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Original Article

The gastric bypass combined ileal transposition having a more significant effect in improving glucose tolerance and islet sensitivity than gastric bypass on type 2 diabetes

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Abstract: Aims: To compare the GBP with IT and only GBP in nonobese type 2 diabetes. Methods: Goto-Kakizaki (GK) rats were used to construct the T2DM animal models. Gastric bypass and joint ileal transposition surgery gastric bypass were done in the two groups. Weight, fasting blood glucose, insulin, C-peptide, IAI, FBCI and the islet β cell of rats were detected and compared between two groups. SPSS 16.0 statistical software was employed for statistics. There was statistically significant difference when $P<0.05$. Results: Postoperative fasting blood glucose, postsurgical glucose tolerance of rats were significantly lower than preoperative in both groups ($P<0.01$). And postoperative insulin level of rats significantly increased than preoperative ($P<0.01$) in both groups. Rats' postoperative C-peptide, insulin sensitivity levels increased significantly than preoperative ($P<0.01$) in both groups. GBP + IT was more significant than the effect of GBP in improving glucose tolerance and enhanced insulin sensitivity persistence. Conclusion: Both GBP and GBP + IT could significantly make a significant treatment effect on type 2 diabetes, while GBP + IT had a more significant effect in improving glucose tolerance and islet sensitivity which could improve persistence.

Keywords: GBP + IT, glucose tolerance, islet sensitivity, 2 diabetes

Introduction

With a prevalence of 10%, diabetes mellitus (DM) is responsible for 1.3 million deaths per year worldwide, and most of them were type 2 DM [1]. By now, the disease has become a major cause of morbidity and mortality and places a huge strain on public health funding [2]. Beyond the traditional drugs, surgeries were more and more employed in the treatment for type 2 DM, such as gastric bypass (GBP), bihopanereati diversion (BPD) and so on. For GBP, as reported, it was commonly used for diabetes treatment, with about 83% short-term cure rate, but the long-term cure rate is only about 57% [3-5]. And it was reported that the duodenal jejunal bypass (DJB) for the treatment of diabetes type 2 in patients with body mass index (BMI) between 22 and 34 was also an effective operation [6]. Others, the ileal transposition (IT) also performed on type 2 DM patients to help the glucose control [7, 8].

Although sustained and significant weight loss is likely to be the key mediator of diabetes remission after GBP, the changes of incretins were reported to improve the early phase of insulin secretion and post-prandial glucose levels, and contribute to a better glucose tolerance [9]. But the IT has been confirmed that the surgical primarily through increased food contact with the distal digestive tract work to have a good hypoglycemic effect [8]. So, we tried to combine these two surgeries together to enhance the effect of the glucose control.

We performed GBP with IT and only GBP in Goto-Kakizaki (GK) rats, the most widely used animal model of nonobese type 2 diabetes. Glucose, insulin, glucose tolerance, insulin sen-

Table 1. The change of body weight between two groups

Group	Presurgery	2 weeks	4 weeks	8 weeks	12 weeks
A	288.99±6.15	253.91±4.36*	302.76±10.85	315.86±15.52	346.65±11.65
B	291.12±4.73	241.20±5.03*	286.33±10.17	298.52±14.95	311.43±5.75
T value	t=0.867	t=6.033	t=3.494	t=2.545	t=8.576
Statistic	P=0.397	P<0.001	P=0.003	P=0.020	P<0.001

Body weight: gram (g). *P<0.05, compared with presurgery.

Table 2. The comparison of fasting glucose between two groups

Group	Presurgery	1 week	2 weeks	4 weeks	8 weeks	12 weeks
A	12.13±2.42	6.93±2.43*	7.13±2.42*	7.31.±2.35*	7.89±1.22*	8.47±2.00*
B	13.71±2.88	6.11±2.88*	6.61±1.84*	6.69±1.42*	7.26±1.76*	7.37±1.23*
T value	t=1.328	t=0.689	t=0.537	t=0.723	t=0.944	t=1.483
Statistic	P=0.201	P=0.499	P=0.598	P=0.479	P=0.358	P=0.155

Fasting glucose (mmol/l). *P<0.05, compared with presurgery.

