

Original Article

Gastric bypass surgery in non-obese patients with type 2 diabetes mellitus: a 1-year follow-up of 58 cases in Chinese

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Abstract: Objective: To investigate the clinical efficacy of gastric bypass surgery in non-obese patients with type 2 diabetes. Methods: Clinical data of 58 non-obese patients with type 2 diabetes (body mass index range from 22.1-25.8 kg/m²) were collected one year after gastric bypass surgery. Collected parameters included fasting plasma glucose, 2-hour postprandial blood glucose, glycosylated hemoglobin, fasting plasma glucagon-like peptide-1 and 2-hour postprandial plasma glucagon-like peptide-1. The insulin resistance index (HOMA-IR = fasting plasma glucose × fasting serum insulin/22.5) and the body mass index were calculated. Results: Of the 58 patients, 48 had stopped taking all hypoglycemic drug treatments and had achieved complete remission (82.8%). Seven patients were unable to completely withdraw from hypoglycemic agents, although their intake of drugs was reduced at least 50% compared to pre-surgical values (12.0%). Three of the cases showed no significant change in blood glucose after surgery (5.2%). In addition, values for fasting plasma glucose, 2-hour postprandial blood glucose, glycosylated hemoglobin and HOMA-IR significantly decreased after surgery. Values for fasting plasma glucagon-like peptide-1 and 2-hour postprandial plasma glucagon-like peptide-1 significantly increased after surgery, and the body mass index at the sixth post-operative month were significantly lower than pre-operative. Conclusion: For non-obese patients with type 2 diabetes, gastric bypass surgery has a significant clinical effect. Potential mechanisms include improvements in insulin resistance and/or increased endogenous intestinal glucagon-like peptide-1 secretion leading to improved insulin secretion.

Keywords: Type 2 diabetes mellitus, gastric bypass surgery, clinical efficacy, glucagon-like peptide-1

Introduction

For many years, gastric bypass surgery has been believed to be a suitable treatment only for obese patients with type 2 diabetes mellitus (T2DM). For example, Kral believes that gastric bypass surgery is only suitable for treating obese patients with T2DM whose body mass index (BMI) is 35 kg/m² or greater [1, 2]. At the "Global Diabetes Surgery Summit Consensus Conference" held in Rome in 2010, the attending experts agree that for patients with a BMI ≥ 35 kg/m² and T2DM that is not effectively controlled by conventional treatment, gastrointestinal surgery (e.g., gastric bypass surgery) is an available treatment [3]. Some studies [4-7] reveal that weight loss is an important factor for the remission of T2DM with obesity. However, little is known concerning surgical

outcomes in non-obese patients with T2DM. More recently, Francesco Rubino, et al [8] observed that Goto-Kakizaki (GK) type 2 diabetic rats could also benefit from gastrointestinal operations without weight loss. This research provides that, in terms of intestinal rearrangements, bypass of the proximal intestine alone is necessary and sufficient to improve diabetes in GK rats. These studies [9, 10] regard that weight loss does not solely account for the antidiabetic effects of gastrointestinal bypass surgery. Should the surgery be necessarily reserved for people with a BMI greater than 35 kg/m²? In China, the majority of patients with T2DM are not obese. In this study, we summarized our observations of the effects of gastric bypass surgery on T2DM in 58 non-obese patients, which had reached the one-year follow-up point.

