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Increased β-Cell Mass in Obese Rats after Gastric Bypass: A Potential Mechanism for Improving Glycemic Control

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Background: Over the past few decades, bariatric surgery, especially Roux-en-Y gastric bypass (RYGB), has become widely considered the most effective treatment for morbid obesity. In most cases, it results in enhanced glucose management in patients with obesity and type 2 diabetes (T2D), which is observed before significant weight loss. However, what accounts for this effect remains controversial. To gain insight into the benefits of RYGB in T2D, we investigated changes in the β-cell mass of obese rats following RYGB.

Material/Methods: RYGB or a sham operation was performed on obese rats that had been fed a high-fat diet (HFD) for 16 weeks. Then, the HFD was continued for 8 weeks in both groups. Additional normal chow diet (NCD) and obese groups were used as controls.

Results: In the present study, RYGB induced improved glycemic control and enhanced β-cell function, which was reflected in a better glucose tolerance and a rapidly increased secretion of insulin and C-peptide after glucose administration. Consistently, rats in the RYGB group displayed increased β-cell mass and islet numbers, which were attributed in part to increased glucagon-like peptide 1 levels following RYGB.

Conclusions: Our data indicate that RYGB can improve β-cell function via increasing β-cell mass, which plays a key role in improved glycemic control after RYGB.

MeSH Keywords: Diabetes Mellitus • Gastric Bypass • Insulin-Secreting Cells • Obesity, Morbid

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Background

Roux-en-Y gastric bypass surgery (RYGB) has been applied for treating morbid obesity for several decades, and in most cases, it leads to the resolution of type 2 diabetes (T2D) [1,2], which occurs before any evidence of noticeable weight loss. The underlying mechanism remains controversial. Studies have shown that T2D remission following RYGB is independent of weight loss, as RYGB has a greater effect on blood glucose control than sleeve gastrectomy, despite similar weight loss effects after surgery [3,4]. Other proposed reasons include reduced food intake [5] and changes in incretin hormones. Increased glucagon-like peptide 1 (GLP-1) secretion has been shown to play a major role in T2D remission [4,6,7]. Other factors, including reduced nutrient absorption, gut bacteria [8,9], and bile acids [10,11], may also contribute.

Another important factor might be the enhanced β-cell function resulting from the increased β-cell mass. Previous studies have revealed that the recovery of β-cell function following bariatric surgery facilitates the resolution of diabetes [12,13]. However, there are several obstacles to generating data using human islets, including the difficulty of obtaining human pancreatic tissue and the wide variation among individuals. Nevertheless, elucidating the changes that occur in β-cells and islets following RYGB is of great significance because it will help reveal the mechanisms by which diabetes remission occurs, as well as helping to identify new strategies for treating obese diabetic patients. Thus, we performed a study using a rat model of obesity and RYGB.

Material and Methods

Animals and diets

Male Sprague-Dawley rats (4 weeks old, the Animal Center of Chongqing Medical University, Chongqing, China) were kept under a 12-h artificial light-dark cycle at 23±2°C and had free access to water throughout the experiment. After 1 week of acclimatization, the rats were given either a Western high-fat diet (HFD) with 45% of kcal derived from fat (#D12451; 4.73 kcal/g, 45% from fat; Research Diets, New Brunswick, NJ, USA) or a normal chow diet (NCD) (#D12450B; 3.85 kcal/g, 10% from fat; Research Diets) as the control. All studies were approved by the Ethics Committee of Chongqing Medical University.

In vivo phenotyping

Body weight was recorded weekly on the same day. An intraperitoneal glucose tolerance test (IPGTT) was conducted 6 weeks postoperatively. After 8 h of fasting, tail vein glucose levels were measured using an automatic glucometer (Accu-Chek, Germany) before (0 min) and 15, 30, 60, and 120 min after glucose administration (2 g glucose/kg bodyweight). Blood (0.75 ml) was collected from the venous plexus at 0 and 30 min to evaluate plasma insulin (catalog no. EZRMI-13K, Merck Millipore, USA) and C-peptide (catalog no. CEA447Ra, Cloud-Clone Corp, USA) levels by ELISA. After sedation with isoflurane, dual-energy X-ray absorptiometry (DXA) (PIXImus densitometer, Lunar Corp., Madison, WI, USA) was used to determine the total fat mass 8 weeks after surgery.

