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ORIGINAL CONTRIBUTIONS

# Roux-en-Y Gastric Bypass Surgery Suppresses Hepatic Gluconeogenesis and Increases Intestinal Gluconeogenesis in a T2DM Rat Model

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**Abstract**
*Background* Roux-en-Y gastric bypass (RYGB) is an effective surgical treatment for type 2 diabetes mellitus (T2DM). The present study aimed to investigate the effects of RYGB on glucose homeostasis, lipid metabolism, and intestinal morphological adaption, as well as hepatic and intestinal gluconeogenesis.
*Methods* Twenty adult male T2DM rats induced by high-fat diet and low dose of streptozotocin were randomly divided into sham and RYGB groups. The parameters of body weight, food intake, glucose tolerance, insulin sensitivity, and serum lipid profiles were assessed to evaluate metabolic changes. Intestinal sections were stained with hematoxylin and eosin (H&E) for light microscopy examination. The messenger RNA (mRNA) and protein expression levels of key regulatory enzymes of gluconeogenesis [phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase)] were determined through reverse-transcription PCR (RT-PCR) and Western blotting, respectively.
*Results* RYGB induced significant improvements in glucose tolerance and insulin sensitivity, along with weight loss and decreased food intake. RYGB also decreased serum triglyceride (TG) and free fatty acid (FFA) levels. The jejunum and ileum exhibited a marked increase in the length and number of intestinal villi after RYGB. The RYGB group exhibited down-regulated mRNA and protein expression levels of PEPCK and G6Pase in the liver and upregulated expression of these enzymes in the jejunum and ileum tissues.
*Conclusions* RYGB ameliorates glucose and lipid metabolism accompanied by weight loss and calorie restriction. The small intestine shows hyperplasia and hypertrophy after RYGB. Meanwhile, our study demonstrated that the reduced hepatic gluconeogenesis and increased intestinal gluconeogenesis may contribute to improved glucose homeostasis after RYGB.

**Keywords** Roux-en-Y gastric bypass · Bariatric surgery · Type 2 diabetes mellitus · Glucose homeostasis · Lipid profiles · Morphological adaption · Gluconeogenesis · High-fat diet · Streptozotocin

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## Introduction

Type 2 diabetes mellitus (T2DM), which is characterized by deteriorative insulin secretion function in pancreatic islets and detrimental insulin resistance in insulin-sensitive target organs, comprises approximately 90 % of all cases of diabetes [1]. Currently, the dominating T2DM treatments include lifestyle interventions, pharmacotherapy, and bariatric surgery. A growing body of evidence indicates that bariatric surgery is the most effective treatment for obese T2DM patients; it leads

to rapid and sustained weight loss and significant improvement or complete remission of diabetes [2, 3]. Along with the rising prevalence of diabetes, there has been a constant increase in the total number of bariatric surgeries performed worldwide over the past 10 years. In 2013, the most commonly performed bariatric procedure in the world was Roux-en-Y gastric bypass (RYGB), followed by sleeve gastrectomy (SG), and adjustable gastric banding (AGB) [4]. However, the underlying mechanisms that mediate the anti-diabetic effects that occur after RYGB are still poorly understood.

Some of the potential mechanisms of action of RYGB include alterations in hormone secretion, gut microbiota, and bile acid recycling [5]. Recently, a novel function of intestinal morphological adaptation and glucose metabolism reprogramming after RYGB has also emerged to explain the therapeutic effect of bypass surgery [6, 7]. Accumulating evidence suggests that intestinal gluconeogenesis may be involved in the metabolic improvement after bypass surgery [8]. Although gluconeogenesis has been well investigated in the liver and intestine, the role of gluconeogenesis after RYGB is still inconclusive [9]. This study aimed to investigate the effects of RYGB on glucose homeostasis, lipid metabolism, and intestinal morphological adaption, as well as hepatic and intestinal gluconeogenesis in a T2DM rat model. The results of this investigation may help to provide new insights into the underlying metabolic mechanisms of diabetes remission after RYGB.