Table 1. Preoperative characteristics of non-obese T2DM patients (n = 58)

Variable	Mean \pm SD	Range
Age (yr)	48.5 \pm 12.3	32-56
Weight (lb)	143.3 \pm 23.5	119.7-172.4
Body mass index (kg/m ²)	23.4 \pm 2.8	22.1-25.8

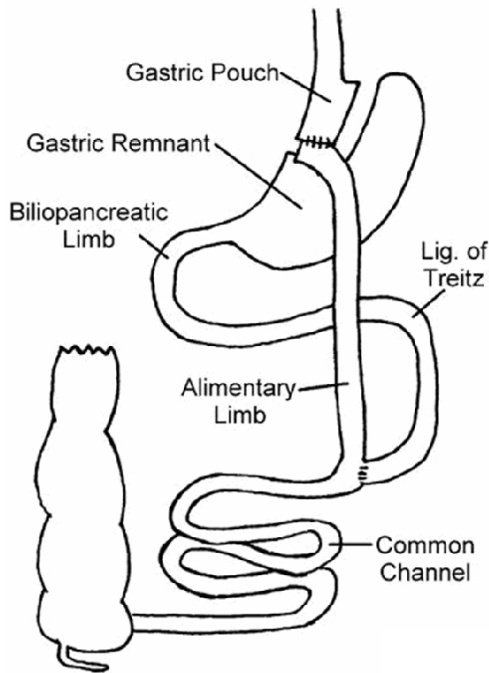


Figure 1. The schematic diagram of operation process.

Data and methods

General information

From March 2009 to August 2009, 58 non-obese T2DM patients were treated with gastric bypass surgery in our hospital and had been followed post-surgery for more than one year. They included 36 males and 22 females, aged between 32 and 56 (48.5 \pm 12.3). Their diagnosis was according to the 2009 American Diabetes Association diagnostic criteria for T2DM [11]. They had been previously diagnosed with T2DM for 1 month to 14 years and their pre-operative BMI range was 22.1-25.8. They had a mean preoperative fasting glucose of 12.0 \pm 3.3 mmol/L and a mean HbA1c of 9.0 \pm 1.8%. None of them had significant complications from diabetes (**Table 1**). Without abdominal surgery contraindications, all patients

voluntarily accepted gastric bypass surgery and signed the informed consent. The surgical plans were discussed and approved by the Hospital Ethics Committee.

Surgical methods

From 2-4 cm to the cardia, the stomach was divided into 2 discrete segments by a surgical stapler: the upper stomach pouch, which was approximately 100 to 120 ml or less in volume, and the lower, bypassed gastric remnant. The jejunum was surgically divided 60 to 180 cm beyond its origin at the ligament of Treitz and reconnected in a Y-shaped fashion so that one arm of the Y (the Roux limb or alimentary limb) drained the small gastric pouch. The Roux limb with about 60 to 140 cm was positioned on the gastric pouch from the front colon (**Figure 1**).

Detection indices and criteria of therapeutic efficacy

Venous blood samples from patients were collected pre-operatively and at 1 week, 2 weeks, 1 month, 3 months, 6 months, 9 months, and 12 months post-operatively. The following indicators were detected: fasting plasma glucose (FPG), 2-hour postprandial blood glucose (2hPG), glycosylated hemoglobin (HbA1c), fasting plasma glucagon-like peptide-1 (FGLP-1) and 2-hour postprandial plasma glucagon-like peptide-1 (2hGLP-1). The insulin resistance index (HOMA-IR = FPG \times FIns/22.5) and the body mass index (BMI = weight in kg/height in m²) were also calculated. A complete remission of diabetes is specified as a fasting glucose level less than the diagnostic criteria for T2DM [11]: fasting blood glucose < 7.0 mmol/L, 2-hour postprandial blood glucose < 11.1 mmol/L, random blood glucose < 11.1 mmol/L.

Statistical analysis

All statistical analyses were performed with SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). Continuous data were presented as mean \pm standard deviation (SD), which were justified as normal distribution by one-sample Kolmogorov-Smirnov test (data not shown). Paired-samples t-test was used to identify differences of FPG, 2hPG, HbA1c, BMI, HOMA-IR, FIns and FGLP-1 detected in pre- and different post-operative time points. $P < 0.05$ was considered statistically significant.

