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ORIGINAL ARTICLE

Ileal transposition rapidly improves glucose tolerance and gradually improves insulin resistance in non-obese type 2 diabetic rats

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Abstract

Background: Many studies have confirmed that ileal transposition can improve type 2 diabetes mellitus (T2DM), accompanied by increased glucagon-like peptide-1 (GLP-1). We performed the experiment on diabetic rats to evaluate the effects and mechanisms of ileal transposition on the glycemic metabolism.
Methods: Twenty Goto-Kakizaki (GK) rats were randomly divided into the ileal transposition group (IT group) and the sham operation group (Sham group). Weight, food intake, fasting plasma glucose (FPG), fasting insulin (F-ins), oral glucose tolerance test (OGTT) and GLP-1 were determined at baseline and 1, 4, 8, 16 and 24 weeks post-operatively. The homeostasis model assessment-insulin resistance (HOMA-IR) index and the area under the curve (AUC) during OGTT were measured. Histological determination of the GLP-1 receptor (GLP-1R) was performed on the pancreas and ileum 24 weeks post-operatively.
Results: In comparison with the Sham group, the IT group showed a higher GLP-1 level and lower AUC at 4, 8, 16 and 24 weeks post-operatively (all $P < 0.05$) and a lower FPG, F-ins levels and HOMA-IR at 8, 16 and 24 weeks post-operatively (all $P < 0.05$). Compared with baseline levels, the plasma GLP-1, AUC and FPG levels decreased significantly at each post-operative time point in the IT group (all $P < 0.05$), but not in the Sham group (all $P > 0.05$); F-ins and HOMA-IR significantly decreased at 8, 16 and 24 weeks post-operatively in the IT group (all $P < 0.05$). GLP-1R expression in the IT group was significantly higher than that of the Sham group in both the pancreas and the ileum at 24 weeks post-operatively ($P < 0.05$).
Conclusions: Ileal transposition ameliorated glucose metabolism without reduction in weight or food intake in GK rats, which may be induced by the increased GLP-1 expression. However, the delayed improvement of insulin resistance, accompanied by decreased plasma insulin levels, might not directly result from the increased GLP-1.

Key words: Type 2 diabetes mellitus; ileal transposition; glucagon-like peptide-1; glycemic metabolism

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Introduction

Metabolic and bariatric surgery (MBS) is a powerful therapy for obese patients with type 2 diabetes mellitus (T2DM) [1–3]. Roux-en Y gastric bypass (RYGB), as a classic procedure of MBS, has several contributors to diabetes remission, namely gastric restriction, nutrient malabsorption, gut hormone changes, peripheral insulin sensitivity improvement, altered bile acid metabolism and changes in gastrointestinal microbiota, etc. [4–9]. Amongst these potential mechanisms, glucagon-like peptide-1 (GLP-1), mostly produced by L-cells located in the distal small intestine and the colon [10], is supposed to be one of the most important factors in the hindgut hypothesis for diabetes remission after MBS [8]. However, studies have shown doubt on the role of GLP-1 in the context of the hindgut hypothesis [5, 11–15]. In GLP-1 receptor (GLP-1R) knockout mice, RYGB still exhibited improved glucose homeostasis [15, 16] and a GLP-1R antagonist did not deteriorate glucose homeostasis in patients who achieved T2DM remission following RYGB [11].

Ileal transposition, also referred to as ileal interposition, is an ideal model to explore the hindgut effect in MBS [8]. It is neither a restrictive nor a malabsorptive procedure. Ileal transposition is not a single technique utilized by T2DM patients, although limited studies have shown that more than 85% of T2DM patients achieve diabetic remission after ileal transposition combined with sleeve gastrectomy with or without duodeno-jejunal diversion [5, 17].

