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Sleeve Gastrectomy with Bypass of Proximal Small Intestine Provides Better Diabetes Control than Sleeve Gastrectomy Alone Under Postoperative High-Fat Diet

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Abstract

Background Sleeve gastrectomy (SG) plus procedures have been developed to strengthen the effect of SG on diabetes control. The aim of this study was to compare diabetes control after SG plus bypass of the proximal small intestine with SG alone under adverse conditions for diabetes remission.

Methods SG plus duodenojejunal bypass (SG-DJB), SG plus jejunojejunal bypass (SG-JJB), SG alone, and sham surgeries were performed in diabetic rats. A high-fat diet (HFD) was fed postoperatively to induce diabetes recurrence. Body weight, food intake, glucose tolerance, insulin sensitivity, serum hormones, hepatic function, and lipid profiles were measured postoperatively.

Results SG-DJB, SG-JJB, and SG groups exhibited significant improvement in glucose tolerance and insulin sensitivity compared with the sham-operated group at 2 weeks postoperatively. Postoperative HFD induced obvious diabetes relapse and re-impaired insulin sensitivity at 16 weeks postoperatively. The SG-DJB and SG-JJB groups exhibited superior glucose tolerance and similar insulin sensitivity to SG alone at 16 weeks postoperatively. Compared with the SG alone, the SG-DJB and SG-JJB groups exhibited similar food intake, weight loss, fasting ghrelin, glucose-stimulated insulin secretion, and higher glucose-stimulated GLP-1 secretion.

Conclusion SG-DJB and SG-JJB provided better diabetes control than SG alone in rats fed a HFD postoperatively. Further clinical studies are expected to confirm the superiority of SG plus bypass of proximal small intestine.

Keywords Sleeve gastrectomy · Sleeve gastrectomy with bypass of proximal small intestine · Diabetes recurrence · High-fat diet

Introduction

A growing number of observational studies and randomized controlled trials have shown that bariatric/metabolic surgery, when used specifically to treat diabetes, promotes dramatic and durable glycemic control [1–4]. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) are currently the most commonly performed bariatric/metabolic surgical procedures [5]. Both SG and RYGB are recommended in the treatment algorithm for type 2 diabetes and have been accepted by diabetes organizations worldwide. RYGB remains the gold-standard procedure for diabetes control, although the optimal procedure is much debated [6, 7].

Although bariatric/metabolic surgeries can provide satisfactory diabetes control, uncontrolled diabetes and postsurgical relapse have been reported in some patients [1, 4]. The incidence of diabetes recurrence ranges from 8.9 to 53% for both RYGB and SG [4, 8–11]. Associated risk factors include longer preoperative duration of diabetes, preoperative insulin use, weight regain, less weight loss, poor compliance, and postoperative high-calorie diet [12, 13].

According to a worldwide survey, SG increased from 5.3% of bariatric procedures in 2008 to 45.9% in 2014, surpassing RYGB in the USA, Canada, Europe, and the Asia-Pacific region [5, 14]. To strengthen the effect of SG on diabetes, pioneer surgeons have combined various novel procedures with SG, involving bypass or transposition of different parts of the small intestine. These procedures, collectively referred to as SG-plus procedures, include SG plus duodenojejunal

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bypass (SG-DJB) [15, 16], SG plus single-anastomosis duodeno-ileal bypass [17, 18], SG plus jejunoileal bypass (SG-JIB) [19, 20], SG plus ileal transposition [21], and others. All these SG-plus procedures have been performed in animals and/or patients and have achieved excellent diabetes control.

The aim of this study was to compare the effect of SG plus bypass of the proximal small intestine with SG alone on diabetes control under adverse conditions for diabetes remission. We performed SG-DJB or SG plus jejunojejunal bypass (SG-JJB) in diabetic rats. A postoperative high-fat diet (HFD) was used to induce diabetes recurrence after surgery [22, 23].

Materials and Methods

Animals and Diets

Eight-week-old male Wistar rats (average weight, 200 g) were purchased from the company. The rats were individually housed with a 12-h light/dark cycle under constant temperature (24–26 °C) and humidity (50–60%). All rats were given 1 week. of adaptive feeding, then fed a HFD (40% fat, 42% carbohydrate, 18% protein, as percentage of total calories; Huafukang Biotech, China) for 1 month to induce fat accumulation and insulin resistance. After a 12-h fast, 35 mg/kg streptozotocin (Sigma Aldrich, USA) dissolved in sodium citrate buffer (pH = 4.2) was injected intraperitoneally to induce a diabetic state. Two weeks after streptozotocin injection, an oral glucose tolerance test (OGTT) was conducted; blood glucose was measured on tail vein samples with a glucometer (Roche Diagnostics, Germany). The criteria for diabetic state in rats include fasting blood glucose of 7.1 mmol/L or higher or 2-h blood glucose above 11.1 mmol/L during OGTT. Forty rats were randomly chosen from among the rats that met the criteria for diabetic state. The Animal Care and Utilization Committee of our center approved all animal procedures in the study.

