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Sleeve Gastrectomy With Modified Jejunoileal Bypass Model in Goto-Kakizaki Rats

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The objective of this study was to develop a nonobese diabetic rat model for sleeve gastrectomy with modified jejunoileal bypass (SG/MJIB) and to investigate its effectiveness and safety for inducing diabetic control. Thirty-five 13-week-old male Goto-Kakizaki rats were randomly assigned to the pair-fed to sham-operated SG/MJIB (PFSO-SG/MJIB), SG/MJIB, PFSO-SG, SG, and control groups. The experimental period was 16 weeks postoperatively. Body weight; food intake; glycemic control outcomes; and ghrelin, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic peptide, and insulin levels were measured. The operated and PFSO groups showed significant weight loss 4 weeks postoperatively compared with the controls. The SG/MJIB and SG groups exhibited a significant improvement in oral glucose tolerance and insulin tolerance compared with the PFSO and control groups. The improved effects in the SG/MJIB group were better than those in the SG group. The SG/MJIB and SG groups showed decreased fasting ghrelin levels and increased levels of GLP-1 secretion 2 and 16 weeks postoperatively. Compared with the SG group, only the SG/MJIB group showed higher glucose-stimulated GLP-1 levels and significantly improved insulin secretion. SG/MJIB may be an effective, steady hypoglycemic surgical model, showing better diabetic control than SG. The hindgut may play a direct role in ameliorating glucose homeostasis.

Key words: Sleeve gastrectomy – Jejunoileal bypass – Goto-Kakizaki rat – GLP-1 – Hindgut

Diabetes mellitus (DM) affects more than 285 million people worldwide, and this is expected to double to approximately 439 million by 2030.[1] More than 90% of patients with diabetes have type 2 diabetes mellitus (T2DM). Even with strict hyperglycemia control, evidence for reducing complications related to T2DM has been reported[2]; nevertheless, current therapies, such as diet, exercise, behavior modification, oral hypoglycemic agents, and insulin, can rarely help patients return

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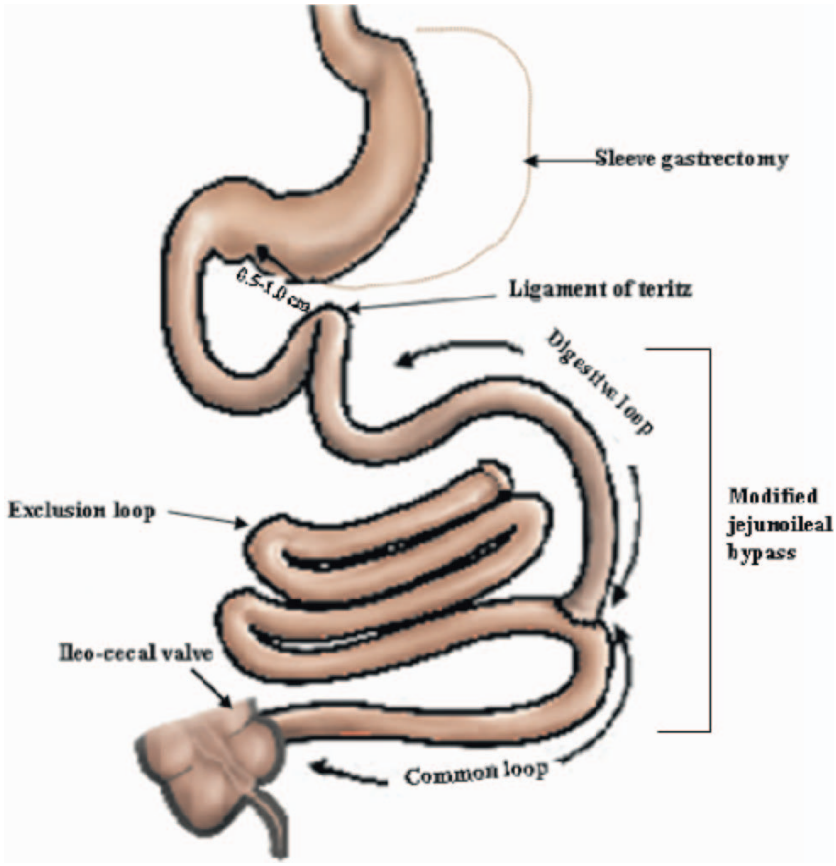

