Changes of blood glucose and gastrointestinal hormones 4 months after Roux-en-Y gastric bypass surgery in Chinese obese type 2 diabetes patients with lower body mass index

Qianlin Wu[1], Zhu Xiao[1], Zhong Cheng[2]*, Haoming Tian[1]*

ABSTRACT

Aims/Introduction: The goal of this study was to evaluate the effect of Roux-en-Y gastric bypass (RYGB) on hyperglycemia and gastrointestinal hormones in Chinese obese type 2 diabetic patients with body mass index (BMI) between 28 and 35 kg/m^2.

Materials and Methods: A total of eight obese type 2 diabetes patients with BMI 28–35 kg/m^2 who underwent RYGB and 10 obese normal glucose tolerance (NGT) patients with no surgery were identified. BMI and blood glucose on baseline, and 2–4 months postoperative, changes of glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY), and oxyntomodulin (OXM) were recorded. Efficacy of RYGB was defined by the percentage of excess weight loss (%EWL) and amelioration of type 2 diabetes.

Results: The %EWL was 53.00 ± 26.25% in 2 month and 63.65 ± 33.71% in 4 month. Glycated hemoglobin changed from 7.2 ± 1.0% preoperative to 6.2 ± 0.9% in 2 month and 6.3 ± 1.2% in 4 month postoperative. The improvement rate of type 2 diabetes 4 months after RYGB was 83.3%. After surgery, area under the curve (AUC) GLP-1 120 increased with no significance. AUC PYY 120 changed from 10.37 ± 5.45 pmol/L/min preoperative to 22.19 ± 10.61 pmol/L/min in 2 month and 22.04 ± 7.73 pmol/L/min in 4 month postoperative. Postoperative AUC OXM 120 was also higher than that of the preoperative level. AUC GIP 120 decreased from 13.06 ± 8.45 pg/mL/min preoperative to 8.71 ± 3.28 pg/ml/min in 2 month and 6.88 ± 2.33 pg/mL/min in 4 month postoperative.

Conclusions: Roux-en-Y gastric bypass has a beneficial effect on weight loss and glucose metabolism in obese type 2 diabetes patients with lower BMI. Postoperative concentrations of GLP-1, PYY and OXM increased, whereas GIP decreased.
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KEY WORDS: Gastrointestinal hormones, Roux-en-Y gastric bypass, Type 2 diabetes

INTRODUCTION

Bariatric surgery is the most effective available treatment for obesity, and is the only treatment that randomized controlled trials have shown to produce effective long-term weight loss and is more effective at ensuring weight loss and controlling comorbidities than medical treatment[1,2]. Bariatric surgery can be divided into three categories: (i) restrictive procedures, such as vertical banded gastroplasty (VBG) and laparoscopic adjustable gastric banding (LAGB); (ii) purely malabsorptive procedures, such as biliopancreatic diversion/duodenal switch (BPD/DS); and (iii) 'hybrid' operations that combine restrictive and bypass components including Roux-en-Y gastric bypass (RYGB). RYGB, the most frequently carried out operation, causes profound weight loss and ameliorates obesity-related comorbid conditions, especially type 2 diabetes mellitus[3]. A systematic review of outcomes after bariatric surgery showed weight loss and remission of type 2 diabetes occurred immediately after Roux-en-Y gastric bypass (RYGB) surgery; after 10 years, excess weight loss was achieved by 52% of patients and 80% of patients experienced an improvement in type 2 diabetes[4]. A large prospective study involving 1,500 patients having a Roux-en-Y gastric bypass reported an excess bodyweight loss of 69% at 1–2 years, and 62% at 3 years[5]. Another systematic review and meta-analysis of the resolution of type 2 diabetes after bariatric surgery found a total remission rate of diabetes in 78% (associated with 55% excess weight loss) of patients and an improvement in 87%[6]. Gastric bypass is thought to exert its beneficial effects through the dual mechanisms of gastric restriction and malabsorption[7]. Besides

