

Original Article

Defining and Predicting Complete Remission of Type 2 Diabetes: A Short-Term Efficacy Study of Open Gastric Bypass

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Key Words

Diabetes · Gastric bypass · Pancreatic function · Remission · Obesity

Abstract

Objective: To investigate the metabolic effects of open Roux-en Y gastric bypass (RYGB) on pancreatic endocrine reserve in overweight/obese Chinese patients with type 2 diabetes during postoperative year 1. **Methods:** Retrospective analysis comparing pre- and postoperative results of oral glucose tolerance tests (OGTT) with determinations of insulin and C-peptide, glycosylated hemoglobin (HbA1c), insulin resistance (HOMA-IR), and BMI at 1, 3, 6, and 12 months in 99 overweight patients (BMI 26.3 ± 4.0 kg/m²; 59 men) with type 2 diabetes at the General Hospital of Chengdu Military Region. **Results:** 79 patients (80%) achieved complete remission (maintaining random blood glucose levels < 11.1 mmol/l, fasting blood glucose levels < 7.0 mmol/l, 2-hour OGTT blood glucose levels < 11.1 mmol/l, and glycosylated hemoglobin < 6.5%). Nine cases (9%) were 'improved' (reduced medication or diet controlled blood sugar), and 11 cases did not meet either criterion ('unchanged'). Patients in complete remission were younger and heavier, more often men, had significantly shorter history of diabetes (4.3 ± 3.8 years vs. 7.6 ± 3.8 years, $p < 0.05$), and exhibited significantly higher fasting and OGTT levels of C-peptide and insulin, and HOMA-IR than the other 2 groups ($p < 0.05$ – 0.01). **Conclusion:** Open gastric bypass achieved complete remission of type 2 diabetes in Chinese overweight/obese, heavier, younger, predominantly male patients with shorter duration of disease exhibiting greater pancreatic endocrine reserve.

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Introduction

China has 92.4 million adult diabetic patients, 93.7% of whom have type 2 diabetes mellitus (T2DM) [1]. Treatment of T2DM has traditionally been dominated by diet and drugs with relatively poor long-term outcomes. In 1967, Mason and Ito [2] first reported the use of gastric bypass, a diversionary operation, to treat morbid obesity. Since then, numerous clinical studies have demonstrated that open gastric bypass effectively treats severe obesity and significantly improves blood glucose and glucose tolerance in patients with T2DM. Pories et al. [3] (n = 330) and Schauer et al. [4] (n = 191) showed that Roux-en Y gastric bypass (RYGB) normalized fasting blood glucose and glycated hemoglobin in 89% and 82% of patients, respectively, and Cummings et al. [5] reviewed 3,568 cases of severely obese RYGB patients, demonstrating remission rates of T2DM of 82–98%. Two recent randomized studies compared laparoscopic gastric bypass to medical therapy, at 1 year [6] and 2 years [7], demonstrating efficacy levels of 42% and 75%, respectively. Gastric bypass is currently recommended for treating obese patients with T2DM in a statement by the International Diabetes Federation from 2011 [8].

In 2001 Kral [9] concluded that treating T2DM patients with gastric bypass at the time was only applicable for severely obese T2DM patients (BMI ≥ 35 kg/m²) in populations with available data appropriate for Caucasian populations. A WHO expert consultation later proposed that the BMI cutoff points for overweight and obesity should be lower for Asian populations than for Caucasians (suggested cutoff points for Asian, >23 kg/m² for overweight and >27.5 kg/m² for obesity) [10]. In November 2010 the Chinese Medical Association instituted Chinese guidelines for diabetes based on racial and regional characteristics. Among the criteria qualified for surgical treatment some BMI criteria were included: i) BMI ≥ 35 kg/m² and ii) BMI 32–34.9 kg/m² with HbA1c $\geq 7\%$. Our clinical research study of 99 patients began in March 2009, before the promulgation of the Chinese guidelines for diabetes. Thus, our 99 patients were neither clinically obese according to Western criteria nor diabetic according to Chinese BMI guidelines.

To fully understand whether gastric bypass is a viable treatment for non-obese T2DM patients, we hypothesized that other factors than BMI affect the efficacy of gastric bypass and are outcome predictors. Our study was designed prospectively to analyze relationships in our Chinese population between BMI related to glucose metabolism, insulin resistance and pancreatic β -cell reserve before and after RYGB.

