Resolution of diabetes mellitus by ileal transposition compared with biliopancreatic diversion in a nonobese animal model of type 2 diabetes

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Background: It has been demonstrated that biliopancreatic diversion (BPD) and ileal transposition (IT) effectively induce weight loss and long-term control of type 2 diabetes in morbidly obese individuals. It is unknown whether the control of diabetes is better after IT or after BPD. The objective of this study was to investigate the effects of IT and BPD on the control of diabetes in an animal model.

Methods: We performed IT and BPD on 10- to 12-week-old Goto–Kakizaki rats with a spontaneous nonobese model of type 2 diabetes, and we performed a series of detection. The rats were observed for 24 weeks after surgery.

Results: Animals who underwent IT and BPD demonstrated improved glucose tolerance, insulin sensitivity and the secretion of glucagon-like peptide-1 compared with the sham-operated animals. Furthermore, IT resulted in a shorter duration of surgery and better postoperative recovery than BPD.

Conclusion: This study provides strong evidence for the crucial role of the hindgut in the resolution of diabetes after duodenum-jejunum bypass or IT. We confirmed that IT was associated with better postoperative recovery than BPD and had a similar control of diabetes as BPD in nonobese animals with type 2 diabetes.

Contexte : Il a été démontré que la dérivation biliopancréatique (DBP) et la transposition iléale (TI) sont efficaces pour faire perdre du poids et permettent de contrôler à long terme le diabète de type 2 chez les personnes atteintes d'obésité morbide. On ne sait pas si le contrôle du diabète est meilleur après la TI ou après la DBP. Cette étude visait à analyser les effets de la TI et de la DBP sur le contrôle du diabète dans un modèle animal.

Méthodes : Nous avons pratiqué une TI et une DBP sur des rats Goto–Kakizaki âgés de 10 à 12 semaines avec un modèle non obèse spontané de diabète de type 2, et nous avons procédé à une série de détections. Les rats ont été observés pendant 24 semaines après l'intervention chirurgicale.

Résultats : Chez les animaux qui ont subi une TI et une DBP, la tolérance au glucose, la sensibilité à l'insuline et la sécrétion de peptide-1 de type glucagon a augmenté comparativement à ceux qui ont subi une opération fictive. De plus, pour la TI, l'intervention chirurgicale a été de moindre durée et le rétablissement postopératoire a été meilleur, par rapport à la DBP.

Conclusion : Cette étude démontre solidement le rôle crucial que joue l'intestin postérieur dans l'élimination du diabète après un pontage duodénojéjunal ou une transposition iléale. Nous avons confirmé que la TI était associée à un meilleur rétablissement après l'intervention que la DBP et permettait de contrôler le diabète de la même façon que la DBP chez les animaux non obèses atteint de diabète de type 2.

Diabetes mellitus presently affects more than 170 million people worldwide, with an increase of at least 50% estimated for 2010.[1] Prevalence of the disease is expected to reach about 300 million by 2025.[2] As the population with type 2 diabetes increases, so does the prevalence of life-threatening complications. By now, the disease has become a major cause of morbidity and mortality and places a huge strain on public health funding.[3] However, its etiology and best treatment remain elusive.

Current therapies, including diet, exercise, behaviour modification, oral hypoglycemic agents and insulin, rarely return patients to euglycemic levels.[4] Recently, investigators found that a number of patients with type 2 diabetes achieved clinical resolution after surgical treatment of morbid obesity.[5] Moreover, recent reports that glycemic control often occurs long before substantial weight loss[6–8] suggested that the control of diabetes may be a direct effect of the operation rather than a secondary outcome of the improvement of obesity-related abnormalities.

It is known that biliopancreatic diversion (BPD) is an effective treatment for diabetes[9] and that this procedure restores normal concentrations of plasma glucose, insulin and glycosylated hemoglobin in 80%–100% of morbidly obese patients.[6,10–12] Furthermore, it also has been demonstrated that not only BPD, but also other bariatric operations, may result in substantial clinical improvement in patients with type 2 diabetes.[7,11–21] Since many of these procedures controlled diabetes in obese and nonobese individuals, which procedure is best? To find the answer, we studied the effect of ileal transposition (IT) and BPD in Goto–Kakizaki (GK) rats, the most widely used animal model of nonobese type 2 diabetes.[22] We report the comparison of glycemic control outcomes between IT and BPD in GK rats during a 24-week period.

METHODS

Animals

We purchased 8- to 10-week-old male GK rats from the National Rodent Laboratory Animal Resources, Shanghai Branch. All animals were housed in individual cages under constant ambient temperature and humidity in a 12-hour light/dark cycle. After obtaining Institutional Review Board approval, animal housing and procedures were carried out according to the National Institutes of Health 1996 *Principles of laboratory animal care*.

Experimental design

The rats were acclimated for 1 week before the start of experiments. First, we measured food intake, weight, fasting glycemia and oral glucose tolerance. Then, 10- to 12-week-old rats randomly underwent 1 of the following procedures: BPD, sham BPD, IT or sham IT. Animals had free access to tap water and were fed ad libitum with a 5% fat rat chow diet.

