Obesity Surgery
https://doi.org/10.1007/s11695-020-04534-z

ORIGINAL CONTRIBUTIONS

Effect of Roux-en-Y Gastric Bypass for Patients with Type 2 Diabetes Mellitus and a BMI < 32.5 kg/m2: a 6-Year Study in Chinese Patients

Guangnian Ji[1] · Weizheng Li[1] · Pengzhou Li[1] · Haibo Tang[1] · Zhaomei Yu[1] · Xulong Sun[1] · Rao Li[1] · Liyong Zhu[1] · Shaihong Zhu[1]

Abstract

Background Roux-en-Y gastric bypass (RYGB) is an effective treatment for morbidly obese patients to improve type 2 diabetes mellitus (T2DM). Recently, T2DM patients with a lower body mass index (BMI) have been receiving more attention, and these patients could benefit from RYGB.

Methods Fifty-two patients with T2DM underwent RYGB between October 2008 and December 2012 in our hospital. Weight, BMI, oral glucose tolerance test (OGTT), insulin release test (IRT), C-peptide release test (CRT), glycosylated hemoglobin (HbA1c), and lipid metabolic parameters were measured at baseline and at 3 and 6 months and 1, 2, 3, 4, 5, and 6 years after surgery.

Results The mean age of the 52 patients was 46.8 ± 9.5 years, and 57.7% were male. The mean duration of T2DM was 6.5 ± 4.6 years. Compared with the baseline values, weight and BMI were significantly decreased at several time points after surgery. HbA1c decreased from 8.2 ± 1.7% at baseline to 6.5 ± 1.4% at 3 months, 6.5 ± 1.4% at 6 months, 7.2 ± 1.3% at 4 years, and 7.5 ± 1.2% at 6 years. OGTT, OGTT-IRT, and OGTT-CRT improved after surgery. There was a decrease in triglycerides (TGs), total cholesterol (TC), and low-density lipoprotein (LDL) and an increase in high-density lipoprotein (HDL). At 6 years after surgery, 16.7% of patients achieved complete remission of T2DM, and 66.7% achieved improvement in T2DM.

Conclusion RYGB may be a safe and effective treatment for T2DM patients with a BMI < 32.5 kg/m^2 in China. However, a long-term study without loss to follow-up is necessary for better evaluation.

Keywords Roux-en-Y gastric bypass · Type 2 diabetes · BMI < 32.5 kg/m^2

Introduction

Type 2 diabetes mellitus (T2DM) is now a global health issue that threatens human health. It is estimated that more than 387 million people are suffering from T2DM, and this number is predicted to be 592 million by 2035 [1]. In Asia, the prevalence of diabetes has increased three- to sixfold within the last 20–25 years [2], and now, China has the highest number of diabetes-related deaths [3].

It is well documented that bariatric surgery could effectively ameliorate T2DM in morbidly obese patients (BMI > 35 kg/m^2), and Roux-en-Y gastric bypass (RYGB) is one of the most effective procedures [4, 5]. Increasing evidence indicates that diabetes remission results not only from weight loss but also from weight-independent mechanisms [6, 7]. Bariatric surgery has recently been investigated as a treatment for T2DM in non-severely obese and even non-obese patients (BMI < 35 kg/m^2) [8, 9]. According to the statement of the International Diabetes Federation (IDF), surgery is an accepted option for patients with T2DM and a BMI > 35 kg/m^2 and an alternative treatment for persons with T2DM and BMI 30–35 kg/m^2. In terms of the characteristics of Asian T2DM patients, the BMI threshold should be reduced by 2.5 kg/m^2 [10].

Chinese T2DM patients are usually of normal weight or mildly overweight, with a mean BMI of 24 kg/m^2 [11] and experience deterioration of islet cell function [12]. Therefore, the investigation of bariatric surgery for patients with T2DM and a lower BMI is of increasing significance. Several studies have focused on the effectiveness of bariatric surgery for Chinese T2DM patients with a lower BMI [13–15]. Unfortunately, these studies lacked long-term outcome data.

