

METABOLIC SURGERY, WEIGHT REGAIN AND DIABETES RE-EMERGENCE*Cirurgia metabólica, ganho de peso e recidiva do diabetes*Josemberg M. CAMPOS¹, Daniel C. LINS^{1,2}, Lyz B. SILVA¹,
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ABSTRACT – Introduction: The poor success of clinical treatment of Type 2 Diabetes Mellitus (T2DM2) increased interest in metabolic surgery, which has been considered a promising alternative for the control of obese or non-obese diabetics. However, there is still no long-term follow-up to evaluate the duration of diabetes remission, and if weight regain would be associated to recurrence. **Aim:** 1) To describe the results of diabetic patients with a BMI < 30 and < 35 kg/m² submitted to the following types of metabolic surgery: ileal interposition and sleeve gastrectomy, Roux-en-Y gastric bypass (RYGB), adjustable gastric banding, duodeno-jejunal exclusion and duodeno-jejunal bypass; 2) to evaluate the possible relapse of diabetes after occurrence of weight regain on long-term after bariatric surgery. **Method:** An expositive and historical literature review about metabolic surgery in diabetic patients with BMI < 30 and < 35 kg/m² was conducted, and systematic review of the association between disease relapse and weight regain after bariatric surgery. **Results:** After analysis of 188 published papers on Medline until 2010, three papers were selected, which included 269 patients who underwent RYGB. Pre-operative BMI was between 37 and 60 kg/m² and follow-up of three to 16 years. **Conclusions:** 1) Two studies showed association between weight regain and recurrence of type 2 diabetes, while the third did not show this association when comparing groups with and without weight regain; 2) metabolic surgery has shown adequate control of T2DM2 in class I obese subjects; however, the non-obese group still need a long-term evaluation, considering the risk of diabetes recurrence when after weight regain.

HEADINGS - Bariatric surgery. Diabetes Mellitus. Recurrence. Weight regain.

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DESCRIPTORES - Cirurgia bariátrica. Diabetes melito. Recidiva. Ganho de peso.

RESUMO – Introdução: O insucesso do tratamento clínico do diabetes melito tipo 2 (DM2) aumentou o interesse em cirurgia metabólica, sendo considerada alternativa promissora no controle de diabéticos com ou sem obesidade. Todavia, ainda não há seguimento em longo prazo para se avaliar a duração da remissão da doença, cuja recidiva pode estar associada ao ganho de peso. **Objetivos:** 1) Descrever os resultados de pacientes com DM2 e IMC <30 e <35 kg/m², submetidos aos seguintes tipos de operações metabólicas: interposição ileal e gastrectomia vertical, derivação gástrica em Y-de-Roux (DGYR), banda gástrica ajustável, exclusão duodeno-jejunal e bypass duodenojejunal; 2) avaliar a possível ocorrência de recidiva do diabetes após ganho de peso em longo prazo. **Método:** Foi realizada revisão expositiva e histórica da literatura sobre cirurgia metabólica em pacientes com DM2 e IMC <30 e <35 kg/m², e revisão sistemática sobre a associação entre recidiva da doença e ganho de peso após cirurgia bariátrica. **Resultado:** Após análise de 188 artigos publicados no Medline até 2010, foram selecionados três estudos, com 269 pacientes submetidos à DGYR, com IMC pré-operatório entre 37 e 60 kg/m² e com seguimento de três a 16 anos. **Conclusões:** 1) Dois estudos mostraram que o ganho de peso está associado à recidiva do diabetes, enquanto o terceiro não confirma este fato, na comparação entre o grupo com e sem ganho; 2) a cirurgia metabólica vem apresentando adequado controle do diabetes em obesos grau I; todavia, o grupo não obeso ainda aguarda avaliação em longo prazo, considerando o risco de recidiva associado ao ganho de peso.