Departments of [1]Endocrinology and Metabolism, and [2]Gastrointestinal Surgery, West China Hospital of Sichuan University, Chengdu, China
*Corresponding authors. Haoming Tian Tel.: +86-1-898-060-1303; Fax: +86-28-8542-3459
E-mail address: hmtian999@yahoo.com.cn
Zhong Cheng Tel: +86-1-898-060-1503; E-mail address: chengzhong63@126.com
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structural change of the gastrointestinal tract, remission of type 2 diabetes and obesity might attribute to the amelioration of incretin levels. The incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which are secreted by cells of the gastrointestinal tract in response to meal ingestion, exercise important glucoregulatory effects, including the glucose-dependent potentiation of insulin secretion by pancreatic β-cells[8]. GIP, secreted from K cells, which are located primarily in the duodenum, promotes secretion of insulin and β-cell proliferation, and its plasma concentration remarkably increases after food intake. GLP-1, produced primarily in the ileum and colon by nutrient-stimulated L cells, is an incretin peptide that increases glucose tolerance by enhancing glucose-dependent insulin secretion, suppressing glucagon secretion, inhibiting gastric emptying, increasing β-cell mass (at least in experimental animals) and possibly improving insulin sensitivity[9]. The incretin effect is greatly reduced in patients with type 2 diabetes mellitus, and this 'defect' plays an important contributory role in the insulin insufficiency and chronic hyperglycemia characteristic of this disorder[10]. However, the preponderance of studies have reported similar GLP-1 secretion levels in response to oral glucose in both patients with type 2 diabetes and normal subjects, although small reductions in GLP-1 levels and in late-phase GLP-1 secretion have been observed in patients with diabetes with poor metabolic control and longer duration of the disease[11,12]. Also, most studies have reported normal or higher GIP secretion in patients with diabetes compared with healthy individuals[13]. In addition, peptide YY (PYY) and oxyntomodulin (OXM) participate in the regulation of appetite and weight balance. Therefore, we tested the four aforementioned hormones in the present study.

Obesity is diagnosed on the basis of body mass index (BMI) ≥28 kg/m^2 in Chinese people[14]. There are few reports showing the effects of RYGB carried out in patients with a BMI of 28–35 kg/m^2, as RYGB is usually carried out in patients with a BMI of > 35 kg/m^2 in the West. All eight obese type 2 diabetes patients in the present study had a BMI of 28–35 kg/m^2, and we focused on changes of bodyweight, glucose and gastrointestinal hormones after RYGB of these patients.

MATERIALS AND METHODS

Participants

A total of eight poorly-controlled type 2 diabetic patients (two males and six females) with BMI 28–35 kg/m^2 were recruited to the study. The mean age was 42.25 ± 9.95 years, BMI 30.12 ± 1.73 kg/m^2, waist circumference 95.50 ± 8.83 cm and duration of type 2 diabetes 4.9 ± 2.7 years. Of the patients, four were using insulin alone before surgery, three were taking antidiabetic drugs alone and one patient was taking oral drugs combined with insulin (Table 1). The range of surgery dates was from March 2009 to December 2010. Another 10 obese normal glucose tolerance (NGT) participants who did not undergo any surgery were recruited as controls. The protocol was approved by the ethics committee of the West China Hospital, Sichuan University. Written informed consent was obtained from all participating before the study.

Surgical Technique

The surgical procedure for RGBP consisted of the creation of a 25–50 mL pouch that was divided from the proximal lesser curvature of the stomach and excluded the fundus. The pouch was anastomosed to a Roux limb of the jejunum created by division of the jejunum 75–100 cm distally to the ligament of Treitz and anastomosing the proximal jejunal stump to the jejunum 100–150 cm distally.

Method and Measurement

Preoperative baseline data included the following: bodyweight, BMI, waist circumference, blood glucose, serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and related gastrointestinal hormones including GLP-1, GIP, PYY and OXM. Patients were followed up 2 and 4 months after surgery. Postoperative data included the following: percentage of excess weight loss (%EWL), BMI, waist circumference, blood glucose, serum insulin, gastrointestinal hormones and adverse events. An oral glucose tolerance test (OGTT; 75 g anhydrous dextrose meal) was administrated at baseline and at every visit after surgery. Venous blood was drawn in fasting 30 and 120 min after a glucose meal. Plasma glucose was measured immediately. Blood samples were collected in ethylenediaminetetraacetic acid tubes, centrifuged for 15 min at 4°C and stored at −80°C until assayed. Serum insulin was measured by radio immunoassay. Glycated hemoglobin (HbA_{1c}) was measured by high-pressure liquid chromatography (HPLC; Bio-Rad-D10; Bio-Rad, Hercules, CA, USA). Total GLP-1, GIP, PYY and OXM were measured by enzyme-linked immunosorbent assay (GBD, San Diego, CA, USA). All hormonal and metabolites measurements were carried out in the Endocrinology and Metabolism Laboratory, West China Hospital of Sichuan University. 'Resolution' of type 2 diabetes was defined by fasting plasma glucose (FPG) <7.0 mmol/L and 120 min postprandial plasma glucose (PPG; OGTT) <10 mmol/L after discontinuing antidiabetic medications. 'Improvement' was defined by a reduction of FPG or 120 min PPG greater than 1.39 mmol/L with a reduced dose or frequency of antidiabetic medications after surgery. 'Uncontrolled' was defined as no change (or even deterioration) of blood glucose or dose/frequency of antidiabetic medications after surgery.

