

From bariatric to metabolic surgery: Looking for a “disease modifier” surgery for type 2 diabetes

Renzo Cordera, Gian Franco Adami

Renzo Cordera, Department of Internal Medicine, University of Genova, 16132 Genova, Italy

Gian Franco Adami, Department of Surgery, University of Genova, 16132 Genova, Italy

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Correspondence to: Renzo Cordera, MD, Professor of Endocrinology, Department of Internal Medicine, University of Genova, Viale Benedetto XV, 6, 16132 Genova, Italy. record@unige.it
Telephone: +39-10-3538947

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Abstract

In this review the recent evolution of the comprehension of clinical and metabolic consequences of bariatric surgery is depicted. At the beginning bariatric surgery aim was a significant and durable weight loss. Later on,

it became evident that bariatric surgery was associated with metabolic changes, activated by unknown pathways, partially or totally independent of weight loss. Paradigm of this “metabolic” surgery is its effects on type 2 diabetes mellitus (T2DM). In morbid obese subjects it was observed a dramatic metabolic response leading to decrease blood glucose, till diabetes remission, before the achievement of clinically significant weight loss, opening the avenue to search for putative anti-diabetic “intestinal” factors. Both proximal duodenal (still unknown) and distal (GLP1) signals have been suggested as hormonal effectors of surgery on blood glucose decrease. Despite these findings T2DM remission was never considered a primary indication for bariatric surgery but only a secondary one. Recently T2DM remission in obese subjects with body mass index (BMI) greater than 35 has become a primary aim for surgery. This change supports the idea that “metabolic surgery” definition could more appropriate than bariatric, allowing to explore the possibility that metabolic surgery could represent a “disease modifier” for T2DM. Therefore, several patients have undergone surgery with a primary aim of a definitive cure of T2DM and today this surgery can be proposed as an alternative therapy. How much surgery can be considered truly metabolic is still unknown. To be truly “metabolic” it should be demonstrated that surgery could cause T2DM remission not only in subjects with BMI > 35 but also with BMI < 35 or even < 30. Available evidence on this topic is discussed in this mini-review.

Key words: Obesity; Severe obesity; Obesity related metabolic co-morbidities; Type 2 diabetes; Type 2 diabetes remission; Type 2 diabetes control; Bariatric/metabolic surgery

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Core tip: In severely obese patients with type 2 diabetes mellitus (T2DM), weight loss after bariatric surgery is often accompanied by long term remission of T2DM

and other obesity co-morbidities, these anti-diabetic outcomes are due both to body fat loss and to still unknown factors specifically regulated by surgery. On the other hand, the same surgical procedures in obese patients with a body mass index < 35, are associated with T2DM remission in only 50% of subjects. These findings raise the question whether bariatric surgery could be considered a metabolic one. We propose that "bariatric" surgery could be considered "metabolic" only in the case that it could demonstrate its effect on long lasting T2DM remission in morbid as well as in non-morbid obese subjects.

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INTRODUCTION

Obesity and severe obesity was a condition well known already in the earlier ancient world: The famous rhetorician Claudius Aelian (170-235 A.D.) includes in his Historical Miscellany the careful report of a massively obese person, Dionysius tyrant of Heraclea, who being ashamed of his great body mass used to give audience to those who wished to confer with him by placing a chest in front of his body so that his whole body remained hidden except for his head^[1]. However, substantially because of food unavailability, of extreme inequalities within population and of short mean life duration, the prevalence of obesity remained almost negligible until the XX century^[2]. During the last 100 years in the Western world a greater availability of food for the great majority of the people, the prodigious improvements of preventive and clinical medicine and the reduction of social gap lead to a progressive increase of life expectancy with the consequent increased prevalence of obesity. In the Western developed countries in the 30's and 40's years of the last century to be slim and in shape became an ethic rather than a health condition: Overweight obese patients unable to loose weight were considered as lazy, ugly and stupid and become the object of a real social stigmatization^[3,4]. After the World War II, bariatric procedures were introduced in the United States as an effective anti-obesity surgical method, that allows significant weight loss also to patients who cannot reduce their usual food intake^[5-7]. Obviously the social, stigmatization of obesity included both the obese patients seeking surgical treatment and the bariatric surgeons: The former are persons without will power, who threat their life for the whim to be slim, the latter are physicians taking care of a worthless issue^[4].

