 2 diabetes and obesity. The acceptance of and the willingness to use this possibility among diabetologic and internal medicine community needs to be bolstered. Research is now focused on the pathophysiologic mechanisms that may explain the effects of bariatric procedures, on the clinical factors that may predict diabetes remission after surgery, on the development of new procedures specifically tailored for type 2 diabetes control, and on the possible effects of metabolic surgery in type 2 non-obese diabetics. All these studies are certainly interesting and will hopefully open new and exciting therapeutic possibilities. However, we believe that a key point still missing remains: the production of high-level controlled trials evaluating the net benefit of bariatric surgery in the prevention of both macro- and micro-vascular hard endpoints specifically in patients with type 2 diabetes.

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