Statistical Analysis

Statistical analyses were carried out with SPSS 17.0 (SPSS, Chicago, IL, USA). All data was calculated as mean ± standard deviation. The area under the curve (AUC) was calculated using the trapezoidal method. Insulin resistance was calculated using the HOMA-IR. Student's *t*-test was used to compare baseline data between surgery and control subjects. Analysis of variance tests were used to determine whether a significant change of each parameter occurred during the postoperative follow-up period, and the pairwise comparison was carried out

Table 1 | Changes of body mass index and glycemia of eight surgery patients

Patient no.	1	2†‡	3	4	5	6†	7†	8
Complications	DN	–	HBP	–	HBP	–	–	HBP/DN
Course of DM (years)	3	10	6	3	2	7	3	5
Preoperative								
Treatment	Met	INS	Aca	Rep	INS	Met + Gli + INS	INS	INS
FPG	8.25	7.14	7.81	7.48	7.04	5.12	9.00	5.58
120 min PPG	17.78	17.77	14.32	20.18	15.88	11.84	18.33	17.40
HbA_{1c}	7	7.0	6.1	7.3	6.3	9.5	7.5	7.2
BMI	32.96	28.72	29.07	30.09	32.47	29.48	28.13	30.04
2 months								
Treatment	–	–	–	–	–	–	INS	–
FPG	4.59	9.93	6.41	6.04	5.20	10.30	8.15	6.08
120min PPG	5.50§	20.03††	5.44§	8.37§	6.80§	16.94¶	10.96††	7.61§
Hb_{A1c}	4.4	7.0	5.4	6.9	5.5	6.8	6.7	6.5
BMI	22.48	26.64	24.44	27.31	27.34	26.70	21.64	26.44
4 months								
Treatment	–	Met	–	–	–	–	–	–
FPG	5.13	10.29	7.35	7.11	5.89	9.95	–	–
120min PPG	3.06§‡‡	20.03¶	2.70††‡‡	5.94††	7.62§	9.23††	–	–
HbA_{1c}	5	8.5	5.8	6.2	5.5	6.7	–	–
BMI	20.96	25.81	22.46	27.39	26.06	25.20		

†Patients who suffered from gastrointestinal adverse events, such as vomiting and diarrhea in the 2 months after surgery.
‡Patient who suffered from gastric fistula and infection at 1 week after surgery.
§Resolution.
††Improvement.
¶Uncontrolled.
‡‡Hypoglycemia.
Fasting plasma glucose (FPG), 120minPPG: mmol/L. Glycated hemoglobin (HbA_{1c}), %. Body mass index (BMI), kg/m^2. Aca, acarbose; DN, diabetic nephropathy; Gli, gliclazide; HBP, high blood pressure; INS, insulin; Met, metformin; Rep, repaglinide.

using the Tukey method. A P-value < 0.05 was considered statistically significant.

RESULTS

Baseline data are presented in Table 2. Obviously, blood glucose and HOMA-IR of type 2 diabetes patients were higher than that of NGT controls. Fasting GIP and AUC GIP 120 of the type 2 diabetes group were higher than the NGT group with no statistical significance. Fasting OXM and AUC OXM 120 of the NGT group were significantly higher than that of the type 2 diabetes group.

All of the eight obese type 2 diabetes patients who underwent RGBP came to follow up 2 months after surgery and six finished the follow up 4 months after surgery. BMI greatly reduced from 30.12 ± 1.73 kg/m^2 preoperative to 25.37 ± 2.25 kg/m^2 ($P = 0.001$) in 2 months and 24.65 ± 2.43 kg/m^2 ($P = 0.000$ vs preoperative) in 4 months postoperative. % EWL was $53.00 \pm 26.25\%$ and $63.65 \pm 33.71\%$ for 2 and 4 months postoperative, respectively. In addition, both bodyweight ($P = 0.004$) and waist circumference ($P = 0.004$) reduced after surgery (Table 3).

Generally speaking, the surgery effectively improved glucose profile. Postoperative HbA_{1c} were $6.2 \pm 0.9\%$ and $6.3 \pm 1.2\%$ in 2 and 4 months, respectively. FPG changed with no significance. The 30-min PPG decreased from 13.53 ± 2.90 mmol/L to 11.77 ± 2.30 mmol/L in 2 months, and then increased to 15.38 ± 3.79 mmol/L in 4 months ($P = 0.105$). The 120-min PPG markedly decreased from 16.69 ± 2.61 mmol/L to 10.21 ± 5.46 mmol/L ($P = 0.041$) and 8.10 ± 6.37 mmol/L ($P = 0.012$ vs preoperative) after 2 and 4 months postoperative, respectively. Compared with baseline, AUC glucose (G) 120 decreased with no significance ($P = 0.100$). Secretion of fasting, 120-min insulin and AUC insulin (INS) 120 decreased with the reduction of HOMA-IR. However, 30-min INS showed an increasing trend after surgery. Postoperative $\Delta I30/\Delta G30$ improved although with no statistical significance (Table 3). Two patients achieved resolution of type 2 diabetes with no antidiabetic therapy at all at 2 months, as well as at 4 months after surgery. Two patients achieved resolution at 2 months, but only achieved an improvement at 4 months postoperative. One patient was uncontrolled postoperative. One patient was uncontrolled at 2 months, but achieved some improvement 2 months after that. In the two patients who were followed up for 2 months only, one achieved resolution and one achieved an improvement (Table 1).