In the last decade this scenario changed radically. At the end of the XX century obesity has become an

increasing social problem in the western developed countries, with a vertiginous increase of prevalence and with great impact on health due severe co-morbidities. The positive trend of longevity obtained in the last years might be stopped and even reversed by the medical problems due to obesity: The baseline conditions being equal, an individual with body mass index (BMI) value over 40 kg/m² has a 50% shorter life expectancy in comparison with a lean persons^[8-10]. Taking into account these epidemiological findings, bariatric surgery is now accepted in the therapeutic armamentarium against obesity, and the surgical option is offered to severely (morbid) obese patients, that are now considered no more as lazy and stupid person but as complicated patients needing complex and tireless cures. Furthermore, the social and scientific consideration of bariatric surgeons, that have to cope with a very difficult task and to fight with the more prevalent chronic disease in the Western world, was sharply increased. At the beginning of XXI century bariatric surgery is regarded as a real branch of abdominal surgery.

The widespread use of bariatric procedures in different populations, by different surgical teams and in different socio-cultural contexts has clearly demonstrated that in the severely obese patients the surgically obtained weight loss is accompanied by the remission or by the improvement of most metabolic and cardiovascular co-morbidities of obesity, with a consequent increase in survival^[11-14] from a research point of view the intriguing observation that most of metabolic effects are obtained well before a clinical meaningful weight loss has raised the hypothesis of a specific gastrointestinal effects of bariatric surgeries^[15,16]. Therefore bariatric surgery community proposed to change the name of their discipline from "bariatric" to "metabolic" surgery, with the purpose of increasing their field of interest and of giving an ever greater deal of scientific background to their clinical practice.

By a pathophysiological point of view, in the obese patients the extra load of fat gives rise to the metabolic complications and to the cardiovascular disorders thus increasing morbidity and mortality: By determining a substantial weight loss and a marked reduction of body fat size, bariatric surgery acts on the metabolic complications only indirectly, and therefore a priori these procedures cannot be defined as true metabolic operations. In fact, in our opinion, a real metabolic procedure would influence the patient's metabolic status regardless of changes in body weight or in body fat size, or at least the body weight changes would play only a secondary role in the process.

Taking into account a clinical and scientific experience of more than thirty years, this brief review puts under close scrutiny the recent bariatric literature, with the aim to establish the possibility to define as "metabolic" the today bariatric surgery, specifically sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGBP) and bilio-pancreatic diversion with its variations (BPD).

The placement of laparoscopic adjustable gastric

banding (LAGB) is the simplest and safest bariatric procedure. The operation causes a gastric restriction and a mechanical obstruction to transit of solid alimentary substrates: By consequence the usual food intake decrease with a resulting weight loss^[17-19]. In the diabetic patients the reduction of food consumption and the drop of body mass size correspond to a normalization of blood glucose in 40%-50% of the cases, while postoperative improvement or resolution of dyslipidemia is only seldom observed^[19-21]. However, in the patients having regained weight after the operation due to incongruous eating habits, the glycaemia increases again and diabetes relapses^[21-24]. These data clearly indicate that the LAGB cannot be considered as a metabolic procedure and that the metabolic benefits experienced by some patients following the operation are essentially due to the weight loss.

In the last decade a great deal of studies have been carried out on the effects of the more complex bariatric procedures, such as the RYGBP, the SG and the BPD with their variations on the type 2 diabetes in the severely obese patients. In summary, published data indicate that in severe obese patients with type 2 diabetes the weight loss obtained following RYGBP is accompanied by diabetes remission in 60%-90% of patients and by an improvement of the diabetes in the remaining case, with a marked reduction of the need of anti-diabetic therapy: These positive results are maintained at 5 and 10 years after the operation^[25-30]. Furthermore, in comparison with non operated severely obese patients with T2DM, the individuals submitted to RYGBP increase their longevity and experience a reduction in the rate of cardiovascular events^[14].

T2DM remission rate is higher after BPD in comparison with the other types of procedures^[26-29], the studies carried out in large cohort of subjects and in different institutions showing a stable and long lasting (10 years) T2DM remission in more than the 86% of patients. The long term positive metabolic outcome RYGBP and SL are similar and nearly occurs in 60% of the cases, though long term results following SG are not yet fully available^[31,32]. Obviously the remission rate after RYGBP and BPD depends on preoperative variables: In the obese patients with a longer pre-operative T2DM duration and in those who were in insulin therapy before the operation the remission rate was about 70% and 50%, respectively, with a marked metabolic improvement in the others^[33-35].