In all groups, weight, food intake, fasting glycemia, fasting insulin, glucose-stimulated glucagon-like peptide-1 (GLP-1), glucose tolerance, insulin tolerance and plasma lipids were measured before and at several time points after the intervention.

The duration of surgery in the BPD and IT groups was strictly recorded. The first defecation time, which served as an indication of postoperative recovery time, and the occurrence of postoperative complications were observed and recorded carefully.

Interventions

Rats undergoing any operation fasted overnight. Inhalation anesthesia with 2% isoflurane and air/oxygen was used during the surgery.

We performed BPD as described by Scopinaro and colleagues.[23] First, a midline abdominal incision was made. Then the duodenum was separated from the stomach, and bowel continuity was interrupted at the level of the distal jejunum, 8 cm from the ligament of Treitz. The distal of the 2 limbs was directly connected to the stomach (gastrojejunal anastomosis), and the proximal limb carrying the biliopancreatic juices was reconnected downward to the alimentary limb at a distance of 10 cm from the ileal valve. In BPD, the gastric volume was maintained intact while the entire duodenum and the proximal jejunum were bypassed. The details of the procedure are illustrated in Figure 1.

We performed IT as described by Strader and colleagues.[20] First, a midline abdominal incision was made, and the cecum was located and removed from the abdomen and placed on saline-soaked sterile gauze. An 8-cm segment of ileum located 5–15 cm proximal to the ileocecal valve was isolated and transected. The segment was carefully placed

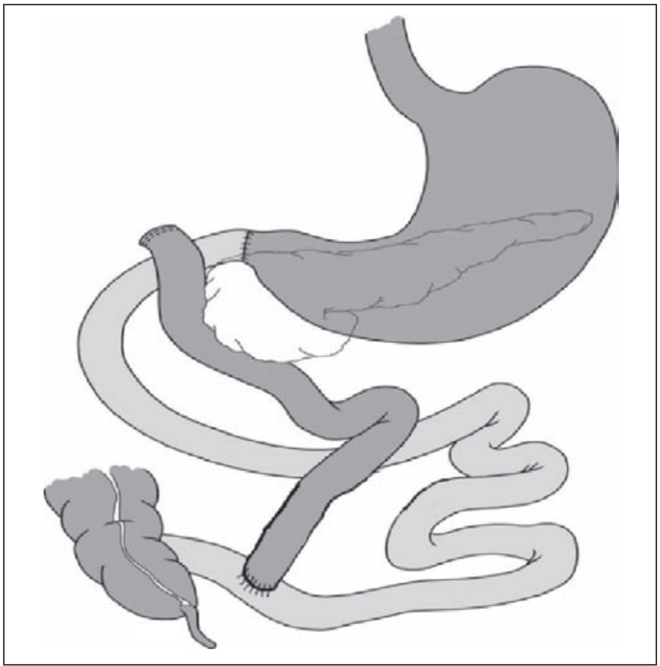

Fig. 1. Biliopancreatic diversion. The duodenum was separated from the stomach, and bowel continuity was interrupted at the level of the distal jejunum (8 cm from the ligament of Treitz). The distal of the 2 limbs was directly connected to the stomach (gastrojejunal anastomosis), and the proximal limb carrying the biliopancreatic juices was reconnected downward to the alimentary limb at a distance of 10 cm from the ileal valve.

on saline-soaked gauze. An anastomosis was then made with the 2 open ends of the ileum, using 8 stitches with 7–0 silk suture (Ningbo Medical Needle Co.). 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. The details of the procedure are illustrated in Figure 2.

Sham surgeries were performed by making transections and reanastomosis of the gastrointestinal tract at multiple sites (corresponding to sites of the enterotomies in the BPD and IT groups). After transection, the intestines were immediately attached by anastomosis. When needed, we prolonged the duration of surgery to produce a similar degree of anesthesiologic stress in rats who underwent sham operations compared with those that underwent BPD or IT.

Measurements

In all groups, we measured weight and food intake daily for the first 2 weeks after the intervention, twice a week for the subsequent 2 weeks, and monthly thereafter.

We measured fasting glycemia using a sure-step plus blood glucose metre (Life Scan Company) once a week for the first 4 weeks and monthly thereafter.

We measured GLP-1 before surgery and 1, 2, 4 and 24 weeks after surgery. Glucose-stimulated GLP-1was measured by blood samples collected from the tail vein in conscious rats 30 minutes after the administration of 1 g/kg of glucose by oral gavages.

