

Received: 2018.10.20  
Accepted: 2018.12.05  
Published: 2019.05.09

# Therapeutic Effects of Sleeve Gastrectomy and Ileal Transposition on Type 2 Diabetes in a Non-Obese Rat Model by Regulating Blood Glucose and Reducing Ghrelin Levels

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Statistical Analysis C  
Data Interpretation D  
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**Source of support:** Departmental sources

**Background:** Nowadays, more than 170 million patients suffer from diabetes mellitus worldwide. This study aimed to investigate the effects of sleeve gastrectomy (SG) and ileal transposition (IT) surgery on the control of diabetes.





**Material/Methods:** Goto-Kakizaki rats were used to establish type 2 diabetes models and undergo SG or IT surgery. At 2 months post-surgery, insulin, glucose, triglycerides (TG), total cholesterol (TC), glucose tolerance, glucagon-like peptide-1 (GLP-1) levels, and insulin sensitivity were evaluated.

**Results:** SG significantly shortened operative time and post-operative recovery time compared to IT surgery ( $P < 0.05$ ). SG and IT surgery resulted in significantly induced weight loss, significantly decreased levels of glucose, and significantly enhanced levels of Ghrelin compared the Sham surgery group ( $P < 0.001$ ). SG and IT surgery resulted in significantly increased GLP-1 levels compared to Sham surgery ( $P < 0.001$ ). SG resulted in better reduction of oral glucose tolerance test (OGTT) glucose compared to IT surgery ( $P < 0.05$ ). SG and IT surgery significantly up-regulated insulin tolerance test (ITT) levels compared to Sham surgery ( $P < 0.001$ ). SG induced better reductions in TC and TG compared to IT surgery ( $P < 0.05$ ).

**Conclusions:** In non-obese rats with spontaneous diabetes, both SG and IT surgery were found to control diabetes by regulating body weight and levels of glucose, Ghrelin, GLP-1, OGTT glucose, insulin, TC, and TG. Moreover, SG demonstrated advantages of shorter operative time, shorter post-operative recovery time, and better control of diabetes compared to IT surgery.

**MeSH Keywords:** **Diabetes Mellitus • Gastrectomy • Ghrelin • Glucagon-Like Peptide 1 • Transposition of Great Vessels**

**Full-text PDF:** <https://www.medscimonit.com/abstract/index/idArt/913705>

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## Background

Nowadays, more than 170 million patients suffer from diabetes mellitus worldwide [1,2]. Diabetes mellitus patients are expected to number 300 million by the year 2025 [3]. In addition to the increased prevalence of type 2 diabetes, many complications of diabetes mellitus have been discovered in clinical settings. In recent years, diabetes mellitus has become the most critical reasons for mortality and morbidity of patients, and has seriously affected public health [4]. However, the etiology of diabetes mellitus and the optimal therapeutic strategies have not been fully clarified.

In clinical settings, there are many therapeutic strategies, including exercise, diet, oral hypoglycemic agents, behavior modification, and treatment with insulin [5–7]. Previous studies have reported that surgical therapy of morbid obesity could clinically alleviate type 2 diabetes with satisfactory clinical outcomes [8,9]. Furthermore, a recent study suggested that diabetes control might be a direct effect of surgery in clinical settings.

In clinical settings, sleeve gastrectomy (SG) and ileal transposition (IT) surgery are the most effective therapies for diabetes control [10,11] and could keep normal insulin levels, plasma glucose concentrations, and glycosylated hemoglobin levels at 80% to 100% of normal range for morbidly-obese patients [9,12]. Moreover, previous studies have indicated that not only SG and IT surgery, but also other bariatric surgeries, might trigger an obvious and satisfactory clinical improvement and outcomes for patients with type 2 diabetes [8,13,14]. However, in the clinical setting, there is controversy regarding which surgical approach to select for treating diabetes. Until now, there have been no investigations or models comparing SG and IT surgery in treatment of type 2 diabetes.

In this study, we investigated the effects of SG and IT surgery using a Goto-Kakizaki (GK) non-obese type 2 diabetes rat model [15] and measured the diabetes associated parameters during a 36-weeks study period.

