

Original Article

Impact of sleeve gastrectomy verses sleeve gastrectomy plus side-to-side jejunoileal anastomosis on weight loss and metabolic control in an obese rat model

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Abstract: Aim: To study the impact of sleeve gastrectomy plus side-to-side jejunoileal anastomosis on weight loss and the remission of type 2 diabetes mellitus. Methods: Thirty-three 7 weeks old male Zucker diabetic fatty rats were randomized into three groups: sleeve gastrectomy plus side-to-side jejunoileal anastomosis (JI-SG group), sleeve gastrectomy (SG group), sham surgery (Control group). Results: The weight of rats in JI-SG group and SG group was significantly lower than control group at 2 weeks postoperatively, and body weight in JI-SG group was lower than SG group since 4 week postoperatively. The blood Glucose was significantly improved for both JI-SG group and SG group, and increased in Control group at 2 weeks after surgery. The serum ghrelin level of rats in JI-SG, SG group was significantly decreased, but without difference between two groups; compared with that preoperatively, the GLP-1 level of rats in JI-SG group was significantly higher at 12 weeks postoperatively; SG group and SO group had no difference in the GLP-1. The serum insulin level in rats was also decreased in JI-SG group and SG group at 6 weeks postoperatively, and plasma insulin level in JI-SG group was significantly lower than those in the SG group at 12 weeks postoperatively. Conclusions: JI-SG is superior to SG as the treatment of type 2 diabetes mellitus and weight control in obese diabetic rodents.

Keywords: Side to side jejunoileal anastomosis, sleeve gastrectomy, type 2 diabetes, zucker diabetic fatty rat

Introduction

Weight loss operation can cure and be beneficial for a long-term improvement of type 2 diabetes mellitus, dyslipidemia, hypertension and other metabolic syndromes [1]. Laparoscopic sleeve gastrectomy (LSG) is one of the main weight loss operations, because the manipulation is relatively simple, safe, with a less post-operative nutritional deficiency and an increasing popularity. However, it has been declared in some studies that the effect of sleeve gastrectomy is still unsatisfactory in weight loss and improving the metabolism [2]. However, the way to take sleeve gastrectomy as a base surgery with other kinds of intestinal bypass is expected to increase the effect of weight loss and improving the metabolism. In this paper, the impact of sleeve gastrectomy plus side-to-side jejunoileal anastomosis (JI-SG) on weight loss and the treatment of type 2 diabetes mel-

litus was discussed by using the Zucker diabetic fatty (ZDF) rat model.

Materials and methods

Animals and grouping

Thirty three 7 weeks old male ZDF rats (Beijing Weitonglihua company, license number: SCXK (Beijing) 2011-0011) were chosen as the animal model. The experimental animals were carried out according to a protocol reviewed and approved by the Animal Committee of Tongji University School of Medicine, China. The rats were taken to operation after 3 weeks feeding by high-fat diet (Purina 5008).

Thirty-three 7 weeks old male Zucker diabetic fatty (ZDF) rats were randomized into 3 groups: sleeve gastrectomy plus side-to-side jejunoileal anastomosis (JI-SG group), sleeve gastrectomy

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(SG group) and sham surgery (Control group). There were 11 rats in each group.

Preoperative preparation and anesthesia

The rats in 3 groups were fasted food without water before surgery more than 12 h. After being weighted accurately, 30 mg/kg cefotiam was injected into the rats' muscle 1 hour before surgery. The rats were anesthetized with 400 mg/kg 10% chloral hydrate by intraperitoneal injection. In order to avoid dehydration during surgery, 5 ml saline was delivered by subcutaneous injection. During the surgery, the supplement of blood should be given depending on particular situations. 5-0 absorbable lines were used in the suture of gastroenterostomy.