Table 3. Comparison of OGTT and AUC of blood glucose in presurgery and 8 weeks after surgery between two groups

	0 min	30 min	60 min	120 min	180 min	AUC
Presurgery of group A	12.51±1.77	25.50±1.77	22.81±1.15	17.68±1.32	13.63±1.54	3448.9307±493.703
Presurgery of group B	13.35±2.65	27.71±2.89	24.68±2.69	17.79±2.34	13.90±1.75	3626.0793±546.835
8 weeks of group A	7.78±1.23	18.74±1.42	16.80±1.04	13.55±1.02	9.76±1.40	2547.1181±347.229
8 weeks of group B	7.21±1.52	17.06±2.04	13.08±1.87	11.32±2.00	8.21±1.30	2142.2192±302.921
T value	t=6.346	t=9.530	t=11.193	t=6.819	t=8.258	t=7.506
Statistic	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001	P<0.001

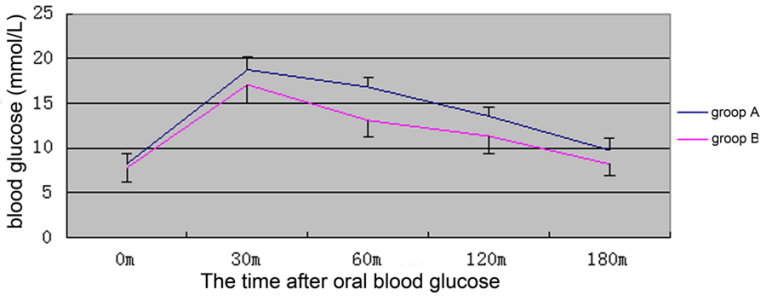

Figure 1. The OGTT of blood glucose after surgery in group A and B.

sitivity, IAI, and FBCI were measured during a 12-week time period.

Materials and methods

Male 8 to 10-week-old Goto-Kakizaki (GK) rats were purchased from National Rodent Laboratory Animal Resources, Shanghai. Animals were housed in individual cages under constant ambient temperature and humidity in a 12-hour light/dark cycle. Care and procedural protocols were evaluated to ensure compliance with National Institute of Health standards [10].

Surgical groups and technique

GBP and GBP combined IT were compared as surgeries for glucose control. A total of 20 rats were then randomized into 2 groups: (1) GBP group, (2) GBP combined IT group. Operations were performed after 1 week of acclimation after an overnight fast and the induction of anesthesia.

GBP surgery was performed as shown in Roux's research [11]. Prior to a midline laparotomy, the abdomen was shaved and disinfected with surgical scrub. The proximal jejunum was divided 15 cm distal to the pylorus to create a biliopancreatic limb. After identification of the caecum, the ileum was then followed proximal-

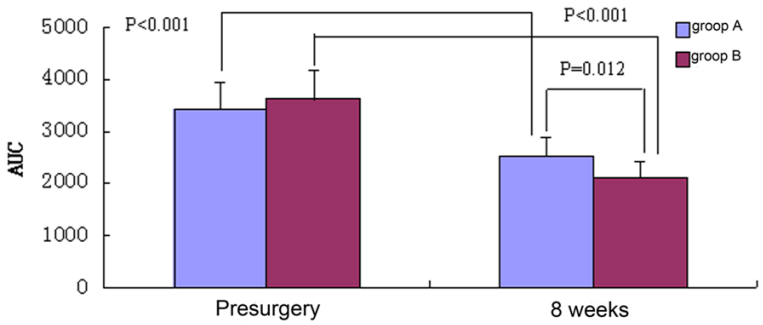

Figure 2. The AUC of blood glucose after surgery in group A and B.

Table 4. Comparison of fasting serum insulin level between two groups

Group	Presurgery	2 weeks	4 weeks	8 weeks	12 weeks
A	0.96±0.13	1.13±0.11	1.21±0.16	1.24±0.13	1.25±0.16
B	1.03±0.24	1.17±0.14	1.24±0.18	1.28±0.22	1.29±0.23
T value	t=0.740	t=0.836	t=0.435	t=0.518	t=0.425
Statistic	P=0.469	P=0.414	P=0.669	P=0.611	P=0.676

Insulin unit (mIU/l). Comparison of presurgery and 12 weeks post surgery in group A (t=4.128, p=0.003). Comparison of presurgery and 12 weeks post surgery in group B (t=3.525, p=0.006).

