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ORIGINAL CONTRIBUTIONS

Predictors of Long-Term Remission and Relapse of Type 2 Diabetes Mellitus Following Gastric Bypass in Severely Obese Patients

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Abstract
Background Diabetes remission is not observed in all obese patients with type 2 diabetes submitted to bariatric surgery. Relapses occur in patients in whom remission is achieved. We investigated the factors associated with long-term (≥3 years) remission and relapse of type 2 diabetes after Roux-en-Y gastric bypass (RYGB) in these patients.
Methods By a retrospective review, we analyzed data from 254 patients with type 2 diabetes who had undergone RYGB from May 2000 to November 2011 and had at least 3 years of follow-up. The criteria for remission and relapse of type 2 diabetes followed the current American Diabetes Association recommendations.
Results Remission was achieved in almost 82% of participants (69.7% complete, and 12.2% partial remission). Of these, 12% relapsed within a mean follow-up of 5.1 ± 2.0 years after surgery. Predictors of complete remission were younger age, better preoperative glycemic control, and shorter diabetes duration. Preoperative insulin use was associated with a ninefold increase in the relapse hazard (HR = 9.1 (95% CI: 3.3–25.4)). Use of two or more oral anti-diabetic agents increased the relapse hazard sixfold (HR = 6.1 (95% CI: 1.8–20.6)). Eighteen point one percent of patients did not achieve any remission during follow-up. However, they exhibited significant improvements in glycemic control.
Conclusions These data indicate that RYGB should not be delayed when remission of type 2 diabetes is a therapeutic goal, and also suggest that the best possible metabolic control should be sought in obese patients who may eventually be candidates for RYGB.

Keywords Diabetes · Bypass · Bariatric surgery · Remission · Relapse

Introduction

Some 8.8% of the adult population worldwide has diabetes mellitus [1]. Part of this prevalence is attributable

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to the increasing frequency of obesity [2]. Therefore, managing obesity is now part of type 2 diabetes guidelines. The American Diabetes Association (ADA) recommends considering bariatric surgery for adults with type 2 diabetes and a body mass index (BMI) >35 kg/m^2, especially if diabetes and associated comorbidities are difficult to control with pharmacological therapy and lifestyle changes. A reasonable A1C goal for many nonpregnant adults with type 2 diabetes is <7% (53 mmol/mol) [3, 4]. In severely obese patients with type 2 diabetes, bariatric surgery has been associated with better glycemic control when compared to medication therapy [5, 6]. It was found to be cost-effective [7, 8], and superior to lifestyle intervention alone for remission of type 2 diabetes [9]. In the Swedish Obese Subjects (SOS) study, bariatric surgery was associated with more frequent diabetes remission and fewer microvascular and macrovascular diabetes complications than usual care [10]. Many specialists consider Roux-en-Y gastric bypass (RYGB) to be a good option for bariatric surgery in patients with type 2 diabetes; this procedure yields satisfactory postoperative results with a low incidence of complications [11, 12].

In 2009, a consensus was reached with regard to defining the criteria for remission, both partial and complete [13]. Partial remission of type 2 diabetes was defined as a glycated hemoglobin (HbA_{1c}) <6.5% (48 mmol/mol) and fasting blood glucose (FBG) levels of 100–125 mg/dl (5.6–6.9 mmol/L) for a minimum of 1 year, without pharmacological treatment. Complete remission was defined as a return to "normal" glycemic levels (HbA_{1c} within normal limits and FBG <100 mg/dl (<5.6 mmol/L)) for a minimum of 1 year without the use of anti-diabetes medication.

Unfortunately, not all patients with type 2 diabetes achieve disease remission after bariatric surgery, and some experience relapse. Studies of factors related to remission/relapse are limited by circumstances such as small number of participants, short observation period, and limited available laboratory data [14–20]. Several studies have evaluated type 2 diabetes remission, but not the factors leading to relapse [21–24]. Moreover, many studies use different criteria for type 2 diabetes remission/relapse [14, 25–28], which might result in falsely elevated incidence rates [29]. To our knowledge, only two studies addressed remission and relapse of type 2 diabetes after bariatric surgery with the 2009 consensus criteria [30, 31].

With the relative lack of information in mind, we have investigated the factors predictive of remission and relapse of type 2 diabetes after RYGB after a minimum follow-up of 3 years, employing the latest standards for reporting bariatric studies.