INTRODUCTION

There is a projection that the number of individuals with diagnosed diabetes will increase by 198%.¹⁴ The disease can lead to several chronic complications, and is poorly controlled with clinical treatment alone. The adequate glycemic control obtained after bariatric surgery has increased interest in developing new techniques; there is also the possibility

of performing the procedure in patients who would not meet the traditional inclusion criteria.^{12, 15, 17} The surgery has been proposed as an option for patients with class I obesity and non-obese patients with poorly controlled type 2 diabetes mellitus (T2DM).

Approximately 84% of diabetic patients experience complete remission of diabetes after undergoing Roux-en-Y gastric bypass (RYGB), often before significant weight reduction. There are several theories that try to explain the mechanisms of how surgery affects the disease and leads to its remission, these theories will be explored further on this article.

Although there is a lot of published data regarding remission of T2DM after bariatric surgery, very limited information is available regarding long-term effects, recurrence or worsening of the disease after a certain period and what would be the factors associated with this diabetes re-emergence.

This study presents a literature review on how metabolic surgery affects control of diabetes in patients with a body mass index (BMI) less than 35 kg/m², discussing the possibility of expanding the surgical indications, focusing on the lack of information on long-term effects of surgery on these patients and what happens when there is weight regain. It also presents a systematic review about the possible recurrence of T2DM associated with weight regain after bariatric surgery on long-term follow-up, independent of preoperative BMI.

METHODS

An expository and historical literature review on surgery and metabolic control of diabetes in patients with BMI less than 30-35 kg/m² was conducted. Aiming to perform a systematic review of the literature on recurrence of T2DM and weight regain simple search on Pubmed/Medline using the following search strategy was held: "bariatric surgery" or "gastric bypass" and "diabetes" and "follow-up studies", limited to studies in humans, and published until 2011. The aim was to include articles that reported and analyzed rates of recurrence and worsening diabetic who had achieved remission after bariatric surgery on long-term follow-up, independent of preoperative BMI. The search yielded 188 studies, and after reading the titles and abstracts, 182 were excluded. The remaining six had their full texts searched, with four of them being excluded after full reading for not reporting recurrence or worsening of diabetes. The two articles included will be analyzed in this study (Figure 1). Was also included data from a study of the institutions involved (Department of General Surgery - UFPE), not yet published, which was made comparing the remission of diabetes among a group who maintained weight loss and another that regained the lost weight.

Surgical mechanisms for the resolution of T2DM

The postoperative control of diabetes is a direct consequence of the rearrangement in gastrointestinal

anatomy, and not merely the reduction in caloric intake and weight. Some theories have been created to explain the mechanisms behind diabetes remission after bariatric surgery.

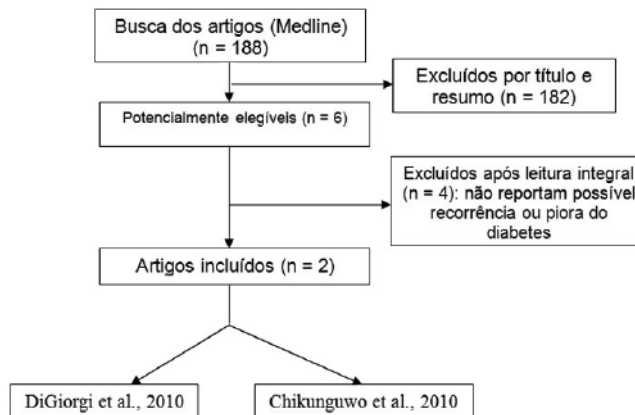


FIGURE 1 - Flowchart of database search and selection process of studies on weight regain and diabetes re-emergence

Hypothesis of minimum food intake and weight loss

Some theories have been created to explain the mechanism underlying diabetes remission after bariatric surgery. The starvation-followed-by-weight-loss hypothesis considers that the glycemic control improves shortly after surgery simply because the patients are not permitted to eat much in the postoperative period, and by the time they start eating regularly again, the insulin-sensitizing effects of dynamic weight loss are acting. There is an extremely rapid postoperative T2DM remission - before substantial weight loss - and if caloric restriction would be the main factor to rapid diabetes remission, it would occur after all bariatric procedures, which is not true. This hypothesis fails to explain the superiority of glycemic control achieved after RYGB vs. equivalent weight loss from dieting or restrictive bariatric operations^{13, 20-21}.