Experimental Protocols

The diabetic rats were randomly divided into a sham surgery group, SG group, SG-DJB group, and SG-JJB group ($n = 10$ in each group). The rats were fed a low-residue diet (10% Ensure, Abbott Laboratories, USA) for 2 days, then nothing per os for 8 h before surgery. All surgeries were performed under general anesthesia with 10% chloral hydrate solution (3 mg/kg, injected intraperitoneally). After surgery, the rats in each group were continuously fed the same HFD as preoperatively, after 3 to 5 days of low-residue diet. Food and water were freely available during the experimental period.

Body weight, food intake, and fasting blood glucose (FBG) were measured once per week for the first 2 weeks after surgery and then twice per week until the end of the study.

OGTT was performed at baseline and at 2, 8, and 16 weeks postoperatively. In addition, homeostasis model assessment of insulin resistance (HOMA-IR), hepatic function indices, fasting lipid profiles and ghrelin, and secretion of glucagon-like peptide-1 (GLP-1) and insulin after glucose gavage were measured at 2 and 16 weeks postoperatively.

Surgical Techniques

Sleeve Gastrectomy

SG was performed as previously described [24] (Fig. 1) and involved: (a) a 4-cm midline abdominal incision beginning at the xiphoid process; (b) dissociation of the greater curvature of the stomach from the cardia to the pylorus by ligation and transection of the vessels of the greater curvature; (c) excision of the entire glandular stomach and most of the gastric body, leaving approximately 30% of the total stomach; (d) reconstruction of the residual stomach cavity with 7–0 silk interrupted suture; (e) abdominal closure with 5–0 silk suture after careful examination.

Sleeve Gastrectomy Plus Duodenojejunal Bypass

SG-DJB surgery combined SG and DJB (Fig. 1). DJB surgery was performed as described in previous studies [24] and involved: (a) transection of the duodenum 0.5 cm distal to the pylorus and closure of the stump; (b) transection of the jejunum 10 cm distal to the ligament of Treitz; (c) end-to-end anastomosis between the distal jejunum and proximal duodenum (duodenojejunal anastomosis); (d) end-to-side anastomosis of the biliopancreatic limb to the alimentary limb 15 cm distal to the duodenojejunal anastomosis in a Roux-en-Y bypass.

Sleeve Gastrectomy Plus Jejunojejunal Bypass

SG-JJB surgery combined SG and JJB (Fig. 1). JJB surgery involved: (a) transection of the jejunum 2 cm distal to the Treitz ligament and closure of the distal stump; (b) exclusion of approximately 25 cm of jejunum distal to the first transection; (c) end-to-side anastomosis of the proximal jejunum to the distal jejunum (jejunojejunal anastomosis).

Sham Surgery

For the rats in the sham surgery group, the abdomen was incised and the stomach, esophagus, and small intestine were exposed as in the surgery groups. No other procedure was performed in these rats. Operative time was prolonged to induce a degree of anesthetic stress comparable to that experienced by the operated rats. The sham surgery group was used to eliminate the influence of surgical stress and general anesthesia on results.

Fig. 1 Diagrammatic drawings of SG, SG-DJB, and SG-JJB surgeries
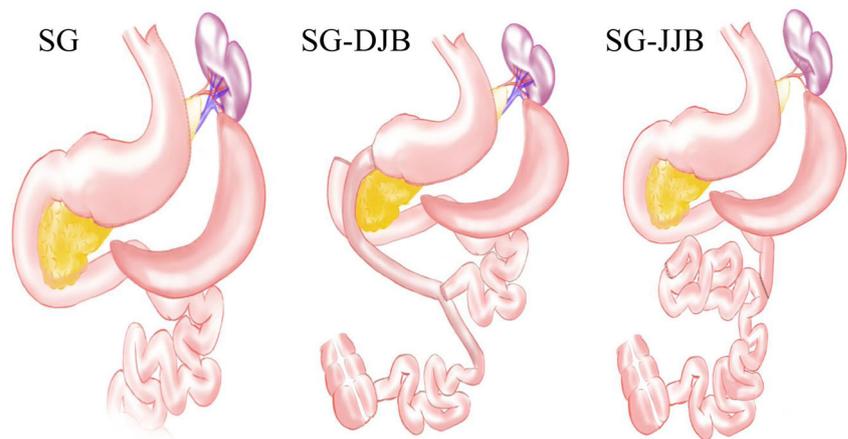
Biochemical Tests

Oral Glucose Tolerance Test

During the OGTT, blood was obtained from the tail by acupuncture, and blood glucose was measured with a Roche glucometer. Before the test, rats were deprived of food overnight. Fasting blood glucose was measured the next morning. Then, the rats were given 1 g/kg glucose by oral gavage. Then blood glucose was measured at 15, 30, 60, 90, and 120 min after gavage.

Homeostasis Model Assessment of Insulin Resistance

Homeostasis model assessment of insulin resistance (HOMA-IR) was used to estimate the degree of insulin resistance and was calculated with the following formula: HOMA-IR = fasting serum insulin (mIU/L) × FBG (mmol/L)/22.5 [25]. Fasting serum insulin and FBG were measured at 2 and 16 weeks postoperatively.