Material and Methods

This retrospective cohort study included patients with obesity, previously diagnosed with type 2 diabetes, submitted to RYGB at Hospital São Lucas (HSL), Pontifical Catholic University, Rio Grande do Sul (PUCRS), Brazil, between 2000 and 2011, with a minimum 3-year follow-up since surgery. Exclusion criteria were conditions that could influence the course of diabetes (treatment with glucocorticoids, pregnancy), or other bariatric procedure besides RYGB. Three hundred and forty-five patients were operated during this period. Ninety-one subjects had incomplete data and/or less than 3 years of follow-up, thus not meeting inclusion criteria.

This study was approved by the Ethics Committees of both HSL and Hospital de Clínicas de Porto Alegre.

Preoperative data included age, sex, height (m), weight (kg), BMI (kg/m^2), excess weight (EW) (Kg), duration of diabetes (years), use of oral agents and/or insulin, blood pressure, waist circumference (cm), cholesterol (total and HDL), triglycerides, FBG (mg/dl), and HbA_{1c} (% (mmol/mol)). Preoperative measurements were obtained within one day before surgery. Dyslipidemia was diagnosed if patient reported the use of lipid-lowering agents or laboratory results were compatible (American Heart Association criteria [32]). Criteria for hypertension included anti-hypertensive medication use and measurements collected during preoperative medical consultations (Eighth Joint National Committee [33]). Known duration of type 2 diabetes mellitus was reported by the patient or the first physician to record the diagnosis; the preoperative diagnosis of diabetes followed the criteria of the American Diabetes Association [34].

The following postoperative parameters were monitored annually: FBG, HbA_{1c}, percentage of EW lost (%EWL), and current medications. EW was calculated by subtracting the weight corresponding to body mass index of 25 kg/m^2 (height squared (m^2) × 25) from the preoperative weight. %EWL was calculated as current weight × 100/EW [35]. Remission and relapse of type 2 diabetes followed the current consensus of the American Diabetes Association [13, 34].

Statistical Analysis

Results are presented as mean ± SD (for normally distributed variables) or medians and interquartile ranges. Categorical variables are expressed as frequencies (%). Hazard ratios (HRs; Cox proportional hazards) and respective 95% confidence intervals (CIs) were calculated (Cox regression method). Univariate analysis was performed with sex, and preoperative data of age, diabetes pharmacotherapy, insulin use, dyslipidemia, hypertension, diabetes duration, weight, BMI, EW, waist circumference, FBG, and HbA_{1c}. Factors significantly associated with remission and relapse in the univariate analysis ($p < 0.05$) were included in a multivariate analysis

model, and backward elimination of variables was used to determine the individual contribution of independent factors in predicting remission and relapse. Subjects were censored in the occurrence of death, loss of follow-up, or end of the study period (January 1, 2015). A 5% level of significance was adopted. Outcomes were compared among the factor categories using the log-rank test. Survival curves were created using Kaplan–Meier analysis. Statistical (SPSS, version 18.0; IBM, Armonk, NY, USA) and electronic spreadsheet software (Excel 2010; Microsoft, Redmond, WA, USA) were employed.

Results

Two-hundred and fifty-four patients met our study criteria. All of them had a minimum 3 years of follow-up and 50.7% had ≥5 years of follow-up. Preoperative characteristics of subjects are shown in Table 1. Figure 1 shows the flow of the study. The majority of patients were female (75.6%). The average patient age was 45.1 ± 10.1 years, and the average preoperative BMI was 47.6 ± 9.1 kg/m^2. Preoperatively, 58.3% of the patients had dyslipidemia, and 86.6% had arterial hypertension. The mean HbA_{1c} (%) and fasting glucose (mg/dl) before surgery were 7.8 ± 2.0 and 160.5 ± 62.3, respectively. A third of patients (33.3%) were on metformin monotherapy, and 20.5% were on insulin, preoperatively. The mean postoperative follow-up was 5.1 ± 2.0 years (range 3 to 13 years). The evolution of postoperative %EWL is presented in Fig. 2a. The %EWL values in the first and third postoperative years were 72.7 ± 20.9 and 71.2 ± 22.1%, respectively. Figure 2b shows total weight loss (kg) during follow-up. Total weight loss in the first and third postoperative years was 41.0 ± 14.4 and 41.2 ± 18.6 kg, respectively.

