



Rapid Improvement in Diabetes After Simple Side-to-side Jejunoileal Bypass Surgery: Does It Need a Ligation or Not?

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Abstract

Background Dual-path side-to-side jejunoileal bypass (SSJIB) can markedly ameliorate diabetes and obesity. However, whether SSJIB requires the ligation of the bypassed loop (single-path) and what is the most appropriate length of the bypassed small bowel remain unknown. The aim of this study was to evaluate the role of ligation and the length of the bypassed small bowel in mediating changes in glucose homeostasis after SSJIB in streptozotocin (STZ)-induced diabetic rats.

Methods Fourteen STZ-induced diabetic rats were randomized into two groups: one group was subjected to 50% SSJIB (SSJIB-50 group) and one group was subjected to sham surgery (sham group). Three weeks later, the SSJIB-50 group was re-operated, and the bypassed segment was ligated (SSJIBL-50 group). Three weeks later, the SSJIBL-50 group was operated again, and 60% of the length of the proximal small intestine was bypassed (SSJIBL-60 group). The measured primary outcomes were body weight, food intake, fasting blood glucose (FBG), and oral glucose tolerance test (OGTT).

Results Body weight in the SSJIBL-60 group was lower than that in the sham group. Food intakes in the SSJIBL-50 and SSJIBL-60 groups were lower than that in the sham group. FBG and OGTT were not improved in the SSJIB-50 group compared with the sham group. However, FBG and OGTT were improved in the SSJIBL-50 group and were further improved in the SSJIBL-60 group.

Conclusions Ligation of the first portion of the bypassed loop is essential to SSJIB, and bypassing approximately 60% of the small intestine length may be appropriate in SSJIBL.

Keywords Metabolic surgery · Side-to-side jejunoileal bypass · Glucose homeostasis · Diabetes mellitus · Streptozotocin (STZ)

Introduction

Jejunoileal bypass (JIB) was commonly performed as a bariatric surgical procedure for massive obesity in the late 1960s and early 1970s but became obsolete by the mid-1980s

because of the severe complications of the procedure, including severe malnutrition, liver failure, and blind loop syndrome [1]. However, JIB is still performed with modifications [2, 3] or in combination with other bariatric surgeries, including sleeve gastrectomy (SG) [4, 5], in some medical centers to date.

The “uncut Roux” reconstructive technique has been successful in promoting myoelectric continuity in the aboral direction and preventing the formation of ectopic pacemakers [6]. Based on these results, a new JIB procedure designated “side-to-side jejunoileal bypass plus proximal loop ligation” (SSJIBL) was developed by our research group. Animal studies showed that SSJIBL induced stronger glucose-lowering effects than end-to-side JIB [7]. Furthermore, intestinal bypass surgery that retained a shorter segment of the distal small bowel yielded stronger antidiabetic effects [8]. Melissas et al. reported that a simple side-to-side jejunoileal anastomosis (SJA) could normalize fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) levels in a non-obese

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diabetic rat model [9]. Furthermore, clinical studies reported that the dual-path side-to-side JIB such as SJA, partial jejunal diversion (PJD) under laparoscope or gastrointestinal endoscopy, and laparoscopic jejunioileal anastomosis (LJISSA) yielded complete or partial remission of type 2 diabetes mellitus in humans with BMI of 28–32 kg/m² soon after these procedures and the preliminary results were encouraging and promising [3, 10–12].

Diverting the food and biliopancreatic secretion to the distal small bowel (hindgut hypothesis) may be the primary mechanism underlying the significant reversal of diabetes following SJA, PJD, and LJISSA. However, our recent study demonstrated that distal small intestinal bypass in which the distal small intestine was almost bypassed yielded long-term improvement in glucose tolerance, and the improvement was similar to that of obese rats subjected to proximal small intestinal bypass [13]. Another study reported that the improved weight loss and antidiabetic effect induced by the longer side-to-side jejunioileal bypass (SSJIB) had a strong relationship with lower food intake [8]. These findings challenged the hindgut hypothesis and the role of malabsorption in the antidiabetic effect achieved with small intestine bypass surgeries.