Hindgut hypothesis

The hindgut hypothesis suggests that faster arrival of digested foods to the end of the gastrointestinal tract improves the metabolism of carbohydrates through an increase in the secretion of the glucagon-like peptide 1 and other anorexigenic peptides. This theory is based on experiments such as ileal interposition, which consists of the transposition of a segment of distal ileum to the jejunum with no gastric or intestinal resection. In rats, interposition has been found to lead to an increase in the secretion of glucagon-like peptide 1 and peptide YY, consequently improving glycemic control⁴.

Foregut hypothesis

The foregut hypothesis suggests that food diverted from the duodenum and proximal jejunum avoids the secretion of as-yet-undefined substances that promote insulin resistance and T2DM. Rubino et al. submitted Goto-

kakizaki rats to duodenojejunal diversion and gastrojejunal anastomosis. The latter technique diverts the same portion of the intestine as duodenojejunal diversion, but allows the passage of food in the proximal intestine. The rats submitted to it achieved an improvement in glucose tolerance, whereas those submitted to gastrojejunostomy demonstrated no improvement in the glycemia profile¹⁹. Multiple mechanisms contribute to T2DM remission following intestinal bypass. The fast arrival of nutrients to the distal intestine intensifies the secretion of glucagon-like peptide 1 and peptide YY, while the exclusion of the duodenum exerts other anti-diabetes effects¹⁸.

Metabolic surgery and BMI <35 kg/m²

The effectiveness of metabolic surgery to lead to improvement and even remission of T2DM through mechanisms that go beyond weight loss raised the question of how non-obese diabetic respond to surgical treatment. The first study proving the anti-diabetic gastrointestinal bypass was performed by Rubino et al., involving non-obese diabetic Goto-Kakizaki rats who underwent duodenojejunal junction and achieved improvement in glucose tolerance.²⁰

Based on the hindgut theory, De Paula et al. performed a combination of ileal interposition and sleeve gastrectomy in the treatment of diabetic patients with BMI<35 kg/m². There was discontinuation on the use of oral anti-diabetes medications and insulin in 87% of the individuals in the postoperative period. However, the long-term effectiveness and safety of the technique remains unknown⁷.

In 2006, Cohen et al. published a case series involving 37 non-morbidly obese diabetic patients with severe comorbidities submitted to laparoscopic RYGB and followed up to 48 months. The remission of all comorbidities occurred in 36 patients and mean excess weight loss was 81%. Only one patient with T2DM, severe arterial hypertension and dyslipidemia maintained mild hypertension in the postoperative period, which was controlled with a single drug. Gastric bypass apparently unites both supposed mechanisms of glycemia control (hindgut and foregut) in the same surgery.

In another study involving a small sample of diabetic patients with a BMI between 30-35 kg/m², treatment with adjustable gastric banding was statistically more effective in the remission of T2DM than clinical treatment. The patients in the adjustable gastric banding group lost more weight and achieved 73% normalization of glycemia, compared to 13% with clinical treatment, in two years of follow-up⁹.

De Sa et al. analyzed 27 patients submitted to RYGB for the treatment of uncontrolled T2DM, with a mean follow-up period of 20 months. In the postoperative follow-up, there was a 23% reduction in mean weight and BMI. The loss of excess weight was 94.5%, and the lowest BMI reached was 20.3 kg/m². Twenty patients (74%) stopped use of all anti-diabetes medications. Thirteen patients (48%) achieved remission of T2DM and 20 (74%) achieved glycemic control without medication. All patients exhibited improvement in glycemia levels when compared to the

preoperative period. The type of medication used in the preoperative period or previous weight did not affect diabetes remission and glycemic control⁵.

Choi et al. compared 66 patients with a BMI of 30-35 kg/m² and comorbidities or with a BMI of 35-40 kg/m² without comorbidities with 438 standard patients who had undergone laparoscopic adjustable gastric banding. The results showed that the short-term weight loss, complications and resolution of comorbidities in both populations were similar, showing that adjustable gastric banding was safe and effective for patients with lower BMIs².