Fig. 1 Sleeve gastrectomy with modified jejunoileal bypass.

to euglycemia.[3] Recent data proved that the most reliable treatment for the long-term management of T2DM is surgical intervention.[4–6] Surgical techniques for T2DM treatment are based on intake restriction, malabsorption, or both of these. However, none of the currently performed operations can provide unanimous treatment effects or a clear therapeutic mechanism.[7,8]

Among the operations performed, adjustable gastric banding achieves hypoglycemia mainly through a limited food intake. Although this surgical method is relatively safe, the glycemic regulatory effect is far from satisfactory; complications, such as intragastric erosion or band slippage, may occur[9]; and the reoperation rate may be >10%.[10] Jejunoileal bypass (JIB) has been the most effective T2DM treatment[11]; however, because of its severe complications, JIB has been abandoned by most surgeons.[12] Other procedures that combine gastritis and malabsorption, such as Roux-en-Y bypass, exclude most parts of the stomach, making this organ and the biliary ducts inaccessible to the usual endoscopic examinations,[13,14] which is not very suitable in high-risk patients.[15]

Recently, sleeve gastrectomy (SG) was reported with a hypoglycemic effect similar to that of Roux-en-Y bypass.[4] However, the use of SG cannot explain the mechanism of T2DM control in detail. According to the latest research findings on T2DM treatment, we modified the JIB in addition to SG, and this surgical technique was named *sleeve gastrectomy with modified jejunoileal bypass* (SG/MJIB). SG/MJIB maintains the normal physiologic environment of the gastrointestinal tract, and it retains about half of the effective length of the bowel, which can provide an adequate absorption of nutrients in vivo to avoid the occurrence of malnutrition; it also shortens the time it takes for food to reach the terminal ileum[16] (Fig. 1).

In this study, we established the effectiveness of the SG/MJIB model in nonobese Goto-Kakizaki (GK) rats by monitoring their body weight, food intake, glycemic control outcome, and levels of gastrointestinal hormones [ghrelin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and insulin] in GK rats during the study period.

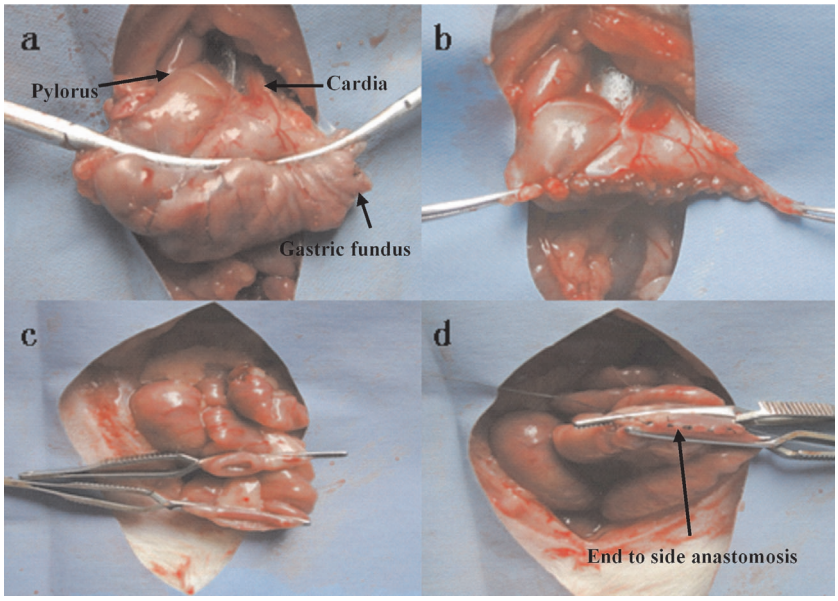

Fig. 2 Surgical procedures. (a and b) Sleeve gastrectomy, in which 70% to 80% of the total stomach is removed from the cardia to the pylorus. (c and d) Modified jejunoileal bypass, in which about 50% of the middle part of the small intestine is excluded, and a jejunojejunal end (remote of the alimentary) to side (proximal side of the common tract) anastomosis was performed using an eversion type interrupted by a polypropylene hand and full-thickness suture.