Studies on different types of rats have shown that a single ileal transposition can improve glycemic metabolism [5, 18], and the increased GLP-1 has been proposed to be an important mechanism of ileal transposition for treating T2DM [8, 19, 20]. However, changes in the secretion of GLP-1 do not explain all the phenomena hypothesized [5]. Furthermore, in a long-term (6-month) study with Zuker rats, a fading effect of ileal transposition regarding glucose tolerance (GT) and GLP-1 level was observed [21], which cast recurrences of diabetes remission that have been reported after MBS, such as RYGB [22], duodenal-jejunal bypass (DJB) [23] and sleeve gastrectomy with duodeno-jejunal end-to-side anastomosis (SG-DJESA) [24]. It could be speculated that a 'jejunization' gradually occurred in the transposed ileum so that the L-cells might eventually impair its incretin-secreting ability [8]. With this possibility, GLP-1 secreting should be gradually decreased. Whether the increased GLP-1 after ileal transposition would be an epiphenomena to the attempt to alter gut morphology to alleviate increased nutrient presentation in the ileum remains unknown [5]. Therefore, further studies are required to examine the role of GLP-1 in glucose metabolism after ileal transposition, and we present a 'long-term' study on non-obese diabetic Goto-Kakizaki (GK) rats.

Materials and methods

Animals and experimental protocol

Twenty male GK rats (aged 9 weeks, purchased from Slac Laboratory Animal Co., Ltd Shanghai, China) were housed individually in a sound-proof environment with a specific pathogen-free (SPF) system. The cages were maintained at a temperature of 20–40°C, relative humidity of 50–70% and 12/12 hours light/dark cycles with a daylight lamp of 40 watts during the day. The rats had free access to water.

After 7 days of acclimation, food intake, body weight, glycometabolic parameters [including fasting plasma glucose (FPG), fasting insulin (F-ins) and blood glucose (BG)] and plasma GLP-1 levels were measured twice a week to obtain pre-operative baseline data 7 days before the planned day of surgery. Oral glucose tolerance tests (OGTTs) were performed at baseline and 4, 8, 16 and 24 weeks post operation, and plasma GLP-1 levels were measured 30 minutes during each OGTT time point. Trapezoidal integration was used to calculate the area under the curve (AUC) of OGTT. AUC was calculated according to the following formula: AUC (mmol·min/L) $= BG0h \times 0.5 + BG1h \times 0.75 + BG2h \times 0.25$ (BG0h, BG1h and BG2h indicated blood glucose levels at 0, 1, 2 hours, respectively). FPG and F-ins were determined at baseline and 1, 4, 8, 16 and 24 weeks post-operatively. The homeostasis model assessment-insulin resistance (HOMA-IR) index was calculated according to the formula: HOMA-IR = FPG (mmol/L) × F-ins (mIU/L)/22.5.

The 20 GK rats were randomly assigned to one of two groups: the ileal transposition group (IT group) and the sham operation group (Sham group). The study protocol was approved by the Ethics Committee for Animal Research of Wenzhou Medical University.

Surgical techniques

Rats undergoing surgery were fasted for 24 hours and anesthetized with an intraperitoneal injection of 1% pentobarbital sodium. In all cases, a small midline incision was performed and the cecum was exposed to identify the terminal ileum. In the IT group, the distal end of the loop to be transposed was selected at ~10 cm from the ileo-cecal valve and the proximal end was identified at ~10 cm from the distal end. The bowel was then dissected with maintenance of an intact mesenteric blood supply (Figure 1). The jejunum was divided 10 cm distal to the ligament of Treitz, and the ileal loop was transposed and end-to-end anastomosed between the jejunal ends (Figure 2). The mesenteric defects were closed before the operation was completed. The sham operation consisted of three transections at the same locations as those in the IT group, but the anastomoses were performed *in situ*. The sham operation time was prolonged intentionally to produce a degree of operative stress similar to that of IT. All of the anastomoses were performed by interrupted sutures using 6–0 Prolene® Blue Monofilament Sutures (Ethicon, Cincinnati, OH, USA).