Surgical operation

Jl-SG surgical methods were as follows: After being anesthetized successfully, the rats were shaved of their abdominal hairs, fixed on the operating table, disinfected with 20% iodophor on the surgical site twice and covered with a square of sterile gauze pad over the wound. Jl-SG includes two operation parts: SG and side-to-side jejunoileal anastomosis: 1) the rats' abdomen were open with a 4 cm median incision, cut the skin and muscle respectively and then open the peritoneum; 2) the retractor was used to get the liver away and broke those ligaments surrounding the stomach and gastroepiploic tissues; 3) resected approximately 70% of the gastric tissue along the greater curvature of the stomach; 4) 5-0 absorbable lines were used to continuous suture the full-thickness gastric section and strengthen the interrupted suture at both two ends and the middle part 5) a 0.5 cm long incision was taken on the point that 10 cm distal away from Treiz ligament, as the site of jejunum anastomosis; 6) a 0.5 cm long incision was taken on the point that 10 cm proximal to the ileocecal ileum, as the site of ileal anastomosis; 7) the single layer side-to-side jejunoileal anastomosis was taken along the food channel direction; (8) fixed the bowel serosa with 5-0 absorbable lines at 1 cm away from both two ends of the anastomosis site respectively; 9) lavaged with warm saline intraperitoneally, checked carefully without any bleeding, and closed the abdominal cavity layer by layer.

Surgical methods of SG group were taken as the same as Jl-SG group. Surgical methods of

Control group: the rats' abdomens were open with a 4 cm median incision, cut the skin and muscle respectively and open the peritoneum. The stomach and the jejunum and ileum were exposed by following the same operation protocol of Jl-SG group. A 2 cm incision was taken along the greater curvature of the stomach, but without removing the stomach tissue, continuous sutured the incision with 5-0 absorbable lines. A 0.5 cm long incision was taken on the same point of Jl-SG group, but without jejunoileal anastomosis, only with simply cutting and suturing. After checking carefully without any abnormal bleeding, closed the abdominal cavity layer by layer, and completed the operation.

Postoperative treatment

After surgery, the rats were restored their body temperature by heating lamps, with 30 mg/kg cefotiam intramuscular injection once. Water deprivation was performed postoperation, and the rats were free access to water after 8 hours postoperation. Three days after surgery, postoperative infection was prevented by 30 mg/kg cefotiam intramuscular injection every day. Three days after surgery, the feeding food was transited from a liquid diet (10% glucose water) to the normal rat food gradually.

Postoperative observation and detection index

Preoperative and postoperative health statuses of the rats in each group were observed daily. The blood-glucose level was determined by using Roche Excellence Gold Rui blood glucose meters and test strips (Roche Diagnostics GmbH, Germany). Meanwhile, Ghrelin, GLP-1, and insulin were measured by Elisa kits (purchased from Becton, Dickinson and Company).

Statistical analysis

SPSS 17.0 statistical software was used for data analysis. Data was presented as means \pm standard deviation. The test indexes before and after the operation were compared with paired t test, and the comparison of each group was using ANOVA analysis. $P < 0.05$ were considered statistically significant.

Results

Survival of rats

During the experiment, the overall survival rate of the animals was 90%. After surgery, none of

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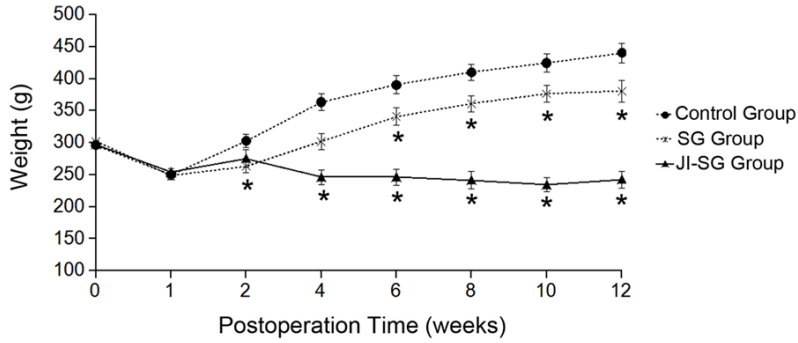


Figure 1. There was no significant difference in the preoperative weight of the rats in three groups. Two weeks after surgery, comparing with Control group, the weights of rats in JI-SG group and SG group were both decreased. *Compared with Control group, $P < 0.01$.