Table 2. The nutrition status of 58 non-obese T2DM patients before and after the gastric bypass surgery

data	Preoperative	Postoperative (1 year)	Normal reference value
Weight (lb)	143.3±23.5	132.4±18.6	
Hemoglobin (g/L)	140.5±17.6	137.8±15.3	115-155
Albumin (g/L)	44.1±8.5	42.7±7.4	35-55
vitamin A (μmol/l)	2.2±0.7	2.0±0.5	1.1-3.1
vitamin B12 (pg/ml)	625±35	591±37	200-900
Vitamin D (ng/ml)	42.1±5.7	39.5±6.2	30-50
Iron (μmol/L)	24.3±3.8	25.1±4.1	10.0-28.5

Results

Surgical outcomes

All of the 58 cases were Chinese, with duration of T2DM less than 15 years. They included 36 males and 22 females, aged between 32 and 56 (48.5±12.3). No serious complications such as anastomotic leaks of the gastrojejunostomy or the jejunojejunostomy, anastomotic bleeding, or other complications occurred after surgery. Fat liquefaction at the incision and delayed wound healing were found in 2 cases. In 5 patients, post-operative frequent diarrhea occurred and the symptoms were gradually relieved after drug treatment. All patients were discharged after a hospital stay of 8 to 17 days (10.3±3.4 days).

All of the 58 patients were followed up for more than one year. Among them, 28 cases used oral hypoglycemic drugs (mean of 2 medications) only, 7 cases used oral hypoglycemic drugs and insulin, and 23 patients used only insulin before the surgical operation. During the postoperative follow-up period, 48 cases (82.8%) achieved disease control, 7 cases (12.0%, 6 cases used insulin only and one used oral hypoglycemic drugs and insulin preoperation) had improvement, and 3 cases (5.2%) had no response. Moreover, the dosage of insulin used in the improved cases was reduced by 50%.

The nutrition status of these patients before and after the surgery

Table 2 lists the mean pre- and postoperative levels of weight, hemoglobin, albumin, vitamin A, vitamin B12, Vitamin D and iron. Vitamins and microelements were routine supplied to all patients after the surgery. Their hemoglobin

and albumin levels 12 month after the surgery were not significantly different from those before the surgery. No case had been diagnosed malnutrition in the one-year follow-up period (**Table 2**).

Test results of blood glucose parameters

Compared to pre-surgical values, FPG, 2hPG, HbA1c, FGLP-1, 2hGLP-1 and HOMA-IR improved significantly in the early post-operative

period (1 month) for the 58 patients, while their BMI was significantly reduced at 6 months post-operative one (**Table 3**).

Discussion

There are 170 million diabetic patients worldwide and these numbers have been forecast to reach 366 million in 2030. T2DM accounts for approximately 85%-90% of all diabetic patients [12]. Effective treatment of T2DM always is a critical issue. Since gastric bypass surgery as a treatment for pathologic obesity was first reported by Mason in 1967 [13], a large amount of clinical data has confirmed that gastric bypass surgery not only is effective in the treatment of pathologic obesity, but also significantly improves blood glucose and glucose tolerance in obese patients with T2DM. After gastric surgery, the majority of these patients are able to maintain normal blood glucose values without hypoglycemic drug treatment. For example, Pories, et al. [14] (330 cases) and Schauer, et al. [7] (191 cases) examined the hypoglycemic effect of gastric bypass surgery in obese patients with T2DM. In 89% and 82% of patients with T2DM, respectively, post-surgical values for fasting blood glucose and glycosylated hemoglobin were in the normal range. Normal blood glucose levels were maintained in these patients for at least 14 years without the use of hypoglycemic drug treatment. In 2003, Schauer's research group reported data from a clinical study of laparoscopic gastric bypass surgery in 1160 obese patients, of which 240 cases were diagnosed with T2DM; in approximately 83% of these obese patients, the blood glucose levels returned to normal values after surgery [7]. In a retrospective analysis of 3568 obese patients treated with gastric bypass surgery, it was found that the diabetes remission