## Materials and Methods

### Animals and Diet Protocols

This animal study was approved by the Animal Care and Utilization Committee of Shanghai Sixth People's Hospital. Twenty 6-week-old male Sprague-Dawley (SD) rats were purchased from Sino-British Sippr/BK Lab Animal Ltd. (Shanghai, China). All animals were kept in individual cages under controlled ambient temperature (24 ± 2 °C) and humidity in a 12-h light/dark cycle. All rats had *ad libitum* access to tap water and food unless otherwise stated. All rats were fed a high-fat diet (HFD) (60 % fat, 20 % carbohydrate, 20 % protein, as a total percentage of calories; Research Diets, Inc., NJ, USA) for 4 weeks to induce insulin resistance, followed by an intraperitoneal injection of streptozotocin (STZ) (3 mg/kg) (Sigma, USA) to induce a diabetic state. Rats with non-fasting blood glucose ≥16.7 mmol/l after 72 h, measured in duplicate from tail vein blood with a glucometer (Sinocare Inc., Changsha, China), were considered diabetic and randomly assigned to the sham ($n = 10$) or RYGB group ($n = 10$). One week after the STZ injection, sham or RYGB surgery was performed.

### Surgical Procedures

After a 24-h fast, the rats were anesthetized with an intraperitoneal injection of 1 % sodium pentobarbital solution (5 ml/kg). RYGB operations were initiated by a 4-cm midline incision. The stomach was divided 5 mm below the gastroesophageal junction from the lesser to greater curvature horizontally. The proximal stomach was closed by 4-0 silk suture (Ningbo Medical Needle, China) in a simple interrupted suture technique to create a small gastric pouch, and the distal stomach was closed in a similar fashion. Then, jejunum was transected 10 cm distal to the ligament of Treitz, and the stump was ligated with 4-0 silk suture. The distal limb of jejunum was brought up to the small gastric pouch, and a 7-mm incision was made on the antimesenteric border of the bowel wall and anterior gastric wall along with greater curvature, respectively. The distal limb of jejunum was anastomosed to the small gastric pouch with a side-to-side gastrojejunostomy. The proximal limb of jejunum carrying the biliopancreatic juices was reconnected downward to the Roux limb at a distance of 15 cm from the gastrojejunostomy with a side-to-side jejunojejunostomy. Both the gastrojejunostomy and jejunojejunostomy were performed in a simple interrupted varus suture technique with an about 7-mm anastomosis using 5-0 silk suture (Ningbo Medical Needle, China). Sham surgeries involved the same abdominal incisions and gastrointestinal transections as those in the RYGB group, and reanastomosis was performed at the same sites.

The rats were fed non-residue diets postoperatively at 24 h and followed by standard rodent chow (10 % fat, 70 % carbohydrate, 20 % protein, as a total percentage of calories; Research Diets, Inc., NJ, USA) at four postoperative days, until the study ended.

In all groups, body weight and food intake were measured daily during the first 2 weeks after surgery and then once a week. All rats were starved overnight and euthanized at 8 weeks postoperatively. Jejunum (the proximal bowel about 17 cm below Treitz ligament in sham group or middle bowel of the Roux limb in RYGB group), ileum (about 10 cm above ileocecal junction in both groups), and liver biopsies were fixed in formalin for routine histology examination or stored at −80 °C after flash frozen in liquid nitrogen for quantitative real-time reverse-transcription PCR (RT-PCR) and Western blotting.

### Oral Glucose Tolerance Test and Insulin Tolerance Test

An oral glucose tolerance test (OGTT) and an insulin tolerance test (ITT) were performed at baseline and at two and eight postoperative weeks. For the OGTT, the rats were administered 20 % glucose (1 g/kg) by oral gavage after an overnight fast. Blood glucose was measured using a glucometer at baseline and 30, 60, 90, and 120 min after the glucose administration. For the ITT, the rats were injected intraperitoneally with human insulin (0.5 IU/kg) after an

overnight fast, and blood glucose was measured in the same manner as OGTT.

### Serum Lipid Profiles

After an overnight fast, blood samples were collected from the tail veins of the conscious rats and placed into chilled tubes containing EDTA solution, and serum was immediately extracted. Serum total cholesterol (TC), triglycerides (TGs), and free fatty acids (FFAs) were measured using enzymatic colorimetric assays (NJJCBIO, Nanjing, China).

### Tissue Histological Analysis

The jejunum and ileum of each rat were embedded in paraffin and sectioned. The sections were stained with hematoxylin and eosin (H&E) for light microscopy examination. For assessment of morphological adaptation of intestine, a pathologist who was blinded to other details evaluated all histological sections under microscopy (×100).