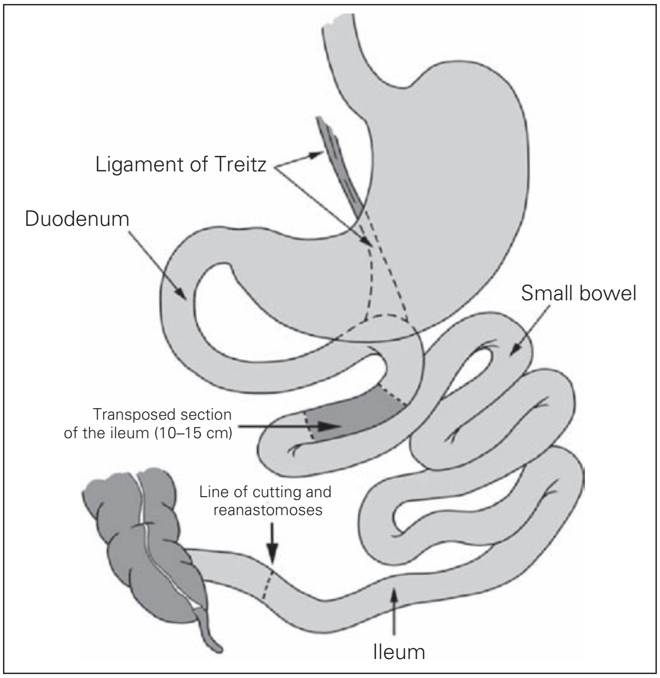

Fig. 2. Ileal transposition surgery was performed by isolating a 10-cm segment of the distal small intestine 5 cm proximal to the ileocecal valve and transposing it to a location within the jejunum 5 cm distal to the ligament of Treitz.

Glucose tolerance (assessed by an oral glucose tolerance test [OGTT]) and plasma insulin were measured before surgery and 10 weeks after surgery. For the OGTT, after 12–14 hours of fasting we measured blood glucose (analyzed by a glucometer) in conscious rats before (baseline) and then 10, 30, 60, 120 and 180 minutes after the administration of 1 g/kg of glucose by oral gavages using the blood collected from the tail. The 0- and 15-minute samples from the OGTT were also used to measure plasma insulin (as described below).

To determine whether the operations cause changes in insulin sensitivity, rats were given an insulin tolerance test 10 weeks after surgery. During this test, a dose of 0.5 UI/kg human insulin was injected intraperitoneally in conscious, fed rats. We selected this dosage after having tested the efficacy of an intraperitoneal injection of different doses of insulin in the same rat model. The sampling methods used were the same as those for other tests, and we measured blood glucose using a glucometer at baseline and then 10, 30, 60, 120 and 180 minutes after insulin injection.

Plasma total cholesterol, triglycerides and free fatty acids were measured both after 12–14 hours fasting and in the fed condition at 12 weeks after surgery. Analytical testing of plasma lipids was performed by the biochemical laboratory of Qilu Hospital.

For plasma hormone measurements, blood samples collected from the tail vein in conscious animals were placed in tubes containing separation gelatin for the determination of lipids and ethylenediaminetetraacetic acid (EDTA). In addition, we used the kallikrein inhibitor aprotinin for the assay of insulin and GLP-1. After centrifugation at 3000 rpm at 4°C for 12 minutes, the plasma was immediately separated and stored at –80°C until analyzed. Rat radioimmunoassay kits (Linco) were used to measure insulin and GLP-1 (performed using equipment from Jingmei Biotech Company).

Statistical analysis

Data are expressed as means and standard deviations (SD). We calculated areas under the curves by trapezoidal integration. Statistical analysis was performed using repeated-measures analysis of variance (ANOVA), Scheffe correction and the Student *t* test, as appropriate. We determined results to be significant at $p < 0.05$.

RESULTS

Before treatments, there were no significant differences between the groups in terms of weight, fasting glycemia, insulin, GLP-1, glucose tolerance and insulin tolerance (Table 1).

Weight loss

Both BPD and IT resulted in significant weight loss compared with the sham-operated rats (p = 0.005, Fig. 3). In addition, BPD resulted in nonsignificant but low nadir weight level compared with IT (p = 0.28). After surgery, paired BPD and IT groups lost a similar amount of weight until postoperative days 10 and 12, respectively, after which the sham-operated groups started regaining lost body weight. However, the rats that underwent BPD or IT lost additional weight before they started regaining weight. The rats that underwent BPD or IT never attained a weight similar to that of the sham-operated groups in the remaining study period (24 wk).

Glycemia

Both BPD and IT markedly reduced postoperative fasting plasma glucose levels, whereas the sham operations did not significantly change blood glucose levels. Glycemia remained consistently lower in the BPD group compared with the sham-operated groups through the entire follow-up period (p = 0.006). There were no significant differences between the BPD and IT groups (p = 0.61, Fig. 4).

Glucagon-like peptide-1

Both IT and BPD resulted in hypersecretion of GLP-1 (p = 0.008 and p = 0.002, respectively) throughout the entire follow-up period (24 wk). Glucose-stimulated GLP-1 in rats that underwent IT was significantly higher than that in rats that underwent BPD (F = 11.44, p = 0.006) and more than twice that of the sham-operated rats (p = 0.008; Fig. 5).