Alteration of gastrointestinal hormones is listed in Table 4. Secretion of GLP-1, PYY and OXM showed an overall trend of

Table 2 | Baseline data

	Obese type 2 diabetes patients (n = 8)	Obese NGT patients (n = 10)	T-value	P-value
Age (years)	42.25 ± 9.95	27.60 ± 6.96	3.675	0.002
BMI (kg/m^2)	30.12 ± 1.73	36.48 ± 5.88	−2.942	0.010
Waist circumstance (cm)	5.50 ± 8.83	114.02 ± 15.71	−2.968	0.009
Bodyweight (kg)	75.81 ± 8.26	102.72 ± 14.69	−4.613	0.000
HbA_{1c} (%)	7.2 ± 1.0	5.3 ± 0.4	5.339	0.000
FPG (mmol/L)	7.18 ± 1.30	5.03 ± 0.57	4.722	0.000
120 min PPG (mmol/L)	16.69 ± 2.61	6.41 ± 0.81	11.856	0.000
AUC G 120 (mmol/L/min)	13.92 ± 2.25	7.40 ± 0.65	8.759	0.000
Fasting INS (mU/L)	25.18 ± 29.07	19.79 ± 11.54	0.538	0.598
120 min INS (mU/L)	83.48 ± 45.07	109.02 ± 70.08	−0.891	0.386
AUC INS 120 (mU/L/min)	56.53 ± 22.88	103.43 ± 45.03	−2.671	0.017
HOMA-IR	7.02 ± 6.24	4.42 ± 2.76	1.187	0.253
ΔI30/ΔG30@	3.05 ± 6.32	28.47 ± 14.06	−4.724	0.000
Fasting GLP-1 (ng/mL)	8.980 ± 4.14	8.18 ± 5.04	0.280	0.783
AUC GLP-1 120 (ng/mL/min)	10.59 ± 3.16	10.70 ± 6.90	−0.044	0.965
Fasting GIP (pg/ml)	14.91 ± 11.56	10.13 ± 5.63	1.155	0.265
AUC GIP 120 (pg/mL/min)	13.06 ± 8.45	8.15 ± 4.01	1.630	0.123
Fasting PYY (pmol/L)	4.78 ± 2.67	6.41 ± 2.38	−1.369	0.190
AUC PYY 120 (pmol/L/min)	10.37 ± 5.45	10.97 ± 3.20	−0.294	0.772
Fasting OXM (ng/mL)	3.13 ± 0.98	4.52 ± 1.44	−2.337	0.033
AUC OXM 120 (ng/mL/min)	3.50 ± 0.70	4.70 ± 1.26	−2.401	0.029

AUC, area under the curve; BMI, body mass index; FPG, fasting plasma glucose; G, glucose; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; INS, insulin; OXM, oxyntomodulin; PYY, peptide YY.

Table 3 | Comparison of metabolic parameters preoperative and postoperative

	Preoperative (n = 8)	2 months (n = 8)	4 months (n = 6)	F-value	P-value
Bodyweight (kg)	75.81 ± 8.26	63.79 ± 7.30**	62.67 ± 5.89**	7.423	0.004
%EWL	/	53.00 ± 26.25	63.65 ± 33.71	t = −0.666	0.518
Waist circumstance (cm)	95.50 ± 8.83	85.75 ± 4.06**	83.33 ± 4.32*	7.706	0.004
BMI (kg/m^2)	30.12 ± 1.73	25.37 ± 2.25*	24.65 ± 2.43*	14.607	0.000
HbA_{1c} (%)	7.2 ± 1.0	6.2 ± 0.9	6.3 ± 1.2	2.444	0.114
FPG (mmol/L)	7.18 ± 1.30	7.09 ± 2.13	7.62 ± 2.10	0.155	0.858
30min PPG (mmol/L)	13.53 ± 2.90	11.77 ± 2.30	15.38 ± 3.79	2.538	0.105
120min PPG (mmol/L)	16.69 ± 2.61	10.21 ± 5.46**	8.10 ± 6.37**	6.055	0.009
AUC G 120 (mmol/L/min)	13.92 ± 2.25	10.60 ± 2.71	11.68 ± 3.98	2.609	0.100
Fasting INS (mU/L)	25.18 ± 29.07	9.55 ± 4.88	9.46 ± 2.82	1.939	0.171
30min INS (mU/L)	44.16 ± 32.05	54.47 ± 31.09	65.35 ± 46.82	0.590	0.564
120 min INS (mU/L)	83.48 ± 45.07	48.58 ± 42.61	37.29 ± 22.42	2.736	0.090
AUC INS 120 (mU/L/min)	56.53 ± 22.88	46.64 ± 23.33	47.84 ± 27.68	0.380	0.689
HOMA-IR	7.02 ± 6.24	3.07 ± 2.07	3.08 ± 0.80	2.466	0.112
ΔI30/ΔG30	3.05 ± 6.32	8.76 ± 8.70	8.67 ± 8.01	1.376	0.277