### Quantitative Real-Time RT-PCR

Total RNA was extracted with TRIzol (Invitrogen, Carlsbad, CA, USA). Quantitative real-time RT-PCR was performed in a Light Cycler System (Roche Diagnostics, Mannheim, Germany). Analyses were performed on 1 μg cDNA using the SYBR® Premix Ex Taq Master Mix (Takara, China), in a total PCR reaction volume of 10 μl, containing 0.2–0.6 μM of each primer. The following primer pairs were used: PEPCK: 5′-GCCTGTGGGAAAACCAACCT-3′ (forward), 5′-CACCCACACATTCAACTTTCCA-3′ (reverse); G6Pase: 5′-CCCAGACTAGAGATCCTGACAGAAT-3′ (forward), 5′-GCACAACGCTCTTTTCTTTTACC-3′(reverse); β-actin: 5′-ACGGTCAGGTCATCACTATCG-3′ (forward), 5′-GGCATAGAGGTCTTTACGGATG-3′ (reverse).

### Western Blotting

Total protein in the liver and intestine tissue was extracted with RIPA lysis buffer containing protease inhibitors (Beyotime, Shanghai, China), and the concentration of protein was determined using a BCA Kit (Beyotime, Shanghai, China). An equal amount of protein was separated using 10 % SDS-PAGE (Beyotime, Shanghai, China). Then, the separated proteins were transferred onto polyvinylidene fluoride membranes (Millipore, USA). Proteins were detected using antibodies against the following: PEPCK (H-300), G6Pase-α (H-60) (Santa Cruz Biotechnology, Santa Cruz, USA), and β-actin (Cell Signaling Technology, USA). After incubation at 4 °C overnight with primary antibody, the membranes were incubated with HRP-conjugated secondary antibody (Cell Signaling Technology, USA) for 60 min. Protein bands were assessed using ECL reagents (Thermo Scientific, USA) and detected by ImageQuant LAS-4000 mini (GE, USA). The band intensity was assessed with ImageJ software (http://rsb.info.nih.gov/ij, National Institutes of Health, USA).

### Statistical Analysis

Quantitative data are presented as mean ± standard deviation (SD). Areas under curves (AUCs) for OGTT ($AUC_{OGTT}$) and ITT ($AUC_{ITT}$) were calculated by trapezoidal integration. For measurements conducted over time, a two-way analysis of variance (ANOVA) with repeated measures was used. For measurements made at one time point, Student's $t$ test was used for unpaired comparisons. $P < 0.05$ represented a statistically significant difference. SPSS Version 20.0 was used for the statistical analysis.

## Results

### Metabolic Parameters

As shown in Fig. 1, there were no significant between-group preoperative differences in body weight, food intake, OGTT, and ITT. In the sham and RYGB groups, body weight reached its lowest value at 1 week postoperatively. In the sham group, body weight was nearly restored to the preoperative values at 2 weeks postoperatively, while the body weight increase in the RYGB group was blunted from week 2 postoperatively. The postoperative body weights in the RYGB group were significantly lower than those in the sham group at week 3 (Fig. 1a). Daily food intake in the RYGB group was significantly decreased postoperatively between weeks 2 and 8 compared with that in the sham group (Fig. 1b).

The rats in the RYGB group showed significant improvements in glucose tolerance at postoperative weeks 2 and 8, as demonstrated by the lower values of $AUC_{OGTT}$ (Fig. 1c). Compared with the sham group, the RYGB group demonstrated lower postoperative values of $AUC_{ITT}$ at weeks 2 and 8, indicating improved systemic insulin sensitivity (Fig. 1d).

There were no preoperative differences in the fasting serum TC, TG, and FFA concentrations between the sham and RYGB groups. At eight postoperative weeks, the rats in the RYGB group showed significantly lower fasting serum levels of TG and FFAs than those in the sham group (Table 1). The fasting serum level of TC decreased slightly in both groups postoperatively, and there was no significant difference between the sham and RYGB groups (Table 1).