Material and Methods

General Information

Between March 2009 and March 2011, a total of 195 consecutive T2DM patients underwent gastric bypass at our medical center, 99 of whom had 1 year follow-up data. Inclusion criteria were age ≤ 68 years or ≥ 18 years and clinically diagnosed T2DM with less than 15 years history. Exclusion criteria were: type 1 diabetes, contraindications to open gastric bypass surgery, and psychological contraindications to purely restrictive gastric procedures. The age of the 99 individuals ranged from 19 to 67 years (mean age 47.5 ± 10.5 years) and included 59 men and 40 women. Mean BMI was 26.3 ± 4.0 kg/m², with 30 patients with BMI <24 kg/m² and 30 with BMI >28 kg/m² ('obese').

22 of the 40 women had reached menopause at ages ranging from 39 to 57 years (mean menopause age 49.0 ± 3.7 years).

All of the patients met the 1999 WHO diagnostic criteria for T2DM: fasting blood glucose (FBG) > 7.1 mmol/l and/or blood glucose levels at the 2-hour oral glucose tolerance test (OGTT) time point (2-hour plasma glucose (PG)) > 11.1 mmol/l, excluding autoimmune diabetes (type 1). The time at which T2DM was clinically diagnosed ranged from 1 month to 14 years before surgery (mean 7.3 ± 3.1 years); preoperative

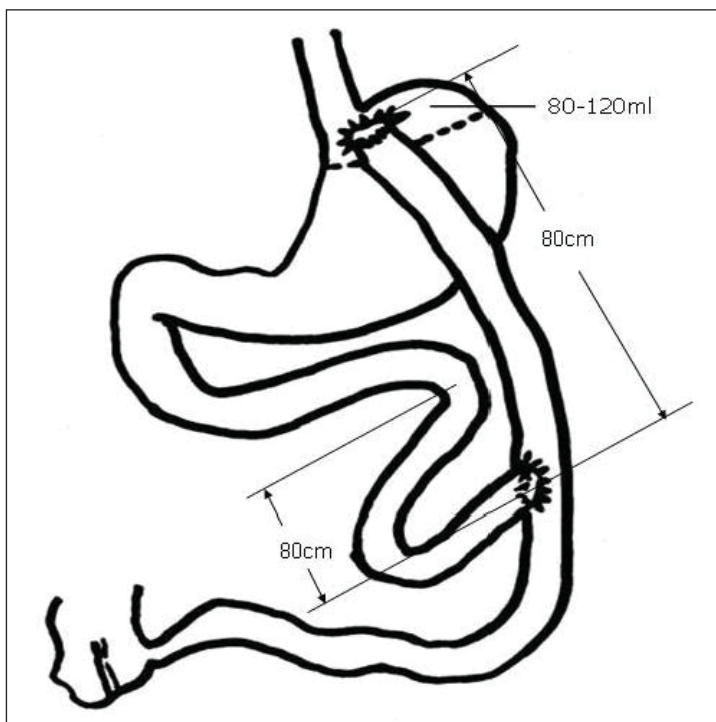


Fig. 1. RYGB consisting of a 80–120 ml gastric pouch with an approximately 3 cm diameter gastro-jejunosomy of the 80 cm Roux-en-Y bypass limb, and an approximately 100 cm biliopancreatic duodeno-jejunal limb. The jejunum is divided 80 cm from the ligament of Treitz, the site of an end-side jejunostomy.

BMI ranged from 23.7 to 48.3 kg/m² (mean 26.3 ± 4.0 kg/m²). None of the patients exhibited diabetic complications. 28 patients were insulin-dependent. All cases were reviewed by the Hospital Ethics Committee and received approval for the operation plan. Subsequently, the patients agreed to gastric bypass surgery and gave written informed consent.

Operation

We followed the procedure described by Tang and colleagues [11]. Through an upper midline laparotomy, the stomach was closed off horizontally 2–4 cm below the cardia resulting in a 100–120 ml proximal gastric pouch, larger than in most series. Approximately 100 cm bilio-pancreatic duodeno-jejunostomy + 80 cm Roux-en Y gastro-jejunostomy approximately 3 cm in diameter were hand-sewn (fig. 1). Vitamin and mineral supplements were routinely started after 1 year.

