Impact of bariatric surgeries on diabetes outcomes

Impacto da cirurgia bariátrica no resultado do diabetes

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ABSTRACT

Obesity and type 2-diabetes (T2D) are associated to dramatically high morbidity and mortality, and their incidence and prevalence are increasing rapidly. Bariatric surgeries, including a variety of gastrointestinal surgical procedures achieve substantial and sustained weight loss in morbidly obese patients, strongly improves diabetes and hypertension control or prevalence, quality of life, decreases incidence of stroke, myocardial infarction and obstructive sleep apnea among other favorable clinical outcomes. Most important, mortality rates decreases. The objectives of this narrative review were the effectiveness of bariatric procedures on diabetes remission or improvement and the implicated mechanisms. It was found that bariatric surgeries induce high rates of short and long-term diabetes remission (from 60 to 95% or improved control), according to the surgical intervention, with low frequency of perioperative and postoperative complications. Rates of diabetes recurrence are not well known, but the time free-of-disease should ameliorate diabetes complications and mortality. The mechanisms are still not completely understood; encompass improved insulin action, better b-cell function, higher adiponectin, lower inflammation and complex changes of hormones of the entero-insular axis, GLP-1 and glucose dependent insulinotropic polypeptide (GIP). Insulin action improves proportionally to weight loss (WL), in most types of surgery, but normalizes after Bilio-pancreatic diversion even in still obese people. b-cell function improves more after bypass than after restrictive surgeries, but does not normalize and baseline function predicts diabetes remission. Efforts to understand mechanisms and predictive factors for diabetes remission may optimize surgical interventions for metabolic disorders even in less obese patients. Finally and more important, they might drive the development of new clinical approaches for T2D.

Keywords: Diabetes Mellitus, type 2; Obesity/surgery; Bariatric surgery; Gastric bypass/methods; Insulin resistance; Anastomosis, roux-en-Y; Body mass index; Weight loss; Biliopancreatic diversion

The incidence and prevalence of obesity and type 2-diabetes (T2D) are dramatically increasing, especially in occidental countries[1-3]. Both conditions are associated to high morbidity and mortality[4]. The predicted diabetes prevalence, 439 millions people by 2030, and complications in the next decades makes the search for effective therapies utterly important[5].

Bariatric surgeries, including a variety of gastrointestinal (GI) surgical procedures have been used in the last 50 years to achieve substantial and sustained weight loss in morbidly obese patients[6] or in patients with a body mass index (BMI) ≥35kg/m^2 associated with comorbidities like diabetes and hypertension[7]. In fact, bariatric surgery has strongly improved prevalence and control of diabetes[8,9] and hypertension, quality of life, decreased incidence of stroke, myocardial infarction and obstructive sleep apnea among other favorable clinical outcomes. Diabetes improvement and remission has been observed following almost all bariatric techniques, at 30% to 95% of the patients. Diabetes control, frequently, precedes substantial weight loss, and persists after the effect of postoperative starvation on the blood glucose has finished. After bariatric surgeries, like Roux-en-Y gastric bypass (RYGB), bilio-pancreatic diversion (BPD) and sleeve gastrectomy, the hyperglycemia decreases within days after surgery and often allows the therapy for diabetes discontinuation. In this way, it is suggested that the metabolic effects are not simply the results of weight loss and decreased caloric intake but might be partly related to endocrine changes resulting from modification of the gastrointestinal tract by the surgery[10,11]. On the other hand, failure to maintain long-term control of diabetes by lifestyle intervention and pharmacological treatment is largely observed, even in developed countries. Recently, bariatric surgery has been proposed to non-obese diabetic patients, denominated "metabolic surgery" and primarily aimed to the treatment of diabetes and metabolic disease[11]. The recent International Diabetes Federation guidelines have identified the need to direct the focus from BMI from the previous guidelines to the metabolic diseases and, suggested to include bariatric procedures in the diabetes treatment algorithms[7].

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Data de submissão: 07/05/2014 – Data de aceite: 08/05/2014
Conflito de interesses: não há.

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To carry out this narrative review we searched MEDLINE using the Medical Subject Headings (MeSH) terms "bariatric surgery" and "diabetes" or "insulin resistance" or "insulin secretion" or "endogenous glucose production", "bariatric surgery" and "mortality", "gastric bypass" and "diabetes" on the last 10 years. Bibliographies of the systematic reviews were also searched and relevant papers were included. Mechanisms of diabetes control or remission were reviewed with particular attention.

There is no consensus in the literature to define remission and control of diabetes. Diabetes control has been evaluated in different ways at variable follow-up length making comparisons among studies very difficult. Buse et al.[12], proposed the term *remission* to achieved glycaemia under diabetes limits in the absence of active pharmacological or additional surgery therapy, being *partial* when fasting glycaemia was between 100 and 125mg/dL and HbA1c <6.5% lasting for at least one year, *complete* for fasting glycaemia <100mg/dL and HbA1c <6.0% for at least one year, and *prolonged remission* is the complete remission for more than 5 years[12]. We searched for these recommendations in the original papers, but frequently they are not clearly reported.

