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NEW CONCEPTS

Safety and Efficacy of Roux-en-Y Gastric Bypass to Treat Type 2 Diabetes Mellitus in Non-severely Obese Patients

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Abstract The efficacy of Roux-en-Y gastric bypass (RYGB) to control type 2 diabetes mellitus (T2DM) has been demonstrated in morbidly obese patients. Surgical procedures primarily focused on T2DM control in patients with body mass index (BMI)<35 kg/m^2 have shown to effectively induce remission of T2DM. However, only few reports have evaluated the safety and efficacy of RYGB in this group of patients. The aim of this study is to assess the safety and efficacy of RYGB in TD2M patients with BMI<35 kg/m^2. All T2DM patients with BMI<35 kg/m^2 and at least 12 months of follow-up who underwent laparoscopic RYGB were included. Safety of the procedure was evaluated according to mortality, need of reoperation/conversion, and complication rates. Metabolic parameters were evaluated at baseline and 6, 12, and 24 months after surgery. Thirty patients were included. Seventeen (56.6%) were women. Age, BMI, and duration of diabetes were 48±9 years, 33.7±1.2 kg/m^2, 4±2.9 years, respectively. No mortality was observed. No conversion/reoperation was needed. Average length of stay was 3.2±0.9 days. Early and late postoperative complications were observed in five (16.6%) and five (16.6%) patients, respectively. Twelve months after surgery, remission was observed in 25 of 30 patients (83.3%). After 2 years, remission was achieved in 13 of 20 patients (65%), and hemoglobin A1c decreased from 8.1±1.8% to 5.9±1.1% and homeostasis model assessment of insulin resistance from 5.7±3.2 to 1.9±0.8 after 12 months. RYGB is a safe and effective procedure to induce T2DM remission in otherwise not eligible patients for bariatric surgery. Evidence from prospective studies is needed to validate this approach.

Keywords Type 2 diabetes mellitus · Gastric bypass surgery · Obesity · Metabolic surgery · Non-severe obesity

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Introduction

Obesity is one of the most important risk factors for the development of type 2 diabetes mellitus (T2DM), and the common finding that obesity precedes diabetes supports a causal relationship between both diseases [1]. In fact, 90% of all T2DM patients are obese or overweight [1, 2]. Currently, surgical procedures for weight loss have demonstrated to be the most effective treatment for morbid obesity and its associated metabolic disorders, especially T2DM. Among the different procedures available, Roux-en-Y gastric bypass (RYGB) is the most commonly performed procedure worldwide [3]. In addition to weight loss, RYGB induces remission of T2DM (normal glucose levels and glycated hemoglobin A1c (HbA1c) after discontinuation of all glucose-lowering agents) in up to 83.5% of diabetic patients [4]. Surprisingly, return to normal insulin and glucose levels occurs days after surgery prior to any significant weight loss [5–7], suggesting the existence of weight loss-independent mechanisms of glycemic control involved in the early normalization of glucose levels after RYGB.

Current indications for bariatric surgery were formulated in the 1991 National Institutes of Health Consensus Development Conference on gastrointestinal surgery for severe obesity [8] and were primarily focused on obesity treatment. In that guideline, eligible patients for surgery were those with severe obesity (body mass index (BMI) >40 or ≥35 kg/m^2 plus an associated obesity-related disease). Recently, some groups have performed bariatric procedures in non-severely obese T2DM patients (BMI<35 kg/m^2) to induce diabetes remission [9–12]. In spite of encouraging results, long-term studies are needed to establish the risks and benefits of surgical treatment of T2DM in non-severely obese patients.

The primary aim of this retrospective study was to evaluate the safety and efficacy of RYGB to induce T2DM remission and weight loss in non-severely obese patients. In addition, we also evaluated the effect of RYGB on hypertension and lipid disorders.

Patients and Methods

Study Design and Patients

We identified all patients with a preoperative BMI 30–35 kg/m^2 who underwent laparoscopic Roux-en-Y gastric bypass (LRYGB) for the treatment of T2DM from August 2001 to April 2008 at the Obesity and Metabolic Surgery Program, Department of Digestive Surgery, Pontificia Universidad Católica de Chile. All patients with at least 12 months of follow-up were included in the final analysis. Prior to surgery, patients were evaluated by a multidisciplinary team and provided informed consent. Diagnosis and classification of T2DM were performed according to the criteria established by the American Diabetes Association [13].