## Material and Methods

### Animals and ethical approval

Male GK rats (age 8 to 10 weeks old) were obtained from the National Rodent Laboratory Animal Resources of China (Shanghai, China). The rats were housed in individual cages under 12-hour/12-hour cycle of light/dark, 40% to 50% humidity, and room temperature. The National Institute of Health standards were administrated to guarantee the care and procedural protocols followed in this study. This research

was approved by the Ethics Committee of People's Hospital of Rizhao, Rizhao, China.

### Experimental procedure and design

One week prior to the experiments start, all of the rats were acclimated. A total of 12 rats were randomly divided into 4 groups: the SG group (n=3), the Sham-SG group (n=3), the IT group (n=3) and the Sham-IT group (n=3). All surgeries were conducted post anesthesia.

The body weight, fasting insulin levels, Ghrelin expression, food intake, glucose stimulated glucagon-like peptide-1 (GLP-1), fasting glycemia, insulin tolerance test (ITT), oral glucose tolerance, and the levels of plasma lipids were measured and evaluated at 2-months post-surgery. We strictly observed and recorded the surgery time of both SG and IT surgery. The operative time and the post-operative recovery time were recorded carefully.

### Surgery

An overnight fast was administrated to all rats prior to performing the surgeries. During the surgical procedures, the rats were anesthetized with 2% isoflurane. SG was conducted according to a previously published study [16]. First, we made a 4-cm mid-laparotomy; the associated structures were observed and identified. The gastric omentum was separated to open the gastric cardium. Second, a thermocautery was used to cauterize vessels of greater curvature, from cardia all the way to pylorus; this arrangement assigned the incision line for the longitudinal SG. The line overlapped the entire lumen and much of gastric fundus was removed: from 70% to 80% of the total stomach. Two bulldog forceps were positioned to limit the flow of gastric content during subsequent suturing. Post exeresis, we cleaned the peritoneal cavity by using saline prior to the gastrectomy. Meanwhile, suture-line integrity and hemostasis were evaluated, followed by an additional stitch application when necessary.

The IT surgery was conducted according to a previously published study [17], with the following modifications: 1) localization of cecum, 2) midline abdominal incision, 3) 8-cm segment of ileum, 4) resected segment placed on saline-soaked gauze, 5) made an anastomosis with 2 open ends of the ileum, 6) implantation of resected ileal limb at transaction sites by making 2 end-to-end anastomoses.

The sham surgeries involved the same abdominal incisions, re-anastomosis, and the transections of multiple sites associated with SG and IT surgery in the gastrointestinal tract. Post transection, the intestine was immediately anastomosed. If necessary, the operative time or surgical period was adjusted or prolonged to produce a similar degree of anesthesiologic stress for the rats that underwent SG or IT surgery.

Upon resuming oral nutrition, all animals were given a liquid diet (glycosaline + Glucopan pet) for 3 days, after which solid nutrition was allowed (standard feed), with the same diet being maintained for 7 days. After day 8, the animals received water and feed ad libitum.

### Fasting glucose examination

Biochemical parameters were evaluated in the blood samples collected and harvested from the tail vein of the study rats. Fasting glucose levels were also evaluated by utilizing the SureStep Plus Blood Glucose Meter (Life Scan Inc., Wayne, PA, USA) at 2-month post-surgery.

### Ghrelin measurement

Ghrelin was measured using an ELISA (enzyme-linked immunosorbent assay) kit using blood samples collected from the tail vein, using pre-chilled tubes containing aprotinin/EDTA solution. Samples were collected before surgery (baseline) and then at 2-months post-surgery. After centrifugation at 4°C, plasma was separated and stored at -20°C until analysis. Total plasma levels of Ghrelin were also examined by using a commercially available radioimmunoassay (Jingmei Biotech Co. Ltd., Beijing, Chia) and utilizing I125 labeled-Ghrelin as the tracer molecule. Meanwhile, a polyclonal antibody synthesized and obtained from rabbit blood against the full-length Ghrelin was used in this study.

### GLP-1 determination

GLP-1 levels were determined before and 2-months post-surgery. Glucose stimulated GLP-1 was evaluated 30 minutes post treatment with 1 g/kg glucose by oral gavages. Moreover, the commercial rat radioimmunoassay kits (Li-Cor Bioscience, Lincoln, NE, USA) were also employed to measure the associated parameters.