A literature review analyzed 16 studies involving a total of 343 diabetic patients with BMI≤35 kg/m² undergoing some type of bariatric surgery in order to treat T2DM. Of the 343 subjects, 85.3% were able to maintain fasting glucose levels close to normal and glycated hemoglobin normal without medications. The BMI reduction and resolution of T2DM were more pronounced in disabsorptive/restrictive procedures, and in patients with a BMI of 30-35 kg/m², when compared to BMI<30 kg/m². There was a low complication rate, and mortality (0.29%). Most patients with low BMI achieved clinical and laboratory resolution of T2DM without inadequate weight loss. However, meta-analysis was not possible to be done, due to the limited number of individuals and study involved and the lack of uniformity of reported data¹⁰.

Metabolic surgery and BMI≤30 kg/m²

In humans, Cohen et al. demonstrated that duodenojejunal diversion normalized glycemia in two overweight patients in the early postoperative follow-up period³. Geloneze et al. selected 12 patients to undergo open duodenaljejunal exclusion surgery, and compare them with a matched control group on standard medical care. All patients were overweight (with a BMI ranging from 25 to 29.9 kg/m²), insulin-treated diabetics. The follow-up period was 24 weeks, and at that point two out of the 12 in the surgery group were on target levels of HbA1c, meanwhile none in the control group. After the 24 weeks, two of the 12 patients remained on insulin therapy, while all the patients in the control group still required insulin. Some improvement in the control group was observed, due to optimization of medical therapy¹¹.

Ramos et al. used the duodenojejunal diversion mechanism in diabetic patients with BMI<30 kg/m² and demonstrated T2DM resolution in 90% of the 20 patients. In the preoperative period, the patients had a mean BMI of 27 kg/m² and maximum duration of T2DM of eight years. Fasting glycemia and glycated hemoglobin were 171 mg/dl and 8.8%, respectively, and decreased to 96.3 mg/dl and 6.8% six months after surgery. The patients presented a 25% increase in the C-peptide following the operation¹⁶.

A group of 69 diabetic non-obese patients were submitted to a laparoscopic ileal interposition associated to a diverted sleeve gastrectomy and followed-up by De Paula et al. Mean preoperative BMI was 25.7±1.9 kg/m² (range 21.8–29.2 kg/m²), 56.5% of patients used only oral

hypoglycemic agents, 7.5% were using only insulin, and 36% were receiving both. Five patients (7.3%) experienced major early complications, and there was no mortality. The mean follow-up period was 21.7 months, after which 95.7% of patients achieved adequate glycemic control without antidiabetic medications, mean HbA1c decreased from 8.7+-2.1% to 5.9+-0.9%. Remission was more frequent among patients with less than five years of T2DM, and for those on oral agents preoperatively. It is important to notice that glucose control was not related to the amount of weight loss. Mean postoperative BMI was 21.8+-4.1 kg/m², 12 patients (17.4%) became underweight, and serum albumin was normal in all patients, with no malnutrition detected (Table 1)⁶.

TABLE 1 - Studies involving patients with a BMI ≤ 30 kg/m²

Author / Year	n	Procedure	Follow-up (months)	Pre-op BMI (mean ± SD)	Diabetes remission	Post-op BMI (mean ± SD)
Cohen 2006 ²⁵	2	DJE	9	30.3 ; 29	100%	27 ; 29.5
Geloneze 2009 ²⁶	12 (surgery)	DJE	6	26.1	16.7% (target HbA1c)	25.6
	12 (control)			26.3	0%	24.2
Ramos 2009 ²⁷	20	DJE	6	27.1	90% (no medications)	24.4
DePaula 2009 ²⁸	69	II + LSG	21.7	25.7 ± 1.9	65.2% (remission); 30.5% (control)	21.8 ± 4.1

BMI=body mass index; DJE=duodenaljejunal exclusion; II=ileal interposition; LSG=laparoscopic sleeve gastrectomy

Systematic Review

Long term follow-up, weight regain and diabetes re-emergence

Much has been published regarding non-morbidly obese and even non-obese diabetic patients undergoing surgical treatment for diabetes, but the data on long-term follow-up is still very limited, leaving unanswered questions on whether surgery really resolves diabetes or if the disease will re-emerge after a given period of time. To our knowledge, only two articles have been published specifically reporting long-term follow-up data, rates of re-emergence of diabetes, or analysis of the possible factors associated with durable remission.