%EWL, percentage of excess weight loss; AUC, area under the curve; BMI, body mass index; FPG, fasting plasma glucose; G, glucose; HbA_{1c}, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; INS, insulin.
*P < 0.01, **P < 0.05 compared with preoperative.

postoperative increase (Figure 1). Fasting, 30- and 120-min GLP-1 and OXM increased after surgery, but the change was not significant. The 30- and 120-min PYY increased significantly after surgery. GIP, however, showed the opposite trend, where its concentration decreased at 4 months at all the time-points during OGTT. The differences of the four hormones between 2 and 4 months were not significant. Postoperative AUC PYY 30/AUC G 30, AUC GLP-1 30/AUC G 30 and

Table 4 | Comparison of gastrointestinal hormones preoperative and postoperative

	Preoperative (n = 8)	2 months (n = 8)	4 months (n = 6)	F-value	P-value
Fasting GLP-1 (ng/mL)	8.80 ± 4.14	10.76 ± 4.06	13.07 ± 9.62	0.853	0.442
30 min GLP-1 (ng/mL)	11.43 ± 3.42	17.33 ± 3.40	19.43 ± 13.12	2.326	0.125
120 min GLP-1 (ng/mL)	10.05 ± 2.91	13.18 ± 3.92	15.65 ± 6.10	2.959	0.076
AUC GLP-1 30 ng/mL/min	10.12 ± 3.71	14.05 ± 3.65	16.25 ± 11.25	1.589	0.230
AUC GLP-1 120 ng/mL/min	10.59 ± 3.16	14.95 ± 3.43	17.22 ± 9.97	2.379	0.120
Fasting GIP (pg/mL)	14.91 ± 11.56	9.47 ± 4.46	8.00 ± 2.93	1.660	0.217
30 min GIP (pg/mL)	14.31 ± 9.11	9.30 ± 3.54	7.34 ± 2.64	2.526	0.106
120 min GIP (pg/mL)	10.78 ± 7.14	7.69 ± 2.91	5.89 ± 1.80	1.909	0.176
AUC GIP 30 pg/mL/min	14.61 ± 9.96	9.38 ± 3.87	7.67 ± 2.74	2.168	0.142
AUC GIP 120 pg/mL/min	13.06 ± 8.45	8.71 ± 3.28	6.88 ± 2.33	2.296	0.128
Fasting PYY (pmol/L)	4.78 ± 2.67	6.73 ± 2.09	7.60 ± 1.52	3.103	0.068
30 min PYY (pmol/L)	13.44 ± 7.22	30.67 ± 16.19**	29.78 ± 11.74	4.767	0.021
120 min PYY (pmol/L)	8.14 ± 4.34	16.04 ± 7.84**	16.54 ± 5.28**	4.556	0.024
AUC PYY 30 pmol/L/min	9.12 ± 4.68	18.70 ± 8.48**	18.69 ± 6.35**	5.177	0.016
AUC PYY 120 pmol/L/min	10.37 ± 5.45	22.19 ± 10.61**	22.04 ± 7.73**	5.171	0.016
Fasting OXM (ng/mL)	3.13 ± 0.98	4.24 ± 1.53	5.13 ± 2.66	2.297	0.128
30 min OXM (ng/mL)	3.90 ± 0.84	4.20 ± 1.81	6.34 ± 4.61	1.647	0.219
120 min OXM (ng/mL)	3.09 ± 0.71	4.31 ± 1.45	5.37 ± 3.32	2.334	0.124
AUC OXM 30 ng/mL/min	3.51 ± 0.84	4.22 ± 1.57	5.74 ± 3.62	1.878	0.180
AUC OXM 120 ng/mL/min	3.50 ± 0.70	4.25 ± 1.58	5.83 ± 3.84	1.895	0.178
AUC GLP-1 30/AUC G 30	1.01 ± 0.48	1.51 ± 0.33	1.37 ± 0.68	2.119	0.148
AUC PYY 30/AUC G 30	0.94 ± 0.53	2.10 ± 1.30	1.71 ± 0.76	3.154	0.066
AUC OXM 30/AUC G 30	0.35 ± 0.10	0.46 ± 0.21	0.51 ± 0.28	1.154	0.337
Fasting GLP-1/fasting GIP	0.74 ± 0.36	1.28 ± 0.64	1.49 ± 0.62**	3.686	0.044
GLP-1 30/GIP 30	1.02 ± 0.44	2.15 ± 1.08**	2.57 ± 0.88*	6.666	0.006
GLP-1 120/GIP 120	1.17 ± 0.50	1.95 ± 1.04	2.74 ± 0.84*	6.370	0.008
Fasting PYY/fasting GIP	0.46 ± 0.30	0.83 ± 0.43	1.01 ± 0.24**	4.942	0.019
PYY 30/GIP 30	1.26 ± 0.76	3.74 ± 2.44**	4.01 ± 0.81**	6.674	0.006
PYY 120/GIP 120	1.03 ± 0.63	2.15 ± 0.91**	2.84 ± 0.69*	10.339	0.001
Fasting OXM/fasting GIP	0.29 ± 0.14	0.51 ± 0.22	0.63 ± 0.15*	6.793	0.006
OXM 30/GIP 30	0.37 ± 0.21	0.54 ± 0.35	0.80 ± 0.30**	3.832	0.040
OXM 120/GIP 120	0.37 ± 0.18	0.62 ± 0.28	0.87 ± 0.34*	6.053	0.009