### Oral glucose tolerance testing (OGTT)

The OGTT was performed prior to and 2-months post-surgery to evaluate sugar control during the progress of SG or IT surgery. Post 12 to 14 hours of fasting, blood glucose levels were tested in conscious rats prior to and 30 minutes, 60 minutes, 120 minutes, and 180 minutes post treatment with glucose at a final concentration of 1 g/kg by oral gavage.

### Insulin tolerance test (ITT)

The ITT was conducted 2-months post-surgery by testing the levels of glucose prior to and at 30-, 60-, 90-, and 120-minutes post intraperitoneal injection of human insulin at a final concentration of 0.5 UI/kg into conscious rats. Free fatty acids (FFA), triglycerides (TG), and plasma total cholesterol (TC)

were also examined at 12- to 14 hours post fasting, and also before and at 2-months post SG or IT surgery. Furthermore, analytical testing was also conducted to evaluate the levels of plasma lipids in the biochemical laboratory of Qilu Hospital (Jinan, China).

### Statistical analysis

All of the data were represented as mean  $\pm$  standard deviation (SD) and analyzed by using SPSS software (version, 16.0, SPSS, Inc., Chicago, IL, USA). The analysis of variance (ANOVA) was used followed by Bonferroni post hoc analysis to analyze difference among multiple groups. Meanwhile, the 2-tailed Student's *t*-test was utilized to analyze the data between 2 groups. The *P* value less than 0.05 was assigned as the significant difference.

## Results

All the parameters of the study rats were tested preoperatively in this study. For comparison of weight, glucose, Ghrelin, and GLP-1 between the 2 groups, there were no statistically significant differences (data not shown).

### SG shortened operative time and reduced post-operative recovery time

Operative time was assigned according to the midline-abdominal incision to the suturing of abdominal incision. SG (47.6 $\pm$ 7.5 minutes) significantly shortened the operative time compared to that of IT surgery (52.8 $\pm$ 9.7 minutes) (Figure 1A, *P*<0.05).

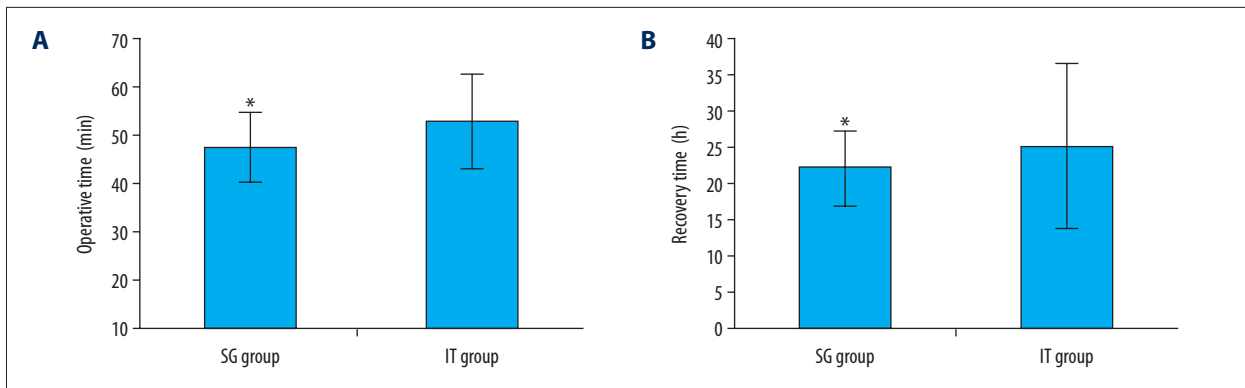
Meanwhile, the post-operative recovery time was assigned according to the end of operation to the first defecation. Results indicated that SG (22.3 $\pm$ 5.2 hours) significantly reduced the post-operative recovery time compared to IT surgery (25.2 $\pm$ 11.4 hours) (Figure 1B, *P*<0.05).