### Histological Changes in the Small Intestine

The jejunum in the RYGB group (Fig. 2b) exhibited marked increases in the length and number of intestinal villi compared

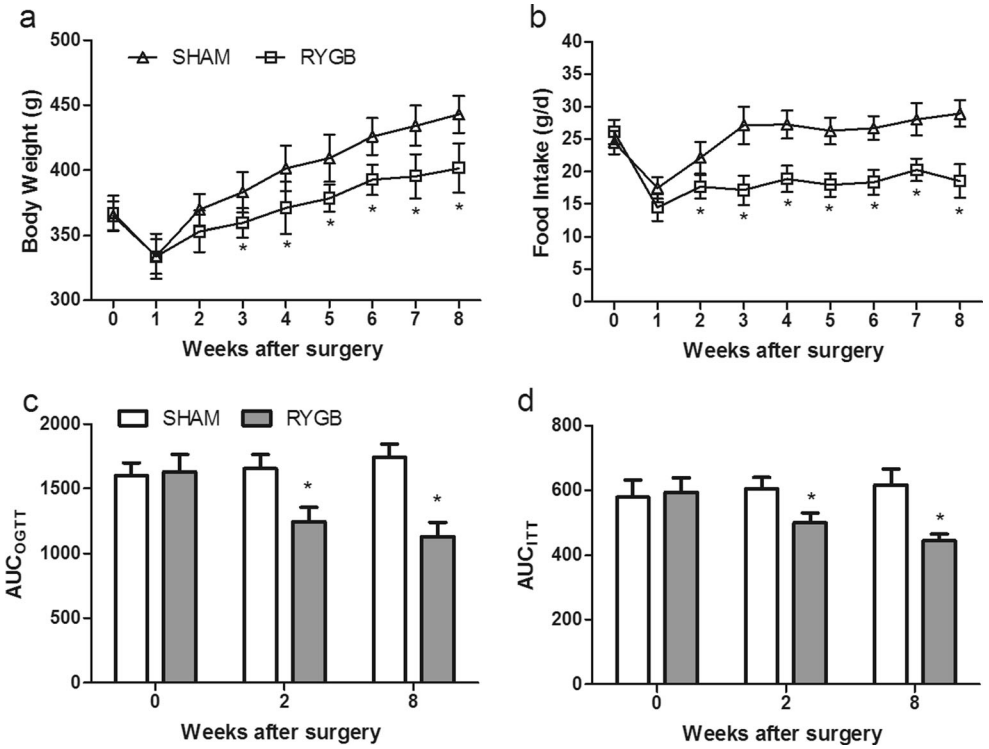


**Fig. 1** Body weight, food intake, $AUC_{OGTT}$, and $AUC_{ITT}$. **a** Body weight of the rats before and after surgery. The RYGB group showed significant weight loss compared with the sham group from postoperative week 3. **b** Food intake of the rats before and after surgery. Food intake of the RYGB group was significantly decreased compared with that of the sham group from postoperative week 2. **c** No difference in the preoperative $AUC_{OGTT}$ values was observed between the sham and RYGB groups. However, the $AUC_{OGTT}$ values were significantly reduced in the RYGB group compared with the sham group at postoperative weeks 2 and 8. **d** There was no significant preoperative difference in $AUC_{ITT}$ between the sham and RYGB groups. However, the $AUC_{ITT}$ values for the rats in the RYGB group were decreased at postoperative weeks 2 and 8 compared with the sham group. Asterisk indicates $P < 0.05$ vs. the sham group

with the sham group (Fig. 2a). Similarly, the ileum in the RYGB group (Fig. 2d) also exhibited marked increases in the length and number of intestinal villi compared with the sham group (Fig. 2c).

### Expression of Key Regulatory Enzymes of Gluconeogenesis

The messenger RNA (mRNA) expression levels of PEPCK and G6Pase in the liver were significantly decreased in the RYGB group compared with the sham group (Fig. 3a). In addition, the protein expression levels of PEPCK and G6Pase in the liver were also markedly reduced in the RYGB group compared with the sham group (Fig. 3b), which was consistent with the results of the corresponding mRNA expression in the liver.

The mRNA expression levels of PEPCK and G6Pase in the jejunum and ileum were significantly increased in the RYGB group compared with the sham group (Fig. 4a, c). The protein expression levels of PEPCK and G6Pase in the jejunum and ileum were also markedly increased in the RYGB group compared with the sham group (Fig. 4b, d), which was consistent with the results of the corresponding mRNA expression in the jejunum and ileum.