AUC, area under the curve; G, glucose; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PYY, peptide YY.
*P < 0.01, **P < 0.05 compared with preoperative.

AUC OXM 30/AUC G 30 increased with no significance (P = 0.148, P = 0.066, P = 0.337). Levels of GLP-1/GIP, PYY/GIP and OXM/GIP on all the time-points during OGTT increased significantly after RYGB (Table 4, Figure 2).

There were no fatal cases, and no patients suffered from pulmonary embolism and severe malnutrition. Of the eight patients who underwent RYGB, three suffered from gastrointestinal adverse events, such as vomiting and diarrhea, in the 2 months after surgery; one patient suffered from gastric fistula and infection at 1 week after surgery; and two patients suffered from dumping symptoms that led to hypoglycemia after surgery (Table 1).

DISCUSSION

In the present study, eight obese type 2 diabetes patients had a BMI between 28 and 35 kg/m^2 before surgery. The percentage of patients who achieved at least an improvement of type 2 diabetes at 2 and 4 months postoperative were 75% and 83.3%, respectively, which was similar to previous studies. The explanation for the additional antidiabetic effects of RYGB is not completely understood. Most human studies of RYGB have reported favorable changes in insulin sensitivity[15,16]. Any short-term reduction in energy intake leads to a rapid improvement in plasma glucose levels. Within a few days after caloric restriction, a rapid reduction of liver fat occurs. Liver fat is important in the pathogenesis of insulin resistance and type 2 diabetes[17]. In the present study, insulin secretion at fasting, 120 min and AUC insulin decreased after surgery with simultaneous reduction of HOMA-IR, which indicated an alleviation of insulin resistance. The improvement of postoperative ΔI30/ΔG30 showed an increasing trend of an early phase of insulin secretion.

Another possible mechanism for remission of type 2 diabetes is the melioration of incretin levels. In the present study, the concentration of GLP-1 was similar between the type 2 diabetes and NGT groups at baseline, whereas the concentration of 'GIP

