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Original Article

Roux-*en*-Y gastric bypass for Chinese type 2 diabetes mellitus patients with a BMI < 28 kg/m^2: a multi-institutional study

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Abstract

Roux-*en*-Y gastric bypass surgery (RYGB) has been demonstrated to be successful for treating type-II diabetes mellitus (T2DM) patients with a body mass index (BMI) <30 kg/m^2, but reports of RYGB for T2DM patients with a BMI <28 kg/m^2 are lacking. T2DM patients with a BMI <28 kg/m^2 were prospectively recruited to participate in this study in four hospitals. The endpoint was T2DM remission (defined by fasting blood glucose (FBG) level <110 mg/dL and hemoglobin (Hb)A1c level $<6.0\%$ at 12 months postoperatively). Predictors of remission were investigated by univariate and multivariate analyses. Eighty-six patients were assessed. Eighty-five patients underwent RYGB, with one conversion to open surgery. We compared the values of various variables before and after surgery. The mean BMI decreased from 24.68 ± 2.12 to 21.72 ± 2.43 kg/m^2 ($P<0.001$). Fifty-eight (67.4%) patients were not treated by drugs or insulin after surgery, and 20 patients (23.3%) had complete remission of T2DM at 12 months after surgery with an acceptable number of complications. The mean HbA1c level in the remission group was significantly lower than that in the non-remission group. Patients with a higher weight, lower HbA1c level, higher C-peptide level, and higher FBG level were more likely to have T2DM remission in multivariate analyses. In conclusion, RYGB was effective and safe for treating T2DM patients with a BMI <28 kg/m^2. Complete remission can be predicted by cases having a higher weight, lower HbA1c level, higher C-peptide level, and higher FBG level.

Keywords: Roux-*en*-Y gastric bypass, type 2 diabetes mellitus, HbA1c, C-peptide, body mass index, metabolic surgery

Introduction

Type 2 diabetes mellitus (T2DM) is worldwide problem. The number of individuals with T2DM is predicted to increase to 439 million by 2030[1,2]. T2DM is associated with increased morbidity and mortality[3]. Control of T2DM by diet, behavior modification and drug treatment is difficult[4–7]. The mean body mass index (BMI) of T2DM patients in China is only 24 kg/m^2 and glucose control is not ideal[5].

In obese patients, bariatric surgery has been shown to be successful for the treatment of obesity and T2DM[8–12]. Importantly, gastrointestinal (GI) metabolic surgery is accepted as effective treatment for T2DM

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patients with a BMI <35 kg/m^2[3,7,13]. Furthermore, GI metabolic surgery has been demonstrated to be successful in the treatment of T2DM patients with a BMI <30 kg/m^2[14].

Studies[7,9,10,14–16] have suggested that preoperative patient factors such as age, duration of T2DM, control of glycated hemoglobin (HbA1c) level, fasting level of C-peptide, and the BMI are associated with improved glycemic outcomes. However, the results of such studies were from obese patients. Dixon and colleagues[14] reported that weight and weight loss have major influences on the outcomes of gastric bypass surgery in T2DM patients with a BMI <30 kg/m^2.

Roux-*en*-Y gastric bypass surgery (RYGB) is the surgical procedure most often used for gastric bypass surgery. RYGB can provide significant and sustained weight loss[11,17–20]. RYGB for the treatment of T2DM patients with a BMI <28 kg/m^2 has not been reported.

The primary aim of the present study was to determine the efficacy and safety of RYGB for the treatment of T2DM patients with a BMI <28 kg/m^2. The second aim was to investigate the predictors of remission of T2DM in a Chinese population.

Patients and methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of each of the four participating hospitals and complied with the Helsinki Declaration. All participants provided written informed consent to be included in the study.

Patients

Between June 2009 and June 2012, patients were recruited to participate in this study from four hospitals prospectively if they met four criteria: (i) absence of well-controlled T2DM after 6 months of medical treatment; (ii) BMI ≤28 kg/m^2; (iii) aged 18–75 years; (iv) acceptance of the risks associated with RYGB. The diagnosis of T2DM was based on the criteria set by the American Diabetes Association and was considered to be valid if established by an endocrinologist or diabetes specialist. The exclusion criteria were: (i) patients who had undergone GI surgery previously; (ii) pregnancy; (iii) latent autoimmune diabetes.