Detection Indices

Preoperative

i) BMI (weight in kg/height in m²). ii) Blood samples were collected in the morning (7:00 to 8:00) after an overnight fast (10–12 h) by venipuncture. Plasma was separated by centrifugation. The glucose oxidase method (Siemens Healthcare Diagnostics, Erlangen, Germany) was used to determine blood glucose levels. Insulin and C-peptide were measured by luminescence immunometric assay (Siemens Healthcare Diagnostics). Glycated hemoglobin (HbA1c) was detected by immuno-turbidimetry (Siemens Healthcare Diagnostics). iii) OGTTs, C-peptide release tests, and insulin release tests were performed. iv) Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin (IU/l) × fasting glucose (mmol/l) / 22.5. Area under the curves (AUC) for plasma glucose, insulin and C-peptide were calculated by total area using the trapezoidal rule [12]. v) Routine urine tests, renal function tests, eye examinations, and gastric endoscopies were performed to evaluate the existence of diabetic nephropathy, diabetic retinopathy, or reflux esophagitis (or esophageal and gastric varices).

Postoperative

i) Venous blood was drawn from each patient 1, 3, 6, and 12 months after surgery to dynamically examine the levels of anti-insulin antibodies and HbA1c; ii) OGTTs, C-peptide release tests, and insulin release tests were performed for each patient. iii) BMI and HOMA-IR were calculated. Finally, the efficacy of the surgery was assessed.

Criteria for Surgical Efficacy

According to the guidelines of diabetes surgical experts in China (2010) [13], patients were divided into three categories to assess the efficacy of gastric bypass for T2DM: i) complete remission, ii) improved, and iii) unaffected. 'Remission' was defined as maintained long-term random blood glucose levels < 11.1 mmol/l, fasting blood glucose levels < 7.0 mmol/l, blood glucose levels at the 2-hour OGTT time point < 11.1 mmol/l, and HbA1c < 6.5% following surgery in the absence of anti-diabetic treatment. 'Improvement' meant a significantly reduced medication dosage or diet-controlled normal blood glucose levels. Patients not meeting these criteria were considered 'unaffected'.

Statistical Analyses

All statistical analyses were performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). We reported categorical variables as absolute and percentages and continuous variables as means \pm standard deviation. Repeated measures analysis of variance (ANOVA) with Bonferroni confidence interval (CI) adjustment was used to compare the postoperative results at individual time points with the corresponding preoperative data. The normal distribution of these data was verified by a one-sample Kolmogorov-Smirnov test (data not shown). Pearson's test, including a correction for continuity, was adopted to test the proportions of males and females, smokers, alcohol users, and patients with hypertension and dyslipidemia among the surgical efficacy groups. One-way ANOVA followed by a least significant difference (LSD) test was used to compare the surgical efficacy groups for age, weight, and BMI. Multivariate analyses were performed using covariance analysis with an LSD test to compare the preoperative indicators among the surgical efficacy groups while adjusting for gender, age, weight, and BMI. The surgical efficacy was assessed at the observational end point (1 year after the surgery). Differences with a p value of 0.05 or less were considered statistically significant.

Multiple stepwise logistic regression analysis was applied to determine the factors independently predictive of remission of T2DM after gastric bypass, reporting their relative risk and 95% CIs.

Results

General Information

There were no major surgical complications in the 99 patients: 5 had delayed wound healing and 9 experienced transient diarrhea which improved following 3-month drug treatment. The hospital length of stay was 8–18 days following surgery (mean 10.3 ± 4.1 days) according to cultural standards of care in the community.

Surgical Efficacy

Preoperative mean weight, BMI, FPG, 2-hour PG, HbA1c, and HOMA-IR were significantly reduced 1 year after surgery (table 1). 79 (80%) patients had remission, 9 (9%) remained dependent on hypoglycemic medication with an approximately 50% drug reduction, and 11 (11%) were unchanged.

