Predictors of type 2 diabetes relapse after Roux-en-Y Gastric Bypass: a ten-year follow-up study

Authors: Diego Moriconi[1], Maria Laura Manca[2], Marco Anselmino[3], Eleni Rebelos[2], Rosario Bellini[3], Stefano Taddei[2], Ele Ferrannini[4], Monica Nannipieri[2]

Affiliations:

[1] Dpt. Surgical, Medical, Molecular Pathology and Critical Care Medicine, University of Pisa, Italy;

[2] Dpt.Clinical and Experimental Medicine, University of Pisa, Italy;

[3] Bariatric Surgery Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy;

[4] Institute of Clinical Physiology, National Research Council (CNR) Pisa, Italy

Correspondence:

Prof. Monica Nannipieri, MD, PhD.

Dpt. Clinical and Experimental Medicine, University of Pisa

Via Savi 10, 56126 Pisa, Italy

Email: monica.nannipieri@unipi.it

Abstract

Aims. - To assess the impact of bariatric surgery on remission and relapse of type 2 diabetes mellitus (T2DM) at 10 years of follow-up and analyze predictive factors.

Materials and Methods. – Eighty-eight obese subjects undergoing Roux-en-Y gastric bypass (RYGB) and 25 subjects assigned to medical therapy (MT) were evaluated every year for 10 years. T2DM remission was defined by the American Diabetes Association criteria.

Results. - Body mass index (BMI), fasting glucose, and hemoglobin A1c (HbA1c) improved more markedly in RYGB than MT patients throughout the 10-year period. Post-surgery remission rates were 74% and 53% at 1 and 10 years, respectively, while remission did not occur in MT patients. One-year post-surgery, BMI decreased more in subjects with remission than in those without, but no further decrease was observed thereafter. By partial-least-squares analysis, T2DM duration, baseline HbA1c, and ensuing insulin therapy were the strongest predictors of remission. Remission was achieved at one year in 91% of patients with T2DM duration < 4 years, and 79% of them remained in remission at 10 years. On the contrary only 42% of patients with T2DM duration ≥ 4 years achieved remission, which was maintained only in 6% at the end of 10 years. By survival analysis, patients with T2DM duration < 4 years had higher remission rates than those with duration ≥ 4 years (hazards ratio (HR) 3.1 [95%CI 1.8–5.7]). Relapse did not occur before two years post-surgery and was much less frequent in patients with < 4- vs ≥ 4-year duration (HR 11.8 [4.9–29.4]).

Conclusions. - Short T2DM duration and good glycemic control before RYGB surgery were the best requisites for a long-lasting T2DM remission, whereas weight loss had no impact on the long-term relapse of T2DM.

Keywords: Bariatric surgery; Diabetes relapse; Gastric bypass; Obesity; Type 2 diabetes mellitus; Weight loss

Introduction

Bariatric surgery is considered to be an effective treatment for morbid obesity and represents a useful adjunct in the treatment of type 2 diabetes mellitus (T2DM) in subjects with severe obesity. The exact mechanisms behind diabetes remission after bariatric surgery are not completely understood, but improvement in insulin sensitivity and ß-cell function as well as changes in the entero-insular axis appear to play an important role [1,2].

Remission rates and diabetes-free time vary across studies, depending on the type of bariatric surgery and severity and duration of T2DM [3,4].

A meta-analysis including 621 studies with variable follow-up reported remission rates of 95.1%, 80.3%, 79.7% and 56.7% in patients who had biliopancreatic diversion (BPD), Roux-en-Y gastric bypass (RYGB), gastroplasty, and gastric banding (GB), respectively [5]. However, as criteria used to define remission varied significantly among studies, these data were not fully confirmed by later analyses [6]. As a consequence, the American Diabetes Association (ADA) consensus panel [7] introduced more stringent criteria to define diabetes remission based on fasting plasma glucose and hemoglobin A1c (HbA1c) concentrations in the absence of anti-hyperglycemic treatment, which led to a significant reduction of remission rates in a subsequent retrospective study [8].