Preoperatively, patients were assessed by a specialized team (surgeon, endocrinologist, anesthetist, psychiatrist, and dietician). All patients underwent a routine preoperative work-up and counseling in addition to a detailed diabetic work-up. Follow-up visits were scheduled at 1 week as well as 1, 3, 6, 9, and 12 months after surgery. Postoperative data collected included levels of fasting plasma glucose (FPG), fasting C-peptide and HbA1c, medication use, and the BMI.

RYGB

RYGB was undertaken by surgeons with >10 years′ experience of GI surgery in all four institutions. The RYGB procedure comprised creation of a subcardial gastric pouch (15–30 mL), a biliopancreatic limb length of 100 cm, and a Roux limb length of 100 cm with a 20-mm gastrojejunostomy. The gastrojejunostomy was performed using linear staplers and a hand-sewn closure of the enterotomy. The mesenteric and Petersen defects were closed.

Remission of T2DM

Remission of T2DM was defined as a FPG <110 mg/dL and HbA1c <6.0% without the use of anti-diabetic medication 12 months after surgery. The patient′s condition was considered to have improved if the FPG level decreased by >25 mg/dL or the HbA1c level fell by >1%. Surgery was considered to have been unsuccessful if glycemic indices showed no significant improvement or became worsened, or if additional anti-diabetic medication was required.

Statistical analyses

Percentiles, the median, the mean ± standard deviation (SD), and range were analyzed for each continuous variable. Patients were divided into two subgroups for univariate analyses: patients with T2DM remission and patients without T2DM remission. Candidate variables in univariate analyses were: sex, age, weight, BMI, level of FBG, 2-h postprandial blood sugar (2-h PPBS), C-peptide and HbA1c, as well as duration of T2DM. Differences between the two groups with regard to the variables stated above were examined using the unpaired *t*-test for continuous variables and the chi-square test for unordered categorical variables. Multivariate logistic analyses were conducted to determine factors associated with T2DM remission. All *P*-values were two-tailed with 5% significance levels. All statistical analyses were undertaken using STATA v10.0 (Computer Resource Center, Chicago, IL, USA).

Results

Patient characteristics

Overall, 86 patients (46 females) with a BMI <28 kg/m^2 were recruited and RYGB was undertaken in all. Of these 86 patients, 80 patients completed the 12-month follow-up and six patients were lost to follow-up. These six patients were excluded from the

data analysis. The median duration of T2DM was 7 (range, 0.5–17) years. The mean age of the patients was 48.52 (range, 22–72) years. The mean BMI was 24.68 (range, 18.69–27.99) kg/m^2.

Complications of surgery

Of these 80 T2DM patients, no mortalities or serious complications (obstruction, requirement of reoperation) were noted. Conversion to open surgery was required for one patient because of injury to mesenteric blood vessels. Hemorrhage of the upper digestive tract occurred in two patients and both were treated successfully by conservative means. One patient died of gastric cancer 15 months after RYGB. No other complications were observed. Anemia was documented in 7 (8.75%) patients, and alopecia in 6 (7.5%) cases.

Efficacy of surgery

Eighty patients completed 12-month follow-up. Hence, various parameters measured before surgery and at the 12-month follow-up were compared. For instance, the mean insulin level decreased from 15.03±13.91 UI/mL before surgery to 12.97±6.65 UI/mL at 12 months after surgery, and this difference was not significant ($P = 0.234$). The mean C-peptide level increased from 1.38±0.72 ng/mL to 1.56±0.64 ng/mL, and this difference was marginally significantly different ($P = 0.086$). The mean FBG decreased significantly from 177.84±81.36 mg/dL to 118.44±22.32 mg/dL ($P < 0.001$), and the 2-h PPBS decreased significantly from 334.62±111.78 mg/dL to 163.80±48.96 mg/dL ($P < 0.001$).

The mean BMI decreased from 24.68±2.12 kg/m^2 to 21.72±2.43 kg/m^2 ($P < 0.001$), and the mean HbA1c decreased from 8.59±2.08% to 6.52±1.06% ($P<0.001$). Of 80 patients, 58 patients (72.5%) were not treated by drugs or insulin after surgery, and 20 patients (25%) had complete remission of T2DM at 12 months after surgery with an acceptable number of complications. Only three patients (3.75%) had an HbA1c level <6% preoperatively, and an HbA1c level <6% was observed in 22 patients (27.5%) at 12 months after surgery. Additional 55 patients (68.75%) were not treated by drugs or insulin after surgery, improved their control of T2DM, and underwent surgery successfully.