Table 1. Comparison of key indicators before and after surgery

	BW, kg	FPG, mmol/l	2-hour PG, mmol/l	HbA1c, %	BMI, kg/m ²	HOMA-IR
Before surgery	71.8 ± 13.7	10.7 ± 3.3	20.0 ± 4.7	9.1 ± 1.7	26.3 ± 4.0	6.1 ± 4.9
1 month after surgery	66.6 ± 13.0	6.9 ± 1.6*	10.3 ± 3.1*	7.5 ± 1.9*	24.4 ± 3.4	3.9 ± 3.6*
3 months after surgery	63.1 ± 14.6*	6.6 ± 1.3*	8.7 ± 3.1*	6.8 ± 1.9*	23.1 ± 3.1	2.8 ± 3.4*
6 months after surgery	61.8 ± 15.8*	6.3 ± 1.3*	8.2 ± 2.7*	6.2 ± 1.6*	22.6 ± 4.0*	2.9 ± 3.7*
1 year after surgery	59.0 ± 14.1*	5.89 ± 1.2*	7.6 ± 2.8*	5.5 ± 1.8*	21.6 ± 3.6*	2.7 ± 2.9*

BW = Body weight; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; HOMA-IR = homeostasis model assessment of insulin resistance.

*Repeated measures ANOVA with Bonferroni CI adjustment, $p < 0.05$ (compared to the corresponding preoperative levels).

Preoperative Predictors of Surgical Efficacy

The statistical analysis results for the preoperative indicators are shown in table 2. Patients in complete remission were more often male and a mean 6 years younger than the patients in the other groups. The mean duration of diabetes among the complete remission group (4.3 ± 3.8 years) was significantly shorter than that in the unaffected group (7.6 ± 3.8 years; $p < 0.05$), with no significant difference between the improved group and the two other groups. Insulin treatment was evenly distributed among the groups (27–36%; $p = 0.75$, data not shown) and thus did not predict outcome. Smoking, alcohol consumption, hypertension, and dyslipidemia were evenly distributed. The mean weights and BMIs of the complete remission group were significantly higher than those of the other two groups ($p < 0.05$). The means of the C-peptide levels at each time point, blood glucose levels at the 30-min and 1-hour OGTT time points, and insulin levels at the 30-min and 1-hour OGTT time points were significantly different between the complete remission group and the other two groups as were the AUC and the peak levels of C-peptide adjusted for gender, age, weight, and BMI ($p < 0.05$ or 0.01). We found no statistically significant sex differences in any parameter except body weight preoperatively or postoperatively (data not shown). Multivariate analysis revealed a shorter duration of disease, larger BMI, fasting plasma C-peptide and 1-hour OGTT insulin to be independent predictors of postoperative T2DM remission (table 3).

Discussion

Our 1-year complete remission rates of T2DM after open gastric bypass are similar to longer-term outcomes of Pories et al. [14, 15] and those of Schauer et al. [4], and superior to the recent small ($n = 50$) 1-year laparoscopic study of Schauer et al. [6]. In contrast to the 2-year study of 20 patients by Mingrone et al. [7], we found that disease duration was predictive of remission, likely owing to our larger study including patients with shorter diabetes duration, which is in agreement with the early results of Pories et al. [14]. Our findings of consistently higher fasting and stimulated C-peptide and insulin levels measured sequentially in the complete remission group support the importance of preoperative islet

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Table 2. ANOVA analyses of factors that may affect the short-term efficacy of gastric bypass