Table 5. Comparison of C-peptide level between two groups

Groups	Presurgery	2 weeks	4 weeks	8 weeks	12 weeks
A	0.12±0.03	0.14±0.02	0.16±0.07	0.16±0.03	0.17±0.05
B	0.13±0.08	0.15±0.05	0.17±0.04	0.18±0.10	0.19±0.02
T value	t=0.238	t=0.592	t=0.270	t=0.585	t=1.062
Statistic	P=0.815	P=0.561	P=0.790	P=0.566	P=0.302

C-perptide unit (mIU/l). Comparison of presurgery and 12 weeks post surgery in group A (t=8.324, p<0.001). Comparison of presurgery and 12 weeks post surgery in group B (t=3.397, p=0.008).

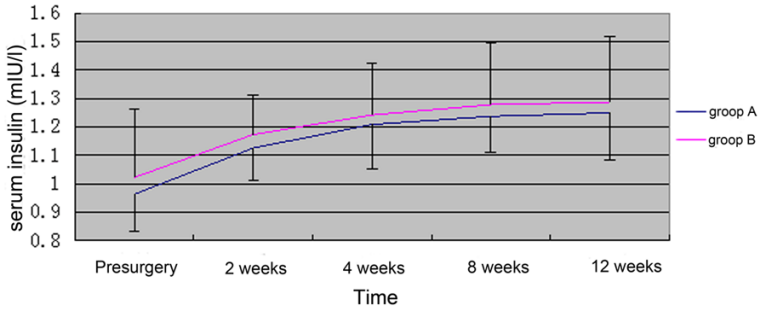

Figure 3. The fasting serum insulin level between two groups.

ly to create a common channel of 25 cm. Here, a 7 mm side-to-side Jejuno-Jejunostomy (running prolene 7-0 suture) between the biliopancreatic limb and the common channel was performed.

GBP combined IT group surgery was performed on the basis of GBP surgery mentioned above. The cecum was located and removed from the abdomen and placed on saline-soaked sterile gauze. An 8-cm segment of ileum located at 5-15 cm proximal to the ileocecal valve was isolated and transected. The segment was carefully placed on saline-soaked gauze. An anastomosis was then made with the 2 open ends of the ileum, using 8 stitches by 7-0 silk suture. The remaining small intestine was then transected 5-10 cm distal to the ligament of Treitz. The isolated ileal segment with full neural innervation and intact vascular supply to the transposed segment was then inserted in the original peristaltic direction by making 2 additional end-to-end anastomoses.

Shame surgery group

For all procedures, operative time, the presence of vomiting (an indication of obstruction), temperature, the time to the first postoperative defecation (deemed the recovery time), and any other complications were recorded. Weight and food intake were measured daily for the first 2 weeks, twice weekly for the next 2 weeks, and then once weekly until the end of the experiment.

Biochemical tests

Fasting glycemia was measured at presurgery and 1, 2, 4, 8, 12 postoperatively on blood obtained from the tail veins by Roche blood glucose meter.

An oral glucose tolerance test (OGTT) was performed at presurgery and 8 weeks postopera-

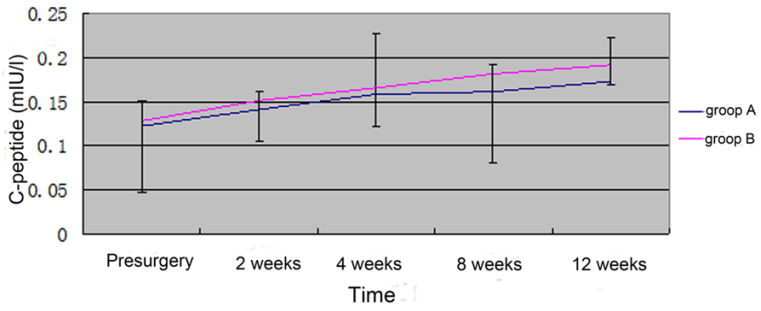

Figure 4. Change of serum C-peptide level after surgery in group A and B.

tively as a measure of the progress of the surgery and sugar control. After 12 to 16 hours of fasting, glucose measurements were performed immediately and then 30, 60, 120, and 180 minutes after the administration of 1 gram glucose by oral gavage.