However, previous studies have shown that the dual-path side-to-side JIB would cause stagnation loop syndrome and liver injury [14]. Changes in the migrating motor complex (MMCs) within the bypassed loop may account for the development of stasis of luminal contents and thereby blind loop syndrome. The single-path bypass model (with proximal loop ligation), in which the propagation of MMCs was maintained for a period of time, could avoid effectively the stagnation of the bypassed loop [15]. The ligation of the first portion of the bypassed segment using silk suture after SSJIBL was the main difference between SSJIBL [7] and JIA [3, 9] or PJD [11, 12] or LJISSA [10]. Based on the findings described above, we hypothesized that SSJIBL might improve weight loss and the antidiabetic effect compared to SJA or PJD or LJISSA because of the more severe malabsorption induced by the decreased intestinal surface area in SSJIBL.

This hypothesis was tested by developing three experimental procedures using streptozotocin (STZ)-induced diabetic rats, a widely used animal model of non-obese diabetes. The three experimental procedures were 50% side-to-side jejunioileal bypass (SSJIB-50), 50% SSJIB with proximal loop ligation (SSJIBL-50), and 60% SSJIB with proximal loop ligation (SSJIBL-60). SSJIB-50, SSJIBL-50, and SSJIBL-60 bypassed 50%, 50%, and 60% of the length of the proximal small intestine, respectively. The analyzed primary outcomes were body weight, food intake, FBG, and OGTT.

The objectives of this study were to systematically evaluate the role of ligation of the first segment of the bypassed loop and the length of the bypassed small bowel in mediating changes in glucose homeostasis after intestinal bypass surgeries in STZ-induced diabetic rats and to establish a suitable

experimental setting to determine the mechanisms underlying the control of diabetes.

Materials and Methods

Animal Model

Twenty-four male Sprague-Dawley (SD) rats weighing 238 ± 8 g were purchased from the Changsha Slac Jingda Laboratory Animal Co. Ltd. The rats were housed in a cage (one per cage) with a 12/12-h light/dark cycle and temperature of 22–25 °C. Water and standard rodent chow were provided ad libitum. The rats were acclimated for 1 week and then received an intraperitoneal injection of streptozotocin at 60 mg/kg [16] (STZ, Sigma, St. Louis, MO, USA). Seventy-two hours after STZ injection, rats with a fed blood glucose level higher than 16.7 mmol/l [17] were considered to be diabetic and were selected for further analysis. The study protocol was approved by the Animal Research Ethics Committee of Nanchang University, China. All surgeries were performed under chloral hydrate anesthesia, and all efforts were made to minimize suffering.

Experimental Protocol

Fourteen STZ-induced diabetic rats were randomly divided into groups of seven rats for the following procedures: SSJIB-50 and sham operation. After 3 weeks, the SSJIB-50 group was re-operated, and the first portion of the bypassed segment was ligated using silk suture (SSJIBL-50 group). After another 3 weeks, the SSJIBL-50 group was operated again and a longer length (approximately 60%) of the proximal small intestine was bypassed (SSJIBL-60 group). The sham group was re-operated twice on the third and sixth weeks after the first operation, respectively. The measured primary outcomes were body weight and food intake. These tests were conducted at weeks 1, 2, 3, 4, 5, 6, 7, 8, and 9 after the operation.

Surgical Techniques

Animals were fasted overnight with free access to water and were anesthetized with 10% chloral hydrate solution (300 mg/kg body weight). The abdomen was shaved, and the peritoneal cavity was accessed via a 4-cm midline incision.