	Complete remission (n = 79)	Improved (n = 9)	Unaffected (n = 11)
Gender*			
Male (%)	50 (85)	4 (7)	5 (8)
Female (%)	29 (73)	5 (13)	6 (15)
Age [§]	45.9 ± 10.0	51.8 ± 10.3	49.4 ± 11.2
Smoker (%)	24 (30)	2 (22)	1 (9)
Alcohol user (%)	9 (11)	1 (11)	0 (0)
Dyslipidemia (%)	46 (58)	2 (22)	5 (45)
Hypertension (%)	10 (13)	1 (11)	2 (18)
Time from diagnosis, year	4.3 ± 3.8	6.6 ± 3.9 ^a	7.6 ± 3.8 ^a
Weight, kg [§]	74.8 ± 13.8	61.8 ± 10.1 ^a	71.2 ± 11.7 ^a
Weight loss	13.7 ± 3.7	10.1 ± 2.6 ^a	8.5 ± 3.3 ^a
BMI [§]	26.9 ± 4.0	23.8 ± 3.6 ^a	23.7 ± 3.2 ^a
BMI drop	4.9 ± 1.4	3.8 ± 1.8 ^b	3.7 ± 1.8 ^a
Fasting C-peptide [#]	2.1 ± 0.8	1.3 ± 0.5 ^b	1.6 ± 0.6 ^a
OGTT 30-min C-peptide [#]	2.8 ± 1.2	1.8 ± 1.0 ^b	2.2 ± 0.9 ^a
OGTT 1-hour C-peptide [#]	3.8 ± 1.7	1.9 ± 0.8 ^b	2.8 ± 1.3 ^a
OGTT 2-hour C-peptide [#]	4.5 ± 2.2	2.8 ± 1.7 ^b	2.8 ± 1.0 ^a
OGTT 3-hour C-peptide [#]	3.5 ± 1.2	2.7 ± 1.5 ^a	2.5 ± 1.4 ^a
AUC _{C-peptide}	10.72 ± 4.04	6.51 ± 3.36 ^b	7.7 ± 2.9 ^a
Peak _{C-peptide}	4.54 ± 1.75	2.85 ± 1.59 ^b	3.22 ± 1.42 ^a
Fasting blood glucose [#]	10.5 ± 3.0	11.0 ± 3.7	11.2 ± 4.0
OGTT 30-min blood glucose [#]	15.8 ± 3.4	16.9 ± 4.9 ^a	16.7 ± 5.2 ^a
OGTT 1-hour blood glucose [#]	19.4 ± 3.8	20.3 ± 5.5 ^b	20.0 ± 4.3 ^a
OGTT 2-hour blood glucose [#]	18.9 ± 4.0	21.4 ± 5.9	21.8 ± 4.7
OGTT 3-hour blood glucose [#]	14.5 ± 4.0	20.4 ± 5.3	16.8 ± 5.5
AUC _{glucose}	51.59 ± 9.77	58.9 ± 15.59	58.01 ± 10.55
Peak _{glucose}	20.71 ± 3.75	23.07 ± 5.63	23.52 ± 3.02 ^a
Fasting insulin [#]	14.3 ± 9.5	9.7 ± 7.9	9.4 ± 5.3
OGTT 30-min insulin [#]	29.4 ± 20.5	17.7 ± 12.5 ^a	17.2 ± 9.8 ^a
OGTT 1-hour insulin [#]	37.2 ± 27.4	16.9 ± 12.1 ^b	23.8 ± 15.9 ^a
OGTT 2-hour insulin [#]	40.3 ± 38.1	26.5 ± 25.5	18.3 ± 14.1
OGTT 3-hour insulin [#]	24.4 ± 16.7	23.3 ± 18.9	16.6 ± 17.8
AUC _{insulin}	93.38 ± 67.71	55.17 ± 41.07	55.59 ± 36.71
Peak _{insulin}	42.88 ± 32.04	26.04 ± 18.74	26.52 ± 19
HbA1c, % [#]	8.9 ± 1.6	9.8 ± 2.7	9.1 ± 0.8
HOMA-IR [#]	6.9 ± 5.5	4.4 ± 3.5	4.8 ± 2.5

*Pearson's χ^2 test with correcting for continuity. [§]One way ANOVA followed by LSD test. [#]Covariance analysis, adjustment for gender, age, weight and BMI. ^aCompared to the complete remission group, $p < 0.05$. ^bCompared to the complete remission group, $p < 0.01$.

Table 3. Multivariate analysis of predictive factors of T2DM remission after gastric bypass

Predictor	Relative risk*	95% CI	p value
Duration of disease/year	-0.139	-0.252 to -0.025	0.017
BMI/kg/m ²	0.167	0.011–0.323	0.036
Fasting plasma C-peptide/ng/ml	1.089	0.083–2.095	0.034
OGTT 1-hour insulin/mU/l	0.043	0.001–0.084	0.044

CI = Confidence interval.

*Indicates effect of '1-unit' difference in independent variable on dependent variable.

β -cell mass and/or function as a predictor of complete remission, as recently demonstrated by Nannipieri et al. [16] in 32 severely obese Caucasian T2DM patients.

Counter-intuitively complete remission was also associated with greater BMI in our population, although it is important to keep in mind that only 30% were 'obese', with a maximum BMI = 26.3 kg/m², and those with complete remission were younger. Greater absolute weight loss and BMI reduction, as typically found in heavier patients after bariatric surgery, are not necessarily causally related to remission [16].