Fasting serum insulin, C-peptide, biochemical indicators of liver and kidney function, and the oral glucose tolerance test of rats in each group, calculated and compared insulin sensitive index (IAI) = 1/(FPG × FINS) and fasting β-cell function index (FBCI) = FINS/FPG at multiple time points before and after the surgery. After the observation, sacrificed the rats and took pancreatic tissue samples for pathological testing. For further research, ELLISA was used to detect the changes in serum glucagon-like peptide-1 (GLP-l), glucose-dependent insulinotropic hormone (GIP) and cyclic adenosine monophosphate (cAMP) levels and the relationship between them. Real-time quantitative RT-PCR was used to detect the expression of GLP-1R and GIPR in pancreatic tissue.

Statisitcs

With the application of SPSS 16.0 statistical software, all data was presented as mean ± standard deviation (mean ± SD), and each of the observation point in time was compared with t-test. There was statistically significant difference when P<0.05.

Results

Operative results

Each 10 rats of group GBP and group GBP combined IT were all survived. The mean time of surgery were 95.75 ± 13.58 min and 173.83 ± 21.86 min, respectively (P<0.01).

The change of body weight in two groups

We found the weight of rats in both groups reduced in the first 2 weeks compared to presurgery (P<0.05). And after 4 weeks, the weight in both groups increased, and group A grew more rapidly than group B (P<0.01). And at the final 12th week, the weight of group A is higher than that of group B (P<0.001). The results were all shown in **Table 1**.

The change of fasting glucose level between two groups

As shown in **Table 2**, the fasting glucose level of both two groups was lower than that of presurgery. The fasting glucose level between two groups had no significantly statistical difference in 1, 2, 4, 8 and 12 weeks after surgery, respectively (P>0.05).

Comparison of OGTT and area under blood glueose curve (AUC) between two groups

Both in group A and group B, the OGTT and AUC of glucose in 8 weeks of surgery were significantly improved compared to those of presurgery (P<0.01).

The improvement in glucose tolerance after surgery, the rats in group B were higher than those of group A (P<0.05). The average blood glucose level at 30 min of group B was lower than that of group A (17.06 ± 2.04 mmol/l vs. 18.74 ± 1.42 mmol/l; P<0.05). The results were all shown in **Table 3** and **Figures 1**, **2**.

Comparison of fasting serum insulin and C-peptide level between two groups

The fasting serum insulin and C-peptide levels after surgery in both group A and B were statistically significantly elevated than the pre-surgery levels (P<0.01). And there were no significantly statistical differences between group A and group B in fasting serum insulin and C-peptide levels after surgery (P>0.05). The results were shown in **Tables 4**, **5** and **Figures 3**, **4**.

Table 6. Comparison of IAI level between two groups

Group	Presurgery	2 weeks	4 weeks	8 weeks	12 weeks
A	0.090±0.021	0.144±0.064	0.127±0.046	0.106±0.023	0.101±0.027
B	0.080±0.034	0.141±0.047	0.128±0.031	0.120±0.047	0.112±0.030
T-value	t=0.791	t=0.079	t=0.028	t=0.839	t=0.878
Statistic	P=0.439	P=0.938	P=0.978	P=0.413	P=0.391

Comparison of presurgery and 12 weeks post surgery in group A (t=1.289, p=0.230). Comparison of presurgery and 12 weeks post surgery in group B (t=3.948, p=0.003).

Table 7. Comparison of FBCI between two groups

Group	Presurgery	2 weeks	4 weeks	8 weeks	12 weeks
A	0.083±0.022	0.184±0.090	0.186±0.078	0.160±0.026	0.156±0.044
B	0.076±0.017	0.191±0.065	0.199±0.073	0.181±0.036	0.177±0.034
T-value	0.761	0.254	0.370	1.541	1.197
Statistic	0.457	0.802	0.716	0.141	0.247

Comparison of presurgery and 12 weeks post surgery in group A (t=3.855, p=0.004). Comparison of presurgery and 12 weeks post surgery in group B (t=9.216, p<0.001).