BARIATRIC TECHNIQUES

The number of bariatric techniques is increasing quickly, new surgeries or modifications of frequently performed surgeries are being proposed to improve efficiency or decrease complications. Laparoscopic techniques are now largely used and they reduced the surgical stress and mortality as compared to the open surgeries. The most frequent surgeries are open or laparoscopic (L) Roux-en-Y gastric bypass (RYGB), adjustable gastric band (AGB) or laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG or LSG), bilio-pancreatic diversion (BPD) and BPD with a duodenal switch (DS) (BPD-DS). Other operations less frequently performed include ileal interposition, laparoscopic duodeno-jejunal bypass with sleeve gastrectomy and, endoscopic or laparoscopic placement of devices in the upper GI[7]. Shortly, RYGB includes a division of the stomach creating a small pouch where the portion of jejunum that has been transected at 30 to 75cm from the ligament of Treitz is anastomosed. The remaining larger portion of the stomach is anastomosed down in the jejunum (75-150cm). In this way, gastric size is reduced and food bypasses the duodenum and proximal jejunum. RYGB changes the bile and nutrients flows, enteric hormone modulation and vagal stimulation [13]. Gastric banding induces a gastric volume restriction by placing an adjustable silicone ring around the upper stomach. In the BPD, 50% horizontal gastrectomy is performed, which is anastomosed to the small intestine, 250cm from the ileocecal valve; the excluded limb carrying the biliopancreatic juice is anastomosed to the ileum, 50-100cm from the ileocecal valve creating a very long bypass. The surgeries including bypasses combine malabsorptive and restrictive mechanisms, the BPD being an essentially malabsorptive operation. SG was initially performed as the first step for weight loss, followed by another operation in a second step. Recently it was proposed as a standalone operation and has been performed more frequently. Involves a stomach resection, along an endoscope initiating about 3cm from pylorus until the angle of Hiss, reducing the gastric volume by 75 to 80%. The duodenal switch, a variation of BPD, includes a sleeve gastrectomy where the stomach is connected to the ileum 2.5-3m from the ileocecal valve[14].

EFFICACY OF BARIATRIC SURGERIES ON WEIGHT LOSS, MORTALITY AND DIABETES

Bariatric surgeries induce important weight loss, mainly in patients with higher baseline BMI. WL improves many obesity complications, as cardiovascular, respiratory, osteo-articular and improves carbohydrate metabolism since obesity is the most important predictor of diabetes development. In the prospective case-matched Swedish Obese Subjects Study (SOS), with surgical and control group, the maximum weight loss, after 1 or 2 years, was 32%, 25% and 20% of baseline for RYGB, vertical banded gastroplasty and gastric band. At 10 years of follow-up, it was stabilized at 25%, 16% and 14% respectively. In that study, 68% of the patients underwent gastroplasty and 13% RYGB. The mean change in body weight at 15 and 20 years were -16% and -18% [15]. About 10% of the participants in both arms, surgical and control, were diabetic. This huge weight loss has been largely reproduced with some variations according to the baseline BMI, surgery procedure and time of observation. In a large meta-analysis, biliopancreatic diversion (BPD) or duodenal switch induced a WL of 70% of the excess body weight followed by gastric bypass with 68% and 62% for gastric band[16]. Sleeve gastrectomy induced lower weight loss until 18 months of follow-up but, similar to RYGB thereafter[17] or, according to other studies, similar already after 1 year[18,19]. In a randomized control study, laparoscopic RYGB induced better weight control than LAGB at 5 years follow-up of, despite of more surgical complications[20]. Quite the reverse, intentional weight loss is difficult to maintain in the long-term.

Several studies have demonstrated an association of obesity and diabetes with cardio-vascular risk and high mortality[21,22]. Long-term reduction of cardiovascular and metabolic risk factors after bariatric surgery has been described many years ago, but a drop in mortality was described more recently. In the SOS, the hazard ratio for the 10 years mortality, adjusted for sex, age, and other risk factors, was 0.71 in the surgery group, as compared with the control group[23]. In a large retrospective study, with a mean follow-up of 7 years, including 7925 pairs of obese patients submitted to RYGB and matched controls from Utah, the surgical group had a 40% decrease of overall mortality, 56% by coronary disease, 92% by diabetes 61% by cancer, whereas mortality due to accidents and suicide increased by 58%[24]. In contrast, improved quality of life and social interactions and lower rates of depression, but not anxiety, have been described in the SOS[25,26].

Furthermore, it is well known that glycemic control decreases long-term morbidity and mortality[27], even if intensive glycemic control, by clinical therapy, in some studies was associated to a higher cardio-vascular risk[28]. Diabetes "remission" after

different bariatric surgery has been repeatedly described in small groups but also in large studies[29-33]. At 2 years of follow-up, 72% of the diabetic patients submitted to surgery in the SOS were in remission, with an adjusted Odds ratio of 8.42 vs. the control group[26]. Even if a relapse of diabetes was reported at 10 years follow-up, remission rates (adjusted Odds ratio vs. control=3.45) are extremely higher than those observed after lifestyle or pharmacological interventions.