During follow-up, 177 subjects (69.7%; 95% CI: 63.8–73.0) achieved complete remission, and 31 (12.2%; 95% CI: 8.2–16.8), partial remission. Overall, 208 patients (81.9%; CI: 76.7–86.1) achieved some degree of remission. Of these, 25 (12.0%; 95% CI: 8.3–17.1) experienced a recurrence of type 2 diabetes (12 after partial remission and 13 after complete remission). Forty-six patients (18.1%; 95% CI: 13.9–23.3) did not meet the criteria for remission. However, these patients obtained a significantly improved glycemic control. Preoperatively, these patients had poorly controlled type 2 diabetes (HbA_{1c} = 9.5 ± 1.9% (80.3 mmol/mol), FBG = 196.8 ± 86.2 mg/dl (10.9 ± 4.7 mmol/L)) [3]. During the first year postsurgery, the mean HbA_{1c} was 6.9 ± 0.8% (51.9 mmol/mol) and FBG was 114.0 ± 36.8 mg/dl (6.3 ± 2.0 mmol/L). Twenty-eight (60.9%; 95% CI: 46.5–73.6) of these patients had used insulin prior to surgery, whereas only 8 (17.4%; 95% CI: 9.1–30.7) required insulin postoperatively. Prior to surgery, only 4 subjects (8.7%; 95% CI: 3.4–20.3) had HbA_{1c} <7%, rising to 26 patients (56.5%; 95% CI: 42.2–69.8) during the first year after RYGB. Figure 2c shows the changes in HbA_{1c} during follow-up in the 254 patients.

Table 1 Baseline characteristic of patients (N = 254)

Characteristic	
Female, *n* (%)	192 (75.6)
Age at surgery (years), mean ± SD	45.1 ± 10.1
Weight (kg), mean ± SD	127.6 ± 27.2
BMI (kg/m^2), mean ± SD	47.6 ± 9.1
Excess weight (kg), mean ± SD	60.4 ± 24.6
Waist circumference (cm), mean ± SD	132.2 ± 17.3
HbA_{1c} (%), mean ± SD	7.8 ± 2.0
Fasting blood glucose (mg/dl), mean ± SD	160.5 ± 62.3
Dyslipidemia, *n* (%)	147 (58.3%)
Hypertension, *n* (%)	220 (86.6%)
Diabetes duration (years), median (IQR)	1.0 (0.1–6.0)
Diabetes pharmacotherapy, *n* (%)	
No medication	91 (36.1%)
Monotherapy with metformin	84 (33.3%)
Two oral anti-diabetic agents	25 (9.9%)
Insulin	52 (20.5%)

BMI body mass index, *HbA_{1c}* glycated hemoglobin, *SD* standard deviation, *IQR* interquartile range

Complete Remission

The rates of complete remission were 59.1% (95% CI: 53.0–65.2), 69.3% (95% CI: 63.6–75.0), and 72.4% (95% CI: 64.7–80.0) in the first, third, and sixth postoperative years, respectively (Fig. 3a). The average time to remission was 1.2 years. In multivariate analysis (Table 2), age < 45 years was associated with a 50% greater chance of complete remission. Patients with diabetes duration ≤5 years had a four times greater chance of complete remission than those with a diabetes duration >10 years. Patients with preoperative HbA_{1c} < 7% (53 mmol/mol) had a 2.4-fold greater chance of complete remission than those with HbA_{1c} levels >10% (86 mmol/mol).

Partial Remission

The average time to achieving partial remission was 1.5 years. In multivariate analysis, partial remission was more likely in patients with a diabetes duration ≤5 years (HR = 4.66 (95% CI: 1.34–16.27)) or 6–10 years (HR = 4.03 (95% CI: 1.11–14.60)) compared to those with duration >10 years. Patients with preoperative HbA_{1c} 7.0–8.5% (53–69 mmol/mol) or >8.5–