There are conflicting data on which is the most resolutive bariatric surgery technique. In a longitudinal multicentric study that included 28,616 patients with T2DM, remission at one year was obtained in 83% of patients undergoing RYGB and in 55% of those undergoing sleeve gastrectomy (SLG) [9], while in other studies the effectiveness of RYGB and SLG in inducing diabetes remission was similar [1,10]. On the other hand, Mingrone and colleagues [11] showed a higher 2-year remission rate after BPD than RYGB (100% and 79%, respectively). A recent review suggests that BPD, RYGB, SLG and adjustable GB impact on diabetes remission in a decreasing order, in parallel with the extent of weight loss [12].

As reported in a randomized control trial [13], after five years of follow-up 53% and 37% of patients in the RYGB and BPD groups, respectively, experienced diabetes relapse. Similarly, the Swedish Obese Subjects (SOS) trial reported that among T2DM subjects with diabetes remission at two years follow-up ~50% had diabetes relapse after 10 years [14]. It is important to underline that, although the efficacy of bariatric surgery on diabetes remission is undeniable, the duration of remission decreases over time after bariatric surgery, as demonstrated in studies with a follow-up of at least five years or longer [15-17]. The predictors of diabetes relapse have not been completely characterized. Several scoring systems have been developed in order to identify factors associated with the probability of diabetes remission before surgery (e.g., DiaRem) [18]. Some data suggest that poorer diabetes control before surgery, longer disease duration, and insulin use before surgery can compromise long-term remission [19], whereas the role of weight regain, often seen several years after bariatric surgery, is uncertain [20, 21].

The aim of this study was to determine the impact of RYGB on T2DM over 10-year follow-up, focusing on the incidence of T2DM relapse after the initial remission in order to identify potential predictive factors.

Materials and methods

One hundred twenty-seven subjects with morbid obesity and T2DM attending the outpatient clinic of the Internal Medicine Unit of the Azienda Ospedaliero-Universitaria Pisana (Pisa, Italy), were enrolled between 2008 and 2009 to take part in a single-center, open, 10-year prospective study. Of them, 96 patients underwent RYGB and 31 refused to undergo bariatric surgery and were recruited into a medical intensive therapy program (MT). Fourteen subjects (8 in the surgery group, and 6 in the medical group) did not attend scheduled follow-up visits in the first two years and were fully excluded from the study.

Inclusion and exclusion criteria: Inclusion criteria were age between 40 to 65 years, body mass index (BMI) ≥ 35 kg/m2, T2DM diagnosis according to ADA criteria [7]. Insulin-taking patients whose age at diabetes onset was ≥ 40 years and who were negative for the presence of islet autoantibodies were also considered to have T2DM. The exclusion criteria were severe medical conditions (malignancies, liver cirrhosis, end-stage kidney disease, connective tissue or endocrine disease), history of type 1 diabetes mellitus or secondary forms of diabetes, previous bariatric surgery or pregnancy. Of the 113 patients completing the study, 88 subjects underwent RYGB, and 25 individuals were under intensive MT. Height, weight, systolic and diastolic blood pressure were recorded pre-surgery, peripheral blood samples were obtained for determination of routine blood chemistry, electrolytes, complete blood count, lipid profile, plasma glucose and HbA1c concentrations; kidney and liver function tests were also recorded. Before surgery, patients were evaluated by a multidisciplinary team, including a surgeon, an anesthesiologist, a diabetologist, a dietician, a psychologist and a psychiatrist.
The protocol was approved by the local Ethics Committee, and all patients signed a written consent form.

Treatment Patients: In the MT group patients were treated by oral anti-hyperglycemic agents and/or insulin based on individual characteristics with the aim of reaching HbA1c levels < 6.5%. Patients received nutritional counseling and a low-calorie diet tailored to achieve a weight loss > 10% of initial body weight. Patients in the surgery group were admitted to our ward two days before surgery and returned three days after the intervention for another three days, in order to check glucose control and adjust drug therapy. On the day of surgery, patients with a fasting plasma glucose concentration >8.0 mmol/l were started on an insulin infusion adjusted to maintain fasting plasma glucose between 6.0 and 8.0 mmol/l during surgery and for the following day, until they started eating again. Before surgery, 27 patients were on insulin therapy, 20 patients were on sulfonylureas plus metformin, and 58 patients took metformin alone. A small group of 8 patients had sulfonylureas alone, due to intolerance to metformin, or a combination of metformin and exenatide.