Serum Parameters

At 2 and 16 weeks postoperatively, blood samples were collected from the retrobulbar venous plexus under diethyl ether anesthesia at baseline and at 15, 30, 60, and 120 min after gavage with glucose. Serum was collected by centrifugation (4000 r × 10 min at 4 °C) and stored at − 80 °C until measurement. Indicators of hepatic function (alanine transaminase [ALT], aspartate transaminase [AST], albumin [ALB]) and lipid parameters (triglycerides [TG], cholesterol [Cho], non-esterified fatty acids [NEFA], high-density lipoprotein [HDL], low-density lipoprotein [LDL]) were measured with the Hitachi automatic biochemical analyzer (Japan). Concentrations of insulin, ghrelin, and GLP-1 were tested with enzyme-linked immunosorbent assay kits (CUSABIO Life Science, Wuhan, China).

Statistical Analysis

All statistical analyses were performed with SPSS version 20.0 (IBM, Chicago, IL, USA). Results are expressed as mean ± standard deviation. Trapezoidal integration was used to calculate areas under curves (AUC) of the OGTT. Statistical analysis was performed with the Bonferroni test for multiple comparisons after one-way analysis. According to the grouping and time after glucose gavage, the curves for OGTT, insulin, and GLP-1 were analyzed with mixed-model ANOVA followed by Bonferroni post hoc comparison. Values of P less than 0.05 were considered statistically significant.

Results

All operations were successful. One (1/10) SG rat died from stomach stump hemorrhage, and one (1/10) SG-JJB rat was found dead due to chronic intestinal obstruction. Two (2/10) SG-DJB rats died from duodenojejunal anastomotic leakage and intestinal obstruction. No deaths or other complications were observed in the sham group.

Weight Loss and Food Intake

Compared with the sham group, the body weight of rats in the other three groups was significantly lower from 4 weeks postoperatively (Fig. 2a) and food intake was significantly lower from 2 weeks postoperatively (Fig. 2b). There were no significant differences in weight loss or food intake among the three surgery groups during the observation period.

Glucose Metabolism

Fasting Blood Glucose

Before surgery, there was no significant difference in FBG levels among the groups, as shown in Fig. 3a. FBG levels in the SG, SG-DJB, and SG-JJB groups were significantly lower than those in the sham group from 1 week postoperatively (*$P < 0.05$). Mean FBG of the SG group was significantly higher than that of the SG-DJB group from 12 weeks postoperatively (at 12 weeks postoperatively, 9.96 ± 1.21 vs. 7.99 ± 1.28 mmol/L, #$P < 0.05$) and was higher than that of the SG-JJB group from 14 weeks postoperatively (at 14 weeks postoperatively, 10.70 ± 1.40 vs. 8.58 ± 1.25 mmol/L, △$P < 0.05$). There were no significant differences in FBG between the SG-DJB and SG-JJB groups within the 16-week observation period after surgery.

Oral Glucose Tolerance Test

The AUC for blood glucose in response to oral glucose tolerance test (OGTT) (AUC_{OGTT}) are shown in Fig. 3b. The blood glucose curves of OGTT at baseline and at, 2, 8, and 16 weeks postoperatively are shown in Fig. 3c–f.

As shown in Fig. 3b, the AUC_{OGTT} did not differ among the groups before surgery. Two weeks postoperatively, the AUC_{OGTT} of the SG (1102.42 ± 181.53), SG-DJB (1061.72 ± 175.48), and SG-JJB (1110.00 ± 220.53) groups were lower than that of the sham group (1843.20 ± 235.38) (*$P < 0.01$); this difference remained until the end of the study.

No significant differences were observed among the SG, SG-DJB, and SG-JJB groups at 2 or 8 weeks postoperatively. However, compared with the SG group (1806.42 ± 228.76), the DJB-SG (1428.84 ± 210.61) and JJB-SG (1469.17 ± 177.94) groups had lower AUC_{OGTT} at 16 weeks postoperatively ($P < 0.05$). The AUC_{OGTT} of the SG, SG-DJB, and SG-JJB groups were significantly higher at 16 weeks than at 2 weeks postoperatively (§$P < 0.01$).