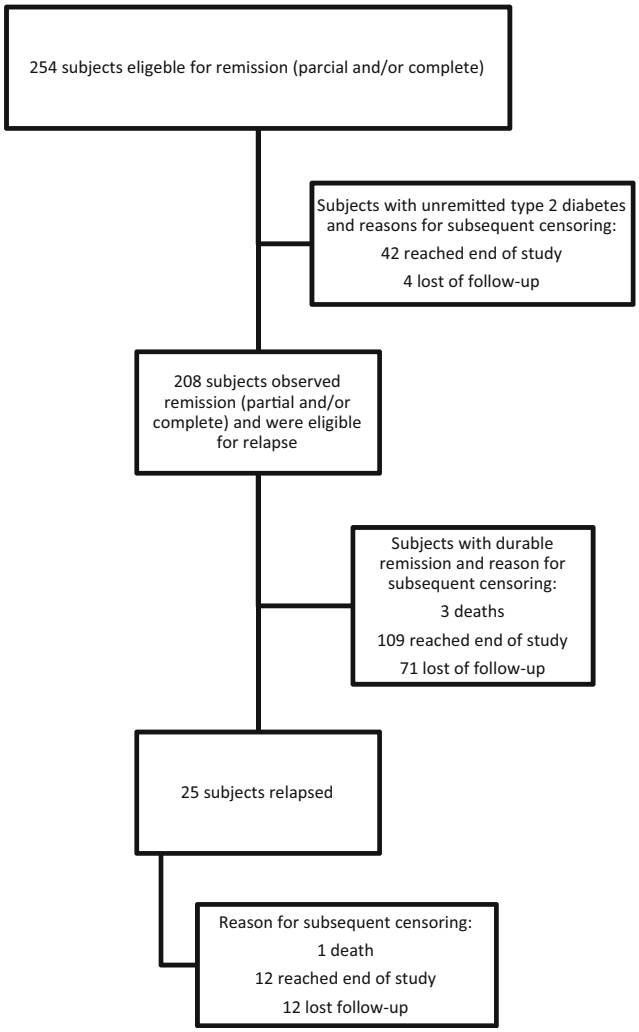


Fig. 1 Flow of subjects through study until outcome or censoring

10.0% (70–86 mmol/mol) had a greater likelihood of partial remission than those with HbA_{1c} levels >10.0% (86 mmol/mol) (HR = 4.7 (95% CI: 1.3–16.9) and HR = 3.8 (95% CI: 1.02–14.3), respectively) (Table 2).

Relapse

Among the 208 patients who achieved complete or partial remission, relapse of type 2 diabetes occurred in 25 (12% (95% CI: 8.3–17.1)), after a median time of 3.0 (1.0–11.0) years after remission. Of the patients who achieved complete remission, 7.3% experienced relapse. Relapse occurred in 38.7% of participants who achieved partial remission. Relapse rates in the third, sixth, and ninth postoperative years were 4.8% (95% CI: 1.8–7.7), 14.9% (95% CI: 7.8–21.9), and 32.9% (95% CI, 15.6–50.1) (Fig. 3b). In multivariate analysis, lower risk of relapse was related to not using anti-diabetic medication (other than metformin monotherapy) preoperatively (Table 2). Using reference categories such as "not using any medication for diabetes," the preoperative use of insulin increased the multivariate risk of relapse ninefold (HR = 9.1 (95% CI: 3.3–25.4); $p < 0.001$), and the use of two oral anti-diabetic drugs increased the risk of relapse sixfold (HR = 6.1 (95% CI: 1.8–20.6); $p = 0.004$). In other words, patients requiring treatment other than diet, exercise, and metformin, preoperatively, have a greater chance of relapse following remission after RYGB.

Discussion

This is one of the very few long-term studies to evaluate both remission and relapse of type 2 diabetes after RYGB in severely obese patients using the 2009 consensus [30, 31]. In our study, 81.9% of patients (95% CI: 76.7–86.1) achieved some degree of remission during the follow-up period. Predictors of remission were younger age, better glycemic control, and duration of diabetes prior to surgery. Of the patients in remission, 12.0% (95% CI: 8.3–17.1) experienced a recurrence of type 2 diabetes. Predictors of recurrence were preoperative uses of insulin, or any anti-diabetic agent other than metformin. Even the 18.1% (95% CI: 13.9–23.3%) of patients which did not achieve any remission experienced significant improvements in glycemia and reduced insulin requirements.

We observed a complete remission rate of 69.7%. This is similar to the rates reported by three other studies that used the new American Diabetes Association definitions of diabetes remission and relapse [15, 18, 30], and only apparently lower than the rates reported in previous studies using more liberal criteria [26, 27, 36]. A recent study of 5-year follow-up reported a complete remission rate of 37% at 5 years after Roux-en-Y gastric bypass [37]. This could be explained by differences in the baseline characteristics of the patients (diabetes duration of 6.0 ± 1.2 years vs 1.0 (0.1–6.0) years in our study, and HbA_{1c} 8.6 ± 1.4 vs 7.8 ± 2.0% in our study) [5, 37]. This stresses our finding that patients with diabetes duration ≤5 years and preoperative HbA_{1c} levels <7% (53 mmol/mol) have greater chance of complete remission.