SSJIB-50

For the SSJIB-50 group (Fig. 1a), the entire small bowel (from the Treitz ligament to the ileocecal valve; the length of the jejunioileum varied from 96 to 109 cm) was measured along the antimesenteric border, and a point 45 cm proximal to the

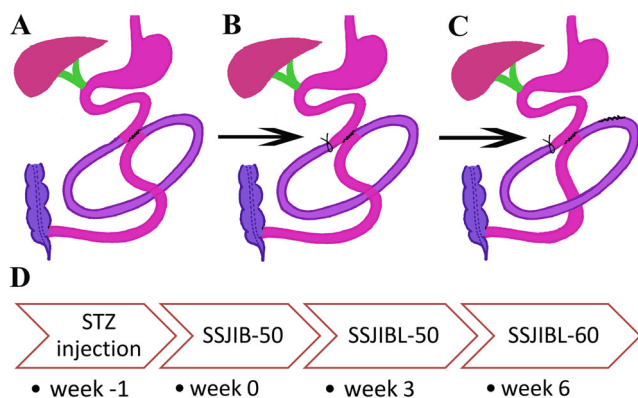


Fig. 1 Surgical procedures. Schematic and operative photograph of the small intestinal bypass models (SSJIB-50, SSJIBL-50, and SSJIBL-60). **a** 50% side-to-side jejunoleal bypass (SSJIB-50). Physiological characteristics of the procedure included (1) preservation of 8 cm of the proximal jejunum and 45 cm of the distal small intestine and exclusion of approximately 50% of the proximal small intestine and (2) side-to-side anastomosis between the proximal jejunum and the ileum. **b** SSJIB-50 plus proximal loop ligation (SSJIBL-50). The physiological characteristics of the procedure included (1) preservation of 8 cm of the proximal jejunum and 45 cm of the distal small intestine and exclusion of approximately 50% of the proximal small intestine, (2) side-to-side anastomosis between the proximal jejunum and the ileum, and (3) ligation of the first portion of the bypassed segment. **c** 60% side-to-side jejunoleal bypass plus proximal loop ligation (SSJIBL-60). The physiological characteristics of the procedure included (1) preservation of 8 cm of the proximal jejunum and 35 cm of the distal small intestine and exclusion of approximately 60% of the proximal small intestine, (2) side-to-side anastomosis between the proximal jejunum and the ileum, and (3) ligation of the first portion of the bypassed segment. **d** Experimental procedure

ileocecal valve was used as the reference point. Starting proximally from this point to 8 cm distal to the Treitz ligament, approximately 50% of the length of the entire small bowel was bypassed, and bowel continuity was restored by performing an isoperistaltic side-to-side anastomosis between the proximal jejunum and the ileum. Enteric anastomoses were performed with a single layer of interrupted 6–0 nylon suture (Hangzhou Huawei Medical Treatment Articles Co., Ltd). The abdominal cavity was closed with 3–0 silk suture (ETHICON SA84G, Johnson & Johnson).

SSJIBL-50

After 3 weeks of the first operation, the SSJIB-50 group was re-operated (Fig. 1b). The peritoneal cavity was accessed via the original incision, and a luminal occlusion was performed by ligating the first portion of the bypassed segment using #7 silk suture (ETHICON SA86G, Johnson & Johnson). After that, the abdominal cavity was closed with 3–0 silk suture.

SSJIBL-60

After 6 weeks of the first operation, the SSJIBL-50 group was re-operated (Fig. 1c). The peritoneal cavity was accessed via

the original incision, and the first anastomosis and ligation in the SSJIBL-50 group were undone and the small bowel continuity was restored using a single layer of 6–0 nylon suture. In the SSJIBL-60 group, 35 cm of the ileum was preserved and a new side-to-side jejunoleal anastomosis was performed using the first 8 cm of the jejunum (measured from the Treitz ligament) and the ileum, thus bypassing approximately 60% of the length of the proximal small intestine. A new luminal occlusion was performed by ligating the first portion of the bypassed segment using #7 silk sutures, and the abdominal cavity was closed with 3–0 silk suture.

Sham Operation

The peritoneal cavity was accessed via a 4-cm midline incision, and the intestine was gently manipulated. The abdominal cavity was closed using 3–0 silk suture. The duration of the surgical procedure was approximately 45 min. At weeks 3 and 6, the sham group was re-operated. All rats were given 10 ml of sterile saline subcutaneously after surgery and were housed in individual cages to recover from anesthesia.