According to Bonferroni post hoc comparison after the mixed-model ANOVA for blood glucose curve of OGTT,
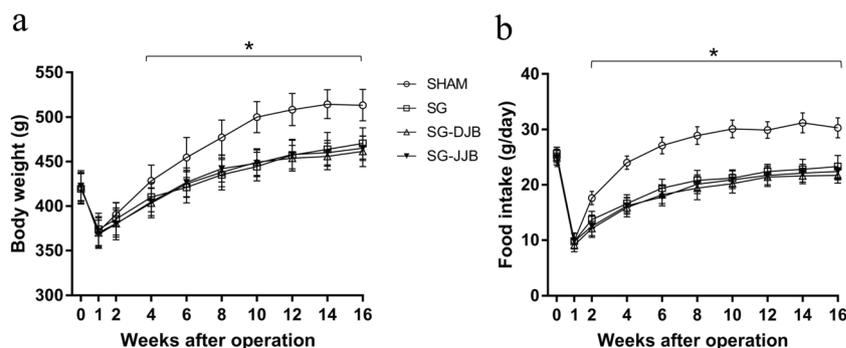
Fig. 3 Fasting blood glucose (**a**), AUC for blood glucose in response to OGTT (**b**), and blood glucose curves of OGTT (**c–f**), before and after surgery. Sham vs. SG, SG-DJB, and SG-JJB, *$P < 0.01$. SG vs. SG-DJB, #$P < 0.05$. SG vs. SG-JJB, △$P < 0.05$. AUC_{OGTT} at 16 weeks vs. 2 weeks after surgery, §$P < 0.01$ (**a**, **b**). Analysis was performed with a mixed-model ANOVA followed by Bonferroni post hoc comparison; P values are shown in rectangular frames (**c–f**). No significant difference was observed between the SG-DJB and SG-JJB groups