Comparison of insulin sensitivity index (IAI) between two groups

Insulin sensitivity index (IAI) is used to roughly evaluate the degree of improvement in insulin sensitivity.

In our research, we found that IAI were significantly improved after surgery in both group A and group B (P<0.01). But, there was no significantly statistical difference between group A and group B (P>0.05). However, as shown in **Table 6**, in group A, the IAI level in 12 weeks after surgery was similar to the presurgical level (P>0.05). It implied that the GBP combined with IT surgery meant a trend of relatively durable improvement in IAI (p=0.003).

Comparison of fasting β cell function index (FBCI) between two groups

Asting β cell function index (FBCI) is used to evaluate the β cell of pancreas. FBCI was significantly improved after surgery in different time point in both group A and group B (P<0.01). But there was no significantly statistical difference between group A and group B (P>0.05). The results were all shown in **Table 7**.

The detection of pathological change of pancreas in different group

After the rats killed after 12 weeks observation, pancreas tissue was stained by HE staining. It showed that both in two groups, islet β cell of rats which originally shrank and disappeared, regenerated again. And both islet β cell hyperplasia in two groups were obviously observed. The results were shown in **Figure 5**.

Discussion

In the surgical treatment of T2DM, especially with a high degree of obesity in patients with T2DM, gastric bypass surgery weight reduction is one of the surgical procedures which the most widely used and effects determined. Its biggest advantage is that in addition to make lasting weight control in obese patients, it can improve the metabolic disorders associated with obesity, which may make the long-term benefit for patients [12, 13]. Compared to gastric bypass surgery, ileal transposition was used less. In our research, we tried to find out the effort of the GBP surgery combined with IT surgery.

Clinical studies have shown that GBP make 83% obese T2DM patients to have normal blood glucose level [14-16]. Other small sample study showed GBP can partially relieve T2DM complications [17]. Moreover, GBP in non-obese patients with T2DM also has the same effect. However, there was still no long-term clinical evidence-based research now.

Our results showed: in 2 weeks after surgery, both two groups of GK rats had the body weight loss. And after that, the bodyweight of both two