### SG and IT surgery induced weight loss in rats

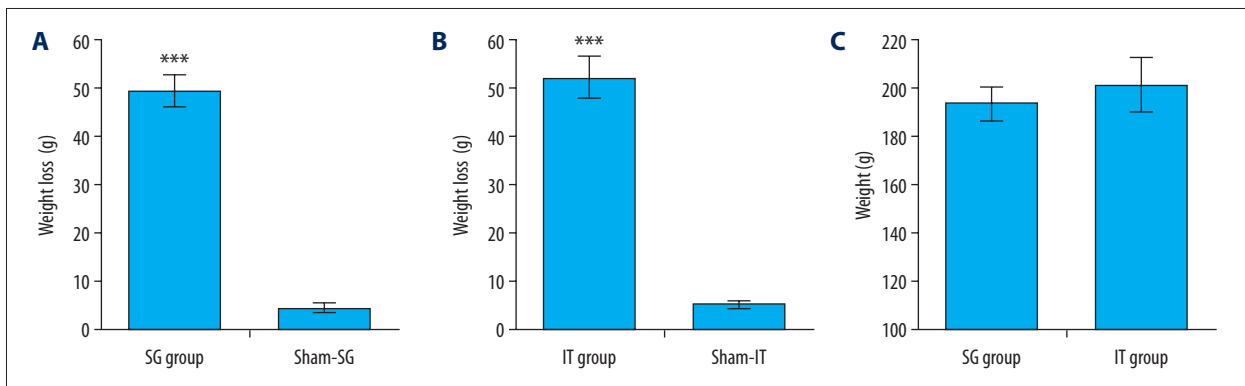
Both SG (Figure 2A) and IT surgery (Figure 2B) caused remarkable weight loss compared to sham-operated rats (Figure 2, *P*<0.001). Moreover, there were no remarkable differences in the mean weights between the SG group and IT surgery group (Figure 2C, *P*>0.05).

### SG and IT surgery decreased levels of glucose

The results showed that glucose levels were significantly reduced in the SG group (Figure 3A) and IT group (Figure 3B) compared to the sham-surgery group (*P*<0.001). Meanwhile, the glucose levels in both the SG and IT surgery groups were



**Figure 1.** Comparison of operative time (A) and post-operative recovery time (B) between the SG group and the IT surgery group. \*  $P < 0.05$  versus Sham-surgery group.



**Figure 2.** Weight loss and body weight of rats in the SG group and the IT surgery group. (A) Comparison of weight loss between SG group and SG-sham group. (B) Comparison for weight loss between IT surgery group and IT-sham group. (C) Comparison for body weight between the SG group and the IT surgery group. \*\*\*  $P < 0.001$  versus Sham-surgery group.

significantly lower compared to the Sham-surgery group (Figure 3C,  $P > 0.05$ ).

### SG and IT surgery enhanced levels of Ghrelin

The results demonstrated that Ghrelin levels in the SG group (Figure 4A) and the IT group (Figure 4B) were significantly enhanced compared to the Sham-surgery group (Figure 4,  $P < 0.001$ ). Furthermore, there were no remarkable differences in the levels of Ghrelin between the SG group and the IT surgery group (Figure 4C,  $P > 0.05$ ).