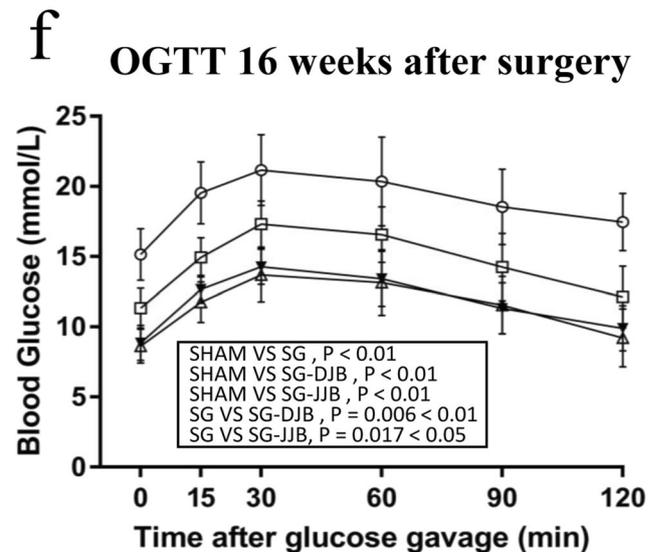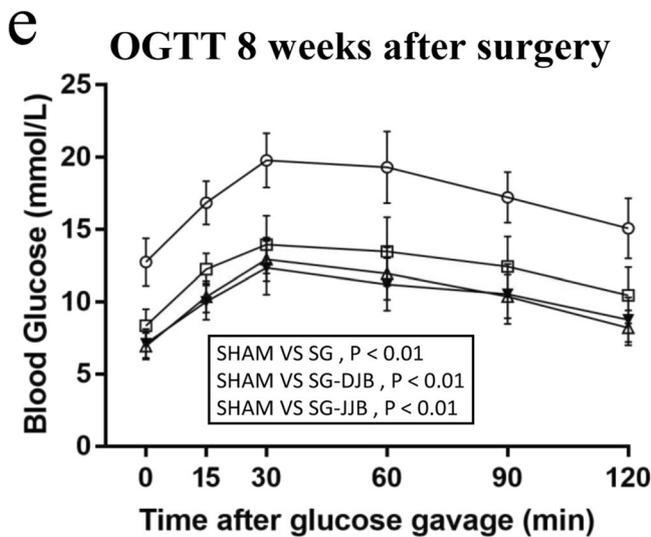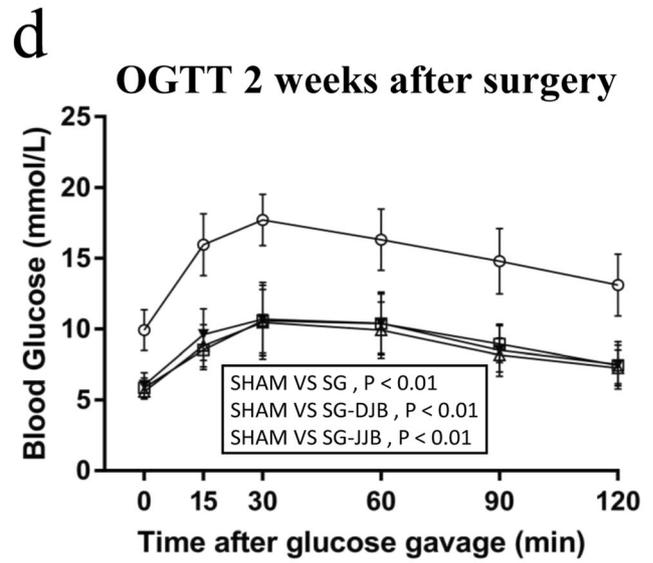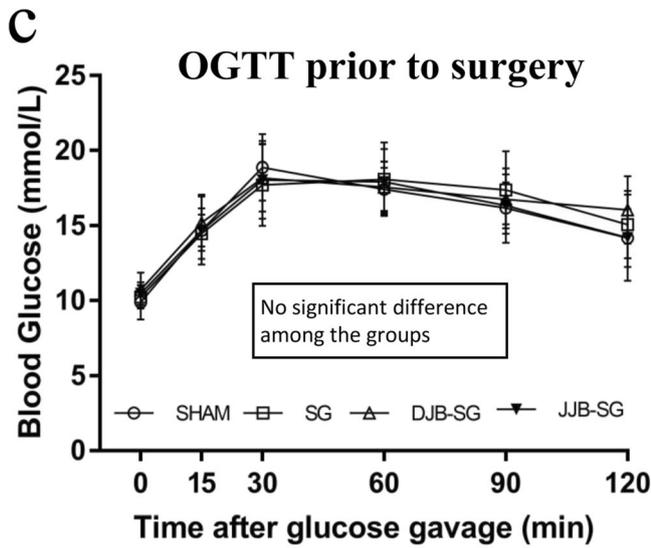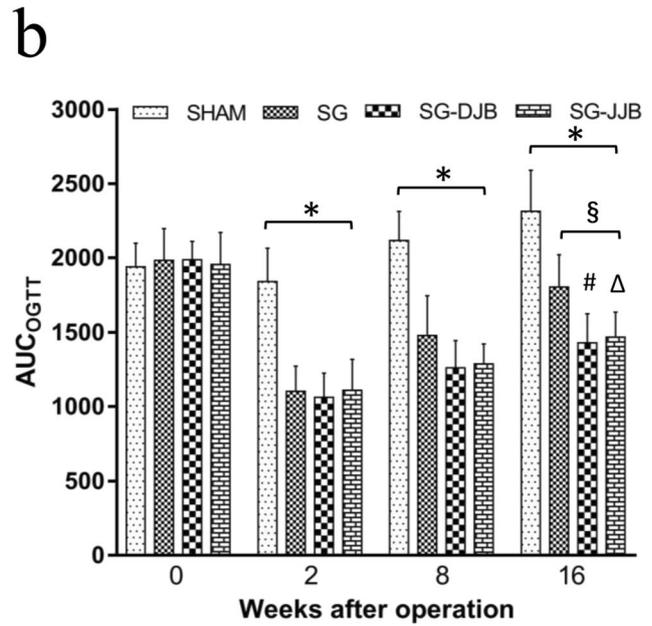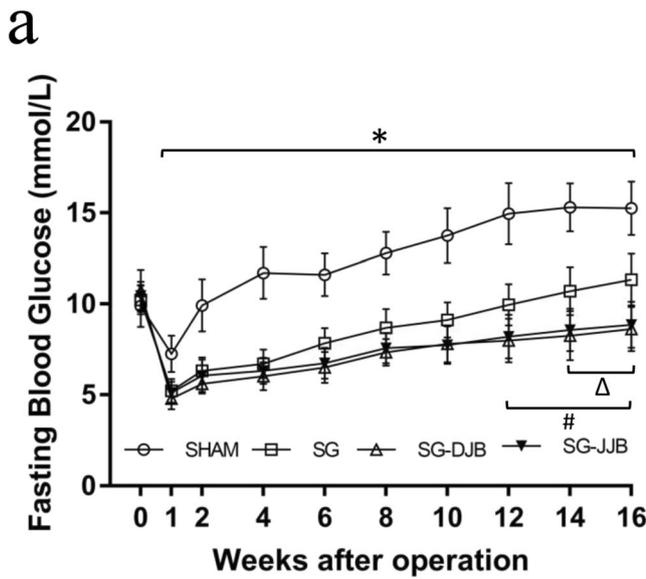
both SG-DJB and SG-JJB groups had lower blood glucose levels than the SG group at 16 weeks postoperatively (Fig. 3f, $P < 0.05$). There was no significant difference between SG-DJB and SG-JJB groups at any time after surgery.
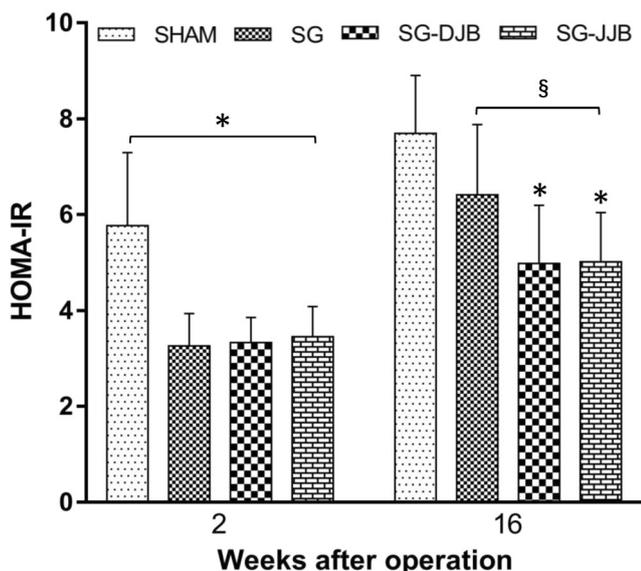
Homeostasis Model Assessment of Insulin Resistance