**Table 1** Serum lipid profiles

| | Before surgery | | Eight weeks after surgery | |
|---|---|---|---|---|
| | SHAM | RYGB | SHAM | RYGB |
| TC (mmol/l) | 3.15 ± 1.07 | 3.11 ± 0.74 | 2.79 ± 0.72 | 2.34 ± 0.80 |
| TG (mmol/l) | 2.66 ± 0.80 | 2.80 ± 0.91 | 2.70 ± 0.71 | 1.93 ± 0.57* |
| FFAs (mmol/l) | 0.92 ± 0.10 | 0.90 ± 0.12 | 0.90 ± 0.11 | 0.52 ± 0.10* |

Data are the means ± SD

*TC* total cholesterol, *TG* triglycerides, *FFAs* free fatty acids

*$P < 0.05$ vs. the sham group

## Discussion

Bariatric surgery was originally developed to induce weight loss in morbidly obese patients; however, it subsequently proved to be an effective treatment for T2DM. Current guidelines recommend that bariatric surgery be considered for people with T2DM and a BMI >35 kg/m$^2$ [10]. Interestingly, many studies have indicated that bariatric surgery in non-

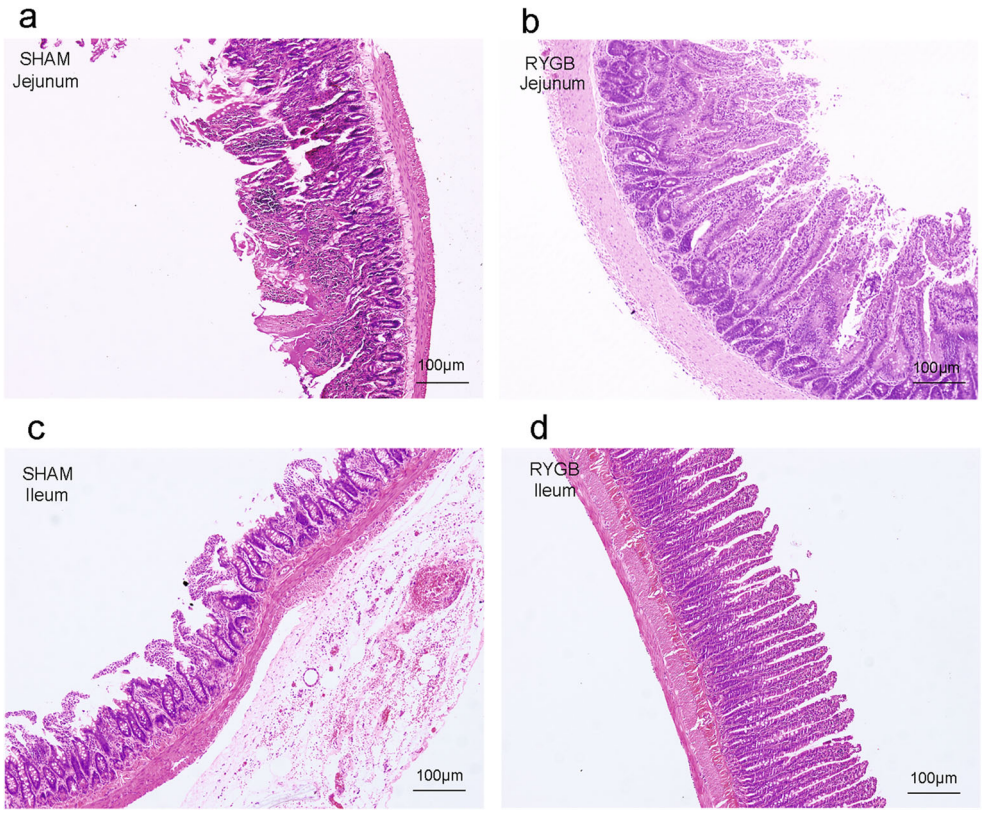


**Fig. 2** Histological changes in the **a**, **b** jejunum and **c**, **d** ileum. The H&E-stained sections (×100) showed histological adaptation of the jejunum and ileum at eight postoperative weeks. The jejunum in the RYGB group (**b**) exhibited marked increases in the length and number of villi compared with the sham group (**a**). The ileum in the RYGB group (**d**) also exhibited marked increases in the length and number of villi compared with the sham group (**c**)

severely obese patients (BMI of 30–35 kg/m$^2$) may also be superior to medical therapy with respect to T2DM remission and glycemic control [11–13]. Recently, the results of three randomized controlled trials have suggested that RYGB is one of the best treatments for T2DM patients with mild–moderate obesity [14–16]. The precise mechanisms underlying the resolution of diabetes after RYGB have not been determined; therefore, the establishment of a RYGB model for T2DM is