Following RYGB and BPD blood glucose control is usually observed early, when BMI values are still in the morbid obesity range, with a rapid fall of serum glucose, insulin and insulin sensitivity values towards physiological range^[15,16]. The new functional - anatomic conditions of the upper gastrointestinal tract due to the operation might causes a change of intestinal hormone secretion patterns, that would be responsible of the metabolic changes observed. The bypass of proximal intestine from the food transit and the early contact of non-digested foods with more distal intestinal

loops increase the secretion of GIP and GLP-1 that have gastrointestinal and insulin-tropic effects^[36-38]. Furthermore, the passage of partially digested aliments through distal ileum cause an increase of secretion in PYY, a distal entero-hormone that specifically stimulates satiety^[39]. For BPD, the fat intestinal malabsorption due to the operation causes a significant lipid deprivation from the fist postoperative days and then a marked decrease of the intracellular lipid storage, that sharply increases muscle insulin sensitivity^[40,41]. After SL similar changes of gastric and intestinal hormones were observed in spite of the lack of duodenal exclusion^[42]. In summary, several studies have demonstrated in both diabetic and non diabetic severely obese patient a metabolic recovery early after the operation, when body weight is still in the obese range. Furthermore, as it results by the clinical experience of many bariatric surgery teams and as it is indicated by a great deal of literature data, the post obese individuals operated of BPD and RYGBP achieve a BMI of stabilization in the overweight range (28-30 kg/m²), that is maintained indefinitely^[26,43-45]. In spite of an higher than normal body weight, in the a cohort of post obese persons submitted to RYGB or BPD the occurrence of a new case of diabetes is highly unusual. In addition, when the severely obese T2DM patients with positive and negative post BPD and post RYGB metabolic outcome were compared, a closely similar weight loss was observed^[34,35], suggesting that diabetes remission could be due not exclusively to surgery but to a combination of surgery with the right subject. These facts clearly evidence the lack of relationship between the weight status and the presence of diabetes after bariatric surgery, and indicate that in these cases the operations have to be considered as true metabolic operation. In the severely obese patients with T2DM submitted to BPD, glucose, glycated hemoglobin serum concentration and insulin sensitivity are normalized for very long time. Also insulin secretion improves as indicated by post surgery recovery of early insulin secretion stimulated by *iv* glucose. The most striking result of surgery is the reversal of the progressive failure of beta cell, as observed instead in non operated T2DM, due to metabolic noxa^[46]. For this reason, in severely obese patients BPD could be considered as a true diabetes modifier therapy^[15,21,47].

As far as lipid metabolism is concerned, in pre-operatively patients with atherogenic dyslipidemia a reduction of serum triglycerides and total cholesterol is usually observed after BPD and RYGBP, and values were satisfactory maintained at long term following operation^[25,44,45,48]. After RYGP the improvement of lipid pattern is substantially due to the reduction of food intake and to qualitative changes in alimentary substrates. On the contrary, after BPD the lipid malabsorption leads to a decrease of distal gut uptake of bile salts, thus obviously determining a size reduction of body cholesterol pool^[45,49]. HDL cholesterol concentration is generally unaffected by bariatric surgery and by the

massive weight loss; but a significant increase of serum HDL cholesterol value was observed at long and at very long term following the bariatric operation, most likely for decreased insulin resistance and lifestyle changes with progressively increases its physical mobility^[45]. Therefore, regarding total cholesterol, BPD acts as a metabolic operation, while the effects of bariatric surgery on the other components of lipid metabolism are substantially accounted for by the weight loss and by the changes in lifestyle and food consumption. The above reported clinical and experimental results are suggestive for the possibility to change the primary aim of bariatric surgery from weight loss to T2DM remission.