Factors associated with remission of T2DM

Preoperative factors in patients with and without T2DM remission were assessed (***Table 1***). The sex distribution between the two groups was not significantly different ($P = 0.126$), nor was mean age ($P = 0.627$). Interestingly, the mean weight in the remission group was higher although the difference was only marginally significant ($P = 0.065$). The mean HbA1c level in the remission group was significantly lower than that in the non-remission group (7.81 *vs.* 8.89; $P = 0.045$). There was no significant difference between the two groups with regard to the BMI, FBG level, 2-h PPBS, C-peptide level, or T2DM duration (all $P > 0.05$).

Multivariate analyses were applied to investigate the factors associated with T2DM remission (***Table 2***). Similar to univariate analyses, patients with higher weights were more likely to have T2DM remission (75.1–90 Kg *vs.* ≤ 60 Kg; odds ratio (OR), 2.70; 95% confidence interval (CI), 1.27–6.72). Compared with patients with a HbA1c level ≤7% before surgery, patients with a HbA1c level ≤9% (OR, 0.03; 95% CI, 0.00–0.26) and >9% (OR, 0.11; 95% CI, 0.01–0.88) were less likely to have T2DM remission. Patients with a higher C-peptide level were more likely to have T2DM remission than patients with a lower C-peptide level before surgery (>2.0 ng/ml *vs.* ≤1 ng/ml; OR, 1.70; 95% CI, 1.04–2.76). Patients with a higher FBG level were more likely to have T2DM remission than patients with a lower FBG level before surgery (>126 mmol/l *vs.* <126 mmol/l; OR, 3.71; 95% CI,

Table 1 **Univariate analysis of preoperative factors in patients with and without T2DM remission**

Factor	Remission	No remission	*P*
Male/female	13/7	24/36	0.126
Age (years)	49.90±10.51	48.53±10.94	0.627
Weight (kg)	69.85±8.89	65.79±8.22	0.065
BMI (kg/m^2)	25.11±2.10	24.56±2.13	0.317
FBG(mg/dL)	165.06±68.22	187.38±86.58	0.298
2-h PPBS(mg/dL)	320.58±104.58	345.06±112.86	0.396
C-peptide(ng/ml)	1.59±0.48	1.30±0.77	0.130
HbA1C(%)	7.81±2.20	8.89±1.99	0.045
Duration of T2DM (years)	6.07±3.70	7.06±4.52	0.388

BMI, body mass index; FBG, fasting blood glucose; PPBS, postprandial blood sugar; T2DM, type 2 diabetes.

2.10–6.56). Other factors associated with T2DM remission were not found in multivariate analyses.

Discussion

Buchwald et al.[17] suggested that of all 22,094 patients who underwent bariatric surgery, T2DM was resolved completely in 76.8% of patients and resolved or improved in 86.0% of cases. However, the patients included in that review were diagnosed with obesity with a BMI >35 kg/m^2. RYGB is known to achieve sustainable resolution of T2DM in obese subjects. RYGB has been accepted to be effective treatment for T2DM patients with a BMI <35 kg/m^2 in a few studies[3,7,13,14], but the results were based on short-term follow-up and a BMI >25 kg/m^2. The mean BMI of patients with T2DM in China is approximately 24 kg/m^2. Therefore, determining the efficacy and safety of GI metabolic surgery for the treatment of T2DM patients with a BMI <28 kg/m^2 is important.

We found that 58 patients were not treated by drugs or insulin after surgery. Of the 86 patients, 20 patients had complete remission of T2DM at 12 months after surgery with an acceptable number of complications. All patients showed improvement or remission with regard to glycemic control. Patients with higher weights, lower HbA1c level, higher C-peptide level, and higher FBG level were more likely to have T2DM remission.

Dixon et al.[14] reported that excellent glycemic control was achieved in 31 (30%) T2DM patients with a BMI <30 kg/m^2 at 12 months. A Korean study of 403 patients with T2DM and mean BMI of 24.7 kg/m^2 found that remission occurred in 15% of patients[21]. Huang et al. reported that 14 (63.6%) patients with a BMI of 25–35 kg/m^2 showed T2DM remission when treated by RYGB[22]. We found that 25.0% of patients had complete remission of T2DM at 12 months after surgery. Therefore, RYGB for the treatment of T2DM patients with a BMI <28 kg/m^2 was effective.