✉ Liyong Zhu
zly8128@126.com

✉ Shaihong Zhu
shaihongzhu@126.com

[1] Department of General Surgery, Third Xiangya Hospital, Central South University, Changsha 410013, China

Published online: 10 March 2020

The aim of this study was to evaluate the effect of RYGB on Chinese T2DM patients with a BMI < 32.5 kg/m^2 in the long term.

Methods

Patient Population

The study was conducted in the Department of Metabolic and Bariatric Surgery of our hospital. This was a retrospective analysis of prospectively collected data on patients with T2DM who underwent RYGB between October 2008 and December 2012. The institutional ethics committee of our hospital approved the study, and written informed consent was obtained from each patient. All patients were assessed by a multidisciplinary team, including surgeons, endocrinologists, nutritionists, and psychologists, considering benefits, risks, and long-term consequences.

Inclusion and Exclusion Criteria

The inclusion criteria included (1) diagnosis of T2DM based on the criteria of the American Diabetes Association (ADA) [16], (2) level of fasting C-peptide in the oral glucose tolerance test > 1 ng/mL and a ratio of the peak to basic value > 2, (3) BMI < 32.5 kg/m^2, (4) age 18–65 years, and (5) T2DM duration < 15 years. Patients were excluded if they had (1) a history of complex abdominal surgery; (2) serious T2DM complications or other diseases, such as liver cirrhosis, malignant tumor, chronic heart failure, myocardial infarction, or stroke; (3) alcohol or drug dependence; or (4) unstable psychiatric illness.

Surgical Procedure

RYGB operations were performed laparoscopically using a 4-port technique. The procedure involved the creation of a small 15–30-mL gastric pouch from the proximal portion of the stomach with a complete stapled transection. The jejunum was divided 50 cm distal to the ligament of Treitz with a linear cutting stapler, creating the biliopancreatic limb. The distal jejunal end was anastomosed to the gastric pouch, and the biliopancreatic limb was anastomosed to the alimentary limb 100 cm away from the gastrojejunostomy. Both anastomoses were created using a linear stapler followed by a single-layer hand-sewn closure. The staple line was sutured with absorbable sutures, and mesenteric defects were closed.

Postoperative Management

All patients fasted for the day of the operation and early ambulation was encouraged. Patients began to consume clear liquid on the fourth day postoperatively, and a liquid diet was initiated on the seventh day and was followed for 3 weeks. After that, a soft diet was begun for 3 months, followed by a normal diet. Patients without fever, abdominal pain, or operation-related complications were discharged. Multivitamin supplements were routinely taken.

Data Collection

Each patient's demographics, weight, BMI, duration of disease, and laboratory workup were collected and recorded into a prospective database. Follow-up visits were scheduled at 3, 6, and 12 months postoperatively and yearly thereafter. Weight, BMI, oral glucose tolerance test (OGTT), insulin release test (IRT), C-peptide release test (CRT), glycosylated hemoglobin (HbA1c), triglycerides (TGs), total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were recorded in preoperative and postoperative periods. Following a 12-h overnight fasting period, the levels of plasma glucose, serum insulin, and C-peptide were assessed at 0, 30, 60, and 120 min after a 75 g of oral glucose load.

Remission of Diabetes

According to the statement of the ADA [17], complete remission was defined as HbA1c < 6.0% and fasting glucose < 100 mg/dl (5.6 mmol/l) for 1 year in the absence of active pharmacologic therapy. Partial remission was defined as HbA1c < 6.5% and fasting glucose 100–125 mg/dl (5.6–6.9 mmol/l) for 1 year without antidiabetic medication. Improvement was defined as a reduction in HbA1c ≥ 1%.

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation (SD), while categorical variables are expressed as numbers and percentages. Paired *t* test was used to compare baseline and follow-up data. All statistical analyses were performed using SPSS statistical software, version 19.0 (SPSS Inc., Chicago, IL, USA). Values of $P < 0.05$ were considered statistically significant.