Materials and Methods

Thirty-five 13-week-old male GK rats with spontaneous nonobese type 2 diabetic models were purchased from the Shanghai SLAC Laboratory Animal Co Ltd (Shanghai, China). The animals had free access to tap water, and they were fed a standard rat chow diet. All of the animals were housed in individual cages under standard conditions (a constant ambient temperature of 22°C and humidity of 60% in a 12-hour light/dark cycle). In this study, the Animal Care and Utilization Committee of Wuhan University approved the animal experiments.

After these rats were acclimated for 1 week, the weight, food intake, fasting plasma glucose (FPG) levels, oral glucose tolerance test (OGTT) values, insulin tolerance test (ITT) values, and ghrelin, GLP-1, GIP, and insulin levels were measured according to the study schedule. The GK rats were randomly assigned to 5 groups: SG/MJIB, pair-fed to sham surgery (PFSO)-SG/MJIB, SG, PFSO-SG, and control.

The operation times (*i.e.*, the time from the beginning of the midline abdominal incision to the end of suturing the abdominal incision) for the SG, PFSO-SG/MJIB, and PFSO-SG groups were prolonged to produce a similar degree of anesthesiologic stress to that of the rats that underwent SG/MJIB. The preoperative fasting of solid food was conducted for 16 to 18 hours, but liquid was permitted during this period. Intramuscular injections of antibiotic prophylaxis (kanamycin solution, 30 mg/kg) and atropine (0.05 mg/kg) were used 30 minutes prior to the procedure. Intraperitoneal anesthetics were applied using pentobarbital sodium (40 mg/kg).

Surgical Procedures

Sleeve gastrectomy with modified jejunoileal bypass

The SG surgery was performed first, as described by Kashyap *et al*[4] and de Bona Castelan *et al*,[17] and 70% to 80% of the stomach volume was removed. The volume consisted of the major part of the stomach and all of the gastric fundus. Second, the ligament of Treitz and the ileocecal valve were exposed. The distance of the ligament of Treitz (approximately 25% of the length of the total small bowel) was the alimentary tract; the distance of the ileocecal valve (approximately 25% of the length of the total small bowel) was the common tract; and the left small bowel was an exclusion tract and was closed by hand sewing. A jejunojejunal end (remote of the alimentary) to side (proximal side of the common tract) anastomosis was performed using an eversion type interrupted by a polypropylene hand and full-thickness suture (Prolene 6-0, Ethicon, Piscataway, New Jersey). Details of the procedure are illustrated in Fig. 2.

Sleeve gastrectomy

SG surgery was performed as the first step of SG/MJIB (Fig. 2a and 2b).

Pair-fed to sham surgery

In the PFSO groups, transections and reanastomosis of the gastrointestinal tract were performed at multiple sites, which corresponded to where the enterotomies were performed in the SG/MJIB and SG groups. The PFSO group was given the same amount of food that the SG/MJIB and SG rats consumed.

Postoperative care

Postoperatively, 10 mL of glucose in normal saline was injected subcutaneously, and the antibiotic was intramuscularly injected on the third day in order to prevent dehydration and infection. The rats being operated on were not given any water or food on the first postoperative day, and were allowed to drink tap water on the second day. After defecation, these rats were allowed to eat a small portion of food. On the seventh postoperative day, these surgical rats were fed a standard solid diet.

Measurements

The rats' body weight and food intake were measured every week for the first postoperative month and 2 weeks thereafter.

The blood samples were collected from the orbital venous sinus in conscious animals during the preoperative stage as well as during the 2nd, 4th, 6th, 8th, 10th, and 16th week postoperatively. The samples were stored in ethylenediaminetetraacetic acid–containing tubes (1.5 μg/mL, Amresco Inc, Solon, Ohio) with a gastrointestinal preservative (aprotinin, 40 μg/mL, Amresco), and they were centrifuged at 3000 rpm at 4°C for 15 minutes. Then, the plasma samples were immediately separated and stored at –80°C until analysis. The ghrelin and insulin levels were measured after 16 to 18 hours of fasting, whereas the GLP-1 and GIP levels were measured 30 minutes after the administration of 3 g/kg glucose by oral gavages. Enzyme-linked immunosorbent assay kits were used for measuring the ghrelin (Linco Research Inc, St Louis, Missouri), GLP-1 (Millipore, Billerica, Massachusetts), total GIP concentration (Linco Research), and insulin (Mercodia AB, Uppsala, Sweden). After a fasting period of 16 to 18 hours, the FPG level was analyzed using the glucose oxidase method (BioSino Bio-Technology and Science Inc, Beijing, China).