Plasma assays

All rats were fasted overnight for 12 hours before the day of blood extraction. Blood for FPG, F-ins and GLP-1 determination was obtained from the angula vein, while blood for BG detection

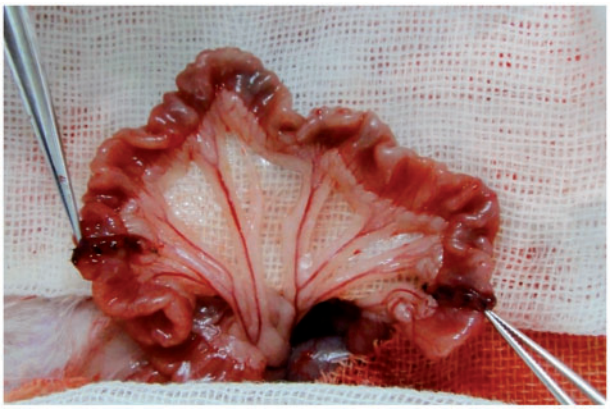

Figure 1. The intact mesenteric blood supply.

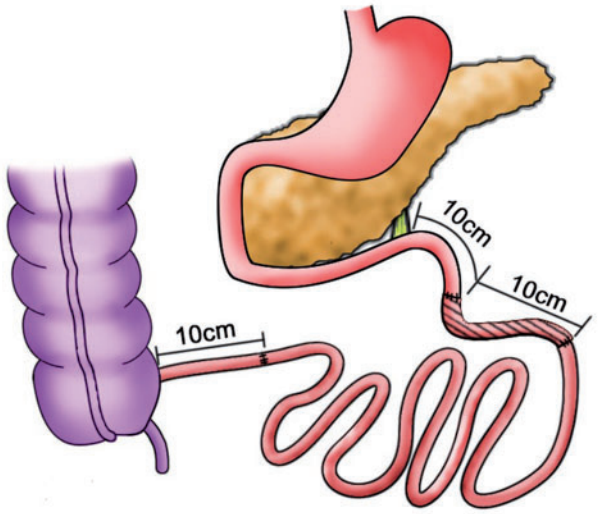

Figure 2. The procedure of ileal transposition.

was obtained from the tail vein. Blood extraction for FPG and F-ins was performed after fasting for 12 hours overnight, separated from the day of OGTT by no fewer than 3 days. BG for the OGTT was measured at baseline and 10, 30, 60 and 120 minutes after administration of 10% w/vol D-glucose solution (1 g/kg body weight) by oral gavage.

Tubes containing blood samples were immediately placed on ice and centrifuged at 5000 rpm for 20 min. Plasma was stored in freezer tubes in a –80°C until assay. FPG was measured via an enzymatic colorimetric assay for glucose (Thermo DMA, Louisville, CO, USA). F-ins and GLP-1 were measured using rat-specific enzyme-linked immunoabsorbent assay kits (Nanjing Jiancheng Bioengineering Institute, China). Dipeptidyl peptidase IV (DPP-4) inhibitor (DPP-4; Linco Research, St. Charles, MO, USA) was added to the solution at a final concentration of 100 μM to assay GLP-1 amide. BG was assessed by a glucometer (Accu-Chek Advantage, Roche Diagnostics GmbH, Germany).

Histological determination

Histological determination on GLP-1R was performed on the pancreas and ileum at 24 weeks post-operatively. GLP-1R mRNA was determinate by RT-PCR, and the protein expression of GLP-1R was detected by Western-blot.

Statistical analysis

Data are presented as mean ± standard deviation (SD) if normally distributed. Paired *t*-tests were used to compare data before (baseline) and after surgery, and independent sample *t*-tests were utilized to compare data between the IT and Sham groups. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) 21.0 (IBM Corp., Armonk, NJ, USA).

Results

No significant differences between the IT and Sham groups in terms of weight, food intake, FPG (or BG), F-ins, HOMA-IR, AUC and plasma GLP-1 levels were observed before operation (all $P > 0.05$).