Moreover, in the SOS study it is noteworthy the lower incidence of diabetes in non-diabetic surgical group: the risk of developing T2D was reduced by 96%, 84% and 78% after 2, 10 and 15 years respectively[34], being the preventive effect more striking in subjects with impaired glucose tolerance (IGT), at baseline. On the other hand, randomized trials of clinical interventions reduced from 14 to about 67% the relative risk of diabetes incidence in high-risk population, like IGT. In the Da Qing study, clinical intervention as diet or physical activity or both were carried out during the first 6 years in IGT patients[35]. At the 23 years follow-up, diabetes incidence was reduced vs. controls (72.6 vs. 89.9%, HR of 0.55), emphasizing long-term clinical benefits. Notably, the delay time to the onset of diabetes was related to better outcomes. Moreover, the mortality drop was significant compared to the control group (28.1 vs. 38.4%, HR=0.71)[35]. These rates seems to be lower than those induced by bariatric surgeries but, the studies include many different lifestyle modifications and/or pharmacological therapy, follow-up length and study populations are different, so the comparison and interpretation of the results are not immediate[36,37].

Factors associated to lack of remission or to recurrence of diabetes are lower BMI, older subjects, longer diabetes duration, insulin therapy, higher HbA1c at baseline and lower weight loss or weight regain[17]. The relapse or recurrence of diabetes parallels the length of the follow-up, from 26% at 5 years to 42% at 15y after RYGB[17]. The type of surgery also influences the weight loss and diabetes outcomes. In fact, relapses or recurrence were not observed 10 years after BPD in a small group of newly diagnosed diabetic patients[31].

Summary: a) Bariatric surgeries are the most effective method to reduce weight; b) BPD; RYGB and SG induces more WL than restrictive procedures like LAGB; c) Bariatric surgeries reduces diabetes comorbidities; d) they reduce overall mortality by 40%; e) are the most effective procedure to treat T2D and to prevent its development in high risk populations.

DIABETES OUTCOMES INDUCED BY DIFFERENT BARIATRIC SURGERIES AND COMPARISON TO MEDICAL THERAPY

Buchwald et al., reported a meta-analysis counting 22094 patients including 1846 diabetic patients. Diabetes resolution (defined as discontinuation of diabetes related medications and blood glucose within the normal range) was achieved by 98.9% after BPD or duodenal switch, 83.7% after gastric bypass, 71.6% after gastroplasty and 47.9% after gastric banding[16]. In a more recent meta-analysis, the same authors found similar results and rates among bariatric techniques in a subset of studies including only diabetic patients[38]. For the laparoscopic adjustable gastric banding, lower weight loss and rates of diabetes resolution, around 60%, were reported[38,39]. Co-morbidities like hypertension, dyslipidemia and sleep apnea also improved more after RYGB[39].

At a 1 year follow-up, the ongoing Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE trial), demonstrated similar diabetes control, defined as glycated hemoglobin ≤6% after RYGB and sleeve gastrectomy, both around 40%. However, 28% of the SG group remained under anti-diabetic drugs therapy, while none of the RYGB group. A third group was submitted to intensive medical therapy alone and achieved higher HbA1c (7.5%) in spite of a larger use of drugs[18]. The just published 3 years follow-up reported a glycemic relapse (defined as a patient who had a HbA1c ≤6% at 1 year but did not maintain at 3 years) of 5%, 24% and 80% for RYGB, SG and medical therapy respectively[40]. In this way, the HbA1c ≤6% was achieved in 38% of RYGB, 24% of SG group and in only 5% of the patients on medical therapy. The diabetic patients in the STAMPEDE study initially had BMI of 27 to 43kg/m^2 and the weight lost at 1 year was similar in the surgical groups and lower in the intensive clinical therapy group but the weight reduction was higher in RYGB than in SG at 3 years follow-up[40]. Another comparison of RYGB and SG (SLEEVEPASS study) revealed similar WL and resolution of obesity-related comorbidities in a post-operative period of 6 months[41]. A very recent meta-analysis reported an overall diabetes remission around 90% after bypass surgeries (pooled data of RYGB and BPD) and 70% after gastric band[42].

Mingrone and al reported even higher diabetes remission rates at 2 y follow-up after BPD (95%) compared to RYGB (75%) in obese patients while none of the patients under optimized medical therapy experienced diabetes remission[43]. All patients of both surgical groups discontinued oral hypoglycemic drugs and insulin therapy within 15 days after intervention. However, the HbA1c drop at 2 y was significantly higher in the BPD than in the RYGB in spite of similar weight loss, and was higher in both surgical groups compared to medical therapy group[43].