The calculated values of homeostasis model assessment of insulin resistance (HOMA-IR) at 2 and 16 weeks postoperatively are shown in Fig. 4. Compared with the sham group, the SG, SG-DJB, and SG-JJB groups had lower HOMA-IR values at 2 weeks postoperatively (*$P < 0.01$). At 16 weeks postoperatively, the SG-DJB (4.97 ± 1.31) and SG-JJB (5.01 ± 1.09) groups continued to have lower values than the sham group (7.69 ± 1.27, *$P < 0.01$). However, there was no significant difference between the sham and SG groups (6.41 ± 1.56, $P = 0.253$). HOMA-IR in the SG, SG-DJB, and SG-JJB groups were significantly higher at 16 weeks than at 2 weeks postoperatively (§$P < 0.01$). There were no significant differences among the SG, SG-DJB, and SG-JJB groups at either time point.

Glucose-Stimulated Insulin Secretion

Insulin secretion curves after glucose gavage at 2 and 16 weeks postoperatively are shown in Fig. 5a, b. At 2 weeks postoperatively, there were no differences among groups in serum insulin concentrations during fasting or in response to glucose gavage (Fig. 5a). However, the insulin secretion levels of the SG, SG-DJB, and SG-JJB groups were higher than those of the sham group at 16 weeks postoperatively ($P < 0.05$). No significant difference was observed in insulin secretion among the SG, SG-DJB, and SG-JJB groups.

Fig. 2 Body weight (**a**) and food intake (**b**) before and after surgery. Sham vs. SG, SG-DJB, and SG-JJB, *$P < 0.05$. No significant differences were found among SG, SG-DJB, and SG-JJB groups
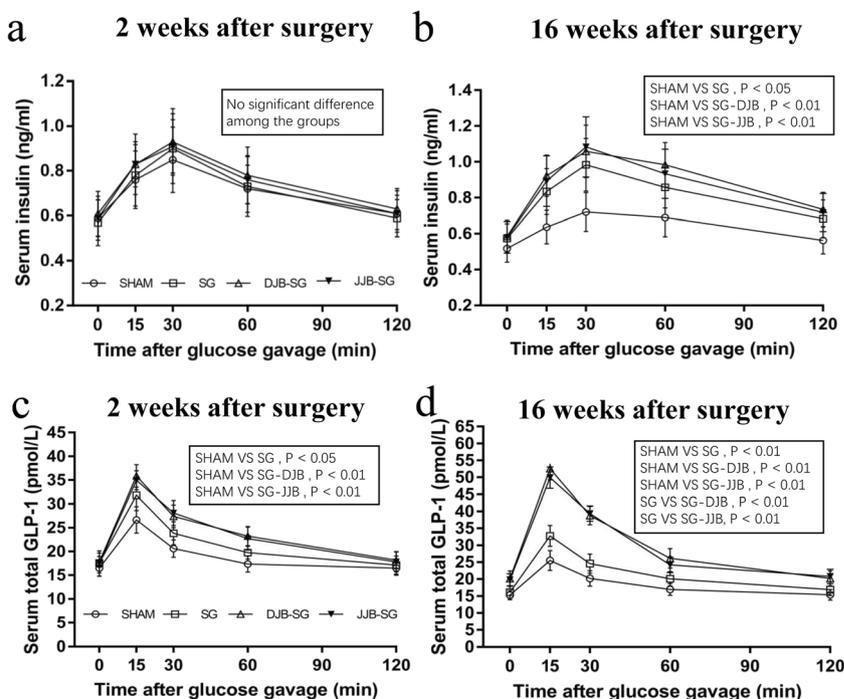
Fig. 4 HOMA-IR results at 2 and 16 weeks after surgery. Sham vs. SG, SG-DJB, and SG-JJB, *$P < 0.01$. HOMA-IR at 16 weeks vs. 2 weeks after surgery, §$P < 0.01$

Glucose-Stimulated Glucagon-Like Peptide-1 Secretion

In Fig. 5c, d, we see that the SG, SG-DJB, and SG-JJB groups secreted more glucagon-like peptide-1 (GLP-1) after glucose gavage than the sham group at 2 and 16 weeks postoperatively ($P < 0.05$). GLP-1 secretion levels in the SG-DJB and SG-JJB groups were higher than that in the SG group at 16 weeks postoperatively ($P < 0.01$). There was no difference in GLP-1 secretion between the SG-DJB and SG-JJB groups.
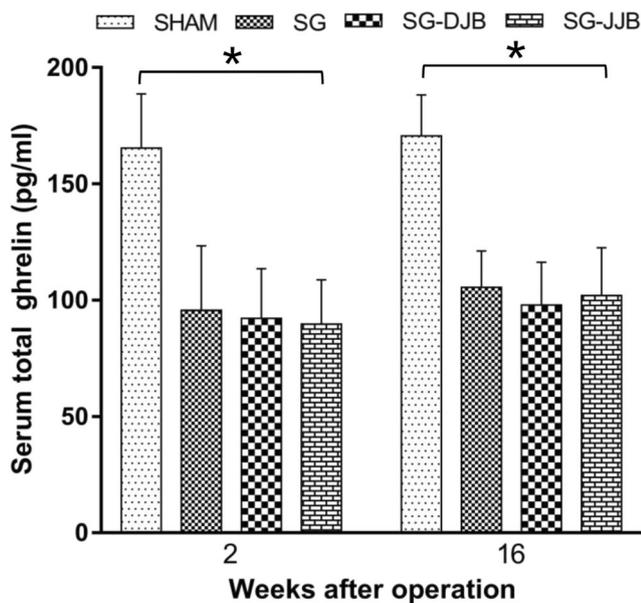
Fasting Serum Ghrelin