Fasting and 2-hour OGTT blood glucose levels are the two most widely used indicators of diabetes and pre-diabetes in epidemiological surveys, hyperglycemia being considered a key pathogenetic factor in T2DM [17]. Therefore, it was of interest to examine whether preoperative blood glucose levels are predictors of gastric bypass outcomes. We found no significant differences in fasting or 2-hour OGTT blood glucose levels between the three groups (complete remission, improved, and unaffected), although levels at the 30-min and 1-hour OGTT time points were significantly different. These results agree with a pediatric study in which Tfayli et al. [18] found that 1-hour OGTT blood glucose levels higher than 155 mg/dl (8.6 mmol/l) in overweight or obese patients identified those likely to develop insulin resistance, leading to T2DM. The implication is that the blood glucose level at the 1-hour OGTT time point is an earlier indicator of β -cell function and insulin resistance than fasting hyperglycemia. Impaired glucose tolerance (as in 1-hour OGTT) is known to appear when β -cell function is reduced by 50%. Our study suggests that it is important to examine blood glucose levels at the 30-min and 1-hour OGTT time points prior to surgery in the absence of fasting C-peptide values, which are superior indicators of pancreatic reserve.

We also found that 30-min and 1-hour OGTT insulin levels, corresponding to the second phase of insulin release, were much higher in the complete remission group than in the improved and unaffected groups, also reflecting β -cell function during this time period [19]. HOMA-IR, a ratio of fasting insulin and glucose levels, is commonly used as a convenient measure of insulin resistance in epidemiologic studies [20]. Our patients had a mean preoperative HOMA-IR level of 6.1 ± 4.9 which decreased to normative values of 2.7 ± 2.9 ($p < 0.05$) following surgery; these results are consistent with 1-year data reported by others [21, 22]. Interestingly, the younger, heavier patients with shorter diabetes history and with complete remission had higher baseline levels of HOMA-IR. Insulin dependence at baseline did not predict 1-year outcomes.

Limitations of this study are as follows: Gastric bypass surgery has only recently been introduced in Southwest China and little is known here about its efficacy in T2DM. Yet we were able to recruit a comparatively large number of representative Chinese patients with T2DM in this 1-year study. All operations were done using an open, non-laparoscopic approach owing to local financial constraints. Nevertheless our perioperative and 1-year complication rates compare favorably with laparoscopic series in other studies, partly attributable to the lower BMI in our Chinese population. Our postoperative lengths of stay were longer than those in Western countries owing to cultural community standards with regard to inpatient preoperative work-up and hospital stay until suture removal approximately 8 days postoperatively, which is generally regarded as the standard for hospital discharge in our region. Our short follow-up of 1 year might entail that our patients were still losing weight and had not reached steady state regarding carbohydrate metabolism, body composition, nitrogen balance, plasma lipids, and other indicators. On the other hand, our exceptionally rigorous follow-up with sequential studies of all patients at 1, 3, 6, and 12 months at which time most parameters had reached plateaus at near-normal values implies that nitrogen balance had been achieved. Our proximal gastric pouch volume of 100–120 ml is larger than that in most series, indicating that the anti-diabetic mechanism is mainly related to the nutrient pathway rather than to gastric restriction, the mechanism of banding operations.

In summary, we found that gastric bypass surgery results in excellent outcomes for overweight/obese T2DM Chinese patients, with complete remission in 80% of patients. Owing to the relatively recent recognition of durable remission of T2DM after bypass surgery, there is controversy over the definitions or criteria of cure or remission of this chronic disease previously considered to represent end-stage pancreatic β -cell failure characterized by hyperglycemia. Several large studies with long-term follow-up (>5 years) have demonstrated remission as well as prevention of incident T2DM. Our short-term study in a largely non-obese Chinese population demonstrates that preoperative measures of pancreatic β -cell reserve, such as high levels of fasting plasma C-peptide and 30-min and 1-hour glucose and insulin during OGTT, are predictive of complete remission defined as random blood glucose levels < 11.1 mmol/l, fasting blood glucose levels < 7.0 mmol/l, blood glucose levels < 11.1 mmol/l at the 2-hour time point of an OGTT, and glycated hemoglobin < 6.5%. Six months after surgery, mean HbA1c levels were 6.2%, decreasing to 5.5% at 1 year postoperatively, entailing superior treatment results than most studies of medical treatment. We are continuing to follow up our patients to obtain long-term results. Based on experiences from several large long-term studies in other populations, most of which were severely obese, it is likely that the favorable outcomes in our overweight/obese Chinese patients can be sustained in the long term.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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