For the oral OGTT, blood glucose was measured after the 16- to 18-hour fasting in conscious rats before (baseline) and then at 30, 60, 120, and 180 minutes after administering 3 g/kg glucose by oral gavage. Blood was obtained from the tail vein and was analyzed using a glucometer (One Touch Ultra; Lifescan Inc, Milpitas, California).

The ITT was performed postoperatively by measuring the glucose levels before and at 15, 30, 60, 120, and 180 minutes after injecting 0.5 UI/kg human insulin intraperitoneally in conscious, fed rats.

The homeostasis model assessment–insulin resistance (HOMA-IR) was calculated at weeks 2 and 16 postoperatively, and the fasting and glucose-stimulated insulin secretions were measured to evaluate the beta cell function using enzyme-linked immunosorbent assay kits. HOMA-IR was used to evaluate insulin resistance according to the formula[18]: HOMA-IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5.

Statistical Data Analysis

The data were expressed as mean ± SD. Areas under the curves (AUCs) of the OGTT and ITT were calculated by trapezoidal integration. Comparisons among the surgical groups were made using a 1-way analysis of variance. A Student *t*-test was used as appropriate. Statistical significance levels were set at $P < 0.05$.

Results

Before the treatments, the weight, FPG, OGTT, ITT, HOMA-IR, plasma gastrointestinal hormones, and plasma insulin had no significant differences among the 5 groups of GK rats.

All of the experimental operations were successful, and the operation times were prolonged to produce a similar degree of anesthesiologic stress. One rat in the SG/MJIB group died from an intestinal obstruction on the seventh day postoperatively. No deaths or complications were found in the other 4 groups.

Body weight loss and food intake

As shown in Fig. 3, after 4 postoperative weeks, the SG/MJIB group had significantly more weight loss than the other 4 experimental groups ($P < 0.0001$). However, the SG, PFSO-SG, and PFSO-SG/MJIB groups had no significant difference in weight loss throughout the study. Because of the surgical stress, the SG/MJIB and SG groups ate less food than the control group (17.8 ± 6.6, 19.1 ± 6.4, and 24.8 ± 1.6

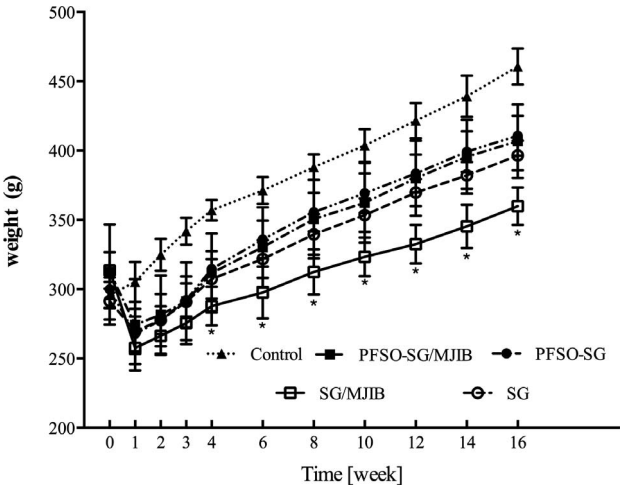

Fig. 3 Body weight loss of the rats in all the groups preoperatively and postoperatively. After 4 postoperative weeks, the SG/MJIB group had significantly more weight loss than the other 4 experimental groups, (*$P < 0.0001$).

g, respectively; $P < 0.001$). However, the food intake of the SG/MJIB, SG, and PFSO groups was not different at any of the stages.

Glucose metabolism

Fasting plasma glucose

The FPG levels of the SG/MJIB and SG groups were remarkably lower than those of the PFSO and control groups at 2 weeks postoperatively ($P < 0.03$). Compared with the SG group, the SG/MJIB group had a lower FPG level ($P < 0.05$; Fig. 4a).