Laparoscopic RYGB: After identification of the Treitz ligament, the jejunum was transected 120 cm from the ligament of Treitz and an entero-enterostomy was performed using a 45-mm linear stapler at 150 cm on the alimentary limb. A subcardial gastric pouch with a 20-30 ml capacity was divided from the gastric remnant by sectioning the stomach with multiple 45-mm linear stapler firings, and a 2.5-3 cm long gastrojejunal anastomosis was performed using a hand-sewn technique.

Follow- up: All patients were checked in our outpatient clinic of the Internal Medicine Unit at 45 days, and 3, 6, and 12 months, and then every six months for the following years. At each visit, physical examination, weight control and laboratory tests were performed; furthermore, all patients underwent dietary assessment conducted by our team (using the EPIC Alimentary Questionnaire). Blood samples included blood count, glycemia, HbA1c, lipid profile, kidney and liver function, electrolytes, urinalysis and albumin-to-creatinine ratio. In both group, medical therapy was adjusted according to the metabolic profile, and discontinuation of medical therapy was considered in case of glycemic normalization.
Sixty-five subjects discontinued antidiabetic therapy within the first 15 days after surgery and were free of antidiabetic therapy for at least one year. Diabetes remission (DR) was defined as the combination of partial and complete remission according to ADA criteria [7]. Specifically, partial remission was defined as HbA1c < 6.5% and fasting glucose 100–125 mg/dL, while complete remission was defined as return to fasting glucose < 100 mg/dL and HbA1c <6.0% for at least one year in the absence of pharmacologic therapy or ongoing procedures.

5y-Ad-DiaRem score: Applying previously described methods [22], we used the 5y-Ad-DiaRem score to assess predictivity both at 5- and 10-year follow up. For this computation, patients in remission were further divided into two categories, partial and total remission, in accordance with ADA criteria.

Statistical analysis: Results are presented as mean ± standard deviation and median [interquartile range] for variables with normal or skewed distribution, respectively. Differences between groups were tested by the unpaired t-test or the Mann Whitney U test, as appropriate; analysis of variance (ANOVA) was used for > 2 groups, correction for multiple testing was applied when necessary. Categorical data were analyzed by the $\chi 2$ test. Repeated measures ANOVA was employed for time series. Remission-free and relapse-free survival curves were generated by the Kaplan-Meier method and, in addition, Cox regression survival analysis was performed.
A mixed linear model (LMM) was constructed to evaluate the impact of insulin therapy and diabetes duration on BMI time course during the 10-year follow-up. Insulin therapy and diabetes duration were included as fixed effects in the model and each subject as random effect. We also included interaction between insulin therapy and duration of diabetes.
Partial least square (PLS) regression was used to identify the baseline variables maximally contributing to the outcome of bariatric surgery after one year: diabetes remission, DR, or non-diabetes remission (NDR) [23]. Variables with a Variable Importance in Projection (VIP) score > 2.50 (a measure of variable relevance in the model) were considered significant for the association with the outcome variable (DR, NDR). The analysis was repeated at 5- and 10-year follow-up. P values < 0.05 were considered significant. Statistical analysis was performed using R and IBM-SPSS packages for Mac.

Results

Surgery vs medical therapy: At baseline, the two groups – RYGB and MT – were comparable regarding age, diabetes duration, BMI, HbA1c, fasting glucose, kidney function, and lipid profile (Table I). Antihyperglycemic treatment was also similar; in particular, 24% of patients were on insulin therapy in both groups, 20% and 17% were on sulfonylureas plus metformin, and more than half of the patients were taking metformin alone (52% and 59%, respectively).

In both groups, BMI, fasting glucose, and HbA1c improved throughout the 10-year follow-up ($P < 0.001$ for all variables). However, BMI decreased more in RYGB than MT patients, as did fasting glucose and HbA1c (Figure 1). At 10 years, RYGB patients had significantly lower concentrations of LDL-cholesterol and triglycerides and higher levels of HDL-cholesterol than MT patients. Estimated glomerular filtration rate (eGFR) declined over time, similarly in the two groups. Blood pressure control, which was similar at baseline, improved in both groups, but patients in the MT group required more anti-hypertensive medications at 10 years. At this time, 32% of the patients on MT required insulin therapy (as compared with 12% of post-RYGB patients); they were also taking a significantly higher number of oral antihyperglycemic drugs (36% vs 6%, MT vs RYGB), including GLP-1 receptor agonists. At study end, none of the MT subjects was in remission, while 47 (53%) of the 88 patients in the surgery group were in remission.