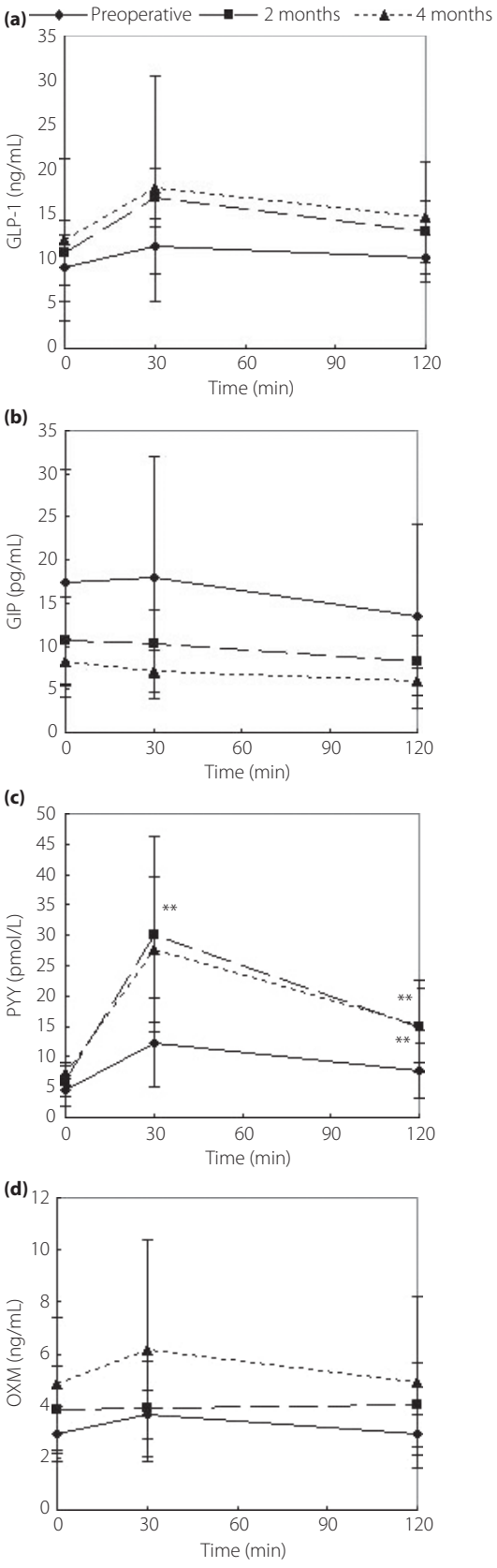

Figure 1 | Glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY) and oxyntomodulin (OXM) levels during the oral glucose tolerance test in patients before and after Roux-en-Y gastric bypass. Data are mean ± standard deviation. $^{**}P < 0.05$ compared with preoperative. ♦, Preoperative; ■, 2 months; ▲ 4 months.

of the type 2 diabetes patients was higher than that of controls'. So the problem seems to be the defects in the insulinotropic responses to the incretins other than impaired secretion. It has been proposed that a GIP post-receptor defect of intracellular machinery and/or a blunted β-cell response to glucose in patients with type 2 diabetes might manifest as an inability of GIP to stimulate late-phase insulin secretion, as it does in healthy individuals[18]; and not only might impairment of GIP activity play a significant role in the pathophysiology of type 2 diabetes, but hypersecretion of GIP might interfere with other metabolic responses to plasma glucose[19]. Even though GLP-1 secretion and activity are maintained, they are unable at physiological concentrations to compensate for the disease-associated impairment of GIP activity. In the present study, plasma concentration of GLP-1 increased while GIP decreased after the RYGB was carried out. These changes might be attributed to the intestinal bypass, which caused an expedited delivery of ingested nutrients to the lower bowel. RYGB creates a gastrointestinal shortcut, which conducts food directly from the stomach to the distal jejunum and diverts nutrients away from the duodenum. GIP-secreting K cells are located primarily in the duodenum. This brings about the decrease of GIP secretion and the unabsorbed nutrients in the distal gut accentuate secretion of GLP-1, as well as PYY and OXM. Low levels of GIP might relieve insulin resistance and regain its insulinotropic effect on β-cells through upregulating the GIP receptor[20]. This explained why the reduction of GIP concentration after surgery was accompanied by the reduction of insulin concentration, as well as HOMA-IR. However, there were also some reports that showed an increase of GIP after bariatric surgery[21]. We speculate that the divergence of GIP levels might be a result of the difference of operation procedure; for example, volume of gastric pouch, position of anastomotic stoma and the distance between the division of the jejunum and the ligament of Treitz. More studies are required to clarify the mechanism of GIP and GLP-1 on regulating glucose metabolism.

Peptide YY is secreted as a 36 amino acid, straight chain polypeptide, and is found in greatest concentrations in the L cells of the terminal ileum, colon and rectum. After secretion, dipeptidyl peptidase IV (DPP-IV) cleaves the N-terminal tyrosine-proline residues from PYY (1–36), producing PYY (3–36). PYY participates in the regulation of appetite and weight balance through hypothalamic-based mechanisms. OXM is released from the L cells of the distal small intestine, 5–30 min after food ingestion and in proportion to meal calorie intake. The raised plasma level of OXM results in postprandial satiety,