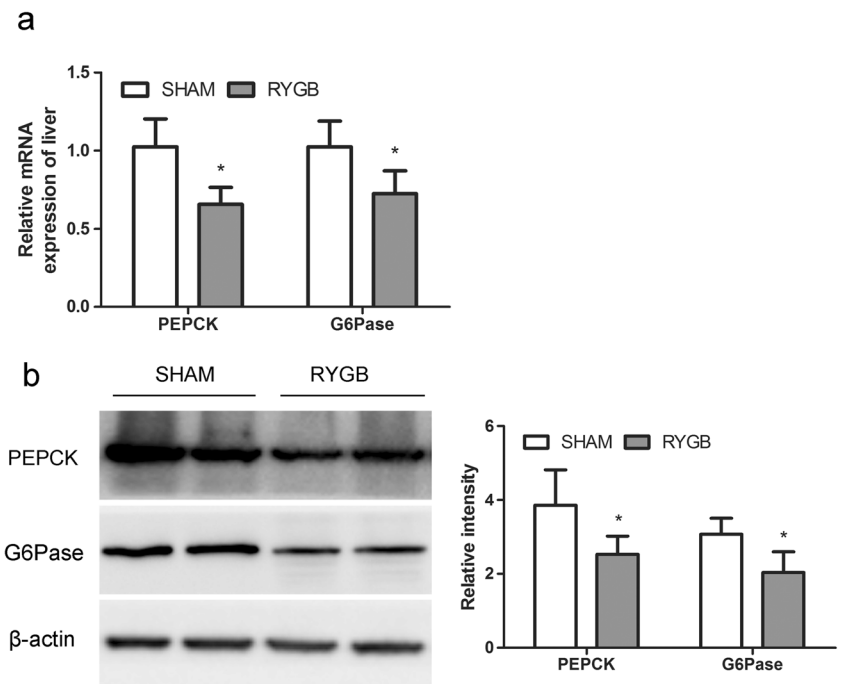


**Fig. 3** Relative mRNA and protein expression levels of the key regulatory enzymes of gluconeogenesis in the liver. **a** The hepatic mRNA expression levels of PEPCK and G6Pase in the RYGB group were significantly lower than those in the sham group at eight postoperative weeks. **b** The protein expression levels of PEPCK and G6Pase were significantly decreased in the RYGB group compared with the sham group at eight postoperative weeks. β-actin was used as an internal control. *PEPCK* phosphoenolpyruvate carboxykinase, *G6Pase* glucose-6-phosphatase. Asterisk indicates $P < 0.05$ vs. the sham group