Surgery

To induce obesity, rats were fed an HFD for 16 weeks; the diet started when the rats were 5 weeks old. RYGB (n=10) or a sham operation (n=6) was then performed. After an overnight fast, each rat was placed on a heating pad under anesthesia induced with sodium pentobarbital (1 ml/kg body weight).

RYGB

The RYGB surgical procedure in rats has been previously described [14]; the stomach was transected distally from the gastroesophageal junction to create a small gastric pouch (approximately 5% of gastric capacity). The remnant stomach was closed with 6-0 sutures. The jejunum was opened at 15 cm distal from the ligament of Treitz; subsequently, the distal jejunum was connected to the small gastric pouch with 6-0 sutures. A new anastomosis was made with 6-0 sutures between the biliopancreatic limb and the alimentary limb 10 cm distal from the gastrojejunal anastomosis to create the common channel. Then, the abdominal wall and skin were closed with 4-0 absorbable sutures using a continuous suturing technique. Before the abdomen was closed, 20 ml/kg saline was administered subcutaneously to compensate for intraoperative fluid loss.

Sham operation

For the sham operation, a 1-cm gastrostomy was performed, which was then closed with 6-0 sutures. The intestines were manipulated gently without transection. The rats were maintained under anesthesia for approximately 1 h, the same duration of the RYGB operation.

Postsurgical management

The rats were closely monitored and housed individually until the end of the experiment. To prevent postoperative infection and pain, cefuroxime and buprenorphine were administered once daily, together with 10 ml of 5% glucose for the first 3 postoperative days. The HFD was continued for 8 weeks after surgery, and the same food intake was maintained in the RYGB and sham rats.

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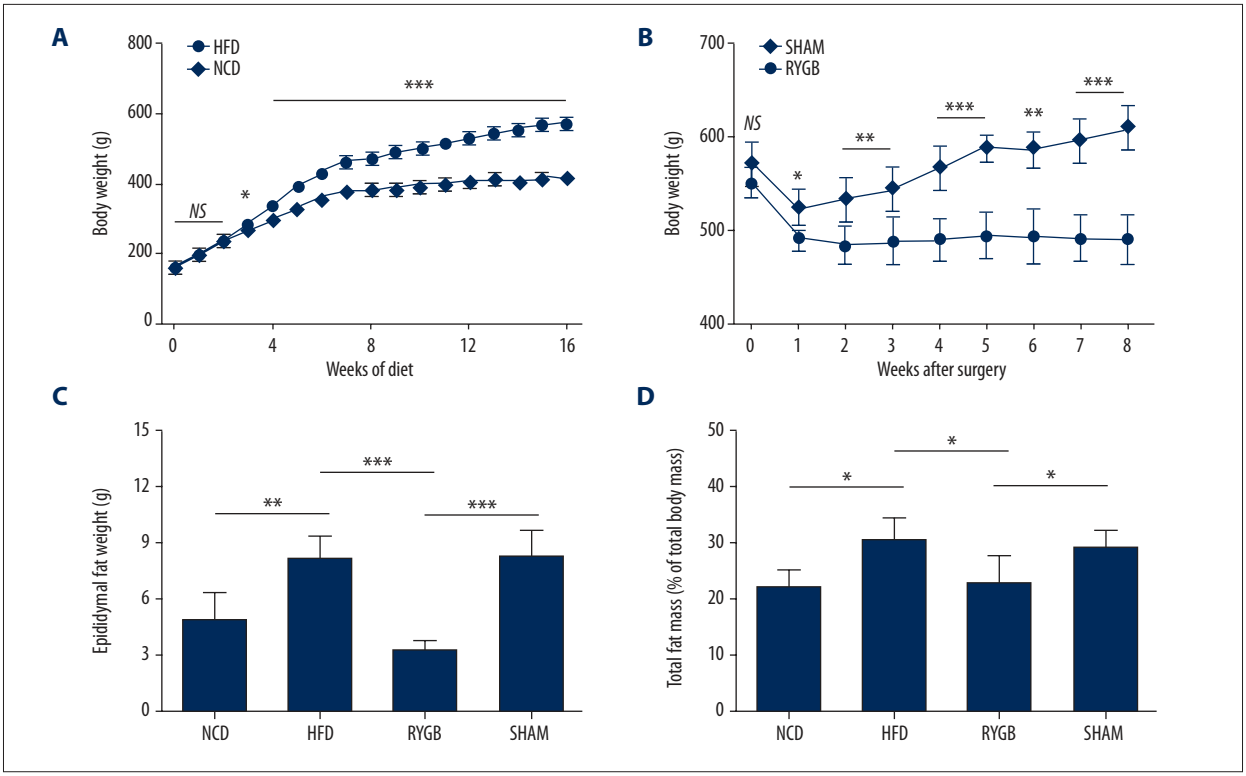