Preoperative Evaluation and Postoperative Management of T2DM Patients

Initial evaluation and characterization of T2DM patients with BMI 30–35 kg/m^2 included duration of diabetes (years), type of anti-diabetic drugs used, fasting insulin levels (FI), fasting plasma glucose, C-peptide, and HbA1c levels. Insulin resistance (IR) is evaluated using the homeostatic model assessment (HOMA-IR = fasting glucose 160×fasting insulin (μU/ml/22.5)) as described by Matthews et al. [14]. Insulin determination was performed by a chemiluminiscent enzymatic immunoassay (Immulite 2000, Diagnostic Product Corp, USA), of which intra-assay and inter-assay coefficients of variation were 4.6% and 5.9%, respectively. The following lipid parameters were also evaluated: serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL), and triglycerides (TG). Lipid disorders were defined according to the following criteria [15]: hypercholesterolemia TC level >201 mg/dl (5.2 mmol per liter), hypertrygliceridemia TG level >150 mg/dl (1.7 mmol per liter), and a low level of HDL <39 mg/dl (1.0 mmol per liter). To identify adult patients with apparent T2DM, who indeed might have latent autoimmune diabetes in adults, we evaluated the presence of the following T1DM autoimmunity markers: (1) glutamic acid decarboxylase autoantibodies, (2) islet cell autoantibodies, (3) insulin autoantibodies, and (4) insulin autoantibody A2. If needed, drug therapy and/or insulin therapy was adjusted in order to optimize glycemic control prior to surgery. After this initial evaluation, patients with negative autoimmunity markers of T1DM underwent the RYGB procedure.

Immediately after surgery, glucose levels were continuously monitored and adjusted at 6-h intervals. After patients reassume oral ingestion of nutrients, anti-diabetic drugs and/or insulin was incorporated to control glucose levels when needed.

Surgical Technique

Laparoscopic RYGB was performed using five ports, constructing a 10–15-cc gastric pouch, with a complete transection of the stomach leaving a 150-cm antecolic antegastric alimentary limb and a 50-cm biliary limb. The gastro-jejunostomy was performed with a hand-sewn double layer technique and calibrated with a 34-F bougie.

Demographic and Metabolic Evaluated Parameters

Data of all patients were collected prospectively and then retrospectively verified. All data were entered into the Obesity and Metabolic Surgery Program database. Other data sources included hospital charts, office charts, follow-up clinical notes, and patient interviews (person–person, telephone). The following demographic parameters were included in the analysis: age, gender, and BMI. Weight loss progression was expressed as percentage of excess weight lost (%EWL). T2DM was characterized as previously described. Criteria for diabetes remission included fasting glucose <100 mg/dl and HbA1c <6.5% without anti-diabetic drugs at the time of evaluation.

Criteria for diabetes improvement included decrease dosage of diabetes medication and fasting glucose 100–125 mg/dl or Hb1Ac decrease greater than 1% but above 6.5%.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation. Continuous variables were compared using Student ANOVA for repeated measure. A two-tailed p value<0.05 was considered statistically significant. Statistical analysis was performed using a commercially available software package (SPSS 15 for Windows, Inc., Chicago, IL, USA). Graphs were made using a commercially available software package (GraphPad for Windows). Continuous variables were graphed as mean ± SEM.

Results

Patients, Demographics, and Metabolic Characteristics

From August 2001 to April 2008, 1,207 patients underwent LRYGB. Thirty-four type 2 diabetic patients with a preoperative BMI 30–34.9 kg/m^2 were identified. Thirty patients had at least 1-year follow-up after surgery and were included in the analysis. Seventeen (56.6%) patients were women. Age, BMI, and duration of diabetes were 48±9 years (28–65), 33.7±1.2 kg/m^2 (30.4–35), and 4±2.9 years (1–12), respectively. One patient was using insulin at the time of surgery. Patients' baseline and postoperative demographic, metabolic, and lipid profile characteristics are summarized in Table 1.

Safety of the Procedure and Early and Late Postoperative Complications

The mean operative time was 112±39 min (70–210). The average length of hospital stay was 3.2±0.9 days (2–6). No early and late mortality occurred. No conversion and reoperation were needed. Ten patients (33.3%) developed early or late complication. Early postoperative complications were observed in five (16.6%) patients and late postoperative complications were reported in five (16.6%) patients. The most common complication was gastrojejunal stenosis developed in four patients (13.3%) that were successfully managed by endoscopic dilatation without complications. Table 2 summarizes the surgical results and complications.