Table 3. Test results of blood glucose parameters before and after the gastric bypass surgery (n = 58)

Time point	FPG mmol/L	2hPG mmol/L	HbA1c %	BMI kg/m ²	HOMA-IR	FGLP-1 pmol/L	2hGLP-1 pmol/L
Pre-	12.0±3.3	15.4±4.5	9.0±1.8	23.4±2.8	6.4±0.5	5.6±1.7	12.3±2.7
1 week	9.6±3.1	12.7±3.7	8.6±1.6	23.3±3.0	5.1±0.6	6.8±2.0	17.5±3.0*
2 week	8.6±2.4*	11.8±3.0	8.1±1.9	22.9±2.9	4.1±0.4*	6.8±3.1*	22.0±3.6*
1 month	6.4±1.6*	9.1±2.7*	7.4±1.5*	22.0±3.2	3.7±0.4*	8.1±2.4*	26.2±3.8*
3 month	6.4±1.1*	8.6±3.0*	5.9±1.3*	22.0±2.8	3.2±0.3*	9.0±2.7*	28.4±4.1*
6 month	6.2±1.0*	8.0±2.3*	5.2±1.3*	21.9±2.8*	2.6±0.5*	9.4±3.2*	31.3±4.7*
9 month	5.9±1.3*	7.8±2.0*	4.7±1.5*	21.8±2.7*	2.6±0.4*	10.2±3.5*	32.0±5.1*
1 year	5.9±1.2*	7.7±1.9*	4.5±1.5*	21.7±2.7*	2.4±0.4*	10.9±4.0*	33.4±5.3*

*Compared to the pre-operative value: $P < 0.05$.

rate after surgery was as high as 82%-98% for patients with concurrent T2DM [15]. In 2004, Buchwald, et al. carried out a meta-analysis on 22,094 cases from 136 publications from the years 1990 to 2003 [16]. The treatment efficacy rate for T2DM was 80% or even higher for obese patients after gastric bypass surgery. Of the patients, 83.7% stayed in long-term remission and 98.9% showed improvements in glucose tolerance. Most patients stopped taking their medication for diabetes, as blood glucose and glycosylated hemoglobin levels returned to normal. Thus, gastric bypass surgery has surprisingly hypoglycemic effects in obese patients with T2DM. Therefore, gastric bypass surgery was adopted in the 2009 Diabetes Treatment Guidelines of the American Diabetes Association. It is now considered the preferred treatment for obesity associated with T2DM [4].

Obese patients with T2DM treated with gastric bypass surgery is well established. However, whether or not this method is suitable for non-obese patients with T2DM has rarely been reported to date. In our opinion, because non-obese T2DM and obese T2DM are essentially the same disease, gastric bypass surgery should be an equally valid treatment for non-obese and obese patients with T2DM. Some data in the literature supported this hypothesis. In one study, a gastrojejunum bypass (GJB) with preservation of an intact gastric volume was performed in 10- to 12-week-old GK rats, a spontaneous non-obese model of type 2 diabetes [17]. Three weeks after surgery, fasting blood glucose had decreased from 159±7 mg/ml to 96.3±0.1 mg/ml ($P < 0.01$). No significant change in fasting blood glucose was observed in the control group that had undergone sham surgery. These results suggested that gastric

bypass surgery could be an effective therapeutic treatment for T2DM in non-obese humans. For the 58 patients in our study, the mean pre-operative BMI was 23.9 kg/m², which is in the non-obese range. The one-year post-operative follow-up found that 48 patients (82.8%) were able to stop taking all hypoglycemic drugs and achieved a complete remission; Seven patients (12.0%) were unable to completely eliminate hypoglycemic agents, but the dosage of insulin required was reduced approximately by 50% compared to pre-surgical needs. However, 3 cases (5.2%) had no response. The clinical indicators of FPG, 2hPG, HbA1c, and HOMA-IR significantly decreased after surgery ($P < 0.05$). Our results suggest that gastric bypass surgery is an effective treatment for the non-obese T2DM.