In clinical practice, the majority of T2DM patients are not morbidly obese, their BMI typically ranging between 25 and 35 kg/m². By the other hand, as said above, BPD and RYGBP act on severely obese patients with a real metabolic mechanism, and T2DM, as well as other comorbidities such as hypertension and dyslipidemia, improve at an early time point after surgery, independent of major weight loss^[15,16,37,38,41]. Recently, both observational^[50-55] and randomized controlled trials^[34,56-61] have indicated that metabolic surgery in severely obese patients might be superior to medical therapy with regard to T2DM remission and glycemic control. Consequently, bariatric-metabolic surgery has been proposed as a treatment option for T2DM also in patients with overweight or obesity of mild degree, because it potentially leads to less morbidity and mortality in the long-term. Furthermore, an adjustment of treatment guidelines favoring metabolic surgery in non severely obese patients would have a major impact on global health care. Recently a very accurate metanalysis and review studies were carried out, that clearly showed the short-term superiority of metabolic surgery to medical treatment, with regard to T2DM remission, glycemic control, and remission of associated comorbidities^[62-64]. However, a relevant heterogeneity of data according to the type of surgical procedure employed and to the characteristics of the patients was observed. In comparison with standard anti-diabetic therapy, in patients submitted to the LAGB or SG the metabolic outcome was better. However, the attainment of normal serum glucose concentration was observed in less than 30% of operated Patients, the results being substantially due to the weight loss and tending to disappear with weight regain^[55,56,61]. The metabolic effect of the more complex procedures was higher, the procedures leading to a fasting blood glucose control or normalization in 50%-60% of the cases within one years after the operation. Therefore both RYGBP and BPD might act as metabolic operations also in T2DM individuals with simple overweight or obesity of mild degree; however the overall results were far less striking and evident than those usually observed in severely obese patients. The rate of postoperative patients with diabetes remission one year after BPD and RYGBP, thought in any case greater than that observed in patients undergoing medical therapy, was consistently

lower in comparison to the rate of postoperative diabetes remission of T2DM in morbidly obese patients. Since the nature of the surgical procedure is the same, the discordant results are most likely due to the diabetes characteristics and/or to the patient's obesity degree. Furthermore, as far as the postoperative diabetes remission in the non morbid obese patients, at the present time only data at short term are available. As said above, type 2 diabetes is a progressive disease, for both a gradual increase in insulin resistance and decrease of beta cell mass due to genetic defects and to glyco-lipotoxicity^[46]. In morbid obese patients, bariatric surgery modifies diabetes natural history by steadily restoring insulin sensitivity of beta cell secretion, evidenced even at five years following surgery^[47].

In T2DM without morbid obesity the picture is still unclear and only the long term functional and clinical results will establish whether RYGBP and BPD act as metabolic operation. An improved and durable rate of diabetes remission could demonstrate that bariatric operation resulted in stopping or reverting the natural history of diabetes, in this demonstrating a metabolic action. On the contrary, if the positive metabolic outcome observed after one year will disappear, it would be demonstrated that the progressive detrimental trend of T2DM is not directly influenced by the operation, and that the metabolic benefits observed at the first postoperative year are substantially accounted for weight loss and by the reduction of insulin resistance, in that excluding a direct metabolic effect of the operation. At one year after BPD, in T2DM overweight-mildly obese patients, the diabetes remission and glycemic control was observed in 40% and 70% of the cases, respectively, while the acute insulin response was not completely restored, differently from what observed in T2DM morbidly obese patients^[47,65-67]. This already suggests that the positive outcome is substantially accounted for by weight loss and by insulin resistance decrease and that BPD has only a little metabolic effect. Longer term studies will clarify this issue.

At the present time, for T2DM patient, bariatric surgery can change to a metabolic one depending on the clinical characteristic of the patient itself. In other words it is possible, even if not completely proofed that the more obese patient before surgery the more metabolically effective is BPD, independently, at least partially, by weight loss. This consideration is based on the assumption that the amount of beta cells is increased in morbid obese subjects, even if already diabetic: recovery from insulin resistance due mostly to a greatly reduction of caloric intake can cure T2DM, because of an enough amount of circulating available insulin.

In summary, this review suggests that the term metabolic surgery should not to be employed as a synonymous of bariatric surgery. Gastric restrictive surgery gives positive metabolic outcomes only in a minority of the patients, and the results are substantially accounted for by the weight loss and are poorly maintained at long term. In the T2DM severely obese patients

RYGBP and BPD obtain astonishing metabolic outcomes independently of weight loss. In this subset of subjects, in spite of the progressive detrimental characteristics of T2DM, the results are maintained throughout the years, so that the operation could be regarded as a true diabetes modifier therapy. In morbidly obese patients BPD and RYGBP actually are metabolic operations. This could not be the case in T2DM patients with simply overweight or obesity of mid degree: However, this lack of metabolic efficacy is not dependent on the operation itself but on the characteristics of the patients.

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