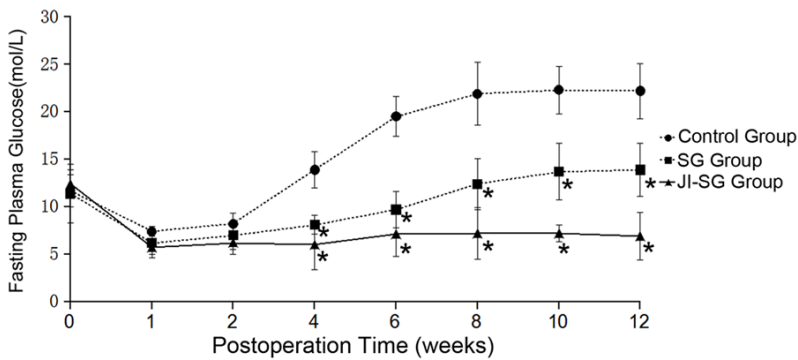


Figure 2. The fasting blood-glucose level of the rats in three groups had no change both before and one week after surgery. However, during the following 2, 4, 6, 8, 10, 12 weeks after surgery, the blood-glucose levels of rats both in JI-SG group and SG group were significantly lower than those in Control group. And in JI-SG group, the blood-glucose level was better controlled compared with SG group. *Compared with Control group, $P < 0.01$.

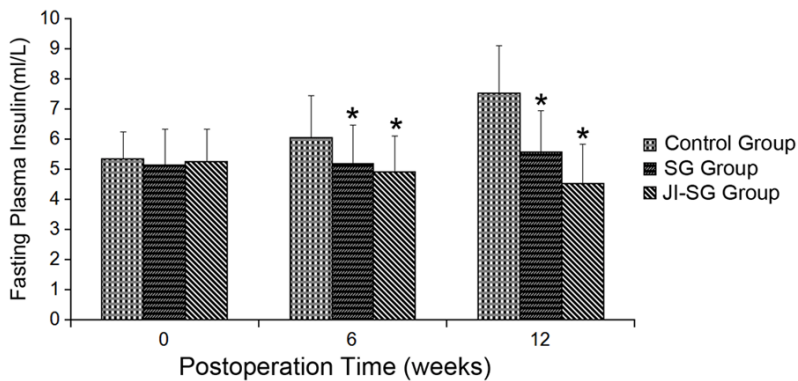


Figure 3. Before surgery, the rats of three groups were no significant difference ($P > 0.05$). 6 weeks after surgery, the insulin levels of rats both in JI-SG group and SG group were significantly lower than those in Control group. 12 weeks after surgery, the insulin level of rats in JI-SG group was significantly lower than those in SG group and Control group. *Compared with Control group, $P < 0.01$.

both in JI-SG group and SG group, there was one rat died of acute intestinal obstruction and intestinal necrosis three days after surgery.

Weight change

The weight of the rats in three groups had no change before and one week after surgery. However, 2 weeks after surgery, the weight of rats in Control group increased quickly, much more than those in SG group and JI-SG group. However, the weight of rats in SG group and JI-SG group had no significantly difference. Two weeks after surgery, the weight of rats in SG group began to rise, while the weight of rats in JI-SG group maintained stable levels. Comparing with the preoperative weight, those in JI-SG group lost weight dramatically 12 weeks after surgery (234 ± 12 g vs. 302 ± 8 g, $P = 0.0034$) (Figure 1).

Blood-glucose change

The blood-glucose level of the rats in three groups had no change before and one week after surgery. However, 2 weeks after operation, the blood-glucose level of rats in Control group increased rapidly. Compared with Control group, the blood-glucose levels of rats in JI-SG group and SG group decreased significantly. After surgery, the blood-glucose level of rats in SG group increased gradually, while the blood-glucose level of rats in JI-SG group was controlled well. 12 weeks after surgery, the blood glucose level of rats in JI-SG group was lower than those

the rats in three groups got an infection to deaths. No animals in Control group died, while

well. 12 weeks after surgery, the blood glucose level of rats in JI-SG group was lower than those

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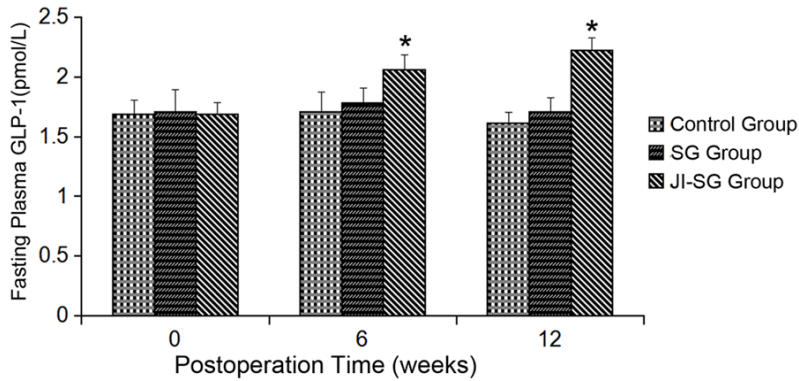