Oral glucose tolerance

Ten weeks after surgery, glucose tolerance was improved in both the BPD and IT groups compared with the preoperation findings for those groups. In particular, BPD

Table 1. Preoperative data of rats undergoing IT or BPD to treat type 2 diabetes

	Group; mean (SD)				
Measure	IT	Sham IT	BPD	Sham BPD	*p* value
Weight, g	279.4 (9.3)	287.4 (8.2)	279.4 (9.3)	287.4 (8.2)	0.68
Fasting glycemia, mg/dL	148.7 (35.0)	153.6 (28.8)	148.7 (35.0)	153.6 (28.8)	0.39
GLP-1, pmol/L	21.8 (5.1)	23.4 (7.3)	18.6 (7.9)	21.2 (6.6)	0.74
Fasting insulin, μU/mL	51.33 (9.49)	57.67 (12.69)	51.33 (9.49)	57.67 (12.69)	0.32
Glucose-stimulated insulin, μU/mL	87.28 (6.89)	82.93 (9.55)	87.28 (6.89)	82.93 (9.55)	0.58

BPD = biliopancreatic diversion; GLP-1 = glucose-stimulated glucagon-like peptide-1; IT = ileal transposition; SD = standard deviation.

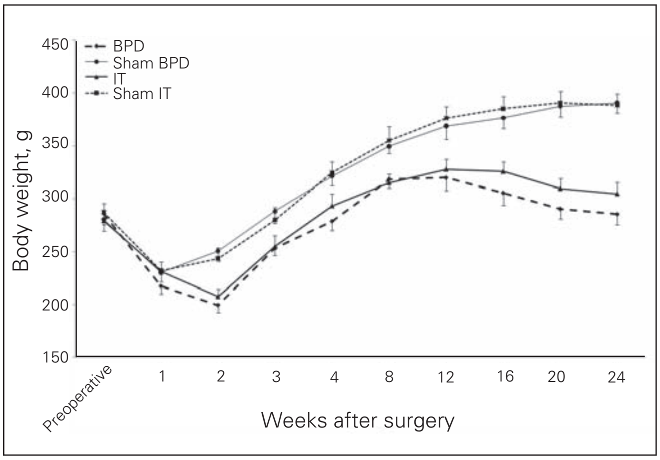

Fig. 3. Body weights of rats (mean and standard errors of the mean). Both the ileal transposition (IT) and the biliopancreatic diversion (BPD) groups showed less weight gain compared with sham-operated groups (2-way repeated-measures analysis of variance; p = 0.005 for BPD–sham comparison and p = 0.002 for IT–sham comparison).

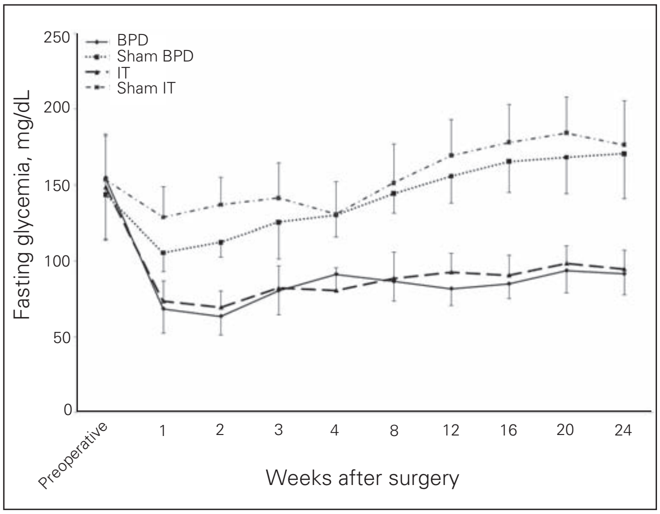

Fig. 4. Fasting glycemia (mean and standard errors of the mean). Mean fasting glycemia remained constantly lower in the rats that underwent ileal transposition (IT) or biliopancreatic diversion (BPD) compared with those that underwent sham operations (2-way repeated-measures analysis of variance [ANOVA]; p = 0.008 and p = 0.006, respectively). There were no significant differences between rats that underwent BPD or IT (2-way repeated-measures ANOVA; p = 0.61).

improved glucose tolerance (Fig. 6), as demonstrated by a greater than 30% reduction of the area under the blood glucose concentration curve, as well as by lower mean 30-minute peak levels (189.4 [SD 22.6] mg/dL v. 346.7 [SD 33.6] mg/dL; $p < 0.001$) and lower mean 2-hour levels (116.7 [SD 34.6] mg/dL v. 255.6 [SD 27.4] mg/dL; $p < 0.001$). Although glucose tolerance among rats that underwent IT revealed significant improvement compared with the sham-IT group (Fig. 6), the rats that underwent IT showed a worse glucose tolerance than those that underwent BPD (a 12.5% bigger area under the curve for the IT group than the BPD group; Fig. 6).

Plasma insulin

Neither BPD nor IT had any effect on plasma insulin concentrations with fasting or after glucose stimulation. The levels were not significantly different among any of the groups ($p = 0.47$ and $p = 0.26$, respectively; Fig. 7).