Postoperative Care

All rats were fasted for 24 h. Free access to tap water was allowed from the first postoperative day to the end of the experiment, and standard rodent chow was provided 1 day after surgery. After the third operation, one rat from the SSJIBL-60 group died from intestinal anastomotic leakage in the postoperative period.

Biochemical Tests

Glucose levels were measured using an electronic glucometer (Accu-Chek Performa®, Roche Diagnostic, Switzerland) on blood collected from the tail vein of conscious rats. The fed blood glucose levels were measured at 8:00 AM. For the measurement of the fasting blood glucose level (FBG), the food was withdrawn starting at 8:00 AM, and after 6 h of fasting, the glucose level was measured at 2:00 PM before surgery and at 1, 2, 3, 4, 5, 6, 7, 8, and 9 weeks postoperation.

An oral glucose tolerance test (OGTT) was conducted before surgery and at 3, 6, and 9 weeks postoperation to determine the effect of operation compared to the sham group. The animals were fasted overnight and glucose level was measured on blood obtained 30 min after the administration of 1 g/kg glucose (20% dextrose) by oral gavage.

Statistical Analysis

Data were expressed as means \pm standard deviation. All analyses were conducted using SPSS version 20.0, and the level of significance was set at 0.05. Body weight, food intake

changes, and 30-min glucose levels in the OGTT and FBG were analyzed using a two-tailed unpaired Student *t* test.

Results

Body Weight

Figure 2a shows the evolution of the average body weight of the operated and sham groups after surgery. There was no significant difference in body weight between the SSJIB-50 and sham groups before surgery and at postoperative weeks 1, 2, and 3 (all at $P > 0.05$). Similarly, there was no significant difference in body weight between the SSJIBL-50 and sham groups at postoperative weeks 4, 5, and 6 (all at $P > 0.05$). However, the SSJIBL-60 group had a lower body weight than the sham group at postoperative weeks 8 and 9 (both at $P < 0.05$).

Daily Food Intake

Figure 2b shows the average daily food intake of the operated and sham groups after surgery. There was no significant difference in daily food intake between the SSJIB-50 and sham groups before surgery and at postoperative weeks 1, 2, and 3 (all at $P > 0.05$). However, there was a significant difference in

this parameter between the SSJIBL-50 and sham groups at postoperative weeks 4, 5, and 6 (all at $P < 0.05$). The daily food intake in the SSJIBL-60 group was significantly lower than that in the sham group at postoperative weeks 7, 8, and 9 (all at $P < 0.01$).

FBG Levels

Figure 3a shows the FBG levels of the operated and sham groups after surgery. There was no significant difference in the FBG levels between the SSJIB-50 and sham groups before surgery ($P > 0.05$) and at postoperative weeks 1, 2, and 3 (all at $P > 0.05$). However, there were significant differences between the SSJIBL-50 and sham groups at postoperative weeks 5 and 6 ($P < 0.01$ for week 5, $P < 0.05$ for week 6). The FBG levels in the SSJIBL-60 group were significantly lower than those in the sham group at postoperative weeks 7, 8, and 9 (all at $P < 0.001$).

OGTT Levels

Figure 3b shows the OGTT levels before surgery and at weeks 3, 6, and 9 after surgery. There were no significant differences