Figure 1. Systemic metabolic effects of the high-fat diet (HFD) and Roux-en-Y gastric bypass (RYGB). (**A**) Body weight progression from the start of the HFD (n=6 per group). (**B**) Body weight progression after RYGB or the sham operation (n=6 per group). (**C**) Epididymal fat weight 8 weeks after surgery (n=4 per group). (D) Total fat mass measured by dual-energy X-ray absorptiometry 8 weeks after surgery (n=4 per group).

Sacrifice

After an 8-h fasting period, the rats were anesthetized with sodium pentobarbital (intraperitoneal injection, 1 ml/kg body weight) and sacrificed by blood sampling via cardiac puncture. Blood was collected into chilled tubes with EDTA and subsequently centrifuged (4°C, 3000 rpm, 15 min) to obtain plasma, which was then stored at –80°C until the GLP-1 (catalog no. EZGLP1T-36K, Merck Millipore, USA) measurements. Epididymal fat and pancreatic tissues were carefully dissected, weighed, and then either frozen at –80°C or preserved for histological analysis.

Morphological and immunohistochemical analyses

The pancreases were routinely fixed in a 4% paraformaldehyde solution and embedded in paraffin; then, 5-µm sections were cut 250 µm apart. To analyze pancreatic morphology, sections were stained for insulin (1: 5000, catalog no. ab 181547, Abcam, UK) and counterstained with hematoxylin.

Relative β-cell volume (RCV) and β-cell mass

To quantify the RCV, 10 sections were randomly selected at 3 levels: the pancreatic head, body, and tail. The observer was blind to the identity of the specimens. These sections were then immunostained with insulin (1: 200, catalog no. ab 181547, Abcam, UK) and counterstained with DAPI (1: 200, Beyotime, China). For each section, 5 randomly selected visual fields were imaged (×10 objective magnification, Leica DM4000B LED, Germany) and analyzed (Image-Pro Plus 16.0) to obtain data on insulin-positive and DAPI-stained surface areas. For each rat, a total of 50 visual fields were analyzed. The RCV was determined as the ratio of insulin-positive area to DAPI-stained area, which was then multiplied by the weight of the pancreas to obtain the β-cell mass in milligrams.

Islet size and number

All islets in visual fields were first examined manually to determine the total number of islets and then together with the DAPI-stained surface area to assess the number of islets per total pancreatic area. To establish islet size, 50 islets from each rat were chosen randomly; subsequently, each of these 50 islets was examined to determine the total insulin-positive area, which was considered the total cross-sectional area of islets. A mean islet size was then determined for each rat.