Was performed a simple search on Pubmed/Medline using the following search strategy: (“bariatric surgery” OR “gastric bypass”) AND “diabetes” AND “follow-up studies”, with the limits “humans” and

“English”. The goal was to include articles that reported and analyzed long term follow-up recurrence and worsening rates on diabetic patients that had achieved remission after bariatric surgery. The search resulted in 148 articles and after reading titles and abstracts, 142 of them were excluded. The remaining six had their full texts assessed, with four being excluded because they did not report recurrence or worsening rates of diabetes. The two included articles are analyzed further on this paper (Figure 1).

Di Giorgi et al. performed a retrospective analysis on 42 post-RYGB patients for a period of over three years, assessing weight loss and T2DM status. Within the first six months of the surgery, all patients had improvement in T2DM, with 64% achieving complete resolution. The preoperative average BMI of the group was 51.4 kg/m², 64% requiring oral medications and 34% insulin. Failure was in 22% of patients not achieving adequate weight loss, and the entire group regained an average of 21% of their lost weight. Of the patients with initial T2DM resolution after surgery, 26% experienced recurrence. Of the patients with initial improvement of their T2DM after RYGB, 20% worsened over time. Those with recurrence or worsening of diabetes had a lower preoperative BMI compared to the ones where diabetes remained resolved or improved (47.9 versus 52.5 kg/m²). The preoperative BMI of patients who required insulin was lower than that of patients who did not require insulin to manage their diabetes⁸.

Chikunguwo et al. retrospectively studied 177 patients with T2DM who had undergone RYGB from 1993 to 2003. Of these, 30 were men (17%) and 147 women (83%). The follow-up length ranged from 5–16 years, with a mean of 8.6 years. Of the 177 patients, 157 (88.7%) had complete remission of their T2DM at some point in their postoperative course. The difference in the percentage of excess weight loss between those who achieved remission and those who did not, was significant. Of the 157 patients with initial remission of their T2DM, 68 (43.3%) subsequently developed T2DM recurrence, this correlated with a regain of lost weight. The long-term durability of diabetes remission did not differ between the varying limb lengths. An interesting fact is that remission was more durable in men (80%) than in women (52.3%). The analysis showed that percentage of weight loss, gender, age and diabetes severity were independent predictors of T2DM recurrence. The strongest predictors were disease stage (oral control versus insulin control) and female gender (Table 2)¹.

TABLE 2 - Studies reporting long-term follow-up and analysis of diabetes recurrence

Author	n	Surgery	Follow-up	Pre-op BMI (mean ± SD)	Initial diabetes remission(%)	Weight regain (%)	Recurrence of diabetes after follow-up (%)	Adequate glycemic control after follow-up (%)
DiGiorgi	42	RYGB	≥ 3 years	51,4 ± 8,7	64%	21% of lost weight was regained	26%	-
Chikunguwo	177		5 – 16 years	50,2 ± 8,1	88,7%	-	43,3%	-
Araujo	15				51,2 ± 6,4		100%	-
	35 (control)		64,8 months	42,8 ± 5,4		0%	-	86,7%

In the first study described, by Di Giorgi et al., lower BMI was considered to be a predictor of diabetes re-emergence. This reinforces the fact that patients who develop diabetes at a lower BMI have a more complicated form of the disease, thus are more susceptible to re-emergence of the disease. If this assumption is true, surgical treatment of diabetes in patients with lower BMIs might be less successful than for those who developed diabetes at a greater BMI⁸.