Clinical variables influencing diabetes remission after surgery: DR (partial or complete) rate was 74%, 60% and 53% at 1, 5 and 10 years, respectively. Partial remission was found in 5 (6%), 2 (2%) and 4 (5%) patients, respectively at 1, 5 and 10 years.

As there were no relapses during the first post-surgery year, from year 2 onward, patients were grouped as DR, NDR and Relapse (Table II).

The NDR group had significantly longer diabetes duration and higher baseline HbA1c, and fasting glucose, but lower BMI, than the DR group, whereas there were no differences between DR and Relapse. At baseline, 93% of DR patients were on metformin alone and none on insulin, against 25% of Relapse and 73% of NDR patients.

For the whole sample, the LMM showed a significant effect of diabetes duration ($P < 0.001$) and of duration*insulin therapy interaction ($P = 0.019$), but not of insulin therapy alone, on the BMI time course. The results of a post hoc analysis dividing the sample into groups of subjects treated or not with insulin showed that BMI did not differ between groups at 5- and 10-year follow-up. A PLS analysis was run using all clinical variables as potential predictors of outcome. Diabetes duration (2 [1–2] vs 12 [9–17] years in DR and NDR, $P < 0.001$) and weight loss (40 ± 13 vs 25 ± 10 kg, $P = 0.014$) were the two variables more closely related to DR at one year. The results at five years still included diabetes duration (VIP: 8.79), but now insulin therapy (VIP: 4.69) and basal HbA1c (VIP: 3.09) were additional predictors of remission. PLS analysis performed at 10-year follow-up also showed that diabetes duration (VIP: 7.39), insulin therapy (VIP: 4.72) and basal HbA1c (VIP: 3.61) were the variables strongly related to remission. On the contrary, weight loss was not related to DR at 5 and 10 years. One-way ANOVA revealed significantly greater values of diabetes duration ($P < 0.001$) and of basal HbA1c ($P < 0.001$) in NRD patients.

When patients were grouped by diabetes duration at the time of surgery into < 4 years and ≥ 4 years, 91% of the patients in the < 4 years group achieved remission at one year, and 88% and 79% of them maintained remission at 5 and 10 years. On the contrary, less than half of patients (42%) with long-term diabetes duration achieved remission in the first year, which was maintained only in 10% and 6% at 5 and 10 years, respectively. By Kaplan-Meier analysis, shorter diabetes duration was associated with a 3-fold higher remission rate within the first ~15 months since surgery, after which time there were no more remissions (Figure 2a). Conversely, relapse started ~2 years after surgery, and had much higher incidence in patients with longer than shorter diabetes duration (Figure 2b).

5y-Ad-Diarem Score estimation: In the bariatric surgery sample, the scoring system correctly predicted the outcome in 97% and 90% of patients, at 5- and 10-year follow-up, respectively, for subjects scoring less than 12 or more than 18. Of the 23 patients with a score ranging between 12 and 17, 70% had T2DM at 5 years (more precisely, 10 Relapse and 6 NDR subjects).

Discussion

The main results of this 10-year follow-up study were: i) bariatric surgery was superior to intensive medical treatment in terms of glycemic control and diabetes remission; ii) at 10 years, half of patients treated by RYGB were considered to be in stable remission; iii) more importantly, a shorter duration of diabetes (< 4 years) predicted better outcome in terms of long-term remission, which was maintained in ~80% of individuals at 10 years, while only half the subjects with longer diabetes duration (≥ 4 years) achieved remission in the first year, and only 6% remained free of diabetes 10 years after surgery.

In the present study patients given medical treatment showed a significant improvement in metabolic control and BMI in the long-term follow-up (Table I). These improvements were apparently better than that reported in a randomized trial [24], but these differences could be explained by baseline differences between the study populations (shorter diabetes duration, higher BMI and weight loss other than better metabolic control in our population compared with that reported by Schauer et al.).