### SG and IT surgery increased GLP-1 levels

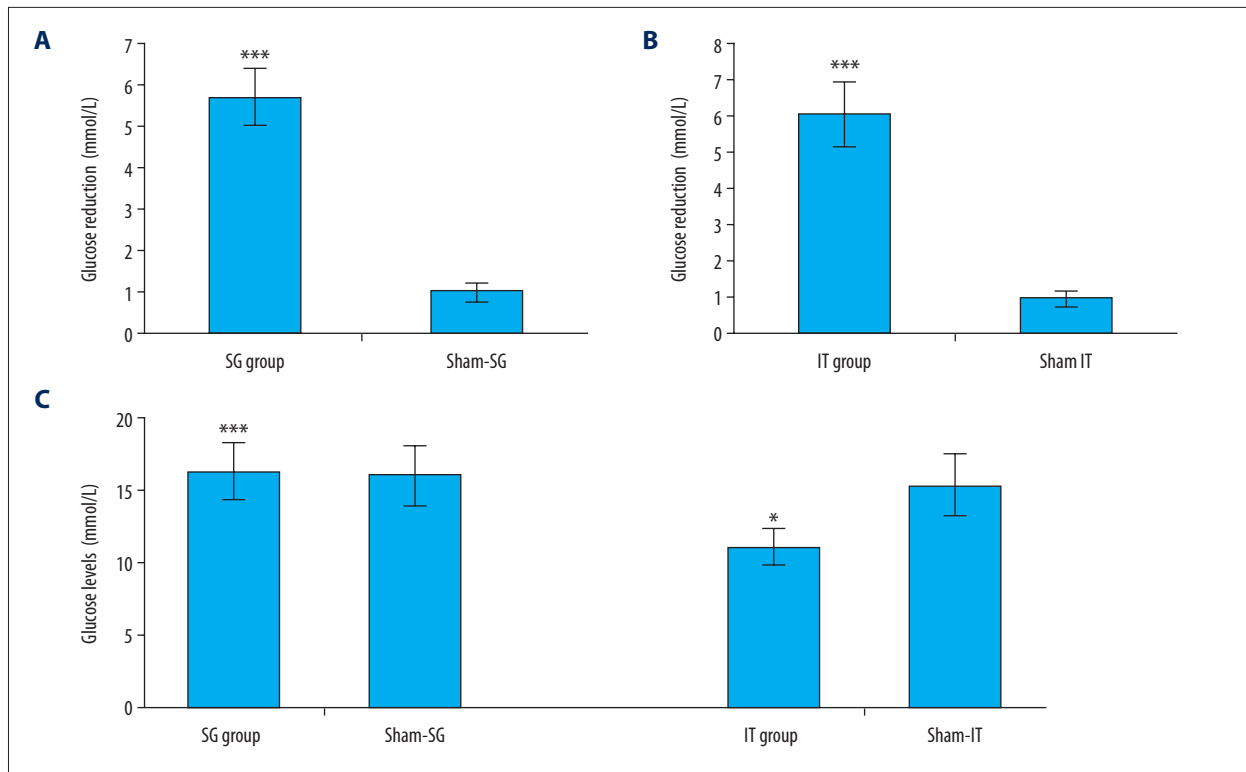
Our results showed that GLP-1 levels in the SG group (Figure 5A) and the IT group (Figure 5B) were significantly increased compared to the Sham-surgery groups ( $P < 0.001$ ). However, the IT group demonstrated better improvement in GLP-1 compared to the SG group (Figure 5C,  $P < 0.05$ ).

### SG exhibited better reduction of OGTT glucose

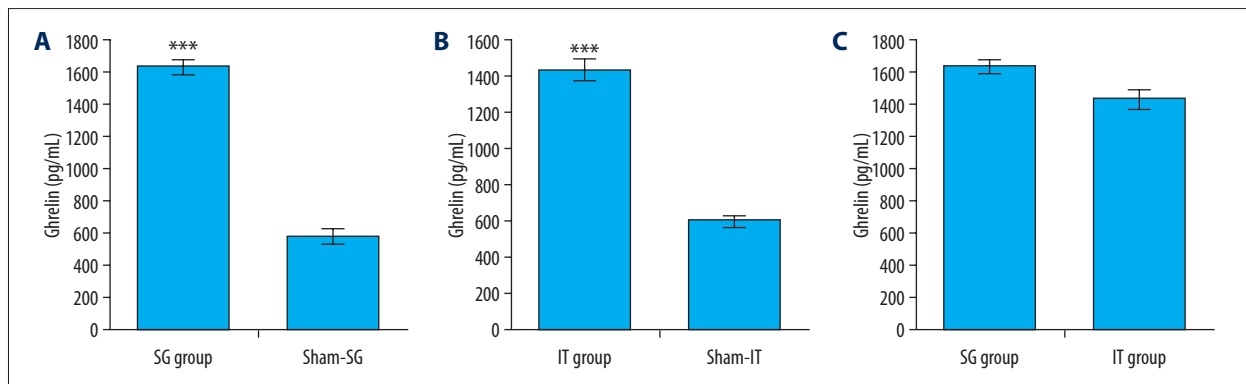
The rats in the SG group showed better improvement in OGTT compared to rats in the IT group by lower average 30-minute peak levels ( $160.5 \pm 9.4$  mg/dL versus  $187.2 \pm 15.6$  mg/dL) (Figure 6A,  $P < 0.001$ ). Meanwhile, for the average 2-hour peak levels, the rats in the SG group demonstrated better improvement in OGTT compared to rats in the IT group ( $99.6 \pm 11.7$  mg/dL versus  $129.5 \pm 20.9$  mg/dL) (Figure 6B,  $P < 0.001$ ).