Oral glucose tolerance test

After 2 weeks postoperatively, the SG/MJIB and SG groups showed an improvement in glucose tolerance, as demonstrated by a significant reduction in the AUC for the blood glucose concentration compared with the preoperative period ($P < 0.01$). This significant effect was not observed in the PFSO and control groups. The AUC_{OGTT} values of the SG/MJIB group were lower than those of the PFSO and control groups at 2, 4, 8, 12, and 16 weeks postoperatively ($P < 0.001$; Fig. 4b). The glucose tolerance of the SG/MJIB group was better than that of the SG group ($P < 0.05$).

Insulin tolerance test

The SG/MJIB and SG groups showed an obviously improved insulin tolerance and lower AUC_{ITT} values compared with the PFSO and control groups at 2, 10, and 16 weeks postoperatively ($P < 0.0001$; Fig. 4c). The SG/MJIB group had a lower AUC_{ITT} than the SG group ($P < 0.05$).

Homeostasis model assessment–insulin resistance

At 2, 8, and 16 weeks postoperatively, the SG/MJIB group showed significantly lower HOMA-IR levels than all of the other groups ($P < 0.001$; Fig. 4d). In addition, the SG group had lower HOMA-IR values than the PFSO and control groups ($P < 0.001$), and no difference was found between the PFSO and control groups.

Hormone measurements

The plasma ghrelin, GLP-1, GIP, and insulin concentrations were measured in the 5 groups.

Ghrelin

Postoperatively, the fasting plasma ghrelin concentrations of the SG/MJIB and SG groups were obviously lower than those of the PFSO and control groups ($P < 0.0001$), and the same tendency was still found during the study period. The fasting ghrelin levels had no significant differences between the SG/MJIB and SG groups ($P > 0.05$; Fig. 5a).

Glucagon-like peptide-1

Compared with the other 4 groups, the SG/MJIB group showed higher GLP-1 levels from 2 to 16 weeks postoperatively ($P < 0.0001$). The GLP-1 levels of the SG group were higher than those of the PFSO and control groups throughout our experiment ($P < 0.0001$; Fig. 5b).

Glucose-dependent insulinotropic peptide

As shown in Fig. 5c, the GIP levels were not significantly different among the groups from 2 to 16 weeks postoperatively ($P > 0.05$).

Insulin

The insulin levels of the SG/MJIB group were obviously decreased at 2 weeks compared with the other 4 groups ($P < 0.001$). Two weeks postoperatively, the insulin secretion in the SG/MJIB group increased, but the total growth tendency was lower than that of the other 4 groups at 2, 4, 6, and 16 weeks ($P < 0.05$). The insulin secretion of the PFSO and control groups was not significantly different throughout the experiment. However, the insulin level of the SG group had a slight tendency to