Insulin tolerance

Both the BPD and IT groups had a greater glucose disappearance rate compared with preoperation levels in those groups and with the sham-operated greoups, indicating better insulin sensitivity (Fig. 8). Moreover, rats that underwent IT showed greater insulin sensitivity compared with those that underwent BPD, as demonstrated by a 10.1% reduction in the area under the curve (Fig. 8).

Lipid profile

Rats that underwent BPD showed similar plasma lipid levels compared with those that underwent IT. Nevertheless, both the BPD and IT groups had lower plasma lipid levels than the sham-operated groups (Table 2).

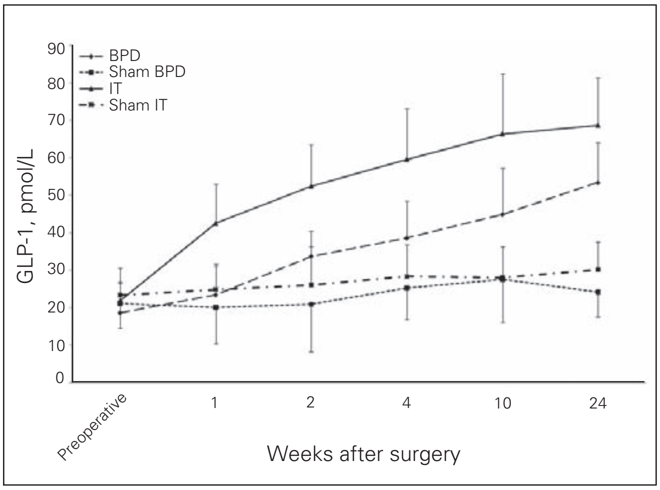

Fig. 5. Plasma levels (mean and standard errors of the mean) of glucose-stimulated glucagon-like peptide (GLP)-1 after ileal transposition (IT), biliopancreatic diversion (BPD) or sham surgery. Both IT and BPD increased plasma GLP-1; these levels were significantly different among rats that underwent IT, BPD or sham operations (2-way repeated-measures analysis of variance; $p = 0.002$ for BPD–sham comparison and $p = 0.008$ for IT–sham comparison).

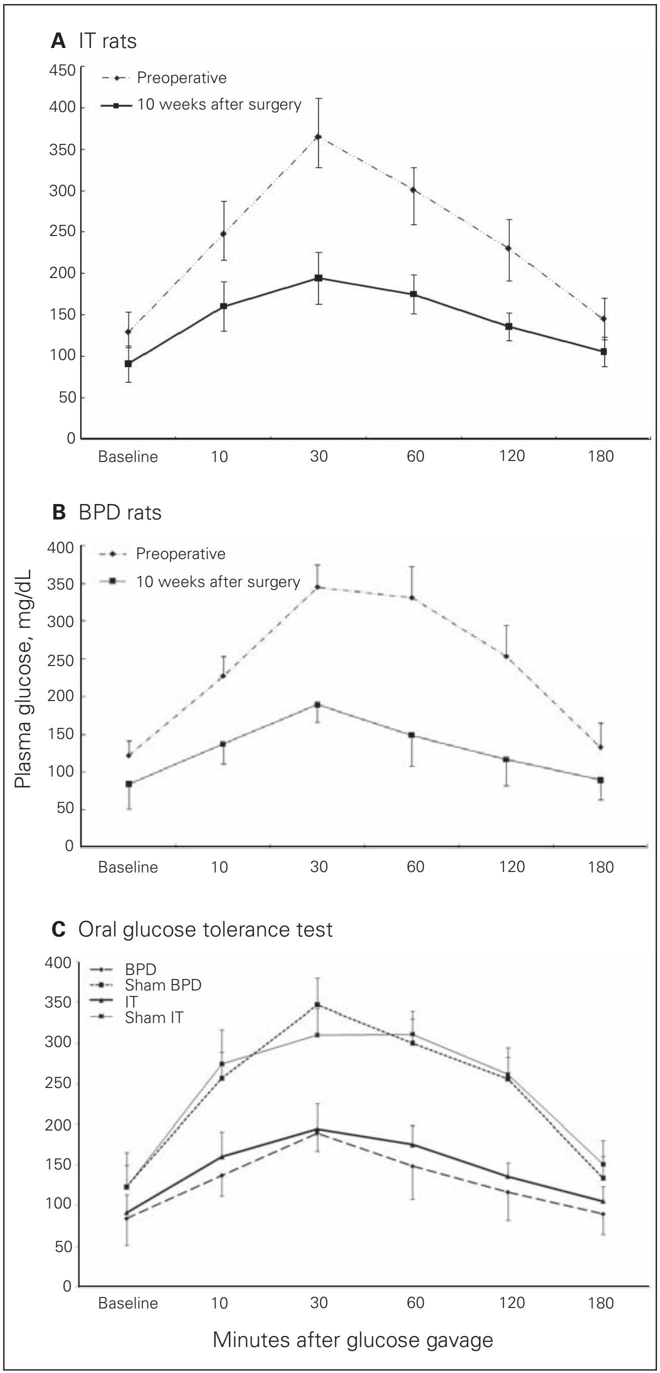

Fig. 6. Glucose tolerance. (**A**) The oral glucose tolerance test (OGTT) performed in rats before and 10 weeks after ileal transposition (IT) showed an improvement of glucose tolerance (40.3% reduction of the area under the curve). (**B**) The OGTT performed in rats before and 10 weeks after biliopancreatic diversion (BPD) showed an improvement of glucose tolerance (45.2% reduction of the area under the curve). (**C**) The OGTT performed in rats 10 weeks after IT or BPD. Rats that underwent IT showed a worse glucose tolerance than those that underwent BPD (12.5% smaller area under the curve for BPD).