Results

This study included 52 patients, 30 women and 22 men, with a mean age of 46.8 ± 9.5 years. Their preoperative mean weight is 76.2 ± 11.4 kg, ranging from 55.2 to 100.5 kg, and their mean BMI is 27.2 ± 3.2 kg/m^2, ranging from 21.0 to 32.1 kg/m^2 (Table 1). There were 13 patients (25.0%) with a BMI less than 25.0 kg/m^2 (normal weight), 15 patients (28.8%) with a BMI from 25.0 to 27.4 kg/m^2 (overweight), and 24 patients

Table 1 Weight and BMI in the preoperative and postoperative periods

	Baseline	3 months	6 months	1 year	2 years	3 years	4 years	5 years	6 years
Follow-up	52	51 (98.1%)	48 (92.3%)	40 (76.9%)	37 (71.2%)	24 (46.2%)	16 (30.8%)	19 (36.5%)	12 (23.1%)
Weight (kg)	76.2 ± 11.4	68.3 ± 10.3*	66.6 ± 7.9*	68.5 ± 9.0*	67.4 ± 10.0*	69.3 ± 8.4*	72.0 ± 6.1*	66.7 ± 9.9*	72.5 ± 7.1
BMI (kg/m^2)	27.2 ± 3.2	24.3 ± 2.6*	25.2 ± 6.3	25.2 ± 3.3*	25.0 ± 3.2*	25.8 ± 2.3*	26.0 ± 1.5	25.0 ± 3.4*	26.3 ± 3.3

BMI, body mass index. *$P < 0.05$ compared with baseline

(46.2%) with a BMI from 27.5 to 32.5 kg/m^2 (class I obesity). The mean duration of T2DM was 6.5 ± 4.6 years, ranging from 3 months to 14 years. Other baseline glycemic indices and metabolic parameters are shown in Tables 2, 3, and 4. All procedures were successfully performed without major complications or mortality. The mean operative time was 206.9 ± 43.7 min.

The changes in weight loss parameters are summarized in Table 1. Compared with the baseline values, weight and BMI were significantly decreased at several time points after surgery. The HbA1c and OGTT showed favorable outcomes, and there are significant and sustained improvements in glycemic parameters after surgery (Table 2). Fasting plasma insulin level decreased from 14.4 ± 18.7 mIU/L to 8.2 ± 10.8 mIU/L at 3 months and decreased at other time points without statistical significance. Plasma insulin levels 30 min after oral glucose showed an increase at 3 months, 1 year, and 4 years after surgery. There was not a statistically significant change in the plasma insulin level at 120 min compared with baseline. The changes in plasma C-peptide levels after the OGTT were similar to those of the insulin levels. Fasting plasma C-peptide levels decreased from 1.9 ± 1.6 μg/L before surgery to 1.4 ± 0.9 μg/L at 6 months and 1.2 ± 0.9 μg/L at 1 year after surgery ($P < 0.05$). However, no statistical significance was observed at 30 or 120 min.

Analysis of lipid metabolic profiles showed a significant improvement in every parameter (Table 3). Compared with the baseline values, the levels of TGs, TC, and LDL decreased at several time points postoperatively. The increase in HDL level was statistically significant only at 4 years after surgery.

Table 4 shows the details of the remission and improvement of T2DM. Complete remission of T2DM was achieved in 30.0%, 27.0%, 20.8%, 31.3%, 21.1%, and 16.7% of the patients at 1, 2, 3, 4, 5, and 6 years after surgery, respectively. After 6 years, the rates of partial remission and improvement were both 25.0%, while 66.7% achieved remission or improvement.

Discussion

Diabetes mellitus is now undoubtedly a global health problem. More than 60% of the diabetes population comes from Asia, and the prevalence is reaching epidemic proportions [2]. Compared with Caucasians, Asians affected by T2DM have a lower BMI and a younger age, and this is partly due to the