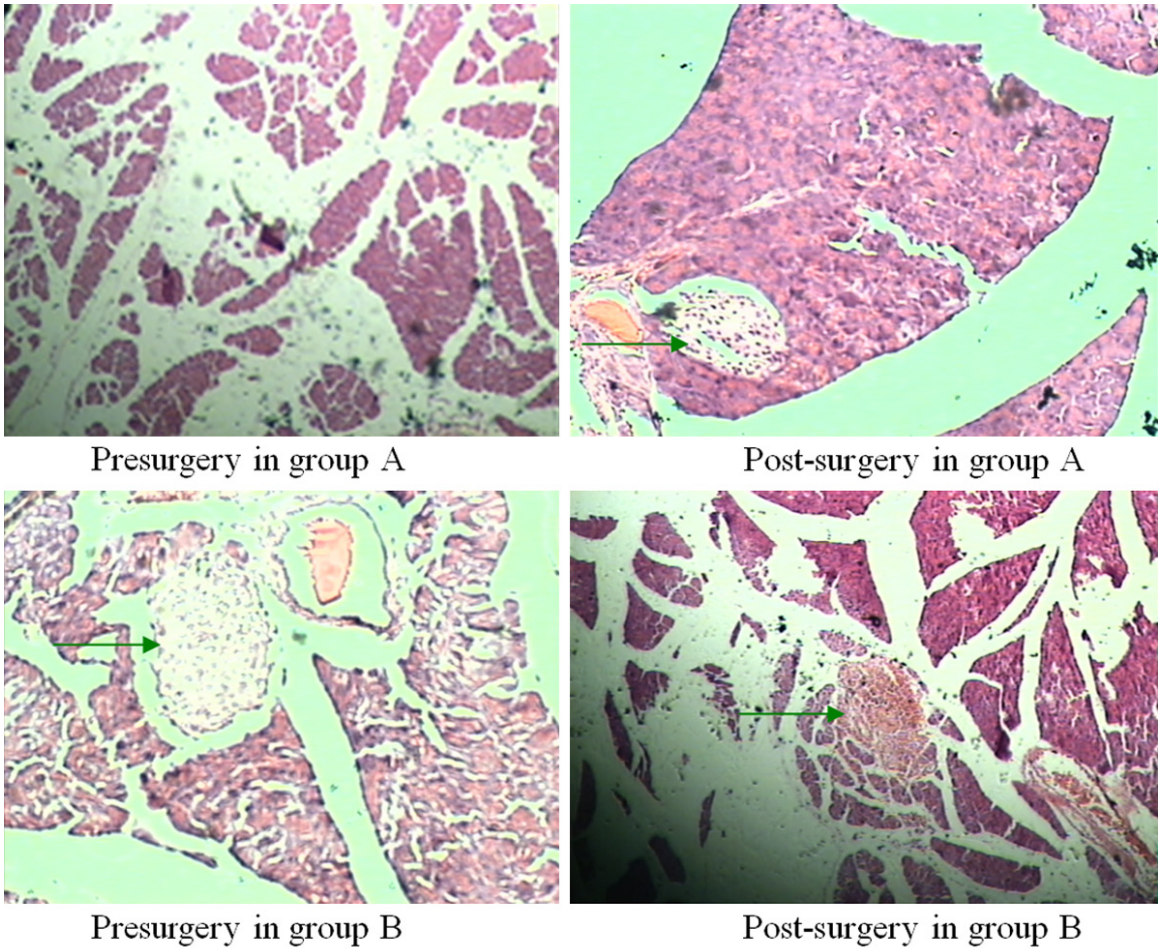

Figure 5. Both islet β cell hyperplasia in two groups were obviously observed to regenerate.

group rats recovered, but GBP + IT group animal weight always was less than the GBP group. The main reason was because the GBP + IT surgery brought more trauma and slow recovery of gastrointestinal function to the experimental animals. And because of trauma, slow healing, and high catabolism, the bodyweight of rats in GBP + IT group was lower compared with GBP alone group.

GBP surgery is to reduce the chance of food contact to the proximal digestive tract, thereby improved blood glucose level in experimental animals, but it is still not ideal on the contact of food and the distal end of the digestive tract [18, 19]. The IT surgery is characterized to increase food contact with the distal end of the digestive tract, thereby increasing the secretion of distal gastrointestinal peptide hormones [20]. So, in theory, GBP combined with IT is better than GBP alone surgery in treatment for T2DM.

Indeed, as shown in this study, as same as the GBP group, GBP + IT surgery can significantly reduce fasting blood glucose, elevated insulin, C-peptide levels, but no significant difference between the two procedures group. However, GBP + IT surgery can more significantly reduce animal blood glucose after glucose challenge test, suggesting that GBP + IT's effect on T2DM surgery may not simply rely on the increase of serum insulin.

More importantly, GBP + IT surgery, such as the IAI trends after surgery, it can be more lasting improvement in insulin sensitivity in experimental animals. In addition, TC and TG levels of GBP + IT group animals were lower than those of GBP group. It may also reflect GBP + IT group experimental animal had lower insulin resistance. The mechanisms of GBP + IT group had such enduring improvement of animal insulin sensitivity is still unknown. As we all known, IT can increase undigested food in contact with

the ileum, and ileum is an important part of the secretion of many hormones affecting glucose metabolism. These results may suggest that GBP + IT had more lasting improvement in glucose tolerance may be realized by changing the ileal hormone secretion. Another important finding of the results in this study is the reproduction and regeneration of islet β cell in experimental animals in the postoperative, suggesting that GBP + IT operation is not directly stimulate the pancreatic β cell proliferation, but indirectly.

In summary, this study suggests that although GBP + IT may exacerbate the trauma on experimental animals compared to the GBP surgery, and the weight is lighter than GBP experimental animals, GBP + IT surgery had not only more significantly improve glucose tolerance compared with surgery alone GBP, but also more lasting improvement in insulin sensitivity in experimental animals, and a better contribution directly to pancreatic β cell regeneration in experimental animals.

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Disclosure of conflict of interest

None.

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