Figure 4. The plasma GLP-1 level was measured in the fasting state. Before surgery, the GLP-1 levels of the rats in three groups were no significant difference. However, after surgery, the GLP-1 level of rats in JI-SG group was higher than those both in SG group and Control group. And, there was no significant difference between SG group and Control group. *Compared with Control group, $P < 0.01$.

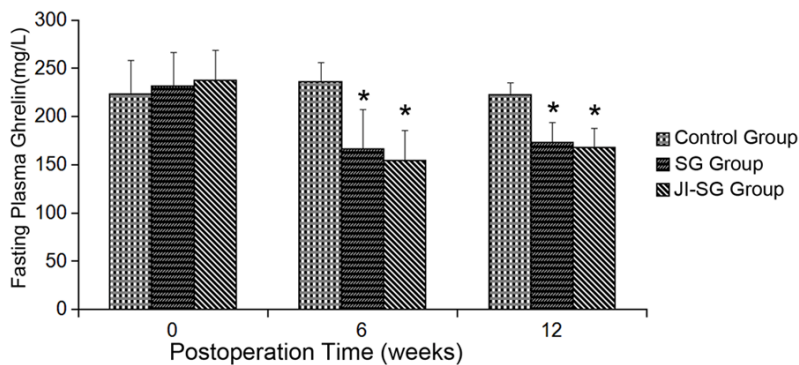


Figure 5. The plasma Ghrelin level was measured preoperatively and 6 and 12 weeks postoperation. 6 weeks after surgery, the Ghrelin levels of rats in JI-SG group and SG group were significantly lower than those in Control group. 12 weeks after surgery, the Ghrelin levels of rats in JI-SG group and SG group were significantly lower than those in preoperation. *Compared with Control group, $P < 0.01$.

in SG group (6.9 ± 2.3 vs. 13.8 ± 2.5 mmol/L, $P = 0.0089$). Comparing with the preoperative level, the blood-glucose level of rats in JI-SG group was improved significantly (6.9 ± 2.3 vs. 12.3 ± 1.1 mmol/L, $P = 0.0045$) (Figure 2).

Fasting insulin, Ghrelin and GLP-1 changes

6 and 12 weeks after surgery, the insulin levels of rats both in JI-SG group and SG group were significantly lower than those in Control group. 6 weeks after surgery, the insulin levels of rats in JI-SG group and SG group were no significant difference (4.91 ± 1.2 vs. 5.02 ± 0.8 , $P = 0.297$). However, when it came to 12 weeks after surgery, the insulin level of rats in JI-SG group was significantly lower than those in SG group

(4.53 ± 1.1 vs. 7.51 ± 1.5 mU/L, $P = 0.0021$) and also lower than itself before surgery (4.53 ± 1.1 vs. 5.24 ± 1.5 mU/L, $P = 0.031$) (Figure 3).

Before surgery, the fasting GLP-1 levels of the rats in three groups were no significant difference. 6 weeks after surgery, the fasting GLP-1 level of rats in JI-SG group was significantly higher than those in SG group and Control group. However, there was no significant difference between SG group and Control group (1.71 ± 0.14 vs. 1.68 ± 0.12 , $P = 0.894$). 12 weeks after surgery, the fasting GLP-1 level of rats in JI-SG group was significantly higher than those in preoperation (2.23 ± 0.11 vs. 1.69 ± 0.12 pmol/L, $P = 0.015$) (Figure 4).

After surgery, the Ghrelin levels of rats in JI-SG group and SG group were decreased significantly. 6 and 12 weeks after surgery, the Ghrelin levels of rats in JI-SG group and SG group were significantly lower than those in Control

group. However, there was no significant difference between JI-SG group and SG group. 12 weeks after surgery, the Ghrelin level of rats in JI-SG group was significantly lower than those in preoperation (168 ± 19.8 vs. 237.7 ± 31.2 ng/L, $P = 0.0034$) (Figure 5).