Our results, like those of recent studies [30, 31, 36], demonstrate the importance of adequate patient counseling with regard to expectations related to a permanent remission of type 2 diabetes, and proper guidance toward realistic objectives. Patients with the best chance of achieving remission were younger and had a shorter duration of diabetes and better glycemic control, thus stressing the importance of not postponing bariatric

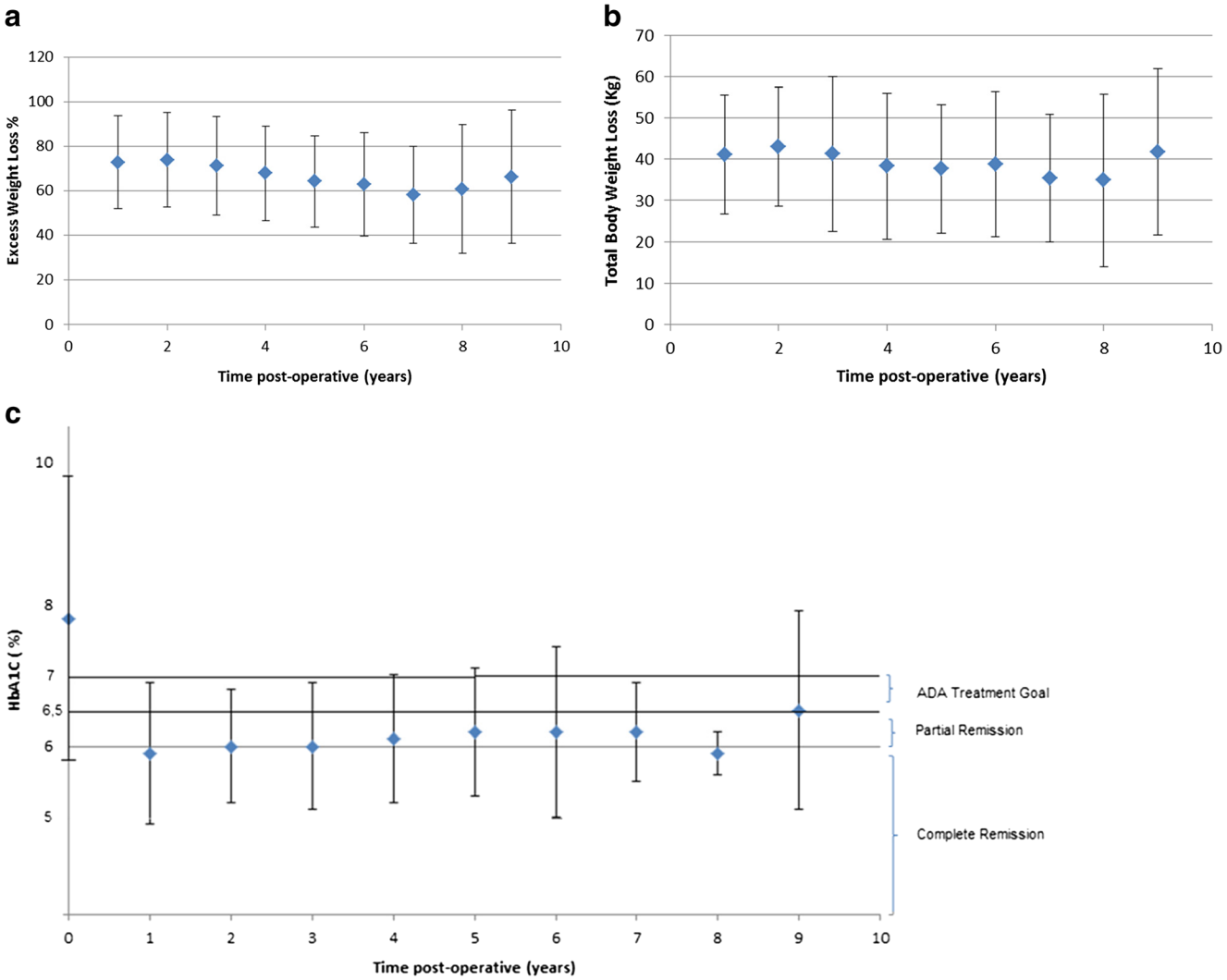
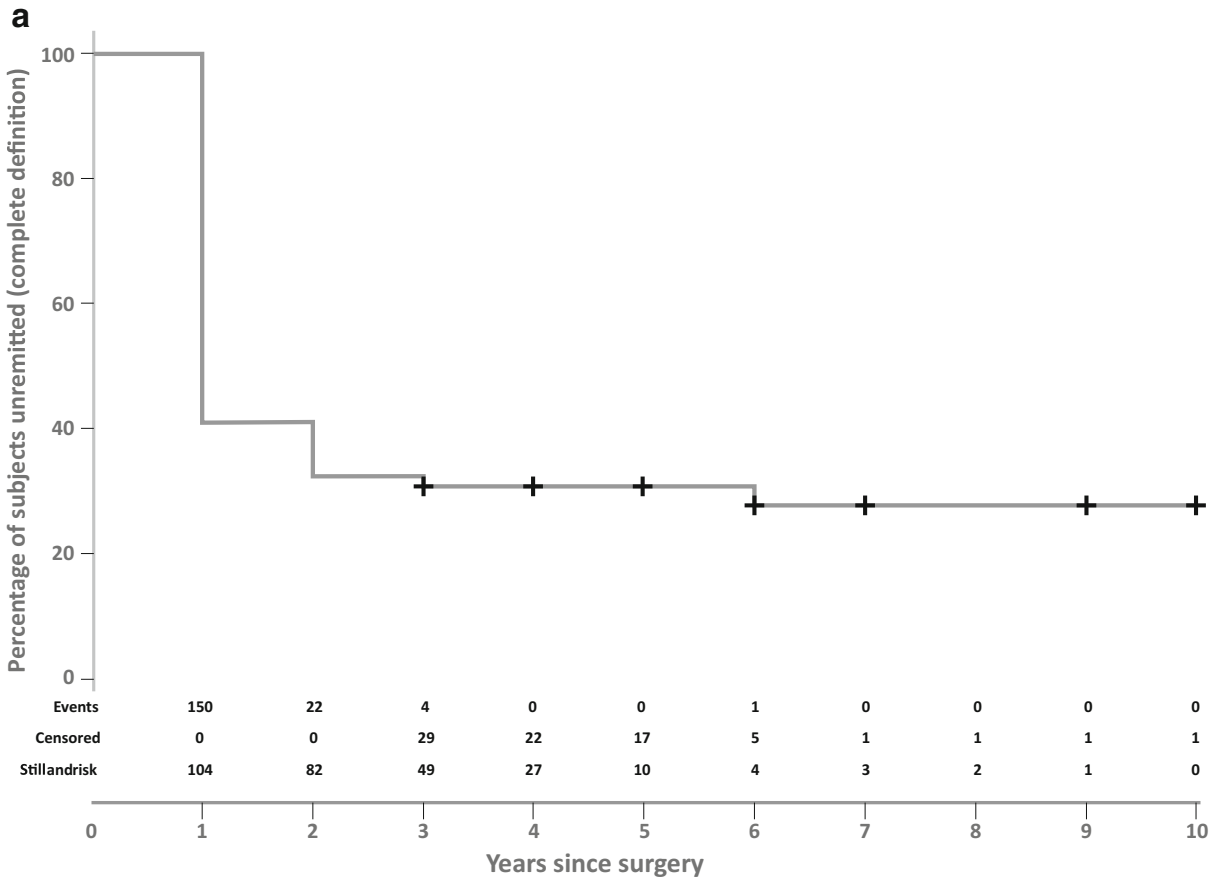