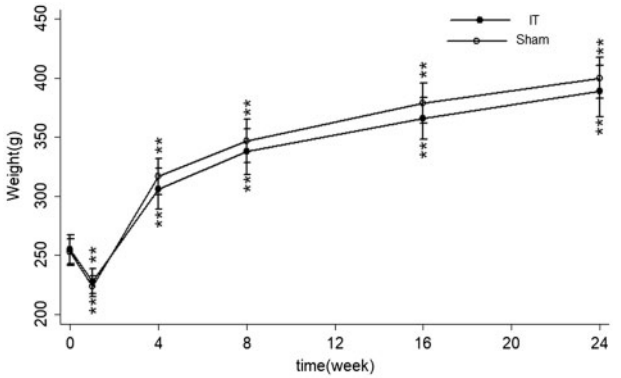

Figure 3. Weight changes after ileal transposition. *$P < 0.05$ and **$P < 0.01$, respectively, by paired samples *t*-test between the post-operative time point and baseline.

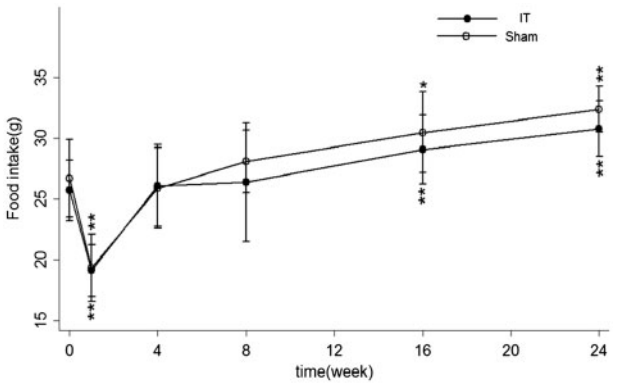

Figure 4. Changes in food intake after ileal transposition. *$P < 0.05$ and **$P < 0.01$, respectively, by paired samples *t*-test between the post-operative time point and baseline.

Weight and food intake

There were no significant differences between the IT and Sham groups in terms of weight and food intake post-operatively. In comparison with the baseline, weight significantly decreased 1 week post-operatively ($P < 0.01$) and significantly increased 4, 8, 16 and 24 weeks post-operatively (all $P < 0.01$) in each group (Figure 3). In comparison with the baseline, food intake significantly decreased 1 week post-operatively ($P < 0.05$) and significantly increased 16 and 24 weeks post-operatively (all $P < 0.01$) in each group. No significant changes in food intake were observed 4 and 8 weeks post-operatively in the two groups (Figure 4).

Glycometabolic parameters

Although no significant differences between the IT and Sham groups were observed 1 and 4 weeks post-operatively ($P = 0.816$ and 0.092, respectively), the IT group showed significantly lower FPG levels than the Sham group 8, 16 and 24 weeks post-operatively (all $P < 0.01$). In comparison with the baseline, FPG significantly decreased at each post-operative time point (all $P < 0.05$) in the IT group, but no significant changes showed at each post-operative time point (all $P > 0.05$) in the Sham group (Figure 5).

The IT group did not show a significantly lower F-ins level than the Sham group until 8, 16 and 24 weeks post-operatively (51.5 ± 11.8 vs 62.9 ± 10.3 pmol/L, $P < 0.05$; 47.3 ± 10.3 vs 65.8 ± 9.8 pmol/L, $P < 0.05$; 39.5 ± 12.2 vs 63.3 ± 13.7 pmol/L,

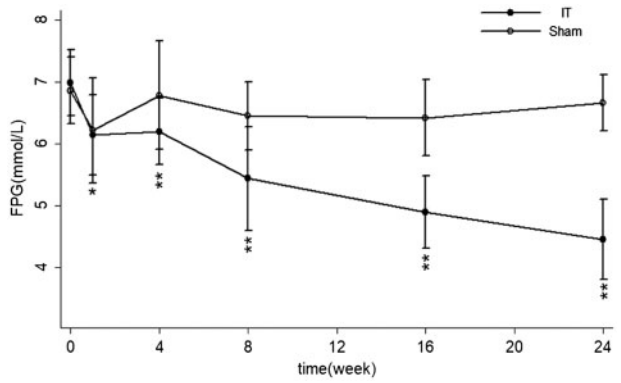

Figure 5. Changes in fasting plasma glucose (FPG) after ileal transposition. *$P < 0.05$ and **$P < 0.01$, respectively, by paired samples t-test between the post-operative time point and baseline.