### SG and IT surgery upregulated ITT levels

The rats in the SG group (Figure 7A) and the IT group (Figure 7B) displayed improvement in ITT levels compared to the Sham-surgery group (Figure 7,  $P < 0.001$ ). However, there were no significant differences for ITT levels between the SG group and the IT group (Figure 7C,  $P > 0.05$ ). Moreover, there were no significant differences in insulin among the SG group, the IT group, and the Sham-surgery groups (data not shown).



**Figure 3.** Glucose reduction and blood glucose of rats in the SG group and the IT surgery group. (A) Comparison of glucose reduction between the SG group and the Sham-SG group. (B) Comparison of glucose reduction between the IT group and the Sham-IT group. (C) Comparison of blood glucose between the SG group and the IT group. \*  $P < 0.05$ , \*\*\*  $P < 0.001$  versus the Sham group.



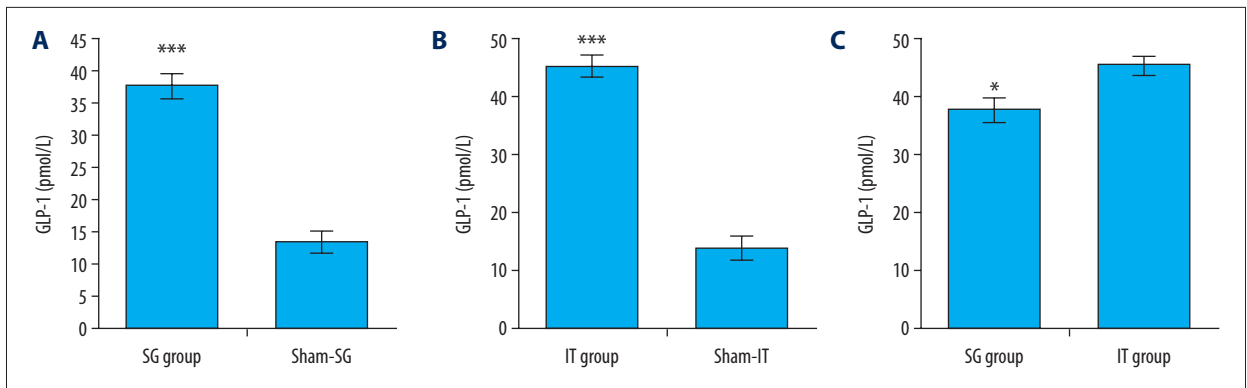
**Figure 4.** Evaluation of Ghrelin levels in rats in the SG group and the IT surgery group. (A) Comparison of Ghrelin levels between the SG group and the Sham-SG group. (B) Comparison of Ghrelin levels between the IT surgery group and the IT-sham group. (C) Comparison of Ghrelin levels between the SG group and IT surgery group. \*\*\*  $P < 0.001$  versus the Sham group.

### SG induced better reduction of TC and TG

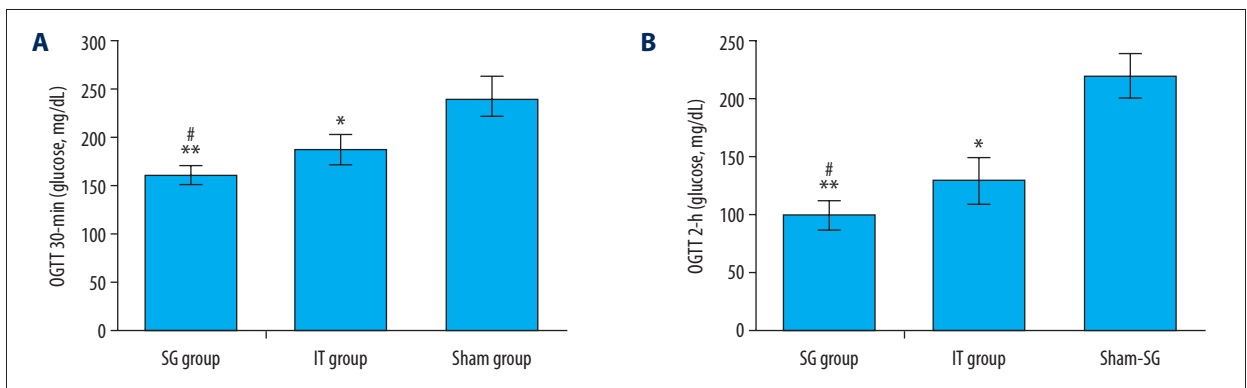
The levels of TC and TG in the SG group and the IT group in non-fasted rats were less significantly reduced compared to the Sham-surgery groups (Table 1,  $P < 0.001$ ). However, the SG group demonstrated significantly lower levels of TC and TG compared to the IT group (Table 1,  $P < 0.05$ ).