In a small case-controlled trial, diabetic complications were reduced 10 years after BPD in very obese diabetic patients as compared to the matched controls. Diabetes remitted in the whole surgical group and insulin sensitivity increased while the prevalence of hypertension and hyperlipidemia strongly decreased or were no more present[31]. The predicted probability of coronary heart disease decreased in the first 2 years and remained low over the follow-up. In the STAMPEDE study at 3 years, cardiovascular biomarkers (blood pressure LDL, HDL cholesterol and Triglycerides) or related medications and albuminuria were significantly improved in the 2 surgical groups as compared to the medical therapy, but the maximal carotid intima-media thickness did not change[40]. Improvements of lipids profile and hypertension control were confirmed in other studies[42] and prevalence of renal dysfunction and or albuminuria also decreased after surgery[31,40].

Summary: a) randomized trials and observational studies provide solid evidence of superior effectiveness of bariatric

surgeries compared to conventional clinical treatment in inducing improvement or remission of diabetes and comorbidities. b) BPD is the most effective procedure to improve diabetes control, followed by the RYGB. c) SG is highly effective but similar or lower rates of WL and diabetes control compared to RYGB were observed. d) Restrictive surgeries are less effective than RYGB and BPD.

BARIATRIC SURGERY IN DIABETIC PATIENTS WITH BMI UNDER 35kg/m²

Fewer studies have addressed a more controversial issue, i.e. bariatric interventions in diabetic patients with a BMI lower than 35kg/m² including the overweight range (25 to 30kg/m²). While morbid obese patients obtain additional benefits, the purposes of surgery in patients under 35kg/m² is mainly diabetes and its complications relief. Observational studies have reported remission or improvement of diabetes and co-morbidities like hypertension and dyslipidemia following different types of bariatric surgeries also in these patients[44,45] with low rates of surgery complications[44-48]. Diabetes control or improvement of metabolic syndrome after gastric banding were superior to usual or intensive clinical therapy, in the BMI range 30 to 40kg/m², as observed in few randomized clinical trials[46,48,49]. As in more obese patients, RYGB prompts better diabetes outcomes than gastric banding[50]. In a prospective study including 66 patients with long standing diabetes and BMI 30-35kg/m², submitted to laparoscopic RYGB, diabetes remission was observed in 88% (HbA1c <6.5%) and improvement in 11% of the patients[47]. These impressive results are similar to those observed in patients with BMI higher than 35kg/m² and in agreement with weight reduction and diabetes remission in patients with BMI <35kg/m² compared to BMI>35kg/m² in the STAMPEDE[40].

High efficacy in this population was reported also for less usual surgical interventions. Laparoscopic mini-gastric bypass, a new surgical procedure, induced a slightly lower weight reduction and diabetes improvement in patients with a BMI <35 compared to those with a BIM >35kg/m² (89 vs. 98%, p=0.09) [51]. DePaula et al., reported a high diabetes resolution or improvement in T2D patients with a BMI <35kg/m² by laparoscopic ileal interposition into the proximal jejunum and sleeve gastrectomy or ileal interposition associated with a diverted sleeve gastrectomy [52].

Importantly, in the STAMPEDE trial, meeting the primary endpoint (HbA1c ≤6%) was predicted by a higher BMI reduction and shorter diabetes duration (less than 8 years), suggesting that surgical interventions should be carried out earlier in the diabetes progression[40]. Accordingly, higher BMI reduction and lower baseline HbA1c predicted the diabetes outcomes after laparoscopic adjustable gastric band[46]. In fact, in diabetic patients with long-standing diabetes and BMI between 25 and 30kg/m², at 1year post-BPD we observed remission (defined as HbA1c <6.5%; fasting glucose <7.0mmol/L and 2 hours into oral glucose tolerance test (OGTT) <11.1mmol/L, without medications) in only 40% of patients, even if diabetes control strongly improved in all of them[33]. In agreement, Scopinaro et al. found a diabetes resolution with less astringent criteria in 83% of T2D with an initial BMI between 25 and 34.9kg/m²[53]. These rates are lower than those obtained for morbidly T2D after BPD and might be on account of the worse b-cell dysfunction in less obese diabetics. However, Cohen et al., did not found correlations of diabetes remission, improvement of HOMA-IR and of a roughly evaluated b-cell function with weight loss or diabetes duration[47], suggesting weight-loss independent mechanisms. These mechanisms eventually are diverse by each type of surgery. In addition, the success rates depend on the baseline diabetes condition, follow-up length and adopted criteria of remission.

Summary: 1) Bariatric procedures are superior to clinical therapy to control or induce remission of diabetes in patients with BMI <35kg/m². 2) The remission rates are higher after RYGB, SG than gastric band. 3) Bariatric surgery seems to be more effective in obese T2D population than in overweight. 4) Longer follow-ups in large study populations are needed to assess the efficacy and durability of diabetes remission in non-obese lower BMI ranges.