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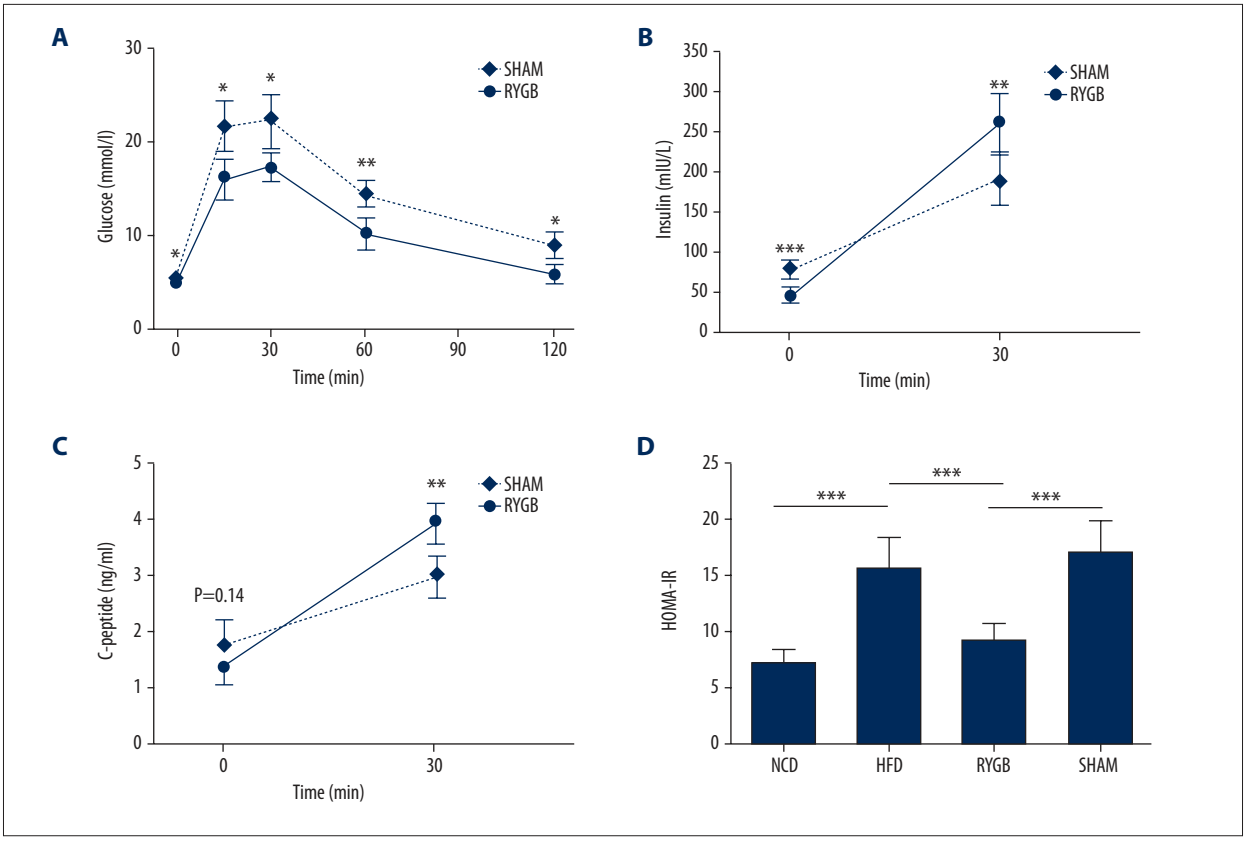

Figure 2. Evaluation of β-cell function after surgery. (**A**) Intraperitoneal glucose tolerance test (after 8 h of fasting, 2 g/kg glucose) 6 weeks after surgery (n=4 per group). (**B**) Fasting and postprandial (30 min after glucose administration) insulin levels 6 weeks after surgery (n=6 per group). (**C**) Fasting and postprandial (30 min after glucose administration) C-peptide levels 6 weeks after surgery (n=6 per group). (**D**) The homeostatic model assessment for assessing insulin resistance index (calculated as fasting glucose level (mmol/L) × fasting insulin level (mIU/L)/22.5) 6 weeks after surgery (n=6 per group).