### Discussion

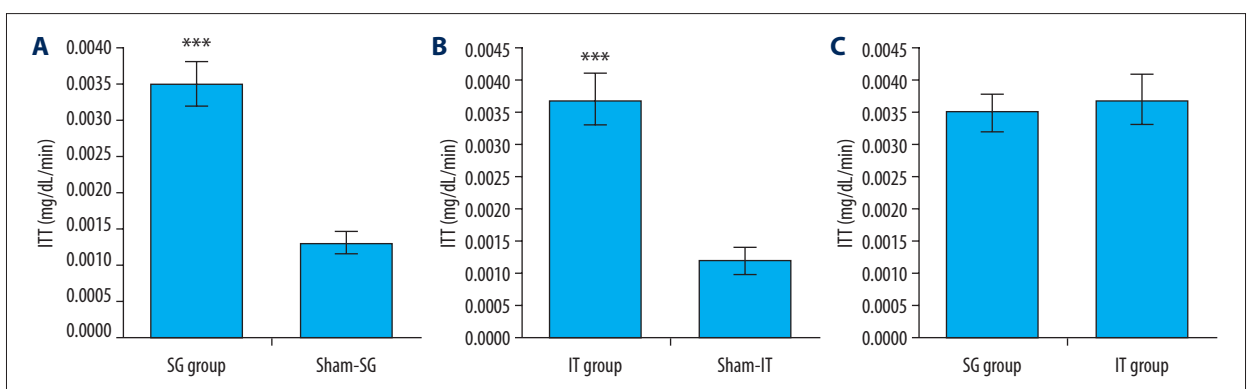
Recently, type 2 diabetes has increased year by year for the general worldwide population [1,18]. To find a better way of controlling diabetes, surgical methods have been researched in recent years. A previous study reported that bariatric surgery was proven to be an effective strategy for the treatment of the type 2 diabetes in clinical settings. However, which



**Figure 5.** Determination of GLP-1 levels in rats in the SG group and the IT surgery group. **(A)** Comparison of GLP-1 levels between the SG group and the Sham-SG group. **(B)** Comparison of GLP-1 levels between the IT surgery group and the IT-sham group. **(C)** Comparison of GLP-1 levels between the SG group and the IT surgery group. \*  $P < 0.05$  versus IT surgery group. \*\*\*  $P < 0.001$  versus the Sham group.



**Figure 6.** Comparison of OGTT glucose levels in rats in SG group, IT surgery group, and Sham group. **(A)** Comparison of OGTT 30-minute glucose levels. **(B)** Comparison of OGTT 2-hour glucose levels. \*  $P < 0.05$ , \*\*  $P < 0.01$  versus the Sham group. #  $P < 0.05$  versus the IT surgery group.



**Figure 7.** Examination of ITT levels in rats in the SG group and the IT surgery group. **(A)** Comparison of ITT levels between the SG group and Sham-SG group. **(B)** Comparison of ITT levels between the IT surgery group and the IT-sham group. **(C)** Comparison of ITT levels between the SG group and the IT surgery group. \*\*\*  $P < 0.001$  versus the Sham group.

surgery is the best therapeutic surgery for the type 2 diabetes has not been clarified. An optimal surgery strategy should cause relative lower morbidity and lower mortality rates for the patients. Moreover, the optimal surgery strategy should

result in significant improvement and obvious resolution of diabetes-associated co-morbidities as well as an increase in quality of life.