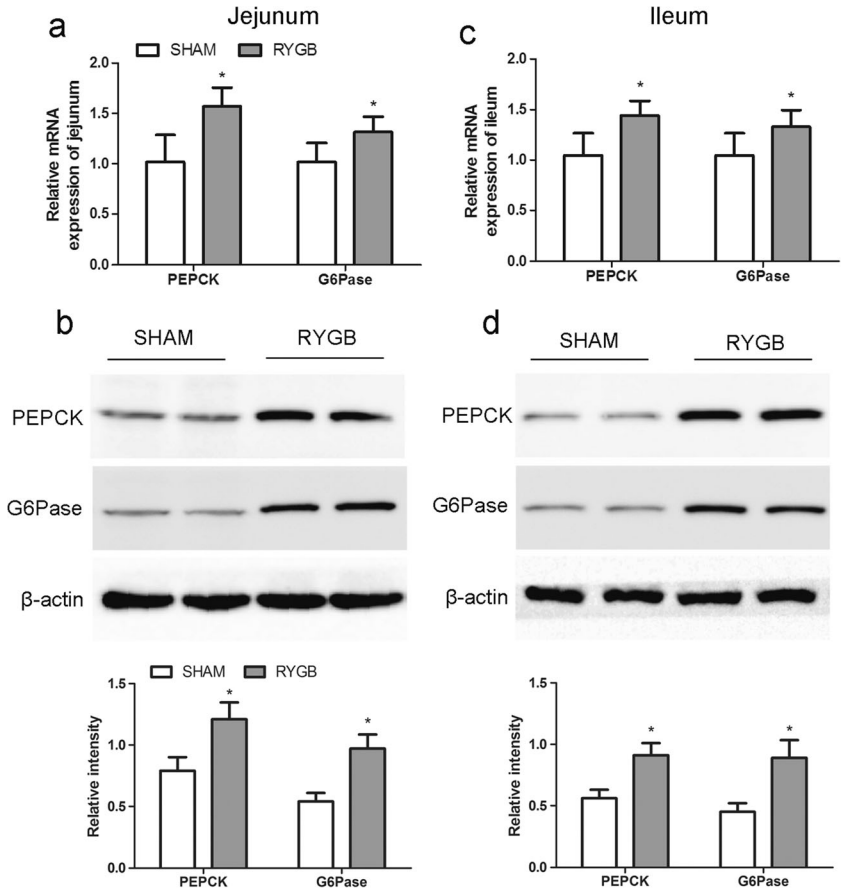


**Fig. 4** Relative mRNA and protein expression levels of the key regulatory enzymes of gluconeogenesis in the small intestine. **a** In the jejunum, the mRNA expression levels of PEPCK and G6Pase in the RYGB group were significantly increased compared with those in the sham group at eight postoperative weeks. **b** In the jejunum, the protein expression levels of PEPCK and G6Pase were significantly increased in the RYGB group compared with the sham group at eight postoperative weeks. **c** In the ileum, the mRNA expression levels of PEPCK and G6Pase in the RYGB group were significantly increased compared with those in the sham group at eight postoperative weeks. **d** In the ileum, the protein expression levels of PEPCK and G6Pase were significantly increased in the RYGB group compared with the sham group at eight postoperative weeks. β-actin was used as an internal control. *PEPCK* phosphoenolpyruvate carboxykinase, *G6Pase* glucose-6-phosphatase. Asterisk indicates $P < 0.05$ vs. the sham group

still important to investigate the intrinsic mechanisms. In the present study, a non-obese T2DM rat model was induced through a HFD and low dose of STZ, which are considered to closely reproduce the pathogenesis and metabolic characteristics of human T2DM [17]. And, this rat model is widely used to study the mechanisms of remission of T2DM after bypass surgery [18–20]. Our preliminary study demonstrated the safety and efficacy of RYGB in non-obese rats with T2DM.

Rapid and sustained weight loss effects after RYGB have been shown in various T2DM rat models [21, 22]. A similar weight-reducing effect was also observed for RYGB in our study, and this effect persisted until the study ended. Comprised of gastric transection and intestinal bypass, it has been well demonstrated that RYGB limits stomach capacity and reduces food intake [23]. In the present study, RYGB also significantly reduced food intake from postoperative week 2 compared with the sham group, indicating the rapid and sustained effect of RYGB on caloric restriction.

In addition to the effects of weight loss and caloric restriction, RYGB also leads to glycemic control or remission of T2DM in more than 70 % of patients [14–16]. Consistent with these results, the present study provided evidence that RYGB induced anti-diabetic effects beginning at postoperative week 2, supported by lower $AUC_{OGTT}$ and $AUC_{ITT}$ values. The OGTT has been the main method of diagnosing diabetes for decades; it detects early diabetes efficiently, as well as subjects with impaired glucose tolerance, according to the mechanisms of glucose homeostasis [24]. This study showed that RYGB lowered the postoperative values of $AUC_{OGTT}$ and improved glucose tolerance. Regarding the ITT, the study showed that RYGB lowered the postoperative values of $AUC_{ITT}$ and improved insulin sensitivity.

Previous studies demonstrated that serum lipid profiles were also improved after bypass surgery in both human and T2DM rat model [15, 25]. Our research showed that serum TG and FFA levels were significantly decreased 8 weeks after

RYGB, which may help to alleviate insulin resistance because excessive serum FFAs are ultimately esterified into TG and both of which promote insulin resistance [26]. These findings raise the possibility that RYGB may improve glucose homeostasis by modulating lipid metabolism.