Both studies found that weight regain was an important factor negatively affecting sustained diabetes remission. It is not clear though if diabetes re-emergence occurs because of the weight regain or because of the increased caloric intake with which it is usually associated. In the study by Chikunguwo et al. there were exceptions; some patients did not enjoy diabetes remission despite a great percentage of excess weight loss, while others achieved full remission with very low percentages of excess weight loss. Their results suggest that perhaps the early diabetes remission that is independent of weight loss is mediated through a different mechanism than the one that mediates long-term remission^{1,8}.

Also reported by both studies was the fact that patients who were preoperatively taking oral medications alone had a better rate and duration of remission than those who were on insulin, indicating that intervention of early diabetic disease would be more beneficial, and the need for insulin therapy might identify those patients in whom weight loss would be insufficient to compensate for the decreased insulin secretory capacity^{1,8}.

A group of 45 patients from our institution, all diabetic and obese, were submitted to RYGB. The patients were analyzed retrospectively and prospectively. All patients lost weight and reached a BMI under 35, but at a certain point in the follow-up period, some of them had regained weight. The group was thus divided in a control group which included patients who maintained weight loss (30 patients) and a group with those who regained weight (15 patients). Glycemic control was analyzed in both groups and there was no significant difference on fasting glucose, oral glucose tolerance test, glycated hemoglobin and diabetes resolution. Complete remission of diabetes was achieved in 73.3% of weight regain patients and in 80% of control patients (p>0.05). The study concluded that weight regain does not significantly influence the resolution of diabetes after RYGB on a mean follow-up of 64.8 months, patients with or without weight regain had a similar diabetes recurrence rate. However, in order for its results to be generalizable, the number of patients involved should be increased and follow-up period should be longer (Table 3).

TABLE 3 - Mean and standard deviation (SD) of age, BMI, follow-up, evaluation of glycated hemoglobin, controlled glycemia, remission of diabetes

Variable	Evaluation time and differences	Group	
		Weight regain (n=15)	Control (n=30)
Age		45,47 ± 12.34	44.77 ± 11,80
BMI (kg/m ²)	Pre	51.18 ± 6.39	42.86 ± 5.36
	Post 1	32.52 ± 1,62	25.30 ± 2,49
	Post 2	39.33 ± 5.49	26.90 ± 2,20
Follow-up	Post 1	17.60 ± 5.77	21.10 ± 10.99
	Post 2	64.80 ± 22.59	48.80 ± 13.35
Controlled HbA1c		n (%)	n (%)
	Post 2	12 (80.0)	26 (86.7)
Controlled glycemia	Pre	4 (26.7)	10 (33.3)
	Post 1	13 (86.7)	28 (93.3)
	Post 2	13 (86.7)	26 (86.7)
Complete remission of T2DM	Post 2	11 (73.3)	24 (80.0)
Complete + Partial Remission of T2DM	Post 2	11 (73.3)	25 (83.3)

T2DM=type 2 diabetes mellitus. Pre = Preoperative. Post = Postoperative

A limitation of the studies was that they fail to report on whether all patients were correctly diagnosed with T2DM. There is a chance that some of these patients, especially the lower BMI ones, were misdiagnosed when they actually had type 1 diabetes mellitus. These patients would have a worst response to metabolic surgery, with bias on the results. Also, it is not certain if patients involved in different researches were on a similar stage of disease. The lack of homogeneity in the papers and among studies, generates difficulties on analyzing and comparing results.

CONCLUSION

BMI alone is not an ideal parameter for defining the indication of surgery for diabetic patients. There isn't no scientific evidence of a BMI cutoff point for selecting the group that will benefit from the surgical procedure. Metabolic surgery performed on patients with BMI<30kg/m², targeting the treatment of diabetes, has been shown to be safe and effective method in short term analysis. As shown in this review, there is insufficient published data on long term follow-up, even in obese patients, and there is still controversy on the factors that could be associated with durable remission of the disease. Due to this lack of information, future studies and discussions of the subject are needed to determine the true position of this procedure as treatment for non-obese diabetic people.

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