MECHANISMS OF DIABETES IMPROVEMENT

Post prandial and fasting plasma glucose levels result from a perfect dynamic equilibrium among peripheral tissue glucose uptake, hepatic glucose production and b-cell function. Tissue insulin sensitivity is the main determinant of peripheral glucose uptake while hepatic insulin sensitivity and portal concentrations of glucagon and insulin determine hepatic glucose release. These major players are under control of many hormones, cytokines, incretins, autonomic nervous system (ANS), etc., which might be modified by surgery. Roughly, T2D results from a variable mix of insulin resistance and b-cell dysfunction. The main metabolic abnormalities of obese patients are peripheral, i.e. skeletal muscle, insulin resistance (IR), due to both impaired oxidative and non-oxidative glucose disposal; low hepatic glucose uptake and increased endogenous (hepatic) glucose production (HGP); increased lipolysis and lipid oxidation. The same abnormalities characterize T2D, but while obesity is associated to hyper insulin secretion, diabetes or impaired glucose tolerance is characterized by reduced insulin secretion in absolute terms or relative to the severity of insulin resistance (by insufficient compensation for IR).

Insulin action after bariatric interventions has been assessed using many measures or indices, the more frequent being plasma insulin concentration and homeostasis model of assessment of insulin resistance (HOMA-IR)[54], but also other surrogates of insulin resistance are reported. Plasma insulin concentration is determined not only by insulin secretion, but also by hepatic insulin extraction and peripheral insulin clearance, a limitation for its use to assess IR or b-cell function. Another limitation is the lack of standardized assays for insulin measurement. HOMA-IR is calculated from a fasting concentration of glucose and insulin, is related to hepatic insulin resistance, is not a dynamic measure and depends of a sufficient residual insulin secretion.

Few studies have evaluated insulin sensitivity (IS) using the gold standard method, hyperinsulinemic euglycemic clamp[55,56]. During the clamp, insulin is infused in a constant rate. A variable rate of glucose, calculated from a frequent measure of plasma

concentration, is associated to maintain glycaemia constant. Higher resistance to the insulin action brings lower tissue glucose uptake, therefore, lower glucose infusion is needed. The clamp assesses the whole body glucose uptake mainly by peripheral tissues; infusion of glucose tracer (radiolabelled or stable isotopes) can be associated to assess hepatic glucose production.

Impact of bariatric surgery on insulin resistance (whole body and hepatic)

The glucose homeostasis control, and the decrease of HOMA-IR within days after RYGB and BPD were similar to those reported following low calorie diets in face of equal and small weight reduction[57]. These results might be attributed to increased hepatic insulin sensitivity and, decline of hepatic glycogen and of glucose release[58,59]. In this way, it is very difficult to distinguish specific effects of the intervention from those of the strong caloric restriction in the early post-op, being the later one probable explanation. After RYGB, HOMA-IR remains low (around 15% of the baseline values) throughout at least 18 months in subjects with normal glucose tolerance (NGT), as well as in diabetic subjects. Unlike the early decrease after RYGB and BPD, HOMA-IR is reduced only 6 months after LAGB[58-60]. In other reports, it improved more and rapidly after RYGB and BPD as compared to the conventional diabetes therapy[40,61]. On the contrary, the long-term HOMA-IR decrease seems to be dependent of the amount of weight reduction[58,62].

In line with HOMA-IR results, clamp studies have demonstrated important improvement of IR in NGT or T2D morbidly obese, but only after relevant weight loss (6 months to 2 years) induced by RYGB, LAGB or SG. The early IR drop was not confirmed[29,63] and insulin sensitivity improvement was predicted and proportional to the achieved body weight, similar to what happens after diet[14,29,63,64]. A 30% BMI reduction predicts insulin sensitivity to increase around 50%[65].

In a series of patients submitted to RYGB, we found that both oxidative and non-oxidative glucose utilization improved, similarly in diabetic and non-diabetic patients[29]. An early (2 weeks) increased lipolysis favoring weight reduction was concomitant to the fall of insulinemia and may have impacted negatively on insulin sensitivity trough lipotoxicity. The lipolysis normalized after 1 year, when body weight reduction flattened and insulin resistance was improved[29]. Conversely, BPD promptly improves insulin sensitivity beyond the effect of weight loss in NGT and in diabetic subjects, reaching levels higher than those of normal subjects[14,43,66]. In fact, normal insulin action on glucose clearance was observed as early as 10 days post-BPD before important WL, in NGT, IGT and T2D subjects[67]. T2D with BMI between 25 and 35kg/m^2 also had their insulin sensitivity normalized already 2 months after BPD[33]. Mechanisms linked specifically to BPD may be the lipid mal-absorption associated to marked reduction of intra-myocellular fat content, and normalization of glucose transporter 4 expression in skeletal muscle [68]. GIP increases fat deposition and insulin resistance and post-prandial levels were reduced by BPD, potentially contributing to better insulin action[59]. However, the mechanisms implicated in insulin action improvement in all these procedures are not totally known.