Table 1 Baseline and postoperative demographic, metabolic, and lipid profile patients' characteristics

	Baseline	6 months	12 months	24 months
Demographics				
Age (years)	48±9 (28–65)			
Diabetes % (*n*)	30		30	20
Remission			83.3 (25)	65 (13)
Improvement			13.3 (4)	25 (5)
No change			3.3 (1)	10 (2)
Hypertension (*n*, %)	20 (66.6%)			20
Remission				55% (11)
Improvement				45% (9)
Antropometric data				
Weight (kg)	93±13	71.6±9.8*	66.8±10*	64.4±10*
BMI (kg/m^2)	33.5±1.2	25.7±1.8*	24.4±2.3*	23.9±2.4*
Diabetes characteristics				
Duration (years)	4±2.9			
FG (mg/dl)	145±61	84.6±8.5*	94.4±31.7*	109.9±55.3*
FI (μUI/ml)	16.9±8.2	6.8±1.9*	8.6±4.3*	6.3±1.3*
HOMA-IR (μUI/ml mmol/l)	5.7±3.2	1.4±0.5*	1.9±0.8*	1.8±0.8*
HbA1c (%)	8.1±1.8	5.9±0.7*	5.9±1.1*	6.5±1.3*
Lipid profile				
TC (mg/dl)	199±34.4	166.2±37.4	181.7±39.5	195.3±37.5**
TG (mg/dl)	191±99	123±51.2	104±50.3	127±47.9*
HDL (mg/dl)	45±8.9	48.5±9.2	58.9±10.9	56.2±11.9*
LDL (mg/dl)	116.6±26.5	95.2±34.3	105±29.4	113±30.9**

All data are reported as mean ± SD

BMI body mass index, *FG* fasting glucose, *FI* fasting insulin, *HOMA-IR* homeostasis model assessment of insulin resistance, *HbA1c* glycated hemoglobin A1c, *TC* total cholesterol, *TG* triglycerides, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

*p<0.05 between baseline and 24 months after surgery; **p>0.05 between baseline and 24 months after surgery

Table 2 Surgical results and postoperative complications (n=30)

Surgical results	
Operative time (min)	112±39 (70–210)
Hospital stay (days)	3.2±0.9 (2–6)
Conversion rate	0
Reoperation rate	0
Mortality rate	0
Postoperative early complications (n, %)	5 (16.6%)
Gastro-jejunal stenosis	4 (13.3%)
Pulmonary atelectasy	1 (3.3%)
Postoperative late complications (n, %)	5 (16.6%)
Gastro-jejunal stenosis	3 (10.0%)
Gallstone disease	1 (3.3%)
Hair loss	1 (3.3%)

Postoperative early complications: complications during the first 30 days after surgery. Postoperative late complications: complication developed after 30 days of surgery

Effect of Gastric Bypass on Diabetes Control

In order to determine the effect of RYGBP on T2DM, we evaluated the following parameters of metabolic control of diabetes: fasting glucose, fasting insulin, HbA1c, and HOMA-IR at 6, 12, and 24 months after surgery. Table 1 summarizes the effect of RYGB on metabolic variables of glycemic control after a mean follow-up of 16 months (range, 12–69 months). All the biochemical parameters that reflect the metabolic control of T2DM were significantly improved. Twelve months after surgery, 25 of 30 patients (83.3%) had remission of T2DM. However, 2 years after RYGB procedure, the number of patients with T2DM remission decreased to 13 of 20 (65%). Two patients had no change in their medical treatment. The patient under insulin therapy decreased the need of insulin from 90 to 12 U/day to maintain metabolic control. Fasting glucose decreased an average of 24% (preoperative FG 144±65.2 mg/dl vs postoperative FG 109±55 mg/dl; $p<0.001$), HbA1c exhibited a substantial decrease of 18.5% (preoperative HbA1c 8.1± 1.8 vs postoperative HbA1c 6.5%±1.3; $p<0.001$), and postoperative fasting insulin levels were 62% lower than the preoperative levels (preoperative FI 16.9±8.2 µUI/ml to postoperative 6.3±1.3 µUI/ml; $p<0.001$). Insulin resistance was dramatically improved after the procedure, as demonstrated by an average reduction of 70% in HOMA-IR (preoperative HOMA-IR 6.1±4.4 µUI/ml mmol/l vs postoperative HOMA-IR 1.8±0.8 µUI/ml mmol/l; $p<0.001$).