Duration of surgery

The duration of surgery was defined as the time from a midline abdominal incision to the suturing of the abdominal incision. Ileal transposition resulted in significant savings of time compared with BPD (50.82 [SD 8.49] min v. 83.44 [SD 15.26] min; $p < 0.001$).

Postoperative recovery time

The postoperative recovery time was defined as the time from the end of the operation to that of the first defecation. Ileal transposition was associated with a significantly shorter postoperative recovery time than BPD (19.29 [SD 7.26] h v. 51.25 [SD 14.7] h; $p < 0.001$).

Postoperative complications

Three of the rats that underwent BPD died on postoperative days 5, 107 and 136, respectively. The deaths were due to stomal leak and metabolism complication. The IT group did not experience any severe postoperative complications.

DISCUSSION

Currently, there is an exponential increase in the prevalence of type 2 diabetes within the population. For this reason, better ways to treat patients with diabetes are needed. There is evidence that bariatric surgery is an effective form of therapy for patients with type 2 diabetes. However, determining the "best" surgical treatment for diabetes is an important task facing the bariatric surgical community. The optimal procedure should have acceptably low morbidity and mortality, resulting in significant and durable glycemic control. It should also lead to the improvement or resolution of diabetes-related comorbidities, as well as increase quality of life.

The main focus of this report is the comparison of glycemic control outcomes following IT and BPD. We demonstrated that IT provides a significant advantage over

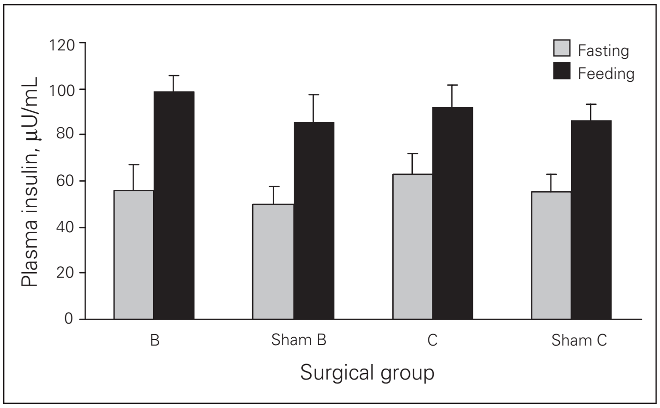

Fig. 7. Plasma levels of insulin (mean and standard errors of the mean). Ileal transposition (IT) and biliopancreatic diversion (BPD) had no effect on fasting or feeding plasma insulin concentrations 10 weeks after operation; these levels were not significantly different in any of the groups (Student *t* test; $p = 0.47$ for BPD and $p = 0.26$ for IT).