Discussion

Weight-loss surgery can improve or cure type 2 diabetes mellitus, dyslipidemia, hypertension and other metabolic disorders as a long-term effect [3]. In the field of treating type 2 diabetes mellitus, weight-loss surgery has played an important role. SG is the one-stage operation of Roux-en-Y gastric bypass (RYGB) surgery. Meta analysis showed that the effect on improv-

ing type 2 diabetes mellitus by SG surgery is not as well as RYGB surgery. The way that adding other kinds of intestinal bypasses on the base of sleeve gastrectomy is expected to increase effects of treatment, which includes sleeve gastrectomy plus jejunoileal diversion, sleeve gastrectomy plus ileal transposition, and sleeve gastrectomy plus side-to-side jejunoileal anastomosis, etc., of which JI-SG surgery was rarely studied [4]. Melissa et al. performed 32 cases of JI-SG surgery, among which 6 cases got better weight loss effect than simply by SG surgery, but without a study on the effect of improving type 2 diabetes mellitus [5]. In this study, the impact of JI-SG on weight loss and the treatment of type 2 diabetes mellitus was investigated by using the rat model.

This study showed that JI-SG and SG surgery had great effects on weight loss and reducing the blood-glucose level. Comparing with SG group, JI-SG group lost weight more and got better blood-glucose control. Researchers have proven that the rapid improvement of type 2 diabetes mellitus resulted from the increasing of insulin sensitivity, which can be recovered by losing weight [6]. The characteristics of ZDF model used in this study were hyperinsulinemia and type 2 diabetes mellitus. After surgery, insulin levels decreased with consequent decreasing of blood-glucose level, which demonstrated that insulin sensitivity would increase after weight-loss surgery. Meanwhile, Buchwald et al. thought that weight loss played an important role in the long-term control of blood-glucose level [7]. In this study, the weight of rats in SG group increased with consequent increasing of the blood-glucose level, suggesting that improved weight had a positive effect on improving of glucose metabolism.

Besides weight loss, increased insulin sensitivity and some other factors, the variations of gastrointestinal hormone are also considered to be one of the important factors in the improvement of type 2 diabetes mellitus [8]. Our study showed that 12 weeks after surgery, the ghrelin levels of rats both in JI-SG group and SG group were significantly decreased than those in Control group. Some scholars believe that the reduced ghrelin level can help lose weight and increase insulin sensitivity [9]. After JI-SG and SG surgery, the fact that the ghrelin level of rats decreased with weight loss and blood-glucose controlling is another evidence

for the ghrelin hormone-related hypotheses. Almost all kinds of mainstream weight loss surgeries involve changes in the stomach, with resultant changes in the ghrelin level, which demonstrates that stomach-related hormonal changes are one of the key factors in all clinical effects. Meanwhile, according to "hindgut theory", the incompletely digested food will go into the terminal ileum, which will stimulate ileal L cells to secrete hormones such as GLP-1 [10]. GLP-1 can promote insulin secretion, increase the sensitivity of insulin and so on [11]. GLP-1 related drugs have served in clinical treatment of type 2 diabetes mellitus. In our study, the ghrelin level of rats in JI-SG group has no difference with those in SG group, but with a higher GLP-1 level. Furthermore, the blood-glucose level, weight control and the insulin level of rats in JI-SG group were better than those in SG group, which demonstrates that GLP-1 plays an important role in improving the metabolism, which also supports the "hindgut theory". In the future, more studies will be undertaken to confirm the precise role of JI-SG surgery in its related hormones' secretion.

For type 2 diabetes mellitus, weight-loss surgery has better treatment effects than traditional medical therapies [8, 12]. In all kinds of surgeries, SG plus other additional bypasses, JI-SG surgery is a novel surgical procedure. We established operational models in ZDF rats successfully. Compared with SG group, JI-SG surgery had better effects in higher GLP-1 level, long-term weight loss, decreased blood-glucose level, and enhanced insulin sensitivity. Besides, JI-SG surgery is safe and simple, for excessive obesity, JI-SG surgery may have better effects.

Disclosure of conflict of interest

None.

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