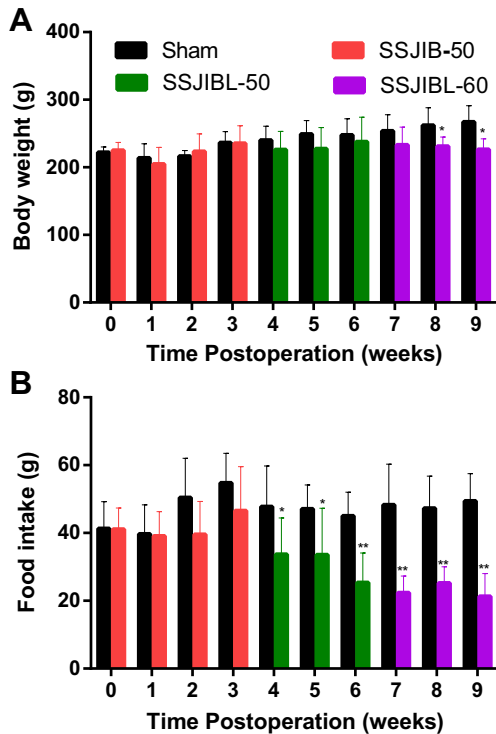


Fig. 2 a Body weight. *Both P 's < 0.05 for SSJIBL-60 versus sham group. b Food intake. *Both P 's < 0.05 for SSJIBL-50 versus sham group; ** $P < 0.01$ for SSJIBL-50 versus sham group; ***All P 's < 0.01 for SSJIBL-60 versus sham group

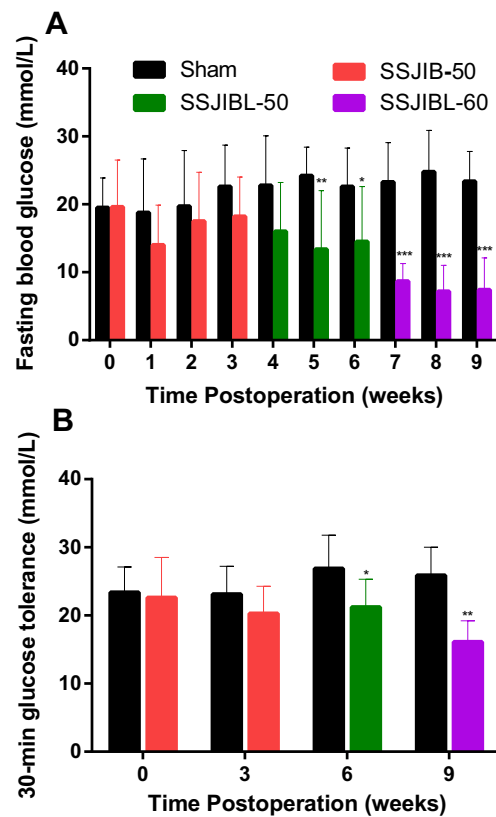


Fig. 3 a Fasting blood glucose levels. * $P < 0.05$ for SSJIBL-50 versus sham group; ** $P < 0.01$ for SSJIBL-50 versus sham group; ***All P 's < 0.001 for SSJIBL-60 versus sham group. b 30-min glucose tolerance test. * $P < 0.05$ for SSJIBL-50 versus sham group; ** $P < 0.01$ for SSJIBL-60 versus sham group

between the SSJIB-50 and sham groups before surgery and at postoperative week 3. However, there was a significant difference between the SSJIBL-50 and sham groups at postoperative week 6 ($P < 0.05$). The OGTT levels in the SSJIBL-60 group were significantly lower than those in the sham group at postoperative week 9 ($P < 0.01$).

Discussion

Blind loop syndrome, also known as stagnant loop syndrome, is a medical condition that occurs when the intestine is obstructed, slowing or stopping the progress of digested food and thus facilitating the growth of bacteria to the point that problems in nutrient absorption occur. The end-to-side JIB necessitates transection of the jejunum, thus creating a blind loop and a stagnant blind loop syndrome with pathological overgrowth of bacteria was one of the factors leading to liver injuries [18]. In order to avoid a blind loop syndrome in intestinal bypass operations for morbid obesity, Stockeld D et al. [14] have tried a JIB with a side-to-side anastomosis. However, this procedure resulted in a very high incidence of liver damage, which puts a question mark to the blind loop syndrome as an etiological factor in producing liver damage. Animal study showed that side-to-side intestinal shunt caused a significantly dilated bypassed loop [15]. Re-entry of the intestinal contents through the lateral anastomosis into the bypass loop and a circulation occurred in the bypassed loop might be related to the stagnation, which was a primary cause of the liver injury [14, 19]. Our previous experimental results showed that the bypassed loop in SSJIBL model was obviously atrophied when compared with the functional loop and the SSJIBL did not cause liver damage in the STZ-induced diabetic rat's model. So, the SSJIBL has been proven to be a successfully modified JIB [8].