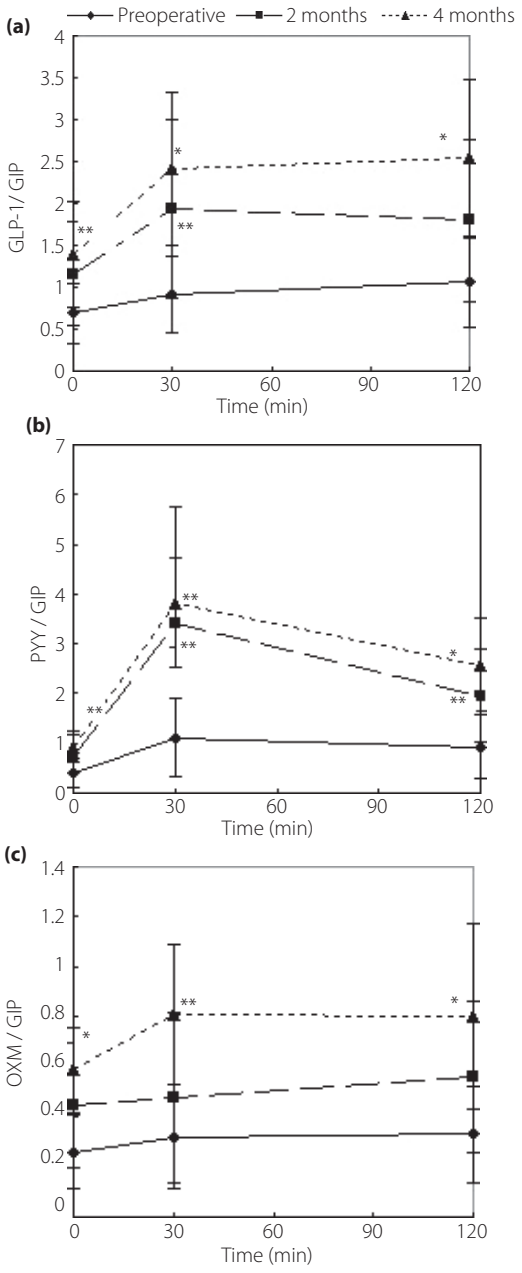

Figure 2 | Levels of glucagon-like peptide-1 (GLP-1)/glucose-dependent insulinotropic polypeptide (GIP), peptide YY (PYY)/GIP and oxyntomodulin (OXM)/GIP during the oral glucose tolerance test in patients before and after Roux-en-Y gastric bypass. Data are mean ± standard deviation. $^{**}P < 0.05$ compared with preoperative; $^{*}P < 0.01$ compared with preoperative. ♦, Preoperative; ■, 2 months; ▲ 4 months.

inhibiting gastric acid secretion and motility. The feeling of satiety produced by OXM is likely because of their effects on the central nervous system, as well as their effect on gastric emptying[22]. OXM might also exert its effects on appetite through suppression of ghrelin, an orexigenic peptide produced by endocrine cells in the oxyntic glands of the stomach[23]. Until now, there were few reports regarding OXM concentration in type 2 diabetes patients and its variation after RYGB. The present study showed type 2 diabetes patients had a lower PYY and OXM concentration than NGT subjects at baseline. Both PYY and OXM increased significantly after RYGB, which might also be attributed to the shortcut procedure that changed the gastrointestinal structure.

In addition, we observed a significant improvement on levels of GLP-1/GIP, PYY/GIP and OXM/GIP (fasting, 30 min, 120 min), which showed that the surgery stimulated secretion of GLP-1, PYY, OXM and inhibited secretion of GIP at the same time.

According to Dixon *et al.*[24], efficacy of surgery for type 2 diabetes is likely influenced by duration of disease, age, severity, β-cell function, whether or not insulin is used, insulin dose, whether or not there are postoperative complications, and lifestyle after surgery. In the present study, the two surgery patients who were uncontrolled at 2 months had longer duration of type 2 diabetes (10 and 7 years), and patient with 7 years duration achieved an improvement at 4 months, whereas the patient with 10 years duration was still uncontrolled at 4 months. This might be because patients with longer duration of disease are apt to lack sufficient residual β-cell mass to recover normal glucose regulation. Usage of insulin reflects the severity of type 2 diabetes on some level. The three patients who did not achieve resolution (patient no. 2, 6 and 7) were using insulin before surgery. Furthermore, patient no. 2 had an irregular diet, overworked, smoked (20 cigarettes/day) and drank frequently after surgery. His diabetes was still uncontrolled 4 months postoperative. Thus, indication for RYGB needs to be strict and cooperation of patients is important for a curative effect of surgery.

Previous studies showed that bariatric surgery procedures were in the lowest category of operative mortality of operations carried out in the USA[25]. Common complications of RYGB were gastrointestinal adverse reactions (gastroesophageal reflux, vomit, diarrhea, etc), anastomotic fistula, pulmonary embolism, infection, dumping symptoms and malnutrition. Patient no. 2, 6 and 7 had frequent vomiting and diarrhea after surgery, and achieved remission by changing dietary habits. Patient no. 2 had gastric fistula and infection at 1 week after surgery. Antibiotics were used and the patient achieved remission later. Patient no. 1 and 3 had dumping symptoms and hypoglycemia at 4 months or so, and they were told to slow their intake. No patient had pulmonary embolism or died in the present study. As the short-term follow up, no malnutrition has been found. The small sample size was the main limitation of the present study. So next step we plan is to enlarge the sample size in our future work.

In conclusion, RYGB might reduce bodyweight and improve blood glucose in type 2 diabetic patients with BMI 28–35 kg/m^2 in a relatively short time, and it might change the secretion of gastrointestinal hormones through altering the gastrointestinal structure that finally affects glucose metabolism.

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There is no conflict of interest.

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