As expected, sustained remission by RYGB was accompanied by greater weight reduction at one year, better lipid profile and blood pressure control, and lower HbA1c with fewer diabetes medications, whereas the need for antidiabetic drugs, including insulin, increased over time in patients on medical treatment. These findings confirm recently published data on long-term follow up and from previous studies with shorter follow-up [13,25]. Specifically, in the 10-year randomized controlled trial conducted by Mingrone et al. [26], more than a third of patients in surgery groups maintained normoglycemia without any medications for the entire study period, in comparison with recently published 5% with conventional medical management.

Of note, in the present study surgically-induced remission at 10 years was higher than that reported by Mingrone et al. [26] (53% vs 25%). This difference could be plausibly attributed to the different duration of diabetes in the two cohorts, which was > 5 years in the Mingrone study while 65% of our patients had a diabetes duration < 4 years. Conversely, if we limit our observations to patients with diabetes duration > 4 years, the impact of RYGB on diabetes remission at 10 years was much lower that reported by Mingrone et al. [26], and this could be likely explained by the longer diabetes duration in our cohort (median 11 vs 6 years, respectively).

Thus, the present data emphasize the importance of taking into account diabetes duration when assessing the comparative success of RYGB and medical treatment. In fact, the present study shows that patients with a short duration (< 4 years) of diabetes experienced better outcome in terms of long-term remission, which was maintained in about 80% at 10 years, while only half of patients with diabetes lasting more than 4 years achieved remission in the first year, remission that was maintained in only 6% of subjects at the end of follow-up. Several investigators [25,27,28] have stressed the importance of early surgical intervention in order to obtain better glycemic control in obese patients with T2DM. Schauer et al. [25], for example, showed that diabetes duration < 8 years was the main predictor of achieving HbA1c < 6.0%, while another study reported that surgical intervention within five years of diagnosis was associated with a high rate of remission [28].

Fewer prospective long-term studies have analyzed the impact of diabetes duration on the relapse rate. The Swedish Obese Subjects (SOS) [29] showed that short diabetes duration at baseline was associated with lower relapse rate between 2- and 10-year follow-up. In that study, overall remission rates (60%, 23%, and 15% for diabetes durations of < 1 year, 1-3 years or > 4 years) were lower than in our cohort. In the SOS study, however, the definition of diabetes remission did not include HbA1c or antidiabetic medication, and three different types of bariatric surgery were pooled for the analysis. Furthermore, the differences between SOS and the present data on diabetes remission and relapse could be due to different types of bariatric surgery that were pooled together in the analyses. However, regardless of the differences between the two studies, both results indicate that the duration of diabetes is a key element for therapeutic success on remission of T2DM. In the study by Mingrone et al. [25], the risk of diabetes relapse appeared to be highest within the first five years after surgery and declined significantly thereafter; also, relapsing patients still had more acceptable glucose control than the medical group, requiring fewer medications.

As previously pointed out by Lebovitz [30], in addition to diabetes duration, worse metabolic control, requiring insulin treatment, also weakens the efficacy of surgery. Our data confirmed this observation, as the need for insulin therapy before surgery was another strong predictor of low surgery success rate. A possible explanation could be the fact that patients needing insulin therapy had a longer diabetes duration, suggesting that β-cell function was more impaired in these patients as expected by the natural history of T2DM. However, patients taking exogenous insulin did not show differences in weight loss or regain at 5 and 10 years compared to patients without insulin treatment.

In the literature, the impact of weight loss on the long-term resolution of diabetes is controversial. A recent study reported that weight loss was unable to predict diabetes remission among patients undergoing bariatric surgery [26], while another study showed that weight loss plays a key role in determining diabetes remission in the first two years [31]. In a long-term follow up study weight variations between baseline and two years after surgery were associated with relapse between two and ten years [29]. In the present study, weight loss influenced diabetes remission in the first year, but not the relapse rate in subsequent years. Importantly, the predominant role of diabetes duration and pre-surgery insulin treatment in predicting long-term remission in the current data does confirm that β-cell glucose sensitivity rather than insulin resistance is the underlying driver of relapse, as demonstrated in our previous study [1].