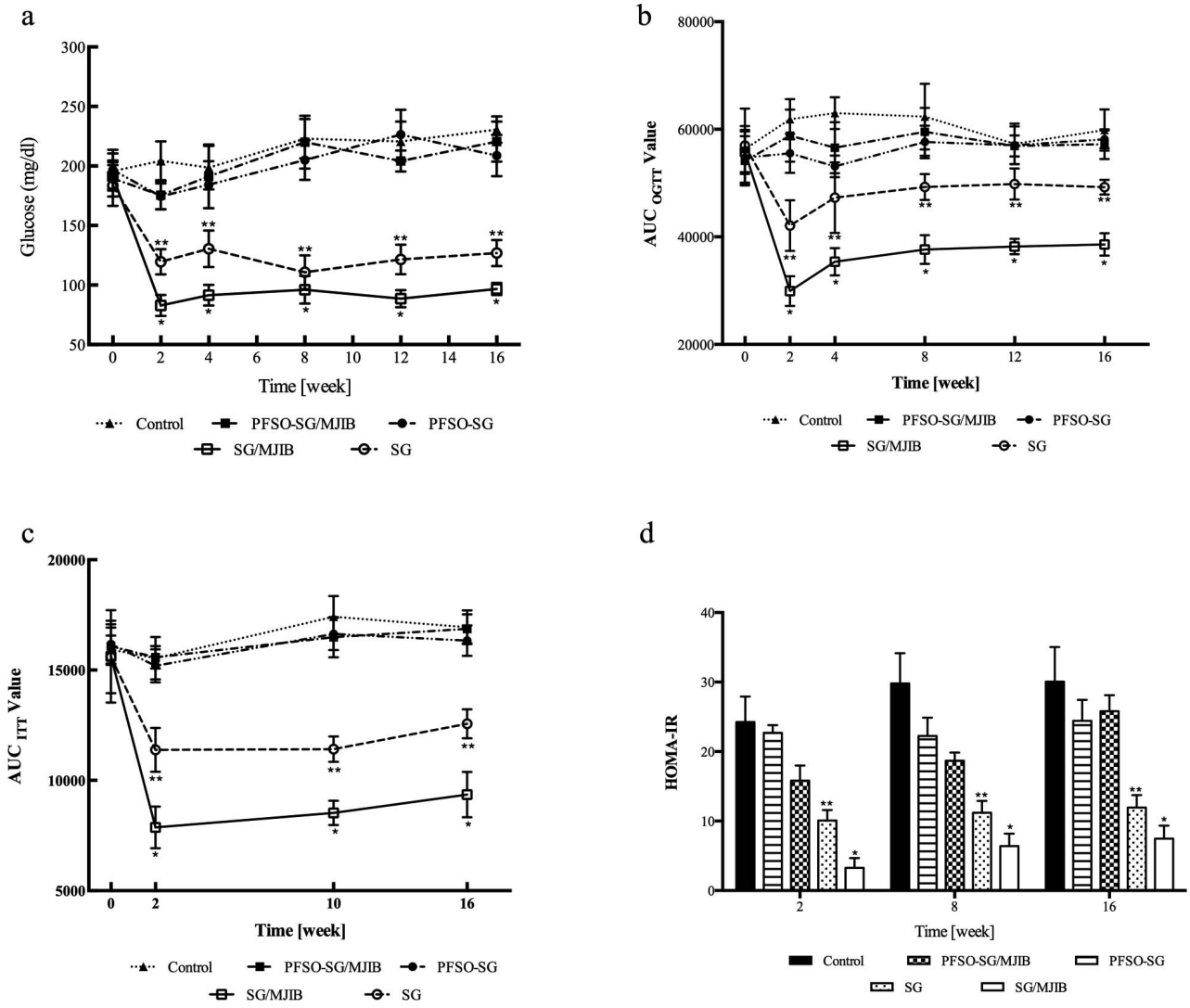

Fig. 4 Glucose metabolism. (a) Fasting plasma glucose. The fasting plasma glucose levels of rats in the SG/MJIB group were lower than those of all of the other groups postoperatively (*$P < 0.001$). In addition, the fasting plasma glucose levels of the SG group were lower than those of the PFSO and control groups (**$P < 0.01$). (b) AUC_{OGTT} values of the SG/MJIB group were lower than those of all of the other groups postoperatively (*$P < 0.001$). AUC_{OGTT} values of the SG group were lower than those of the PFSO and control groups postoperatively (**$P < 0.02$). (c) AUC_{ITT} values for rats in the SG/MJIB group were lower than those for all of the other groups at 2, 10, and 16 weeks postoperatively (*$P < 0.001$). AUC_{ITT} values of rats in the SG group were lower than those of the PFSO and control groups at 2, 10, and 16 weeks postoperatively (**$P < 0.01$). (d) HOMA-IR. At 2, 8, and 16 weeks postoperatively, the HOMA-IR values of rats in the SG/MJIB group were lower than those of all of the other groups (*$P < 0.001$). At 2, 8, and 16 weeks postoperatively, the HOMA-IR values of rats in the SG group were lower than those of the PFSO and control groups (**$P < 0.01$).

decrease, and the total changes had no significant difference (Fig. 5d).

Discussion

Understanding various metabolic effects has helped bariatric surgery evolve into multiple forms in recent decades, which has led to a paradigm shift from bariatric surgery, a solely weight-reducing procedure that affects the whole-body metabolism.[19] SG has a similar hypoglycemic effect to Roux-en-Y bypass.[4] JIB was a widely performed procedure for morbid obesity during the 1970s, and it led to intestinal malabsorption for reducing weight and decreasing blood glucose; however, because of the