This study investigated the effects of different intestinal bypass surgical procedures on weight loss and glucose regulation using an STZ-induced diabetic rat model. This study is the first to compare the curative effects of SSJIB-50 and SSJIBL-50 on weight loss and glucose homeostasis. Our results demonstrated that SSJIBL-50 improved the antidiabetic effect and glucose tolerance compared to SSJIB-50 in STZ-induced diabetic rats. Moreover, food intake in the SSJIBL-50 group was significantly lower than that in the sham group whereas food intake in the SSJIB-50 group was not significantly different from that of the sham group.

Of note is that the SSJIBL-50 group, but not the SSJIB-50 group, had lower global food intake and improved FBG and glucose homeostasis compared to sham rats. The main difference between SSJIBL-50 and SSJIB-50 was the ligation of the first portion of the bypassed segment using silk suture in the former. We hypothesized that SSJIB-50 was not sufficient to cause nutritional malabsorption because SSJIB-50 did not involve luminal

occlusion at the beginning of the bypassed loop, and ligation in SSJIBL-50 prevented the chyme from entering the bypassed small intestine and reduced the digestion and absorption area of the digestive tract, leading to the reduced calorie intake, which explains the marked improvement in diabetes control.

The glucose-lowering effect was stronger and the length of the functional distal small bowel was shorter in the SSJIBL-60 group than in the SSJIBL-50 group. Furthermore, body weight and food intake were significantly lower in the SSJIBL-60 group than in the SSJIBL-50 group. Therefore, we hypothesized that the length of the functional small intestine was a primary contributor to glucoregulation in SSJIB procedures. Furthermore, our results demonstrated that a bypass of 60% (i.e., the maintenance of 40% of the distal small bowel) of the length of the proximal small bowel was suitable. Malnutrition and diarrhea were likely to occur when this threshold was exceeded in rats, and weight loss and the glucose-lowering effect were absent or mild in cases in which the bypass length was shorter than this threshold. Other studies and our previous study supported these findings [8, 9, 20].

The hindgut hypothesis suggests that JIB surgery should increase the passage of food to the terminal ileum, increase the secretion of incretins, and activate satiety signals to reduce caloric intake [21]. Our results indicated that SSJIB-50 did not cause a reduction in food intake, body weight, and FBG (Figs. 2 and 3), although SSJIB-50 bypassed 50% of the length of the proximal small intestine and increased the passage of food to the terminal ileum. Moreover, the increase in the passage of nutrients to the distal small bowel was not significantly different between SSJIB-50 and SSJIBL-50. Therefore, our findings do not support the hindgut hypothesis.

Our previous study demonstrated that the significant effects on diabetes control after 60 to 70% SSJIBL were dependent on alterations in food intake [8]. Furthermore, some authors believe that reduced calorie intake explains the marked improvement in diabetes control observed after Roux-en-Y gastric bypass [22]. In this study, SSJIBL-60 induced lower food intake and a better glucose-lowering effect than SSJIBL-50, suggesting that nutritional malabsorption causes changes in glucoregulatory mechanisms in SSJIBL.

In conclusion, this study provides experimental evidence that ligation of the first portion of the bypassed loop is essential and important to SSJIB, and bypassing approximately 60% of the length of the proximal small intestine may be appropriate in SSJIBL. SSJIBL surgery induced a stronger antidiabetic effect compared to SSJIB surgery, and the longer SSJIBL yielded improved and more sustained weight loss and a stronger antidiabetic effect compared to the shorter bypass in an STZ-induced diabetic rat model. However, further clinical studies are needed to evaluate the safety and efficacy of this simple procedure.

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Compliance with Ethical Standards

The study protocol was approved by the Animal Research Ethics Committee of Nanchang University, China.

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

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