As shown in Fig. 6, the fasting serum total ghrelin levels in the SG, SG-DJB, and SG-JJB groups were lower than those in the sham group at 2 and 16 weeks postoperatively ($P < 0.01$). No significant differences were found in ghrelin levels among the SG, SG-DJB, and SG-JJB groups after surgery.

Hepatic Function and Lipid Profiles

The main serum indices of hepatic function (ALT, AST, ALB) and lipid profiles (TG, Cho, NEFA, HDL, LDL) after surgery are listed in Table 1. At 2 weeks postoperatively, fasting tri-glycerides and NEFA levels of rats in the SG, SG-DJB, and SG-JJB groups were lower than those in the sham group ($P < 0.05$). These differences lasted until 16 weeks postoperatively (Table 1). Serum ALT, AST, and fasting cholesterol of rats in the three surgery groups were lower than those in the sham group at 16 weeks postoperatively, but not at 2 weeks postoperatively. No significant differences were seen in serum ALB, HDL, or LDL among the four groups postoperatively. In addition, there were no significant differences among the SG, SG-DJB, and SG-JJB groups.

Discussion

The principal finding of the present study was that SG plus DJB or JJB provided more persistent improvement of diabetes than SG alone in rats fed a HFD postoperatively. SG-DJB was

Fig. 5 Serum insulin and total GLP-1 secretion after glucose gavage at 2 and 16 weeks after surgery. Analysis was performed with mixed-model ANOVA followed by Bonferroni post hoc comparison (a–d). *P* values are shown in rectangular frames

Fig. 6 Fasting serum total ghrelin levels of all groups at 2 and 16 weeks after surgery. *$P < 0.05$ vs. sham group, no significant difference among SG, SG-DJB, and SG-JJB groups

initially performed in a porcine model and was reported in 2008 [26]. We compared SG-DJB with SG in a previous animal study and found similar improvements in diabetes [16]. However, later clinical studies consistently showed that SG-DJB was superior to SG in promoting diabetes remission [27, 28]. A possible reason for this discrepancy is that both SG and SG-DJB provide good diabetes control, and that the effect is so quick and durable in diabetic animals that the superiority of SG-DJB is not obvious. Therefore, we added a HFD postoperatively in this study to disrupt the improvement in diabetes after SG-DJB and SG-JJB. As expected, both SG plus procedures showed superior diabetes control compared with SG

alone. This result is consistent with our previous study of SG plus jejunojejunal or jejunoileal loop [22].

Although this study suggests that adding bypass of the proximal intestine strengthens the antidiabetic effects of SG, duodenal exclusion seems not to be absolutely necessary. Based on previous mechanical researches, duodenal exclusion is essential for metabolic surgeries to regulate glucose homeostasis. In addition to SG-DJB, SG plus single-anastomosis duodenal switch, such as single-anastomosis duodeno-ileal bypass with sleeve gastrectomy (SADI-S) and stomach intestinal pylorus sparing (SIPS) procedure, has been designed and gains popularity in surgeons [29–32]. Currently, SG-DJB, SADI-S, and SIPS have been reported by many centers and offer similar or superior weight loss and diabetes control compared with RYGB [31–34]. Compared with these SG plus duodenal switch/bypass procedures, SG-JJB keeps the duodenum intact and is less invasive and technically easier. Thus far, no clinical study has evaluated the safety and effect of SG-JJB on weight loss and diabetes control. Whereas SG-JIB, a similar version of SG-JJB, has been reported to obtain significant improvement of diabetes in some clinical studies [19, 20]. What is more, SG plus jejunojejunal or jejunoileal loop, which does not exclude the duodenum, are also proved effective and achieve better diabetes control than SG alone in one of our previous animal studies [22]. These clinical and animal evidences suggest that although duodenal exclusion has powerful antidiabetic effect, it is not the unique or essential procedure to strengthen the effect of SG. Furthermore, the less invasive and technically easier SG-JJB compared to SG-DJB is worth more extensive attention and recommending for further clinical investigation.