Table 2 HbA1c and OGTT outcomes in the preoperative and postoperative periods

	Baseline	3 months	6 months	1 year	2 years	3 years	4 years	5 years	6 years
Follow-up	52	51 (98.1%)	48 (92.3%)	40 (76.9%)	37 (71.2%)	24 (46.2%)	16 (30.8%)	19 (36.5%)	12 (23.1%)
HbA1c (%)	8.2 ± 1.7	6.5 ± 1.4*	6.5 ± 1.4*	7.3 ± 1.5	7.6 ± 1.5	7.4 ± 1.7	7.2 ± 1.3*	7.6 ± 1.8	7.5 ± 1.4*
OGTT (mmol/L)									
0 min	7.9 ± 2.4	6.0 ± 1.8*	6.6 ± 1.6*	6.7 ± 1.5*	6.4 ± 1.9*	6.7 ± 2.2	6.7 ± 2.0*	7.5 ± 2.1	7.7 ± 2.3
30 min	12.8 ± 3.5	11.5 ± 2.9*	12.4 ± 2.7	12.7 ± 2.1	11.8 ± 4.2	11.0 ± 4.4	12.8 ± 3.5	12.1 ± 2.6*	10.9 ± 2.8
120 min	17.0 ± 4.1	11.4 ± 4.6*	12.8 ± 4.1*	12.6 ± 4.2*	13.1 ± 4.4*	12.6 ± 4.1*	13.1 ± 4.1*	12.0 ± 3.5*	12.5 ± 3.1*
OGTT-IRT (mIU/L)									
0 min	14.4 ± 18.7	8.2 ± 10.8*	7.3 ± 7.8	9.0 ± 7.6	8.4 ± 5.7	8.0 ± 4.1	9.1 ± 6.1	5.9 ± 4.3	6.2 ± 4.2
30 min	23.8 ± 23.7	40.4 ± 52.5*	52.3 ± 71.5	59.6 ± 80.4*	36.8 ± 50.3	30.8 ± 16.4	47.2 ± 40.2*	38.8 ± 43.3	53.8 ± 67.7
120 min	40.9 ± 41.8	32.5 ± 29.3	31.1 ± 29.3	30.1 ± 23.8	27.0 ± 16.1	35.3 ± 29.0	45.9 ± 50.1	32.0 ± 31.0	26.8 ± 18.5
OGTT-CRT (μg/L)									
0 min	1.9 ± 1.6	1.4 ± 1.3	1.4 ± 0.9*	1.2 ± 0.9*	1.3 ± 0.8	1.8 ± 1.2	1.4 ± 0.4	1.4 ± 0.6	1.7 ± 1.0
30 min	3.0 ± 2.2	4.3 ± 4.4	4.4 ± 4.3	4.4 ± 4.8	3.3 ± 3.1	4.5 ± 2.1	3.9 ± 2.5	3.9 ± 2.3	4.3 ± 2.9
120 min	5.2 ± 3.3	4.9 ± 2.9	5.6 ± 3.7	4.8 ± 2.9	5.1 ± 3.2	5.7 ± 3.8	4.5 ± 2.4	4.7 ± 3.0	4.7 ± 2.7

HbA1c, glycosylated hemoglobin; *OGTT*, oral glucose tolerance test; *IRT*, insulin release test; *CRT*, C-peptide release test. *$P < 0.05$ compared with baseline

Table 3 Lipid metabolic parameters in the preoperative and postoperative periods

	Baseline	3 months	6 months	1 year	2 years	3 years	4 years	5 years	6 years
Follow-up	52	51 (98.1%)	48 (92.3%)	40 (76.9%)	37 (71.2%)	24 (46.2%)	16 (30.8%)	19 (36.5%)	12 (23.1%)
TGs (mmol/L)	2.3 ± 1.6	1.4 ± 0.8*	1.5 ± 1.0*	1.6 ± 1.4	1.3 ± 0.7*	1.5 ± 0.8	1.5 ± 0.9*	1.6 ± 0.9	1.9 ± 1.2
TC (mmol/L)	4.7 ± 1.1	4.3 ± 0.9*	4.3 ± 1.0	4.1 ± 1.0	4.7 ± 1.8	3.9 ± 1.2*	4.2 ± 1.3	4.7 ± 1.2	4.0 ± 1.7
HDL (mmol/L)	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	1.2 ± 0.5	1.2 ± 0.4*	1.2 ± 0.4	1.1 ± 0.4
LDL (mmol/L)	2.5 ± 0.9	2.4 ± 0.6	2.3 ± 0.7	2.2 ± 0.7	2.4 ± 0.8	2.0 ± 0.8*	1.9 ± 0.8	2.2 ± 0.6	2.0 ± 0.7*

TGs, triglycerides; *TC*, total cholesterol; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein. $^{*}P < 0.05$ compared with baseline

differences in body composition and insulin sensitivity. Asians are prone to developing central obesity with abdominal fat deposition, which may lead to insulin resistance [18]. The mean BMIs of patients with T2DM are 32.3 kg/m^2 in the USA, 29.4 kg/m^2 in the UK, 23.1 kg/m^2 in Japan, 24.9 kg/m^2 in Korea, and 24 kg/m^2 in China [8, 19].