Fig. 2 Evolution of postoperative %EWL, total body weight loss, and HbA_{1c}. **a** Average percentage excess weight loss in the postoperative period. **b** Average weight total loss in the postoperative period. **c** Mean values of glycated hemoglobin (HbA_{1c}). The horizontal lines indicate HbA_{1c} levels according to ADA therapeutic goal (<7%), definition of partial remission (HbA_{1c} between 6 and 6.5%), and complete remission (HbA_{1c} < 6%). *ADA* American Diabetes Association

surgery, when indicated, in these individuals. Patients who used ≥1 oral anti-diabetic drugs and/or insulin had a greater risk of relapse after remission; this might be related to a lower pancreatic reserve or a more extensive metabolic derangement [38]. Although these findings were first suggested in 2003 [39], the state of affairs has not changed, worldwide, in terms of provision of bariatric surgery.

It is important to note that all patients, even those who did not achieve remission, exhibited improved glycemic control. After bariatric surgery, patients have been reported to experience improvements in quality of life and other comorbidities (e.g., systemic hypertension, sleep apnea, arthritis), as well as reduced risks of cardiovascular disease and mortality [10, 40, 41]. Therefore, a relatively lower chance of type 2 diabetes remission should not be an obstacle to recommending bariatric surgery when indicated. Several studies [42, 43] have demonstrated that achieving the best possible metabolic control early in the course of type 2 diabetes, and maintaining it for as long as possible, has value in reducing the incidence of microvascular complications and their rate of progression. This would be a further argument in favor of not postponing surgery whenever it is indicated. Patients in whom relapse of type 2 diabetes occurs pose a particular clinical challenge. The empiric idea that, once surgery has been carried out and diabetes relapsed, the physician is left "empty handed," is probably prejudiced, since surgery still led to better glycemic control, and would likely pave the way for optimized clinical.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Percentage of subjects unremitted (complete definition)
100
80
60
40
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0
Events 150 22 4 0 0 1 0 0 0 0
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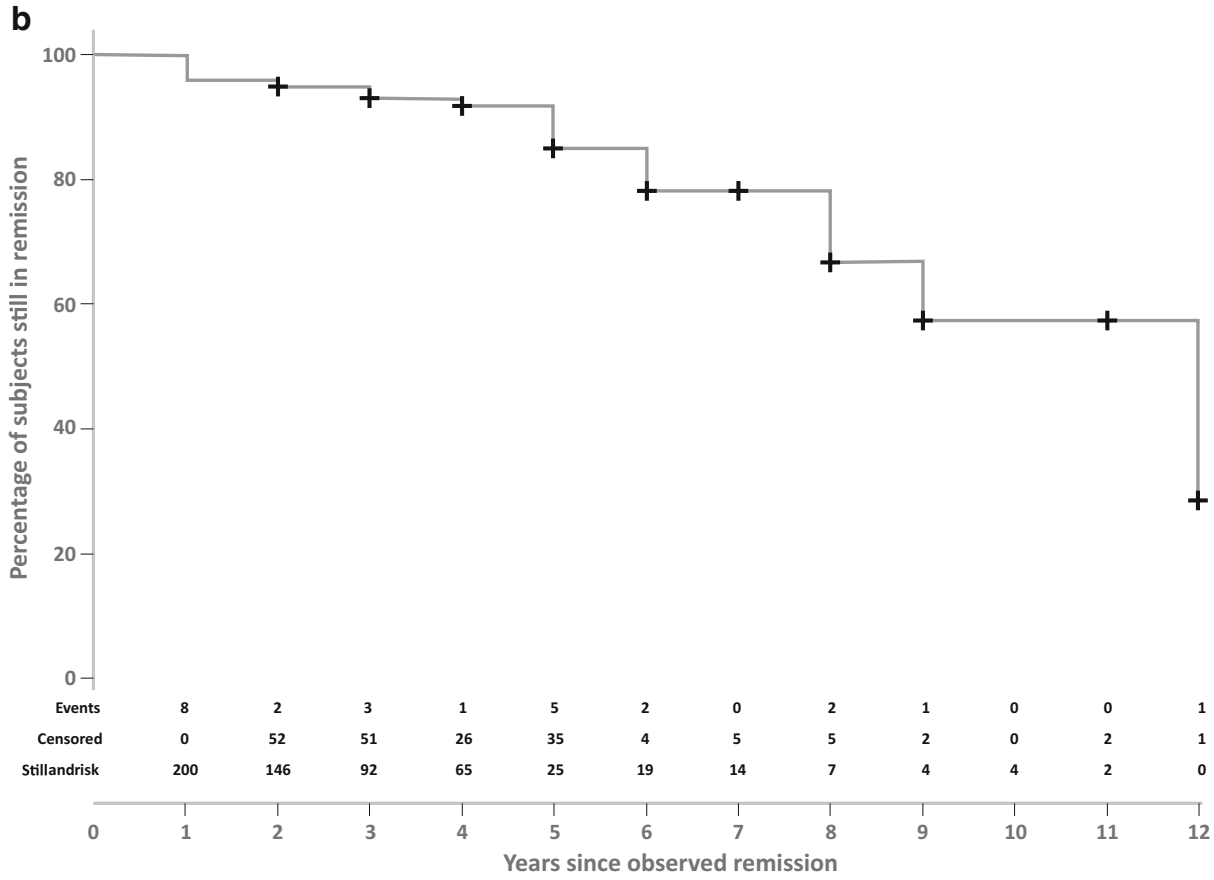
Years since surgery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Years since observed remission