Finally, the 5y-Ad-Diarem score was created to predict diabetes remission and identify patients at risk for relapse five years post-surgery [22]. Our data confirm the performance of this score in identifying almost all patients in remission at five years with a score < 12. These data can be extended to 10 years with very good agreement. However, of the 23 patients with a score between 12 and 17, six individuals were NDR and 10 relapsed at 5 years). This suggests that the cut-off for predicting long-term diabetes relapse may be lower.

The present study has some strengths including complete long-term follow-up, surgery performed by the same surgical team, and a single research group using homogeneous inclusion criteria. On the other hand, the main limitation of the present prospective study is that it is not randomized and controlled, although the control group had similar baseline characteristics as the surgery group.

In conclusion, the present study suggests that RYGB is more effective in achieving remission of diabetes in subjects with shorter duration of the disease, in which the remission is maintained for at least 10 years. Moreover, another important finding is that weight loss did not impact diabetes relapse. Further long-term follow-up study will be help to better understand the mechanisms and prognostic factors of diabetes relapse after metabolic surgery.

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Contribution Statement: DM contributed to acquisition and interpretation of data and drafting the article; ER contributed to acquisition of data; LMM contributed data analysis; ST and EF revised the manuscript; MA and RB contributed to data resources. MN was responsible for the conception of the study, and interpretation of data and drafting the article. All authors approved the final version. MN is responsible for the integrity of the work as a whole.

Figure 1. Time course of glycated hemoglobin and BMI over the 10-year follow-up in RYGB vs MT groups. The values are expressed as average ± SEM. Repeated measures ANOVA was performed to compare the groups. Full lines denote HbA1c in MT (red line) and RYGB (blue line). Dotted lines represent BMI in MT (red line) and RYGB (blue line).