Another important finding of this study was that a postoperative HFD induced obvious diabetes relapse, even after SG-DJB or SG-JJB. Few studies have focused on relapse of

Table 1 Main serum indices of hepatic function and lipid profiles of the four groups at 2 weeks and 16 weeks after surgery

	2 weeks after surgery				16 weeks after surgery			
	Sham	SG	SG-DJB	SG-JJB	Sham	SG	SG-DJB	SG-JJB
ALT (U/L)	65.88 ± 12.0	61.36 ± 10.12	57.11 ± 7.51	55.63 ± 13.60	70.45 ± 9.80	38.70 ± 7.65*	37.39 ± 6.50*	37.97 ± 11.35*
AST (U/L)	140.33 ± 34.07	136.63 ± 17.18	134.41 ± 30.30	136.26 ± 36.49	196.28 ± 23.63	140.94 ± 18.47*	136.4 ± 26.33*	141.11 ± 34.43*
ALB (g/L)	39.38 ± 2.74	37.2 ± 3.31	37.99 ± 3.00	38.38 ± 3.36	39.54 ± 3.26	38.7 ± 2.53	36.69 ± 2.63	39.27 ± 2.21
TG (mmol/L)	2.31 ± 0.50	1.77 ± 0.31*	1.63 ± 0.25*	1.70 ± 0.26*	2.63 ± 0.54	1.51 ± 0.49*	1.36 ± 0.44*	1.44 ± 0.44*
Cho (mmol/L)	2.14 ± 0.63	1.84 ± 0.51	1.81 ± 0.39	1.80 ± 0.48	2.86 ± 0.38	1.90 ± 0.38*	1.71 ± 0.47*	1.74 ± 0.50*
NEFA (μmol/dL)	50.6 ± 11.98	35.22 ± 6.30*	34.75 ± 7.89*	32.30 ± 10.77*	54.9 ± 11.78	38.89 ± 9.90*	33.38 ± 6.20*	34.67 ± 9.45*
HDL (mmol/L)	1.18 ± 0.23	1.20 ± 0.17	1.24 ± 0.20	1.22 ± 0.30	1.15 ± 0.18	1.29 ± 0.16	1.36 ± 0.25	1.35 ± 0.24
LDL (mmol/L)	0.38 ± 0.11	0.32 ± 0.11	0.34 ± 0.09	0.33 ± 0.11	0.39 ± 0.10	0.34 ± 0.09	0.33 ± 0.06	0.34 ± 0.12

*$P < 0.05$ vs. sham group

diabetes after bariatric/metabolic surgeries. However, such recurrence is common. Diabetes relapse after initial remission has been reported after SG, RYGB, and biliopancreatic diversion. Seki et al. reported that 10.8% of SG-DJB patients experienced recurrence during the follow-up period [35]. In the present study, all rats experienced quick improvement in glucose tolerance and insulin sensitivity after SG and SG plus procedures. However, the improvement was slowly reversed after adding the HFD. We previously reported that a HFD reversed improvements in glucose tolerance after DJB in two diabetic rat models. Our later studies on SG plus jejunojejunal or jejunoileal loop confirmed the adverse effect of a HFD on diabetes improvement. Therefore, as the clearest pathogenic factor in diabetes, a HFD must be strictly limited postoperatively.

Animal models of diabetes relapse after initial remission provide an opportunity to understand the mechanisms of diabetes remission after bariatric/metabolic surgeries. All SG, SG-DJB, and SG-JJB rats experienced weight loss after surgery, and no significant difference was observed among these groups in diabetes remission or recurrence. Therefore, weight loss was confirmed to be less associated with diabetes remission after surgery than other factors. Insulin sensitivity, which was assessed with HOMA-IR, varied with glucose tolerance. This finding suggests that improvement and worsening of insulin sensitivity was the main cause of diabetes remission and recurrence, rather than β-cell function, which was reflected by glucose-stimulated insulin secretion. It seems that SG and SG plus bypass of the proximal intestine protected but did not improve β-cell function. Serum GLP-1 and ghrelin varied after surgery but not together with diabetes remission and recurrence. This finding suggests that these hormones were only associated with diabetes remission.

There were some limitations in the present study. We only compared SG-DJB and SG-JJB with SG, and all rats were given a HFD postoperatively. A more comprehensive study with DJB- and JJB-alone groups, and with groups fed with a normal diet, would be preferable. Secondly, we did not conduct further studies on why SG-DJB and SG-JJB provided better diabetes control than SG alone, especially studies of the morphological and functional changes of bypassed proximal intestine. In addition, all findings were derived from an animal model, not humans. Clinical studies are needed to confirm our results.

In conclusion, the present animal study revealed that SG-DJB and SG-JJB provided better diabetes control than SG alone under the interference of a postoperative HFD. The improvement and worsening of insulin sensitivity was associated with diabetes remission and HFD-induced diabetes relapse after surgery. Duodenal exclusion was not essential in SG plus procedures. Our results should be confirmed with further clinical studies.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This study was performed in accordance with the National Institutes of Health Guidelines on the Use of Laboratory Animals and was approved by the Ethics Committee on Experimental Animals of Qilu Hospital, Shandong University.

Statement of Informed Consent Does not apply.

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