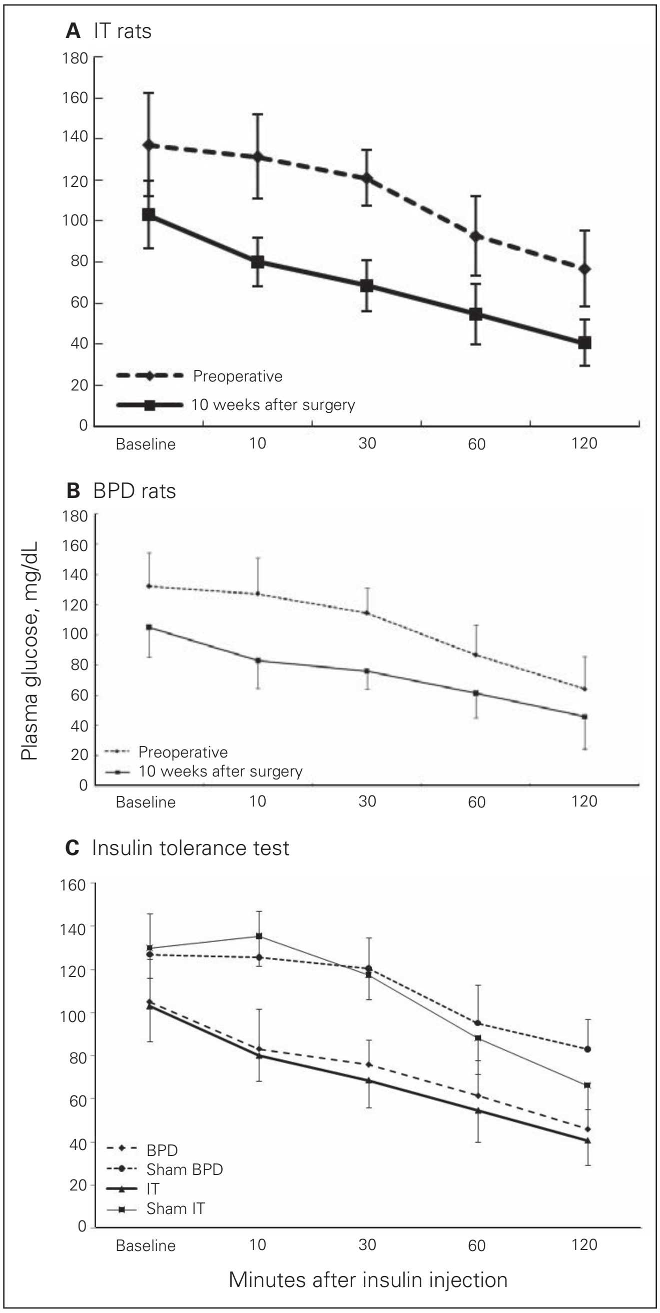

Fig. 8. Insulin sensitivity. (**A**) The insulin tolerance test performed in rats before and 10 weeks after ileal transposition (IT) showed an improvement of insulin sensitivity (39.1% reduction of the area under the curve). (**B**) The insulin tolerance test performed in rats before and 10 weeks after biliopancreatic diversion (BPD) showed an improvement of insulin sensitivity (26.7% reduction of the area under the curve). (**C**) The insulin tolerance test performed in rats 10 weeks after IT or BPD. Rats that underwent IT demonstrated better insulin sensitivity than those that underwent BPD (10.1% reduction of the area under the curve).

BPD when comparing insulin sensitivity and GLP-1. A similar effect with BPD on glycemia, plasma insulin, glucose tolerance and plasma lipids was demonstrated. Both IT and BPD showed sustained effect in the resolution of diabetes. Similar to previous observations, these surgeries achieved normal concentrations of fasting glycemia and fasting plasma insulin,[6,7,11,12] restored insulin sensitivity,[6,8,21,24] prevented progression in impaired glucose tolerance[21,25] and reduced mortality from diabetes.[26] In this study, IT yielded a better result than BPD in insulin sensitivity and GLP-1. Moreover, irrespective of the statistical results, animals that underwent IT had a better absolute value in plasma glucose levels and lipid profile than those that underwent BPD. Results in the BPD group suggest that IT shows a superior glycemic control than BPD. Furthermore, we speculate that IT might provide a significantly better result than BPD in further experiments with larger samples. These data give strong evidence that the role of the hindgut in the resolution of diabetes is at least similar, if not more crucial than, bypass of the proximal bowel.

An alternative explanation for our findings is the hypothesis that high levels of plasma GLP-1 reported after jejunoileal bypass[27] play a crucial role in the mechanism of diabetes control after bariatric surgery.[28,29] Additionally, it has been well-documented that rats with elevated GLP-1 with deletions or mutations in the GLP-1–metabolizing enzyme dipeptidylpeptidase-IV show improved glucose tolerance.[30,31] Previous studies have indicated that ileal segments transposed into the duodenojejunal region become extremely hypertrophied after transposition and secrete significantly more enteroglucagon compared with sham-operated rats.[32,33] Likewise, the rats that underwent IT showed a significantly increased GLP-1 level over those that underwent BPD or the sham operation in our study. Thus, we speculate that because of the positive effect of IT on GLP-1, IT achieves superior control of diabetes than BPD. The increased GLP-1 levels after IT and BPD suggest that greater production of GLP-1, triggered by the earlier presentation of undigested food in lower segments of the bowel, might be involved in the glycemic control resulting from bypass procedures for the treatment of obesity.[28] In the present study, the fact that rats that underwent IT demonstrated lower glucose tolerance but more insulin sensitivity and similar postoperative plasma glucose levels compared with rats that underwent BPD showed that GLP-1 results in the long-term remission of diabetes by improving insulin sensitivity through restoration of insulin signalling.[34] Interestingly, it has been demonstrated that the bypass procedure significantly increases GLP-1 levels of morbidly obese nondiabetic patients but not of diabetic patients.[35] Moreover, a study of bypass procedures concluded that GLP-1 was not a critical factor for the early changes in glucose tolerance.[36] Another study also reported that bypass procedures have been shown to produce substantially increasing GLP-1 levels in obese patients with type 2 diabetes.[37] Although the present study did not conclusively assess the effect of bypass procedures on GLP-1 in type 2 diabetes, the possibility of an effect of bypass procedures on GLP-1 is of interest. Increases in signalling pathways are considered to be among the most critical alterations underlying type 2 diabetes,[38] in which the incretin-like effect of GLP-1 is characteristically attenuated secondarily to decreased expression of GLP-1 receptors.[39]