Bariatric surgery, especially Roux-en-Y gastric bypass, has been widely acknowledged as the most effective treatment for T2DM among morbidly obese patients [4, 5]. Increasing evidence has indicated that the glycemic control followed by RYGB is due to hormonal and metabolic mechanisms, not merely reduced calorie intake and weight loss [6, 20]; therefore, the use of RYGB to treat T2DM in mild or even non-obese patients is being considered and implemented. A series of studies have demonstrated the safety and efficiency of RYGB in patients with T2DM and a BMI < 35 kg/m^2 [21–23]. A meta-analysis also showed that Asian patients with T2DM and a BMI < 30 kg/m^2 could achieve significant improvement in glycemic control and lipid profiles in the short and medium terms after bariatric surgery [8].

This study may provide further preliminary evidence that RYGB is an effective option for treating T2DM in non-severely obese Asian patients (BMI < 32.5 kg/m^2) in a mid-term follow-up. Glucose metabolism was shown to improve immediately within 1 year, and the improvement was sustained up to 6 years after surgery. The reduction in mean HbA1c was 1.7% at 3 and 6 months and 0.7% at 6 years after surgery, all with statistical significance. The FPG values decreased significantly within 2 years but decreased slightly in the long term. However, an obvious reduction in the postprandial plasma glucose at 120 min was observed postoperatively and was sustained for up to 6 years. Although there was not much statistical significance in the changes in plasma insulin level when compared with the baseline values, the mean fasting plasma insulin level decreased, while the postprandial plasma insulin levels increased at 30 min and decreased at 120 min. These changes remained stable for up to 6 years, in agreement with the results reported by other studies [24, 25]. The rapid stimulation of beta cells 30 min after the OGTT showed that the delayed insulin secretion pattern ameliorated the early secretion pattern after RYGB. In addition, the C-peptide level is widely used as a surrogate index of pancreatic function. Fasting C-peptide levels decreased and postprandial C-peptide levels at 30 min increased, with trends similar to those observed in other studies [26, 27], suggesting that beta cell function also achieved improvement after surgery. The lipid metabolism indices decreased slightly, as shown in Table 3, including triglycerides, total cholesterol, and LDL, with statistical significance at several time points after surgery.

After gastric bypass surgery, some patients achieved remission or improvement of T2DM, although the rate gradually showed a downward trend over time from 1 to 6 years. Up to 6 years, we achieved a complete remission and total improvement rates of 16.7% and 66.7%, respectively (Table 4), which is a promising evidence for T2DM treatment in mildly obese or non-obese individuals. The remission rates were lower than those of several previous studies. Lee et al. [21] reported that complete remission of T2DM was achieved in 57% of patients with a BMI < 35 kg/m^2 at 1 year and 55% at 2 years after surgery. In Boza's study [23], the highest T2DM complete remission percentage (55.3%) was achieved in the first postoperative year. In the third postoperative year, a total of 53.2% of patients achieved complete T2DM remission. In the another cohort of 64 patients [12], the total (complete and partial)