◀ **Fig. 3** Kaplan–Meier survival curve for diabetes remission and relapse. **a** Time to complete diabetes remission following bariatric surgery. **b** Time to relapse of diabetes following bariatric surgery and initial remission

In contrast to previous studies [14, 27, 31], weight loss and/or gain were not predictors of type 2 diabetes remission or relapse. The average time to complete remission was 1.2 years. In other words, patients achieved type 2 diabetes remission in a relatively short time, a process that may be primarily influenced by hormonal factors and caloric restriction. The sudden postoperative caloric restriction after gastric bypass appears to improve insulin sensitivity, particularly in the liver, and significantly reduces fasting glucose levels [44, 45]. Changes in the secretion of intestinal hormones, particularly glucagon-like peptide-1 (GLP-1), occur on the first postoperative day and promote improved pancreatic cell beta function [45]. Weight loss appears to contribute to a long type 2 diabetes remission [45–47]. Nevertheless, may not be a strong predictor of remission [20, 26, 48].

Our study is limited by its retrospective nature and the fact that some socio-demographic variables such as race/ethnicity, socio-economic levels, and education levels could not be evaluated; these could have impacted our results. We note, however, that previous studies also did not evaluate these variables [14, 26, 30, 31, 36]. It was not possible to compare our results with those of a non-surgical treatment group. However, in another study, bariatric surgery appeared to confer better type 2 diabetes control than conservative treatment [5]. A selection bias can occur because the group lost to follow-up might be subject to with poorer glycemic outcomes, not included in analyses. However, we analyzed baseline characteristic of both groups and they did not differ significantly. Finally, duration of diabetes depended on patient reports, information in medical charts, and preoperative examinations, and was thus subject to measurement bias.

In conclusion, gastric bypass effectively induces remission of type 2 diabetes in 81.9% of patients with morbid obesity. Nevertheless, up to 12% of these patients relapsed. Age, duration of type 2 diabetes, degree of control, and prior therapeutic regimen were found to be predictive of type 2 diabetes remission and relapse.

Compliance with Ethical Standards

Funding This study received funding from the Brazilian National Research and Development Council (CNPq).

Conflict of Interest Dr. Lopes Preto de Oliveira was the recipient of a grant from the Brazilian National Research and Development Council (CNPq); Gianluca Pioli Martins was the recipient of a grant from the Brazilian National Research and Development Council (CNPq); Dr. Rizzolli has nothing to disclose; Dr. Mottin has nothing to disclose; Dr. Friedman reports grants from this study. It received funding from the Brazilian National Research and Development Council (CNPq) during the conduct of the study.

Ethical Approval All procedures were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Does not apply

Table 2 Predictors of remission and relapse of T2DM after RYGB–Cox regression analysis (adjusted model)

		Complete remission		Partial remission		Relapse	
		HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (years)	<45	1.5 (1.1–2.1)	0.02*				
	≥45	1 (Ref.)					
HbA_{1c} (%)	<7	2.43 (1.18–5.04)	0.017*	2.34 (0.38–14.20)	0.356		
Diabetes duration (years)	7–8.5	1.81 (0.88–3.74)	0.107	4.68 (1.30–16.94)	0.019*		
	8.51–10	1.17 (0.51–2.70)	0.717	3.83 (1.02–14.3)	0.045*		
	>10	1 (Ref.)		1 (Ref.)			
	≤ 5	4.15 (1.65–10.40)	0.002*	4.66 (1.34–16.27)	0.016*		
	6–10	1.93 (0.70–5.32)	0.205	4.03 (1.11–14.60)	0.034*		
	>10	1.0 (Ref.)		1.0 (Ref.)			
Diabetes pharmacotherapy	No medication					0.14 (0.05–0.38)	<0.001*
	Monotherapy with metformin					0.09 (0.02–0.32)	<0.001*
	Two oral anti-diabetic agents					0.84 (0.29–2.45)	0.844
	Insulin					1.0 (Ref.)	

RYGB Roux-en-Y gastric bypass, *HR* hazard ratio, *95% CI* 95% confidence interval, *Ref.* reference category, *HbA_{1c}* glycated hemoglobin
*$p < 0.05$

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