The second issue we tried to address was the comparison of postoperative recovery and complications between IT and BPD. We demonstrated that postoperative recovery in rats that underwent IT was faster than that in rats that underwent BPD. It has been previously shown that rats that underwent IT had no malabsorption problems and needed little postoperative management.[40] The easier the procedure, the shorter the postoperative recovery. The present data strongly support this association. Moreover, we found that IT was associated with a shorter duration of surgery (50.82 [SD 8.49] min v. 83.44 [SD 15.26] min; $p < 0.001$), faster postoperative recovery (19.29 [SD 7.26] h v. 51.25 [SD 14.7] h; $p < 0.001$) and a significant decrease in both major and minor postoperative complications compared with BPD. In contrast, bypass procedure research in

Table 2. Lipid profiles of rats that underwent IT, BPD or sham operations for type 2 diabetes

	Lipid; test time; mean (SD) mmol/L					
	Cholesterol		Triglycerides		Free fatty acids	
Group or comparison	Fasting	Feeding	Fasting	Feeding	Fasting	Feeding
BPD	1.32 (0.57)	1.72 (0.43)	2.23 (0.91)	1.11 (0.39)	0.85 (0.13)	0.37 (0.09)
Sham BPD	2.86 (0.55)	2.65 (0.37)	2.37 (0.65)	1.92 (0.58)	1.36 (0.40)	0.92 (0.28)
IT	1.74 (0.29)	1.43 (0.31)	2.16 (0.41)	1.17 (0.73)	0.83 (0.30)	0.57 (0.23)
Sham IT	2.91 (0.38)	2.77 (0.33)	2.23 (0.74)	1.70 (0.30)	1.17 (0.39)	0.90 (0.13)
p value*						
IT v. BPD	0.09	0.12	0.10	0.36	0.56	0.07
IT v. sham IT	< 0.001	< 0.001	0.11	0.33	0.45	< 0.001
BPD v. sham BPD	< 0.001	< 0.001	0.15	0.036	0.28	0.006

BPD = biliopancreatic diversion; IT = ileal transposition; SD = standard deviation.
*Student *t* test.

humans showed that the overall early complication rate ranges from 3% to 15%,[41,42] and because of possible iron and vitamin B_{12} deficiency, there is a need for long-term supervision and vitamin and mineral replacement.[43] Both operations appear to be reasonably safe, with low 30-day mortality, particularly considering that this series includes our initial experience with IT.

These findings are in agreement with the observations published in a series of laparoscopic approaches for bypass procedure documenting an overall mortality of 0.2%[41] and a large series documenting a 0.4%–0.8% mortality for BPD.[6] This issue is an important point because it indicates that IT is an alternative method of providing long-term control of glycemia and normal levels of insulin with lower mortality compared with BPD.

In addition to providing good glycemic control, the results of both operations presented herein corroborate and extend previous work in several ways. First, both operations appeared to result in stable weight loss compared with a carefully constructed sham surgical procedure (involving transections and anastomoses). Previous research has shown that rats that underwent IT have been able to maintain weight loss and reduced food intake for as long as 6 months after surgery,[44] and similar results have been reported in studies of BPD. In our study, the net weight difference of the BPD and IT groups compared with the sham-operated groups was persistent and maintained at more than 70 g 24 weeks after surgery. Second, it has been suggested recently that the low levels of free fatty acids found after BPD might reflect dependence on some degree of fat malabsorption and might have played a role in improving glycemic control.[23] In our research, we demonstrated that both operations can effectively lower the levels of free fatty acids compared with the sham operation. Indeed, it has been demonstrated previously that high levels of free fatty acids induce insulin resistance,[45] and lowered levels of free fatty acids are associated with improved insulin sensitivity in hyperlipidemic human patients.[46] Third, in our study the control of diabetes induced by both IT and BPD was not dependent on the resolution of obesity-related abnormalities because we used a nonobese model. The effect on glucose metabolism seems to be a direct consequence of the duodenal jejunal exclusion and the IT rather than weight loss. Decreased food intake can also be ruled out as a cause because the rate of food ingestion was the same in all study groups, including the sham-operated groups. These findings are consistent with those reported in previous studies in humans that indicated the plasma glucose and insulin levels after bariatric surgery occurred before substantial weight loss.[47]

CONCLUSION

Safely obtained significant and sustained glycemic control is the key goal of metabolic surgery. Our direct comparison of IT with BPD demonstrated that IT provided superior glycemic control with better clinical recovery in an animal model of type 2 diabetes compared with BPD. In the absence of either restriction or malabsorption, large changes in intestinal hormone secretions and synthesis were evident. Our findings confirm at the preclinical level that IT is a surgical procedure of possible relevance in the therapy of type 2 diabetes in nonoverweight and mildly obese patients. Of course, IT is not yet an established procedure in the treatment of diabetes. Further study and follow-up will be needed to confirm and extend the present findings, especially in humans, including a comparison of nutritional outcomes, resolution of comorbidities and quality of life. In this way, an evidence-based rationale for procedure selection can be developed. With time and further development, IT may become an efficient method of surgically curing diabetes.

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