Weight Progression

Gastric bypass induced a significant weight loss in all patients. %EWL after 6, 12, and 24 months was 92±21.6%, 109±28%, 114±30.4%, respectively (Fig. 1). Two years after the procedure, the average BMI was 23.9±2.4 kg/m^2, which represents a 28.4% decrease with respect to their preoperative BMI of 33.5±1.2 kg/m^2 ($p<0.001$). At the end of the follow-up, all patients achieved a BMI<30 kg/m^2.

Effect of Gastric Bypass on Hypertension and Lipid Disorders

Two years after surgery, 11 patients (55%) had hypertension remission and 9 (45%) had a significant improvement, accounted by a reduction in the number and/or dosage of their anti-hypertensive medication (Table 1). RYGBP induced a significant increase in HDL levels and induced a significant reduction in TG levels. However, no significant changes were observed in TC and LDL levels (Table 1).

Discussion

Current guidelines for surgical treatment of severe obesity are reserved for patients with BMI>35 kg/m^2 plus an associated obesity-related disease, or BMI>40 kg/m^2 [8]. The early normalization of glucose levels after surgery, before a significant weight loss has occurred [5–7], suggested the existence of weight loss-independent mechanisms of glycemic control triggered by the surgical manipulation of the gastrointestinal tract. Evidence from non-obese rodent model of T2DM demonstrated a weight loss-independent improvement in glucose homeostasis [16–18]. These observations suggested that surgical treatment of T2DM in non-severely obese patients can be as effective as the surgical treatment of T2DM in severely obese patients to induce diabetes remission. In this retrospective study, we have shown that RYGB in non-severely obese T2DM is effective to induce diabetes

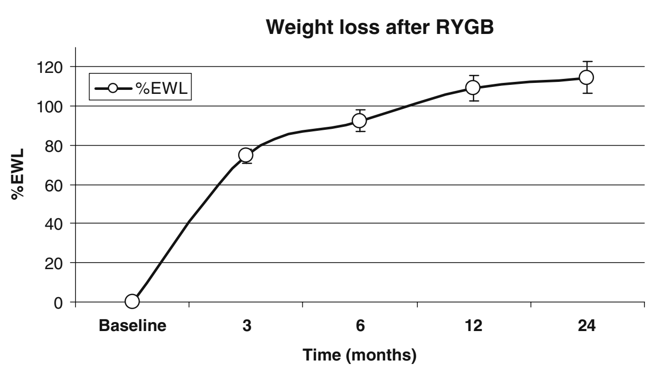

Fig. 1 Weight loss after RYGB in non-severely obese T2DM patients. Postoperative weight progression curve expressed as percent of excess weight loss. Data are presented as mean ± SEM