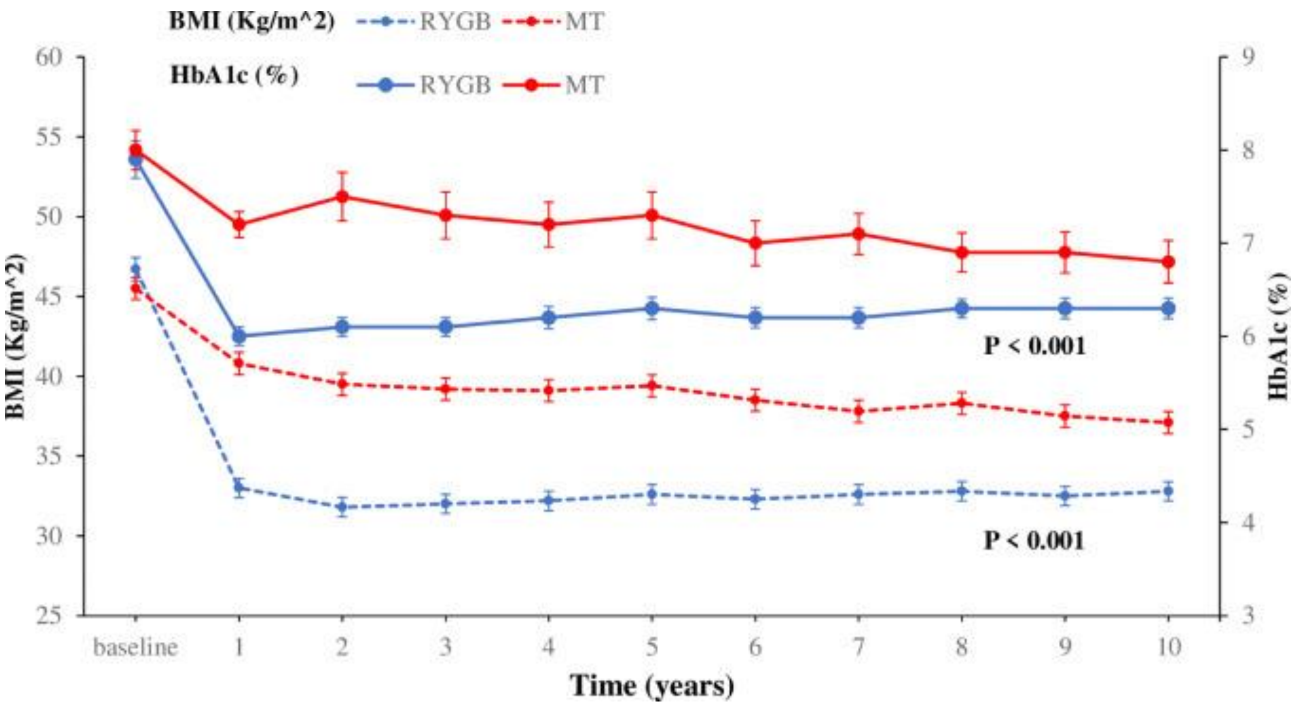

Figure 2. Kaplan-Meier curves for remission-free survival (A) and relapse-free survival (B), in the group of patients with diabetes duration ≥ 4 years (blue line) and in the group of patients with diabetes duration < 4 years (red line)

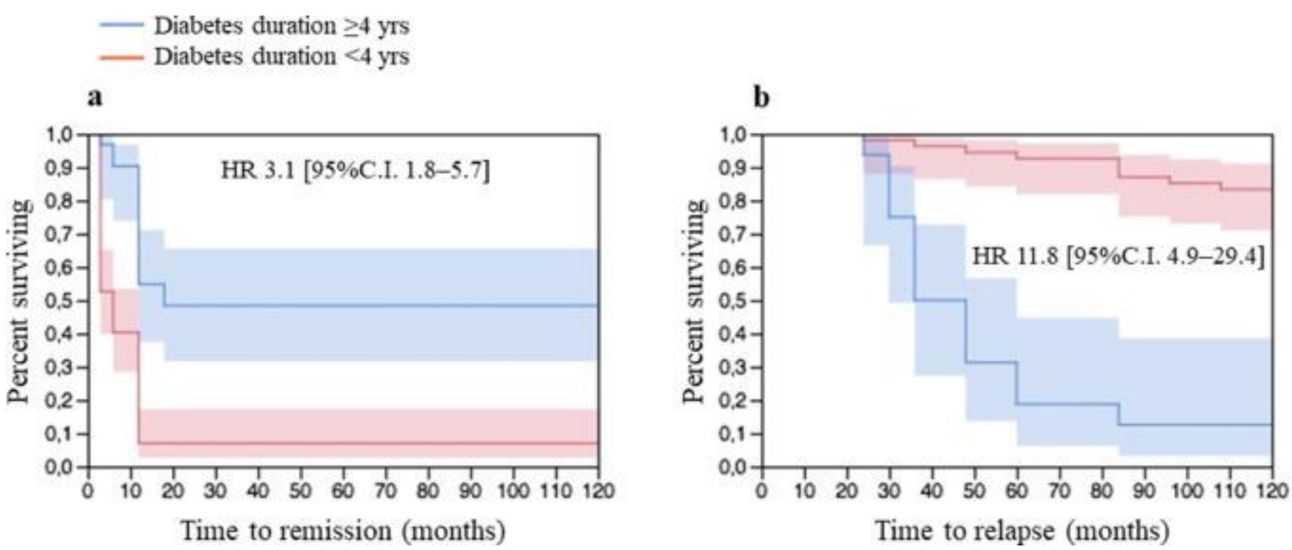

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Table 1. Anthropometrics and time-course of clinical features of subjects on medical or surgical treatment.