Mean size of individual β-cells

Ten islets stained for insulin from each rat were imaged (×40 objective magnification) to generate data on the insulin-positive area (μm²). The nuclei located within the insulin-stained area in the islets were counted manually to compute the mean size of individual β-cells.

Statistical analysis

GraphPad Prism 6.0 was used to conduct all statistical analyses. Data are presented as the mean ±SD. To determine significant differences between 2 groups, an unpaired *t* test (parametric samples) or the Mann-Whitney test (non-parametric samples) was used. One-way ANOVA or the Kruskal-Wallis test was performed to determine differences among more than 2 groups. Post hoc analyses were performed using Tukey's multiple comparisons test (parametric samples) or Dunn's multiple comparisons test (non-parametric samples); $p<0.05$ was considered statistically significant. Significance is shown as * $p<0.05$, ** $p<0.01$ or *** $p<0.001$. NS indicates no significant difference.

Results

HFD induced early obesity, and subsequent RYGB induced sustained weight loss and decreased fat mass

Compared with the NCD rats, the HFD rats exhibited a significantly higher body weight from 3 weeks after the start of the diet (Figure 1A), as well as an increased epididymal fat weight (Figure 1C) and an increased fat mass, as measured by DXA (Figure 1D). After 16 weeks of the HFD diet, RYGB or a sham operation was performed. The survival rate was 100% in the sham group (n=6) and 60% in the original RYGB group (n=10); the causes of death were anastomosis bleeding (n=3) and mechanical ileus (n=1). Only RYGB rats that survived the entire experiment (n=6) were included in the analysis. Body weight in both groups decreased during the first week after surgery due to the surgical stress. From week 2 after surgery, the sham-operated rats slowly regained weight, ultimately exceeding their preoperative weight by the end of the experiment. In contrast, the RYGB mice maintained their lower body weight throughout the experiment, despite the continued HFD (Figure 1B). In addition, decreased epididymal fat

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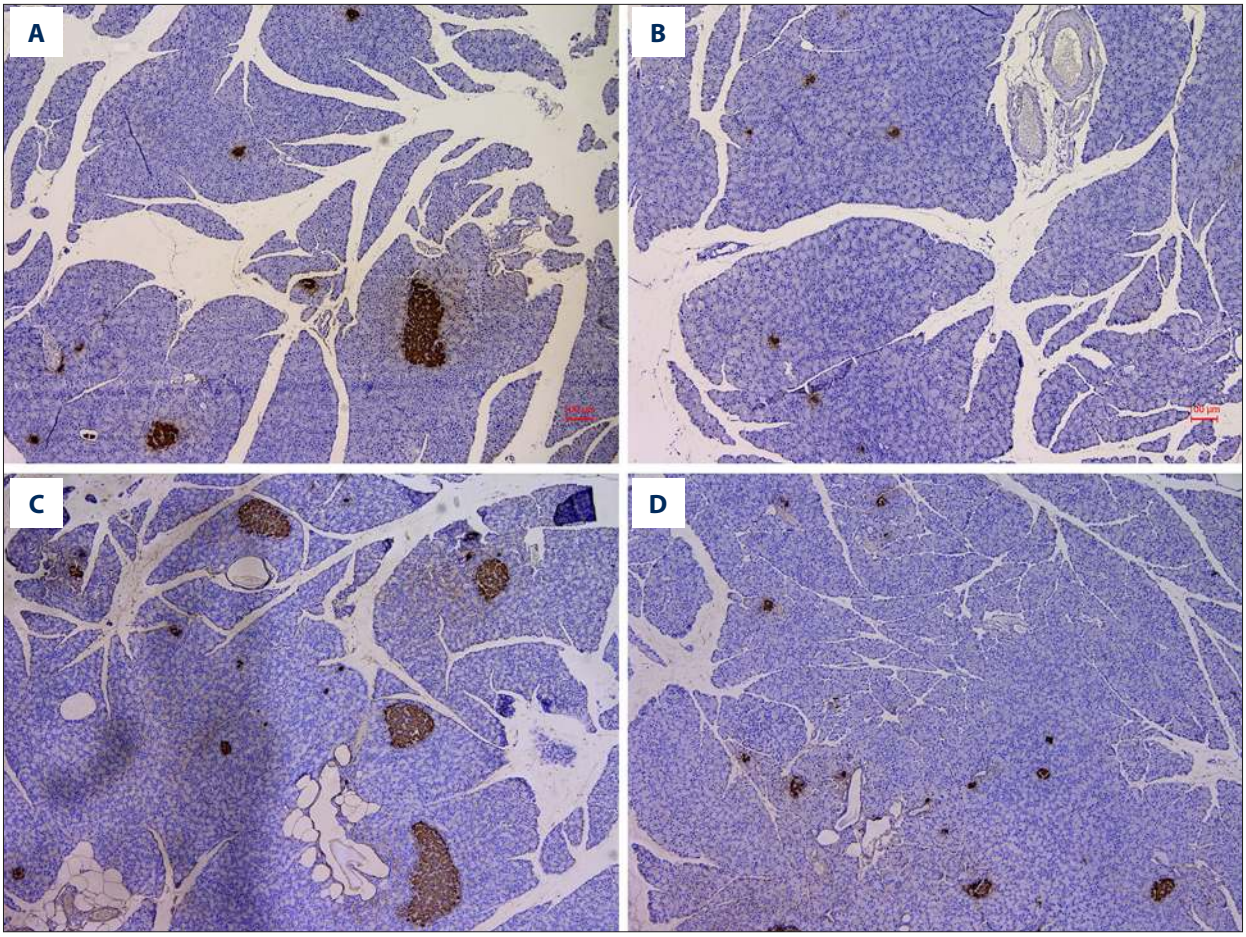