Gastric bypass surgery has positive effects on T2DM. However, the exact mechanism is not yet fully understood. At present, the primary hypothesis is the "intestinal neuroendocrine theory" [8]. This hypothesis states that the regulation of glucose metabolism by intestinal hormones after gastric bypass surgery is an important mechanism treating T2DM. This hypothesis includes two parts: the foregut and the hindgut hypotheses. The foregut hypothesis states that, in patients with T2DM, the movement of food through the digestive tract stimulates the production of an "insulin resistance factor" that causes insulin resistance, the primary cause of T2DM. After gastric bypass surgery, the food bypasses the upper gastrointestinal tract (the duodenum and the proximal jejunum), reducing the amount of "insulin resistance factor" that is released. Consequently, insulin resistance is reduced or eliminated [18]. The hindgut hypothesis states that after gastric bypass surgery, the entry of undigested or incompletely digest-

ed food into the ileum induces the synthesis and secretion of endocrine hormones in the ileum. These hormones regulate pancreatic endocrine function through the intestinal-pancreatic axis. The results include an increase in the synthesis and secretion of insulin and improved insulin sensitivity of the peripheral tissue, which results in improved control of blood glucose levels [19]. In addition, the weight lost in patients after gastric bypass surgery plays an important role in blood glucose control. Reductions in body weight increase insulin receptor expression in muscle and enhance adiponectin levels. These changes are believed to reduce the hyperglycemic toxic effects of glucose and lipids on pancreatic beta cells and to improve beta cell function. However, our data in this study showed that the values of FPG, 2hPG and HbA1c significantly decreased with significant hypoglycemic effects one month after surgery, while the BMI values did not decrease significantly until six months after surgery. These results suggest that the improvements in diabetics after gastric bypass surgery are not directly related to weight loss. In addition, our study found that the insulin resistance index significantly decreased from 6.4 ± 0.5 to 2.4 ± 0.4 one year after surgery ($P < 0.01$). Therefore, the reduction in insulin resistance in patients with T2DM after gastric bypass surgery might be one of the major mechanisms of treatment of non-obese patients with type T2DM.

The peptide hormone GLP-1 is an important product of pancreatic pro-glucagon. It is primarily secreted by L-cells in the ileum and colonic mucosa. GLP-1 accelerates the synthesis of insulin (pro-insulin), inhibits the secretion of glucagon, increases insulin sensitivity of peripheral tissue, inhibits apoptosis, and promotes the regeneration of pancreatic beta and islet cells, among other actions. Nauck reported that in patients with T2DM, GLP-1 secretion was impaired and the injection of exogenous GLP-1 significantly increased the secretion of insulin [20]. Type 2 diabetics on injectable GLP-1 are able to reduce or eliminate post-prandial insulin. Studies of obese patients with T2DM treated with gastric bypass surgery showed that GLP-1 levels increased significantly and blood glucose lowered after surgery [21, 22]. Studies of the effect of gastric bypass surgery on GLP-1 levels in non-obese T2DM are lacking. In our study, it was observed that non-

obese T2DM showed improved GLP-1 levels after gastric bypass surgery, simultaneously with lower levels of blood glucose, both fasting and post-prandial. Accordingly, we speculate that after the surgery, incompletely digested or undigested food reaches the ileum and the colon too early, stimulating the secretion of GLP-1 by L cells. In turn, insulin secretion is promoted and/or insulin sensitivity is increased, with the result of blood glucose control. Therefore, we propose that GLP-1 plays an important role in blood glucose control in the non-obese T2DM after gastric bypass surgery.

Our research shows that non-obese T2DM patients could also benefit from gastric bypass surgery without weight loss. Changes of intestinal hormone, especially GLP-1, and the exclusion of the proximal small intestine may play important roles in the anti-diabetic effect after surgery.

Disclosure of conflict of interest

None.

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