The safety of RYGB in the treatment of T2DM patients with a BMI <28 kg/m^2 is also important. Changes in the BMI at 12 months in comparison with the mean preoperative BMI value were significant. Nevertheless, BMI values remained within the normal

Table 2 **Multivariate analyses of preoperative factors in patients with and without T2DM remission**

Variable	OR	95% CI	*P*
Weight (kg)			
≤60	1	Reference	
60.1–75	2.23	0.84–5.73	0.104
75.1–90	2.70	1.27–6.72	0.039
Weight difference (kg)			
≤5	1	Reference	
5–10	3.05	0.49–18.95	0.232
>10	1.17	0.16–8.61	0.876
BMI (kg/m^2)			
≤24	1	Reference	
24–25.9	0.96	0.10–9.36	0.970
26–28	2.26	0.19–26.83	0.519
Duration of T2DM (years)			
≤5	1	Reference	
5.1–10	1.06	0.25–4.60	0.936
>10	0.16	0.01–4.01	0.267
C-peptide (ng/ml)			
≤1	1	Reference	
1.1–2.0	2.34	0.90–8.50	0.067
>2.0	1.70	1.04–2.76	0.034
FBG level before surgery (mg/dL)			
≤126	1	Reference	
>126	3.71	2.10–6.56	0.026
HbA1C level before surgery (%)			
≤7	1	Reference	
7.1–9	0.03	0.00–0.26	0.002
>9	0.11	0.01–0.88	0.037

range. Some studies focusing on RYGB undertaken on patients with low BMI values corroborate the finding of a less dramatic postoperative change in the BMI[14,22]. The reason why patient weights did not continue to decrease is not clear. Scopinaro et al. postulated that a homeostatic mechanism permits weight loss relative to the amount of calories, for which the procedure facilitates the absorption of calories. Furthermore, a "blunting" of weight loss is observed[23].

We found that anemia occurred in 7 (8.75%) patients and alopecia in 6 (7.5%) individuals. After diet modification and nutrient supplementation, anemia and alopecia were cured. No malnutrition occurred in our 80 patients. Furthermore, the prevalence of complications after surgery was low and, in general, acceptable. Our prospective multi-institutional study suggested that RYGB in the treatment of T2DM patients with a BMI <28 kg/m^2 was safe.

Univariate and multivariate analyses were applied to investigate the predictors of T2DM remission. Patients with higher weights, lower HbA1c levels, higher C-peptide levels, and higher FBG levels were more likely to have T2DM remission. Studies have suggested that a higher BMI is associated with a higher prevalence of T2DM remission[14,17]. In the present study, the BMI was not significantly associated with the prevalence of T2DM remission, and while preoperative weight was significantly associated with the prevalence of T2DM remission, the weight loss was not. This finding confirms that normalization of glycemic indices is not related to weight loss. Dixon and colleagues showed that weight loss has a major influence on outcomes[14]. In the present study, levels of C-peptide and HbA1c were found to be associated with the prevalence of remission. C-peptide is a reflection of beta-cell function. The mean C-peptide value increased marginally after surgery, but a higher C-peptide level was associated with a higher prevalence of remission. In patients with a BMI <28 kg/m^2, the C-peptide level was an important predictor. Furthermore, a lower level of HbA1c was associated with a higher prevalence of remission. We suggest that drug control of T2DM before surgery may be important.

Our results are encouraging, but the prevalence of remission in patients with a BMI <28 kg/m^2 is lower than that in obese patients. However, an additional 55 patients (64.0%) were not treated by drugs or insulin after surgery. In view of our findings, preoperative weight and levels of HbA1c, C-peptide and FBG are important factors for patient selection when considering surgical treatment for T2DM patients with a BMI <28 kg/m^2.

The present study had three main limitations. First, the follow-up duration was short and long-term results are needed to confirm our findings. Second, although this prospective study was multi-institutional, the sample size in the four centers was not identical. Third, differences of habits and customs in the four regions in which the patients were recruited were not assessed.

In conclusion, our prospective study showed that RYGB for T2DM patients with a BMI <28 kg/m^2 is efficacious, safe and associated with low early morbidity. A total of 25.0% of patients with a BMI <28 kg/m^2 had complete remission of T2DM at 12 months after RYGB with an acceptable number of complications. Complete remission was predicted by higher weight, lower HbA1c level, higher C-peptide level, and higher FBG level. Our findings are interesting, but future studies with a larger sample size (especially in an Asian population) are needed to confirm them.

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