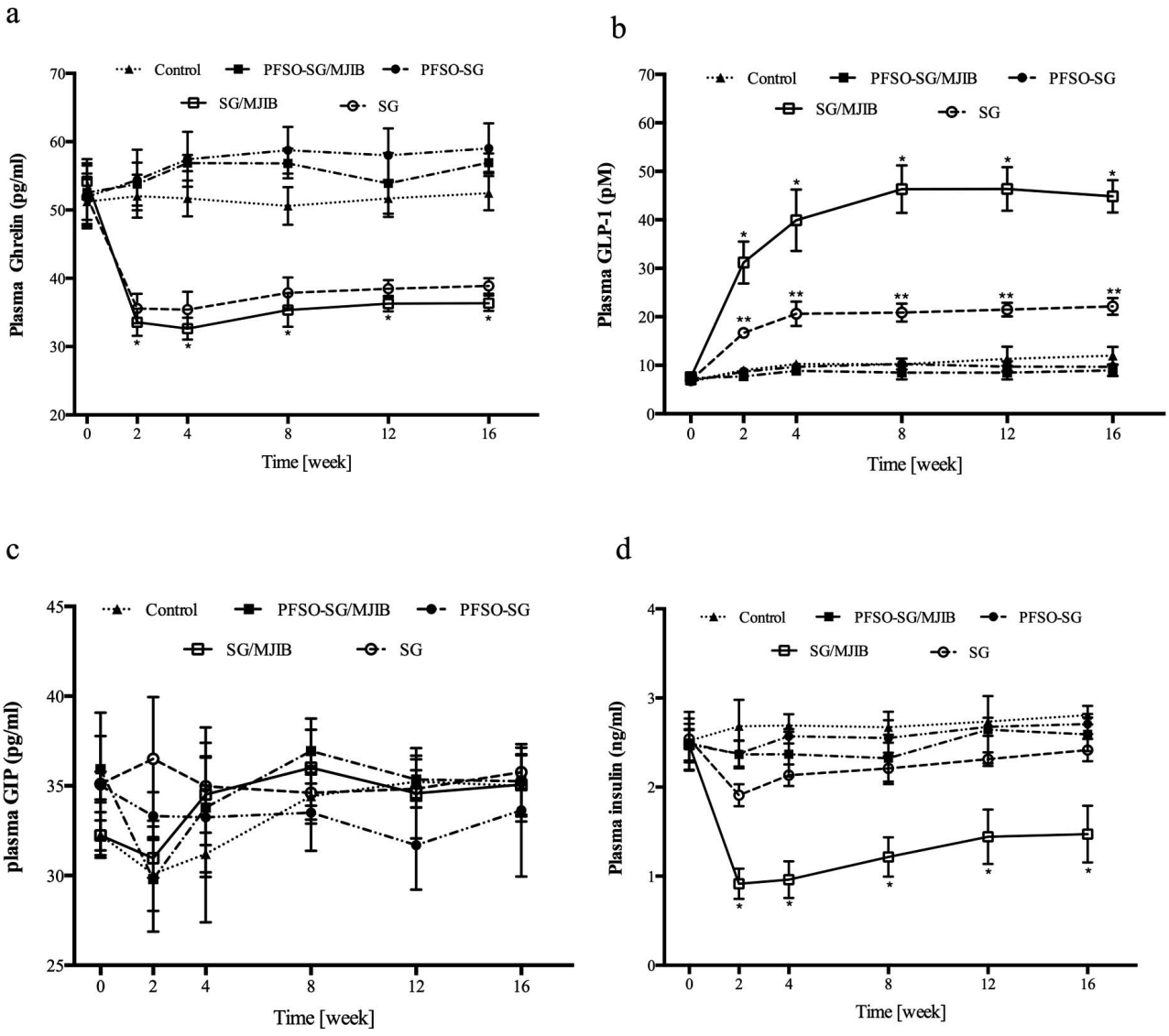

Fig. 5 Glucose metabolism–related hormones. (a) Fasting plasma ghrelin of rats in all of the groups postoperatively. During the postoperative weeks, the fasting plasma ghrelin levels of rats in the SG/MJIB and SG groups were lower than those of the PFSO and control groups (*$P < 0.0001$). (b) Plasma GLP-1 concentrations after an oral glucose gavage (3 g/kg) postoperatively. The GLP-1 levels of rats in the SG/MJIB group were higher than those of all of the other groups postoperatively (*$P < 0.0001$). The GLP-1 levels of rats in the SG group were higher than those of the PFSO and control groups postoperatively (**$P < 0.0001$). (c) Plasma GIP concentrations after an oral glucose gavage (3 g/kg) postoperatively. The plasma GIP levels were not significantly different among the groups ($P > 0.05$). (d) Fasting plasma insulin of rats in all of the groups postoperatively. The fasting plasma insulin levels of rats in the SG/MJIB group were lower than those of all of the other groups (*$P < 0.05$).

high morbidity rates, its popularity declined, and most surgeons no longer perform the operation.[11,12] Yet, with modifications to the JIB, it is still being performed in certain centers in order to reduce severe complications.[20–22] Therefore, we first established the surgical model of SG/MJIB in GK rats and explored a possible solution to stabilize the lasting improvement of diabetes.