Figure 3. Representative images of pancreatic sections immunohistochemically stained for insulin (dark brown). All slides were counterstained with hematoxylin and imaged at ×5 objective magnification. (**A**) Pancreatic section from a rat fed the normal chow diet. (**B**) Pancreatic section from a rat fed the high-fat diet. (**C**) Pancreatic section from a rat that underwent Roux-en-Y gastric bypass. (**D**) Pancreatic section from a rat that underwent the sham operation. Scale bars=100 μm.

weight (Figure 1C) and fat mass (Figure 1D) were observed in the RYGB rats compared with the sham rats.

HFD induced decreased insulin sensitivity and RYGB rats exhibited improved glucose control and enhanced β-cell function

At 6 weeks after surgery, HFD rats developed more severe insulin resistance, as the HOMA-IR index of the HFD rats was more than twice that of the NCD rats (Figure 2D). Then, an IPGTT was performed in the RYGB and sham rats to assess β-cell function. The RYGB rats had a significantly better glucose tolerance than the sham rats (Figure 2A). Fasting insulin (Figure 2B) and C-peptide (Figure 2C) levels were lower in the RYGB rats than in the sham rats, and the homeostatic model assessment for assessing insulin resistance level was reduced 1.8-fold in the RYGB rats (Figure 2D), suggesting increased β-cell sensitivity to glucose. In contrast, plasma insulin and C-peptide concentrations rapidly increased in the RYGB rats during the first 30 min after glucose administration (Figure 2B, 2C), reflecting enhanced β-cell secretory function after RYGB.

RYGB induced pancreatic hyperplasia, as reflected in increased RCV and β-cell mass, in part due to increased islet number and size

In the NCD and RYGB rats, abundant insulin staining was observed in the images of the pancreatic tissue, which showed clear boundaries and normal structures (Figure 3A, 3C). In the HFD and sham rats, the insulin-stained areas were sparse and markedly reduced in size (Figure 3B, 3D).