	Medical treatment group (n = 25)				**Bariatric surgery group (n = 88)**			
	baseline	**1 year**	**5 years**	**10 years**	**baseline**	**1 year**	**5 years**	**10 years**
Age (years)	54 ± 7				53 ± 8			
Gender (F/M)	12/12				67/21			
BMI, kg/m^2	45.5 ± 5.1	40.8 ± 4.6	39.4 ± 5.0	37.1 ± 4.9	46.7 ± 6.8	33.0 ± 5.6	32.6 ± 5.7	32.8 ± 5.6
T2DM duration (years)	2 (1-4.5)				2.5 (1-10)			
Fasting glucose (mmol/L) $^{*,\#}$	8.53±1.34	7.97±1.45	8.22±2.04	7.81±2.29	8.54±2.84	5.50±1.17	5.86±1.81	5.96±1.75
HbA_{1c} (%)$^{*,\#}$	8.0 ± 1.1	7.2 ± 0.7	7.3 ± 1.2	6.9 ± 1.1	7.9 ± 1.6	6.0 ± 0.7	6.3 ± 1.0	6.4 ± 1.1
Total Chol. (mg/dL)$^{*,\#}$	180 ± 24	147 ± 62	176 ± 33	157 ± 30	197 ± 38	168 ± 34	174 ± 35	170 ± 32
HDL Chol. (mg/dL)$^{*,\#}$	41 ± 12	42 ± 13	45 ± 13	43 ± 12	42 ± 11	51 ± 13	57 ± 15	59 ± 17
LDL Chol. (mg/dL)$^{*,\#}$	112 ± 28	101 ± 39	101 ± 34	83 ± 29	129 ± 31	99 ± 31	98 ± 33	94 ± 40
Triglycerides (mg/dL)$^{*,\#}$	168 (120-203)	148 (100-195)	159 (105-210)	140 (108-206)	158 (122-215)	105 (75-133)	92 (74-122)	106 (78-148)
Systolic BP (mmHg)$^{*,\#}$	141 ± 15	137 ± 9	138 ± 13	133 ± 17	139 ± 14	129 ± 13	128 ± 10	130 ± 11
Diastolic BP (mmHg)$^{*,\#}$	96 ± 17	84 ± 5	84 ± 6	80 ± 10	85 ± 8	77 ± 8	76 ± 7	73 ± 9
eGFR	89 ± 16	83 ± 13	80 ± 22	72 ± 21	88 ± 21	96 ± 22	89 ± 22	81 ± 21
Insulin therapy (n,%) $^{*,\#}$	6 (24%)	6 (24%)	7 (28%)	8 (32%)	21 (24%)	7 (8%)	11 (12%)	11 (12%)
N. of medications	1.7 (0.7)				1.5 (0.9)			
≥ 2	56%	52%	56%	60%	49%	11%	24%	27%
1	44%	48%	44%	40%	51%	10%	15%	19%
None	0%	0%	0%	0%	0%	78%	60%	53%

* P ≤ 0.05 for the time factor

\# P ≤ 0.05 the time x group (MT vs RYGB) interaction

Table 2. Anthropometric and clinical baseline characteristics of type 2 diabetic subjects in remission (DR) or not (NDR) or relapsing into diabetes after bariatric surgery

	DR	NDR	Relapse	P-value
N	46	22	20	
Age (years)	51 ± 8°	53 ± 8	55 ± 5	ns
Sex (m/f)	7/39	7/14	6/14	ns
BMI (kg/m^2)	47.2 ± 6.5	44.3 ± 6.5	48.5 ± 7.2*	ns
Diabetes duration (years)	2 [1-2]	12 [9-17]	6 [2-11]	< 0.0001
Fasting glucose (mg/dL)	7.83 ± 1.94	10.70 ± 4.07§	7.63 ± 1.24*	< 0.0001
HbA$_{1c}$ (%)	7.4 ± 1.3	9.3 ± 2.0§	7.6 ± 0.9*	< 0.0001
Total cholesterol (mg/dL)	194 ± 35	197 ± 43	207 ± 44	ns
HDL (mg/dL)	43 ± 11	40 ± 9	40 ± 8	ns
LDL (mg/dL)	123 ± 27	135 ± 31	135 ± 36	ns
Triglycerides (mg/dL)	138 [110-191]	210 [140-290]§	177 [138-209]*	0.002
eGFR (Ml/min^{-1} 1.73 m^{-2})	94 ± 19	75 ± 27§	82 ± 21	0.01
Hypertension (n,%)	28 (61%)	16 (73%)	13 (65%)	ns
SBP (mmHg)	138 ± 10	144 ± 12	143 ± 20	ns
DBP (mmHg)	84 ± 8	87 ± 8	81 ± 8	ns
Metformin alone (n,%)	43 (93%)	3 (14%)	4 (20%)	< 0.0001
Insulin therapy (n, %)	0 (0%)	16 (73%)	5 (25%)	< 0.0001

*NDR vs Relapse; § NDR vs DR; ° Relapse vs DR