Hepatic insulin resistance has a substantial role in the development of impaired glucose metabolism via both, high fasting glucose release and low postprandial hepatic glucose uptake. HGP is inhibited by insulin and stimulated by glucagon, and has been evaluated at fasting, during the euglycemic hyperinsulinemic clamp or during a meal test in yet fewer studies and in small populations due to the complex experimental setting. We have observed a small non-significant decrease of fasting HGP, 2 weeks after RYGB, in presence of lower insulinemia, thus suggesting an improvement of hepatic insulin resistance. A significant fasting HGP decrease was observed 1 year later[29]. On the other hand, Weijer et al reported a significant decrease already 14 days after RYGB[69]. A more complex study assessed hepatic glucose metabolism in morbidly obese with NGT or T2D before and 6 months after RYGB or SG using positron emission tomography, magnetic resonance spectroscopy and euglycemic hyperinsulinemic clamp. Before surgery, hepatic glucose uptake at fasting was similar to controls, whereas during clamp it was reduced and increased by 30-40% after intervention in association to the reduction of visceral adipose tissue. This finding agrees with the concept that visceral fat releases large amount of free fatty acids that impairs hepatic glucose uptake, increases hepatic insulin resistance, triglycerides in the liver and peripheral insulin resistance. This study also reported a normalization of HGP and of liver fat content while liver volume reduced but remained higher than normal[70].

In addition, we also assessed HGP during a meal tolerance test before and after RYGB. Fasting HGP was higher and post-prandial HGP less suppressed in normal glucose tolarance (NGT) obese or T2D obese subjects as compared to lean controls. One year later, fasting HGP was unchanged while post prandial HGP was even greater (or still less suppressed) than before surgery. This result is in contrast to the above clamp results. Really, the time course of HGP curve changed, reminding a "dumping" pattern, since the peak occurred during the second and third hours postprandial, when glycaemia was already back to fasting levels or even lower levels[71]. The glucagon response to the meal is typically higher in T2D[72] and paradoxically it increased even more after RYGB[71,73]. The insulin-to-glucagon ratio decreased with the same time course of HGP, likely partially accounting for the increased HGP[71]. Similarly, insulin-to-glucagon ratio increased after BPD and, post-prandial HGP did not normalize, remaining less suppressed than in controls[33]. Taken all results together, both RYGB and SG seem to improve hepatic insulin resistance by decreasing glucose production and increasing uptake. The unexpected increase during the postprandial period after RYGB and BPD needs to be further investigated.

Summary: a) the similar early post-operative and post-diet decrease of HOMA-IR might be attributed to caloric restriction effect on HGP. b) Insulin resistance improves after RYGB, SG and LGB proportionally to weight reduction, whereas BPD improves IR early and normalizes it even in still obese subjects. c) The improvement of insulin sensitivity, similar between diabetic and non-diabetic obese patients, includes oxidative and non-oxidative

glucose utilization. d) At long-term, hepatic glucose metabolism improves or normalizes in concert with decreased visceral fat, but the response to the meal deserves more investigation. e) More studies are needed especially in T2D patients with lower BMIs.

Impact of bariatric surgeries on Insulin secretion and gastrointestinal hormones

In T2D there is a failure of b-cell function, even if insulin secretion frequently is higher than in NGT subjects. The glucose intolerance starts when secretion is insufficient to compensate for the prevailing IR[62,74]. The ability of weight loss, induced by diet or bariatric surgery, to decrease plasma insulin has been repeatedly reported, but as discussed above the interpretation of insulinemia may be biased, not given accurate information of "real secretion" and not allowing the assessment of many functional parameters of b-cell function. Fasting measures does not reproduces the dynamic changes induced by meal and does not assess the entero-insular axis control, which is stimulated by meal. The insulin response to intravenous glucose gives an estimation of glucose-dependent insulin secretion, excluding the effects of the entero-insular axis. In this case, the most used are the intravenous glucose tolerance test (IVGTT) and the hyperglycemic clamp. In the later, plasma glucose is acutely raised and maintained high by a continuous glucose infusion. The induced hyperglycemia stimulates endogenous insulin secretion. Both tests allow evaluation of the acute and early insulin secretion, or first phase (first 10 minutes after glucose infusion), and the late second phase[75]. The most frequently performed oral tests are glucose tolerance test (OGTT) and many kinds of meal tolerance test (MTT). The rate of glucose absorption and effect during an OGTT are quite different of a usual meal that contains fat, proteins and fibers. On the other hand, OGTT is a standardized test while MTT has been applied with many different nutrient composition and calorie amounts in liquid or solid formulas making comparisons very difficulty. However, MTT seems to be the more physiological approach. Mathematical models, using the results of insulin, glucose and C-peptide concentrations from the OGTT and the MTT, are carried out to investigate some other aspects of b-cell function. Thus, insulin secretion can be calculated from C-peptide deconvolution and mathematical modeling and, a curve of secretion is constructed. The most important parameter is the dose-response relationship between insulin release and plasma glucose concentrations. The mean slope of the dose-response function is taken to represent ß-cell glucose sensitivity, i.e. the sensitivity of ß-cells to glucose. Characteristically, it is very low in diabetic patients[76].