Morphometric analyses of the pancreas were performed to understand the enhanced β-cell secretory function in the RYGB rats. Compared with the HFD and sham rats, the ratio of pancreas weight to body weight was increased in the RYGB rats (Figure 4A). The RCV, expressed as relative insulin-positive area, was increased by ~40% in the RYGB rats (Figure 4B), and β-cell

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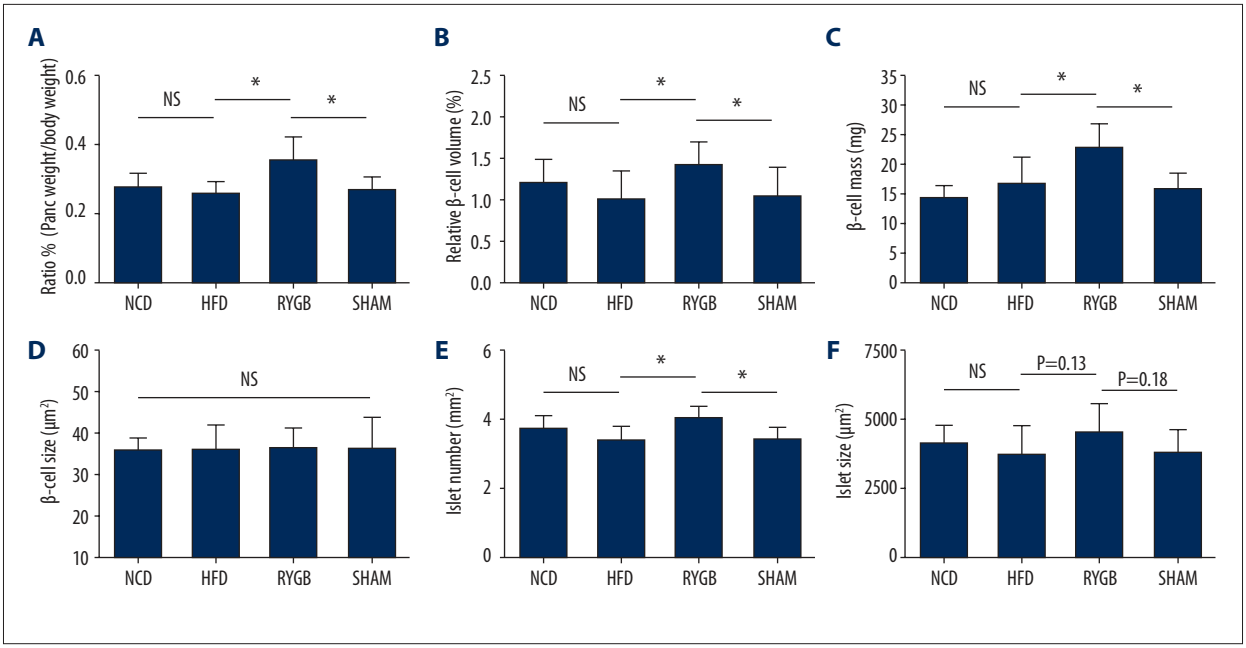

Figure 4. Pancreatic morphology in the different groups. (**A**) Ratio of pancreas weight to body weight (%). (**B**) Relative β-cell volume (RCV, %). (**C**) β-cell mass (mg, quantified by multiplying pancreas weight by RCV). (**D**) Mean size of individual β-cell. (**E**) Number of islets per unit area of total tissue. (**F**) Mean islet size of rats in the different groups. N=6 per group for all assays.

mass was significantly higher in the RYGB rats (Figure 4C). The increased RCV in the RYGB rats was due to an increased β-cell number since the individual β-cell size did not vary among the groups (Figure 4D). In agreement with the increased β-cell mass, the number of islets was increased 1.2-fold in the RYGB rats (Figure 4E). While the islets tended to be larger after RYGB, this difference did not reach significance (Figure 4F).

Potential mechanism underlying pancreatic hyperplasia

In consideration of the beneficial effects of incretins on glucose metabolism, we also measured fasting GLP-1 levels, and we found that these were significantly higher in the RYGB rats (Figure 5).