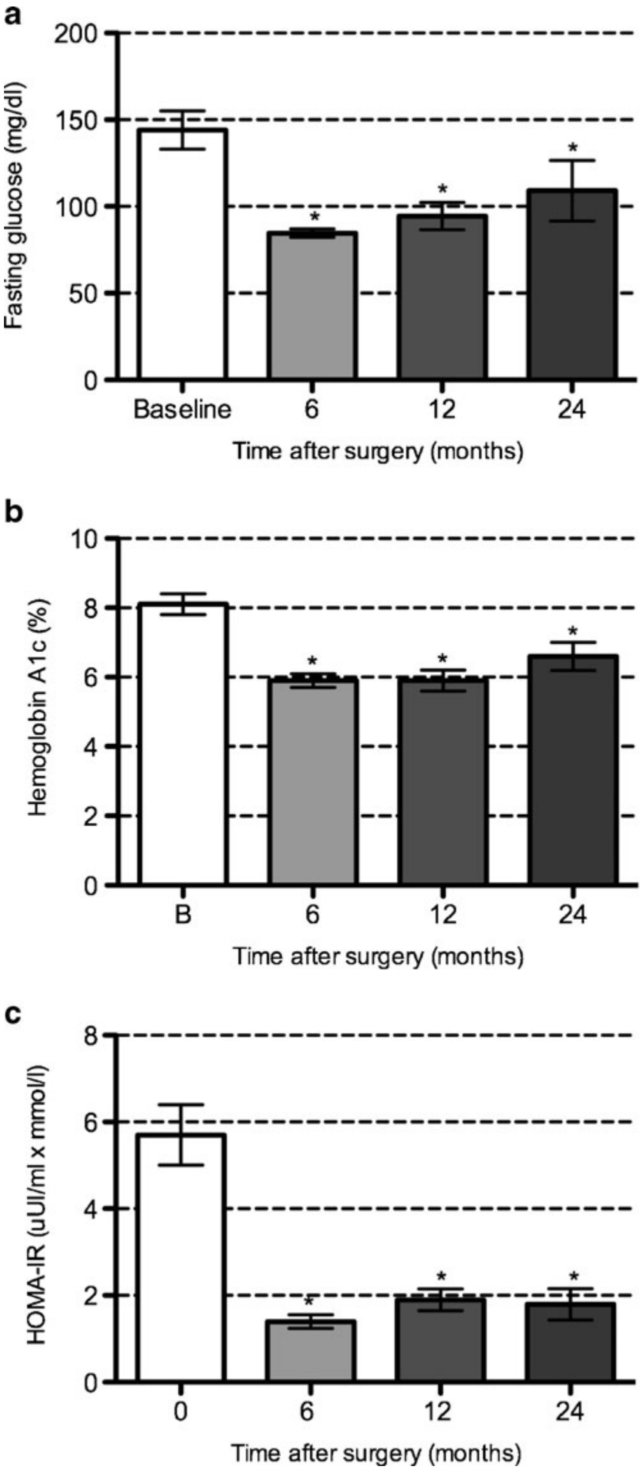

Fig. 2 Glycemic control after RYGB in non-severely obese T2DM patients. **a** Fasting glycemia: a significant and sustained improvement on fasting glycemia were observed after RYGB. **b** Glycated hemoglobin A1c: HbA1c levels reflect blood glucose levels over the last 2–3 months of both pre- and postprandial glycemia. **c** HOMA-IR: insulin resistance was dramatically improved after surgery, indicated by significant reductions in HOMA-IR. *$p<0.05$ baseline vs each time point after surgery. Data are presented as mean ± SEM

remission, can be safely performed, and induces a significant weight loss in otherwise not eligible candidates for bariatric surgery (Fig. 2).

In comparison to mortality rates of other procedures performed in US hospitals, aortic aneurism 3.9%, coronary artery graft bypass 3.5%, esophagectomy 9%, and pancreatectomy 8.3%, laparoscopic RYGB has a low mortality, with hip replacement procedure as the safest surgery with a 0.3% mortality. It has been estimated that overall mortality rate for RYGB is 0.5% [4] and that mortality after open and laparoscopic RYGB ranges from 0% to 1.5% [5, 19–23]. In this study, there was no mortality, no conversion, and no need of reoperation. Previously, we have reported no mortality and 1.3% conversion rate after 1,500 consecutive LRYGB [24]. Other series have also shown low mortality and morbidity rates. After the mini-gastric bypass surgery in T2DM patients, Lee et al. reported a 0.12% mortality rate and an overall morbidity of 2.6% [25]. Cohen et al. report no mortality and no morbidity in a series of 37 patients after LRYGB [9]. The most frequent early and late complication was gastro-jejunal stenosis (Table 2) that was successfully managed by endoscopic dilation (Savary-Gilliard) [26]. Combined, these results indicate that RYGB in non-severely obese T2DM patients can be performed with a low mortality rate and that most of the associated complications can be successfully managed.

Few studies have reported the efficacy of RYGB to treat T2DM in patients with a BMI<35 kg/m^2. One study included 37 T2DM patients (mean BMI 32.5, mean age 34 years, none with insulin treatment) that underwent LRYGB. After a mean follow-up of 20±5.4 months, 97.3% (36/37) patients experienced diabetes remission (fasting glucose levels <100 mg/dl and HbA1c <6% without glucose-lowering agents). Another study included 15 patients (mean preoperative BMI of 28.9±4, mean HbA1c levels of 10%). Three months after the RYGB procedure, the patients experienced diabetes remission [27]. In this study, RYGB induced remission of T2DM in up to 83.3% of patients 12 months after surgery, which is in accordance with the 83.5% and 80% remission rate previously reported in two meta-analysis [4, 28]. Two years after surgery, data from 20 patients were available to determine diabetes response to surgery. Of those, 13 patients meet criteria of diabetes remission reducing the percentage of diabetes remission from 83.3% to 65%. However, when combined to patients with improved glycemic control, RYGB significantly improved glycemic control in 90% of patients. This result highlights the importance of long-term studies to determine remission rates of diabetes and to identify and characterize the group of patients who experience diabetes remission or improvement and those in which surgery did not improve glycemic control. Unfortunately, in a small proportion of patients, RYGB fails to induce remission or improvement of glycemic control. These patients most likely will require glucose-lowering agents to improve their metabolic control. Different clinical predictors of poor response to RYGB of diabetes have been reported including duration of T2DM, elevated HbA1c, and insulin usage. In contrast, the magnitude of the weight loss has been positively associated with diabetes remission [6]. Identification of predictors of diabetes response to surgery will increase the risk/benefit profile of this surgical procedure and will provide another tool to physicians and patients to determine whether or not surgery is a cost-effective alternative to treat T2DM. Despite the observed decreased in the rate of diabetes remission 2 years after surgery, the benefits of RYGB in the glycemic control of T2DM patients are unquestionable, have been consistently reported in different studies and meta-analysis, and are superior to any currently available medical therapy [4, 6, 28, 29].