Regarding surgical effects, RYGB, BPD and SG induces rapid reduction of fasting plasma insulin[23,29-33,43,59]. MTT and OGTT carried out after RYGB confirmed the large decrease of fasting insulinemia and important changes of the time course of glucose, insulin, C-peptide and insulin secretion curves were observed[32,71]. The new distorted pattern follows the oral glucose appearance into the plasma (investigated by glucose kinetics). There is a faster and greater peak with most glucose absorbed during the first hour and a steeper decrease thereafter[71], as outlined in Figure 1. A similar shift to left of glucose and insulin secretion curves was observed after 15 days and 1 year post SG[32]. The total insulin secretion and the insulin concentrations during oral tests do not change substantially even if plasma glucose was decreased, demonstrating an improved relationship of insulin secretion with glucose[70,71]. Nevertheless controversial results regarding insulin secretion during OGTT or MTT have been reported[58].

Fasting plasma insulin concentrations decrease not only due the reduced secretion but also due to increased insulin clearance induced by weight loss after RYGB, BPD and SG[70,71]. After many surgical interventions, ß-cell glucose sensitivity increases to double or more in obese T2D patients. Nonetheless, ß-cell glucose sensitivity rests still markedly depressed in comparison with lean healthy individuals[32,31,70,71,77].

In T2D patients with BMI under 35kg/m^2, the improvement of ß-cell glucose sensitivity post-BPD was higher in those that experienced diabetes remission (remitters) *vs.* non-remitters, even if both groups had a marked amelioration of glucose control[33]. In these patients, insulin sensitivity improved till normal range, equally in diabetes remitters and non-remitters, supporting the hypothesis that worse diabetes outcome must be a consequence of poorer initial and lesser recovery of b-cell function[33]. The better or worse outcome of glucose tolerance is related to the initial degree of ß-cell dysfunction also in morbidly T2D submitted to RYGB[78]. The still impaired b-cell function,

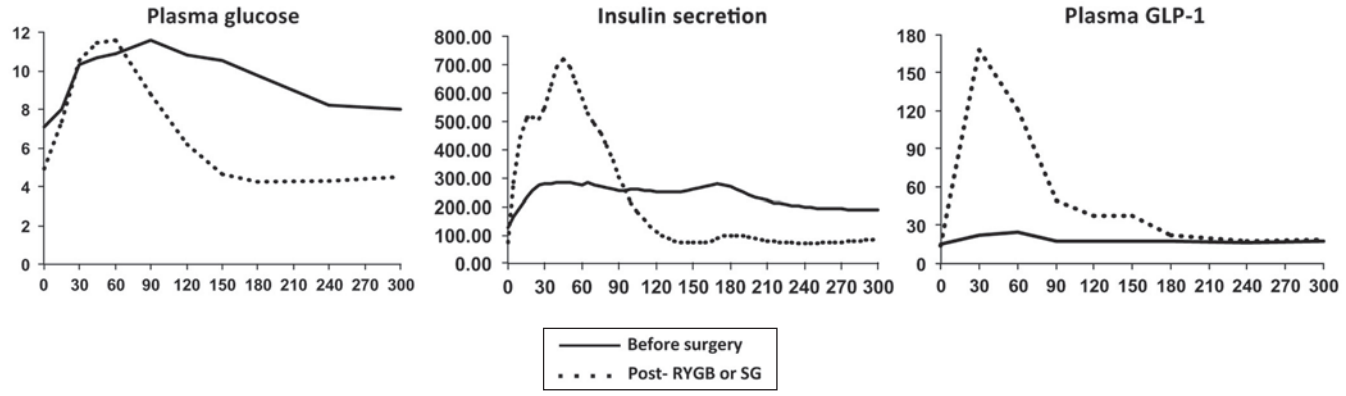

Figure 1.

especially the decreased glucose sensitivity, may therefore signal the possibility of diabetes relapse if the disease progress or if weight is regained worsening insulin sensitivity.

The amelioration of ß-cell dysfunction has many possible mechanisms: caloric restriction lowers glucose and insulin concentrations, the consequent removal of glucose toxicity may enhance glucose sensitivity; the drop of insulin resistance reliefs the workload of b-cells; and increased action of entero-insular axis on b-cells.

Oral glucose stimulates insulin release above intravenous glucose infusion even when plasma glucose levels are the same. This difference of insulin secretion, termed *incretin effect*, is mainly mediated by the gastrointestinal hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The incretin effect is blunted in diabetic patients[79,80]. The gastrointestinal L cells and K cells in contact with ingested nutrients release GLP-1 and GIP, thus potentiating secretion after glucose ingestion. Among other effects, GLP-1 inhibits while GIP stimulates glucagon release by pancreatic a-cells[81]. GLP-1 is decreased in many but not in all diabetic patients[82] and, its administration improves diabetes control through improved ß–cell function, decreased glucagon release and decreased HGP[83,84]. RYGB and SG, but not gastric band or diet, induces an equally and massive increase in GLP-1 concentration and an increased incretin effect, early as at 1month follow-up, that are maintained for years[59,71,73,78]. Interesting, the time course and shape of GLP-1 and GIP responses are similar to oral glucose appearance, plasma glucose and insulin curves[71], suggesting that the altered gastrointestinal transit over stimulates GLP-1 secretion. The meal-induced hyperglucagonemia[71,73] might, partially, be attributed to increased GIP levels, even if the causes remain undetermined. However, the effect of bariatric surgery is controversial, since increased, decreased or unchanged post-prandial glucagon and GIP levels were shown[58]. The relationship between GLP-1 increment and insulin secretion improving diabetes control after bariatric surgery as a weight-independent mechanism is far from to reach a consensus. If the putative weight-independent effects of bypass surgeries on glycemic control are important after weight stabilization are still unanswered.