Several studies previously described that the Roux limb displays morphological changes after RYGB [27, 28]. In accordance with previous studies, we confirmed that the jejunum and ileum both exhibited hyperplasia and hypertrophy after RYGB. However, the importance of the morphological adaptation of the small intestine in terms of the metabolic effects of RYGB remains largely unknown. As direct contact with undigested nutrients appears to be the most potent factor in inducing mucosal adaptation of the small intestine [29], the number of enteroendocrine cells increased passively as the intestine adaptation and that the increased total number of L and I cells is likely to contribute to the higher circulating levels of GLP-1, PYY, and CCK, potentially leading to metabolic improvement after RYGB [7]. The role of intestinal glucose metabolism in T2DM remains largely unknown. A recent study showed that the Roux limb exhibits reprogramming of intestinal glucose metabolism to meet the increased bioenergetic demands of intestinal remodeling changes after RYGB [6]. Saeidi et al. proposed that the reprogramming of intestinal glucose metabolism renders the intestine a major organ for glucose disposal, contributing to glucose homeostasis after RYGB. Therefore, we hypothesized that the morphological and glucose metabolism adaptation of the intestine may occur in response to its advance exposure to undigested nutrients and that it may play an important role in improving glucose homeostasis.

In this study, we also observed postoperative gluconeogenic enzyme changes in the liver and intestine. The mRNA and protein expression levels of PEPCK and G6Pase were increased in the intestine but decreased in the liver after RYGB. PEPCK and G6Pase are key regulatory enzymes of gluconeogenesis, and regulation of these enzymes is important in the control of endogenous glucose production. It is well known and documented that the impaired suppression of gluconeogenesis in the liver promotes hepatic glucose production and aggravates insulin resistance [30]. Hepatic insulin resistance, which is characterized by impaired suppression of hepatic gluconeogenesis and glucose output by insulin, plays a crucial role in the pathogenesis of hyperglycemia and glucose intolerance [31]. Given that hepatic gluconeogenesis plays an important role in glycemic control, the downregulation of hepatic gluconeogenesis may be involved in the improved insulin sensitivity and glucose tolerance resulting from RYGB.

Because RYGB induces morphological changes in the intestinal tract, we reasoned that the expression levels of PEPCK and G6Pase increased to adapt to the changes triggered by RYGB and that the increased expression levels of PEPCK and G6Pase may benefit glucose homeostasis. An intestinal/hepatic regulation hypothesis has been proposed that the shunting of nutrient delivery to distal small intestine after bypass surgery enhances intestinal gluconeogenesis, which activates hepatoportal glucose sensor and decreases food intake and suppresses hepatic glucose production, then improves glucose homeostasis [32]. Recently, Soty et al. found that intestinal gluconeogenesis can signal the hypothalamus and, thus, is capable of modulating numerous functions associated with whole body metabolism that are under the control of the hypothalamus [33]. Thus, the findings in the current study suggest that increased intestinal gluconeogenesis may result in increased portal glucose concentration and decreased hepatic gluconeogenesis, as well as translate a neural signal to the hypothalamus and modulate metabolism throughout the body. These findings are consistent with the findings of previous studies that have demonstrated that enhanced intestinal gluconeogenesis after bypass surgery is responsible for ameliorating hyperglycemia in rats [34, 35].

The present study demonstrated improvements in glucose homeostasis and lipid metabolism accompanied by weight loss and calorie restriction, as well as hyperplasia and hypertrophy of the small intestine after RYGB. The present study also demonstrated that gluconeogenic enzymes were attenuated in the liver and increased in the intestine after RYGB. Together, these study results suggest that RYGB surgery suppresses hepatic gluconeogenesis and stimulates intestinal gluconeogenesis, which may then improve glucose homeostasis. Further studies are needed to determine the role that morphological and metabolic adaption of the small intestine plays in glucose homeostasis after RYGB.

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**Compliance with Ethical Standards**

**Conflict of Interest** All authors declare that we have no conflict of interest.

**Statement of Informed Consent** Informed consent does not apply to this study.

**Statement of Human and Animal Rights** All applicable institutional and national guidelines for the care and use of animals were followed.

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