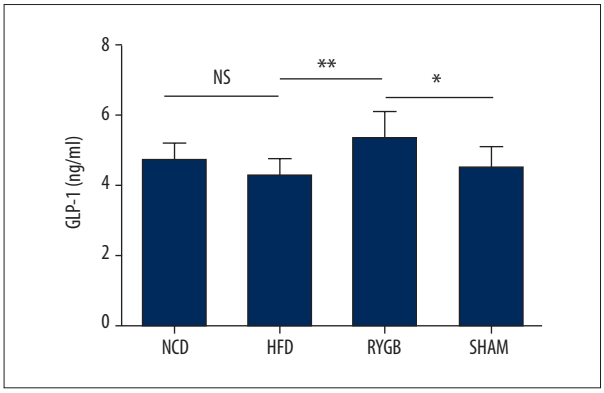

Figure 5. GLP-1 levels after surgery (after 8 h of fasting, n=6 per group).

Discussion

Obesity is associated with chronic metabolic disorders such as T2D and lipid disturbances [15]. RYGB has been shown to be more effective than intensive drug interventions for the long-term management of blood sugar in patients with diabetes [16] and it may even reduce incidence of obesity-related cancer [17]. In fact, T2D remission often occurs before significant weight loss in T2D patients who undergo RYGB [18]. Mounting evidence suggests that β-cell function plays a major role in the long-term relief of diabetes after RYGB [19,20]; however, the exact mechanism of the recovery of β-cell function following RYGB remains unknown. Here, we show that RYGB results in increased RCV and β-cell mass, followed by enhanced β-cell function, as well as increased incretin secretion in obese rats.

Human and rodent studies have reported rapid improvement in glucose regulation, insulin resistance, and β-cell function after bypass surgery [21,22]. In the present study, we found lower post-fasting and postprandial glucose levels in the RYGB rats early after surgery. We also found reduced insulin and C-peptide levels after fasting and a rapid increase in insulin and C-peptide secretion during the first 30 min after glucose administration, suggesting improved glucose metabolism and β-cell function after RYGB. Thus, our data are in agreement with previous human studies on the effect of RYGB on glucose metabolism and insulin release [4,13].

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Decreased β-cell mass in T2D has been reported in previous human studies, which may be caused in part by increased β-cell apoptosis [23]. Hence, approaches designed to induce β-cell formation might be significant therapeutic options for the management of T2D. Interestingly, our research suggests that the RCV and β-cell mass increased after RYGB, in part due to increased islet number and size, despite being in severely obese rats with a mildly abnormal glycometabolism. These results are consistent with those of previous studies. Lindqvist et al. [24] found that pigs had an increased β-cell mass after RYGB. For most obese patients with T2D, an increased β-cell mass after RYGB enhances β-cell function and thus reduces the use of diabetes medications. However, sometimes the effect is too large and leads to nesidioblastosis, resulting in hyperinsulinemia and postprandial hypoglycemia [25–27]. However, there are contrasting repots; Meier et al. suggested that β-cell mass was not affected by RYGB [28].

The exact mechanism underlying the RYGB-induced increase in β-cell mass remains unclear; however, the regulation of gut hormones may contribute to the stimulation of β-cell trophic factor secretion [29]. Consistent with this hypothesis, GLP-1 levels were increased in the RYGB rats. The increased islet number is attributed in part to increased islet neogenesis [30]. Other potential reasons include β-cell redifferentiation after RYGB; recent studies have shown that metabolic stresses may result in β-cell dedifferentiation and that dedifferentiated cells can subsequently redifferentiate into mature β-cells following insulin therapy [31]. Further studies are required to determine the mechanism underlying increased β-cell mass after RYGB, which will facilitate the development of new strategies for the treatment of obesity and T2D.

Conclusions

In the present study, RYGB improved β-cell function and β-cell mass in obese rats, which were key determinants of improved glucose tolerance after RYGB.

Declaration

The authors declare no conflicts of interest.

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