Adiponectin and inflammatory markers

Adiponectin, a hormone secreted by adipose tissue, paradoxically reduced in obesity and in diabetes, is directly related with insulin sensitivity and indirectly to HGP. Weight loss, mainly the large reduction after bariatric surgeries increases adiponectin potentially impacting on insulin sensitivity and decreasing hepatic steatosis[13,59]. The changes of and the role of leptin and resistin post bariatric surgeries even if intensely studied are still controversial[13,59], and will not be reviewed here.

Obesity and T2D are low-grade inflammatory diseases. Many inflammatory molecules are released by the adipose tissue and they can contribute to diabetes development by impacting on insulin action or insulin secretion. Weight loss is associated to an important decrease of these inflammatory markers[85]. The extent of their influence improving IR and insulin secretion after bariatric surgeries still warrants more investigation.

Intestinal microbiota

Another area of intense research is intestinal microbiota and its influence on nutrient absorption, energy extraction and expenditure and inflammation. In animal models of obesity and in obese humans there is, among other microbiota modifications, a shift towards more *Firmicutes* and reduced *Bacteriodetes* (the 2 major bacteria phyla of gut microbiota) [13]. Alterations in the composition and capacity of gut microbiota potentially contribute to obesity and insulin resistance, lead to systemic inflammation and to non-alcoholic fatty liver disease development[86]. Furthermore, dietary interventions and gastric bypasses modify the microbiota pattern. Particularly the microbe *Faecalibacteriumprausnitzii*, less abundant in diabetics and obese persons and inversely related to inflammatory markers, increases after gastric bypass[86-88]. If modifications of gut microbiota are maintained at long-term, the cause-effect relationship with obesity, weight loss, inflammation, and insulin action are not well understood.

Summary: a) RYGB, BPD, SG and ileal interposition improve ß–cell function, doubles the b-cell glucose sensitivity, without reach normal values. b) Insulin secretion time course is synchronous to the accelerated glucose absorption and a massive GLP-1 release. c) There is a paradoxical increase of meal-induced hyperglucagonemia in some studies on diabetic patients. d) Relief of inflammation and intestinal microbiota modification are promising but deserves more investigation. e) Diabetes and ß–cell function improvements seem to be less marked in less obese patients. f) More importantly, the extent of previous ß–cell dysfunction is predictive of diabetes remission both in obese and in non-obese patients.

COMPLICATIONS OF BARIATRIC SURGERIES

Even if bariatric interventions are associated with low rates of complications and good outcomes, the risk-benefit should be weighted. Perioperative complications were more frequent after RYGB than AGB, even if the mortality of both techniques is lower than 0.3%[39]. As bariatric techniques have changed a lot in the last decade, Chang and cols[42] performed a meta-analysis with more up-to-date data, starting at 2003 till 2012, counting about 160 000 patients from randomized clinical trial (RCT) and observational studies. The performed surgeries were grouped as those including bypasses (RYGB and BPD), AGB, vertical banded gastroplasty and sleeve gastrectomy. They reported low rates of overall perioperative (<30 days) mortality of 0.08 in randomized clinical trials and 0.22 in observational studies and, postoperative mortality (>30 days) of 0.31 and 0.35 respectively [42]. Complications like bleeding, stomal stenosis, leak, vomiting, reflux and nutritional or electrolyte abnormalities were higher for Gastric Bypasses than gastric banding (21 vs. 13 in RCT and 12 vs. 78% in observational studies), while reoperations were more frequent for adjustable gastric band (3 vs. 12; and 5 vs. 7%)[42]. The nutritional deficiencies are very frequent after

bypasses, in particular after BPD, requiring a lifelong vitamins and trace elements supplementation. Furthermore, the reported low complications usually are from academic institutions and may be lower than observed in general clinical settings; the work of the surgical and clinical team and the surgeon expertise are very relevant for the intervention success. Really, greater surgical skill of the bariatric surgeon is associated with fewer rates of postoperative complications[89].

In conclusion, bariatric surgeries induce high rates of short and long-term diabetes remission or improvement, diverse according to the surgical intervention and with low frequency of complications. Rates of diabetes relapse are not well known, but the time free-of-disease should ameliorate diabetes complications and mortality. The mechanisms are still not completely understood; encompass many effects like improved or normalized insulin action, better b-cell function, lower inflammation and complex changes of gastrointestinal hormones. Efforts to understand these mechanisms may boost the development of new clinical approaches for T2D and may allow optimization of the "metabolic surgeries".

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