In this study, although the SG/MJIB and PFSO-SG/MJIB groups had no significant differences in weight and food intake, the SG/MJIB group had a better effect on glucose homeostasis, and the resolution of diabetes was sustained compared with the PFSO-SG/MJIB group. There were similar findings in the SG and PFSO-SG groups, but the effect of the improved diabetes was worse than that

in the SG/MJIB group. This suggests that the effective improvement of T2DM was mediated by the improvement in the insulin sensitivity and secretion levels, which was independent on the weight loss and food intake, and this effect was exhibited throughout the study.

Changes in the gastrointestinal hormones may be the key factors for improving T2DM.[23–25] In the current study, we found that the SG/MJIB and SG surgeries induced a decreased fasting ghrelin and increased GLP-1 levels at 2 and 16 weeks postoperatively. Ghrelin, which is mainly produced by the gastric fundus, can inhibit insulin sensitivity and secretion.[26–28] Current studies support that decreased ghrelin levels are linked to improved insulin sensitivity.[26,27] In the SG/MJIB and SG groups, the decreased ghrelin level was accompanied by a decreased blood glucose level, which provides evidence for the ghrelin hypothesis. In contrast, the elevation of glucose-stimulated GLP-1 levels after the SG/MJIB and SG surgeries provides further evidence for the hindgut hypothesis, which proposed that the rapid delivery of undigested nutrients to the distal bowel upregulated the production of L-cell derivatives, such as GLP-1.[29,30] GLP-1 is capable of regulating insulin synthesis and proinsulin gene expression, as well as the secretion of glucagon and somatostatin,[31] and GLP-1 analogues have been administered to patients with type 2 diabetes.[32] Among all of the groups, there was no obvious difference in plasma GIP levels, which is responsible for insulin resistance[33]; thus, this indicates that GIP may not be associated with the antidiabetic effect. Although our study showed that the decreased ghrelin and elevated GLP-1 secretions were accompanied by improved insulin sensitivity and secretion levels, the relationship between the ghrelin and GLP-1 after bariatric procedures in diabetic subjects remains unclear.

In our study, the SG/MJIB procedure was safe and feasible, with little postoperative complications, which was comparable to SG. Simultaneously, we observed a better diabetic control induced by SG/MJIB than by SG in GK rats. To our knowledge, comparisons of the effects of SG/MJIB and SG surgeries in nonobese diabetic subjects have not been performed. Our present study suggested that the SG/MJIB procedure might be better as an animal model for demonstrating the hypoglycemic mechanism.

There are limitations to this study. All of the findings for the SG/MJIB and SG procedures originated only from the nonobese diabetic rat model, and it was a short study period. However, the SG/MJIB rat model is effective for investigating the effects of SG/MJIB surgery. Our study showed that SG/MJIB surgery was better for ameliorating diabetes than SG, and it had higher glucose-stimulated GLP-1 levels than the SG group. These findings indicated that SG/MJIB produces more GLP-1 via the quick transfer of nutrients to the distal ileum. Thus, our findings support the hindgut hypothesis. However, the effects of SG/MJIB surgery on many other hormones and the relationship of ghrelin and GLP-1 are still unclear. Therefore, further studies are needed to study the effects of SG/MJIB on glucose metabolism and the relationship of the hormones.

In conclusion, we developed a valuable animal model for studying the metabolic effects of the SG/MJIB procedure on nonobese diabetic subjects. Our study showed that SG/MJIB surgery is effective and safe for improving type 2 diabetes associated with a reduction in the fasting ghrelin and an elevation in GLP-1. In our study, SG/MJIB demonstrated better effects on metabolism than SG. Further comparative studies and long-term follow-up in nonobese diabetic subjects are necessary to confirm these findings and to evaluate the effectiveness of SG/MJIB.

Acknowledgments

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