**Table 1.** Levels of total cholesterol (TC) and triglycerides (TG) in SG and IT surgery groups.

Lipid	SG group	IT group	Sham group
TC (mg/dL)	115.4**,#	125.46*	154.65
TG (mg/dL)	132.46**,#	146.32*	210.32

\*  $P < 0.05$ , \*\*  $P < 0.01$  versus Sham group. #  $P < 0.05$  versus the IT surgery group.

This study was conducted to compare glycemic control outcomes in a rat model of diabetes, between SG and IT surgery. The results showed that both SG and IT surgery demonstrated sustained effects on the resolution of diabetes. However, by comparing Ghrelin levels, we found that SG surgery demonstrated a more significant improvement in rats compared IT surgery. However, there were similar effects found in the SG group compared to the IT surgery group in glycemia levels, OGTT levels, levels of plasma lipids, and plasma insulin levels. Both SG and IT surgery have been shown to achieve normal levels of fasting plasma insulin [19,20], fasting glycemia levels, insulin sensitivity [21], and the glucose tolerance [21]. Our findings were consistent with previously published studies. Both SG and IT surgery have been shown to reduce the mortality potentially in diabetes mellitus patients [22]. Our study also demonstrated the role of Ghrelin in progression and resolution of diabetes. SG surgery demonstrated better improvements in glycemic control and other values compared to IT surgery. However, we found relatively lower levels of GLP-1 in the SG group compared to the IT surgery group. Both SG and IT surgery have been shown in other studies to demonstrated critical roles or functions in controlling diabetes [23].

In this study, the SG procedure showed superior or better control of diabetes compared to the IT procedure. Research has shown that higher glucose tolerance, increased insulin sensitivity, and lower levels of plasma glucose triggered by Ghrelin result in long-term diabetes remission via activating the insulin signaling pathway [24,25].

In this study, we also compared the post-operative recovery between SG and IT surgery. The results showed that SG surgery demonstrated faster post-operative recovery compared to IT surgery. Rats that have had SG surgery have exhibited a few limitations, such as no mal-absorption [26]. It is well-known that the easier the performance of surgery, the sooner the patient will recovery post-operation. In our study, the SG

surgery was related to a faster post-operative recovery period ( $22.3 \pm 5.2$  hours versus  $25.2 \pm 11.4$  hours) and a shorter surgery time ( $47.6 \pm 7.5$  minutes versus  $52.8 \pm 9.7$  minutes) compared to the IT group (all  $P < 0.05$ ). Also, the procedure of SG has been proven to be safe as demonstrated by lower mortality rates [27]. Therefore, SG surgery could be considered as an alternative strategy for long-term glycemic control and retaining normal insulin levels, as well as providing better clinical outcomes compared to IT surgery.

The present study extended and enhanced previous investigations in several ways. First, FFA levels have been correlated with glycemic control and insulin resistance in hyperlipidemic patients [24,28]. Our study results also showed SG could decreased FFA levels effectively compared to the IT surgery group and the Sham-operated group. Second, for non-obese models, control of diabetes has not been correlated with resolution of obesity-associated abnormalities, as shown in other research [29].

Although this study had some interesting results, there were also a few limitations. First, the sample size of this study was inadequate, which might affect the accuracy of the findings. Future studies should employ a large sample size. Second, the follow-up time for the applied therapy was relative short, therefore, future investigations should prolong the follow-up time to confirm out study conclusions. Third, this study did not observe the post-operative complications of both SG and IT surgery. Future studies should evaluate the complications of these 2 surgical approaches.

## Conclusions

The present study demonstrated that SG might provide superior glycemic control for type 2 diabetes compared to IT surgery and sham surgery; however, this finding needs further confirmation using longer treatment periods. In addition, further investigation and longer follow-up periods are needed to verify our study results, such as resolution of co-morbidities, nutritional outcomes, and quality of life studies using rat models. Thus, it is critical to discover easy and available surgical strategies that have lower mortality rates and lower morbidity rates, as well as better glucose control. If SG is done in a clinical setting, it could be an alternative choice for the cure of diabetes by providing long-time control of glycemia.

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