Table 4 The remission and improvement of T2DM

	Baseline	3 months	6 months	1 year	2 years	3 years	4 years	5 years	6 years
Follow-up	52	51 (98.1%)	48 (92.3%)	40 (76.9%)	37 (71.2%)	24 (46.2%)	16 (30.8%)	19 (36.5%)	12 (23.1%)
Complete remission	–	20 (39.2%)	19 (39.6%)	12 (30.0%)	10 (27.0%)	5 (20.8%)	5 (31.3%)	4 (21.1%)	2 (16.7%)
Partial remission	–	12 (23.5%)	11 (22.9%)	8 (20.0%)	7 (18.9%)	7 (29.2%)	3 (18.8%)	3 (15.8%)	3 (25.0%)
Improvement	–	13 (25.5%)	9 (18.8%)	10 (25.0%)	8 (21.6%)	5 (20.8%)	4 (25.0%)	5 (26.3%)	3 (25.0%)
Total	–	45 (88.2%)	39 (81.3%)	30 (75.0%)	25 (67.6%)	17 (70.8%)	12 (75.0%)	12 (63.2%)	8 (66.7%)

remission rate achieved with the RYGB procedure was 75% at 1 year and 57.4% at 3 years. However, Scopinaro et al. [28] revealed that diabetes could be considered remitted in only 5 (25%) patients with a BMI of 30 to 35 kg/m^2 who underwent gastric bypass surgery at 1, 2, and 3 years. Differences in remission rates were possibly due to racial characteristics, patient selection, follow-up rate, or criteria for remission. Additionally, differences in remission rates may be related to the differences in bypass lengths. The biliary and alimentary limbs were 50 cm and 100 cm, respectively, in our study. However, the biliary/alimentary configuration was 80/120 cm in Lee et al.'s study [21], 50/150 cm in Boza et al.'s study [23], and 100/250 cm in Scopinaro et al.'s study [28]. Such differences may result in varying degrees of diabetes control. According to the ADA, the remission of T2DM was defined as HbA1c in the normal range and FPG < 5.6 mmol/L, without pharmacologic therapy for at least 1 year [17]. The remission rate of T2DM for metabolic surgery was lower when using the new definition than when using the previous definition [29]. However, a meta-analysis, including 5 randomized controlled trials and 6 observational cohort studies, showed the superiority of metabolic surgery to medical treatment in regard to remission of T2DM and comorbidities in patients with a BMI lower than 35 kg/m^2 [30].

These results demonstrated the insufficiency of the existing BMI cutoff as the surgical standard for patients with T2DM to receive metabolic surgery. Therefore, a more comprehensive predictor of diabetes remission is of great significance for Chinese patients and even Asian populations. Several preoperative factors have been reported to be associated with glycemic control, including age, diabetes duration, BMI, and fasting C-peptide level [31–33]. T2DM is acknowledged as a progressive disease with initial insulin resistance and a compensatory increase in insulin production and then followed by beta cell dysfunction. Patients with younger age and shorter duration of T2DM will achieve better surgical outcomes, as the pancreatic reserve can be stimulated by endocrine regulation. Fasting C-peptide is an indicator of insulin secretion and residual beta cell function and could predict the success of metabolic surgery. Fasting C-peptide increases at the early stage of T2DM as a compensation for insulin production, while it decreases as beta cell function is progressively destroyed at the later stage of disease [14]. Therefore, metabolic surgery should be performed on diabetic patients early to achieve the best outcomes, and surgeons should not wait until impaired pancreatic function is found.

The limitations of this study are its relatively small sample size and retrospective nature. The lack of randomization may lead to a selection bias. The major limitation is incomplete follow-up, a common problem in retrospective and long-term studies, which would undoubtedly affect outcome assessment and remission rates. The rates of remission and improvement could be obviously reduced by the patients lost to follow-up, as these patients may have no improvement, which is the mathematical probability. In addition, we need to evaluate the predictors of diabetes remission to choose the most appropriate patients to receive metabolic surgery in the future. However, this is a rare study to evaluate RYGB as a treatment for T2DM in Chinese patients with a BMI < 32.5 kg/m^2 with a long-term follow-up, and the promising results encourage larger and prospective studies in such Asian patients.

Conclusion

Our study shows that RYGB is a safe and probably effective treatment for remission or improvement of T2DM in Chinese patients with a BMI < 32.5 kg/m^2 in the midterm. RYGB could be considered comprehensively as an intervention for Asian patients with T2DM and lower BMI to establish the efficacy of the procedure in Asian populations. Larger prospective studies without loss to follow-up are needed to confirm our findings.

Funding Information The paper was supported by the National Natural Science Foundation of China (81600431).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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