Weight loss after surgery is highly variable among patients. Hatoum et al. [30] reported that %EWL after RYGB exhibited a normal distribution with a mean of 64.8% and standard deviation of 20.5%. In that study, they found that higher initial BMI, limited physical activity, followed by T2DM (among others) were preoperative predictors of less body weight loss after surgery. Other studies have also shown that T2DM patients who underwent surgery lose less weight compared to non-diabetic patients [31–33]. The clinical relevance of the lower weight loss reported in T2DM after surgery on the glycemic control has not been properly studied. In this series of patients, RYGB induced a progressive and sustained weight loss (Fig. 1), which stabilized 1 year after surgery. Also, all patients stabilized their body weight on the range of normal or overweight body weight (mean BMI 23.9 kg/m^2; 20.3–28.9). Finally, the average %EWL at 2 years was 114±30.4% (60–160), which is higher compared to the mean %EWL of 81% reported by Cohen et al. [9]. In this perspective, the lower weight loss observed in T2DM patients in some studies after surgery does not affect the capacity of RYGB to induce diabetes remission and to substantially improve insulin sensitivity.

A major cause of morbidity and mortality among T2DM patients is heart disease [34], due to the greater number of atherogenic risk factors (hypertension, lipid abnormalities, obesity, etc.) compared to non-diabetic patients [35, 36]. Hypertension was presented in 66.6% (20/30) of the patients; after surgery, hypertension was resolved in 55% (11/20) and the 45% remaining (9/20) had a significant improvement, reflected by the decrease in the number of anti-hypertensive drugs (data not shown). In T2DM patients, obesity, insulin resistance, and the relative decreased insulin production are associated with hypertrygliceridemia, low HDL concentration, and sometimes elevated LDL levels [37, 38]. This pattern of lipid abnormalities is thought to be secondary to insulin resistance and/or hyperinsulinemia [39]. RYGB induced a significant improvement in TG and HDL levels (Table 1), which might be related with the weight loss and improved insulin resistance. In the largest prospective Swedish Obese Subjects Study, researchers evaluated the effect of surgery on cardiovascular risk factors and determined that patients who underwent surgery had a greater rate of recovery from hypertrygliceridemia and low levels of high-density lipoprotein, whereas recovery from hypercholesterolemia did not differ with medically treated patients [29]. Our study supports these findings, in which RYGB induced an improvement of hypertrygliceridemia and low HDL levels, yet no improvement on TC levels. RYGB has been also associated with improvements in cardiovascular risk factors, and induced weight loss predicts a 10-year reduction in cardiovascular events and death [40]. The improvement on the lipid profile, along with better glucose control after surgery, might explain the cardiovascular benefits reported in those studies. We could speculate that these patients, although not having the classical indications for bariatric surgery, have improved all their cardiovascular risk factors that could influence their life expectancy in the next years, a goal difficult to achieve with medical treatment.

Conclusions

In summary, this study demonstrated that RYGB is safe and an effective procedure to induce remission of T2DM in non-severely obese patients, otherwise not eligible for bariatric surgery. Additionally, RYGB induced a significant weight loss that was accompanied by significant reductions in blood pressure and normalization in the lipid profile. Combined, these encouraging results provide evidence about the safety and efficacy of this procedure in non-severely obese T2DM patients. Considering that a significant proportion of patients with T2DM have an adequate metabolic control with medical therapy, surgical treatment of T2DM should be considered in those patients in which an adequate glycemic control cannot be achieved despite lifestyle modifications and glucose-lowering agents. Evidence from long-term studies is needed to support this approach and the present study provided the necessary evidence to further support this approach. An adequate selection of T2DM patients will increase both the risk/benefit and safety/efficacy profile of this surgery which would benefit millions of patients around the world [41].

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Conflicts of Interest None.

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