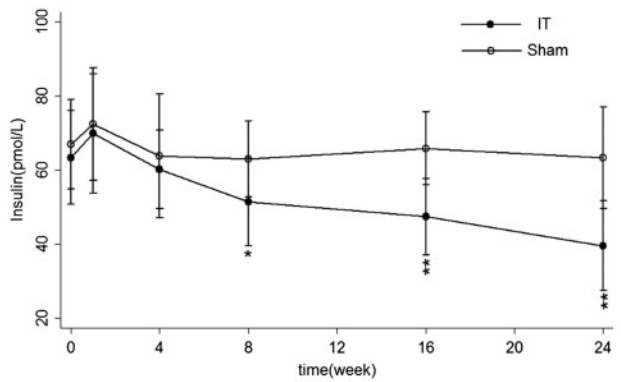

Figure 6. Changes in fasting insulin levels after ileal transposition. *$P < 0.05$ and **$P < 0.01$, respectively, by paired samples t-test between the post-operative time point and baseline.

$P < 0.01$, respectively). In comparison with the baseline, F-ins significantly decreased at 8, 16 and 24 weeks post-operatively in the IT group ($P < 0.05$, $P < 0.01$, $P < 0.01$, respectively) but showed no significant change in the Sham group post-operatively (Figure 6).

The IT group did not show a significantly lower HOMA-IR index than the Sham group until 8, 16 and 24 weeks post-operatively (1.7 ± 0.5 vs 2.8 ± 0.6, 1.4 ± 0.5 vs 2.7 ± 0.5, 1.1 ± 0.4 vs 2.6 ± 0.4, respectively, all $P < 0.01$). In comparison with the baseline, HOMA-IR significantly decreased 8, 16 and 24 weeks post-operatively in the IT group (all $P < 0.01$) but showed no significant change in the Sham group post-operatively (Figure 7).

As for OGTTs, the IT group showed a significantly lower AUC than the Sham group 4, 8, 16 and 24 weeks post-operatively ($P < 0.01$, $P < 0.05$, $P < 0.01$, $P < 0.01$, respectively). In comparison with the baseline, AUC significantly decreased 4, 8, 16 and 24 weeks post-operatively (all $P < 0.01$) in the IT group but showed no significant changes in the Sham group at each post-operative time point (Figure 8).

Plasma GLP-1 levels

The IT group showed significantly higher plasma GLP-1 levels than the Sham group 4, 8, 16 and 24 weeks post-operatively (all $P < 0.01$). In comparison with the baseline, plasma GLP-1 levels significantly increased (all $P < 0.01$) in the IT group but showed

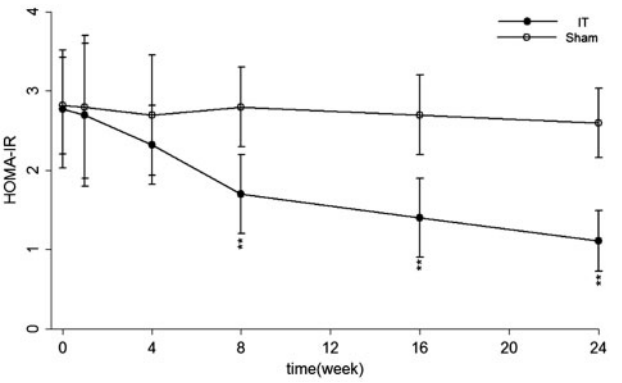

Figure 7. Changes in the homeostasis model assessment-insulin resistance (HOMA-IR) index after ileal transposition. *$P < 0.05$ and **$P < 0.01$, respectively, by paired samples t-test between the post-operative time point and baseline.

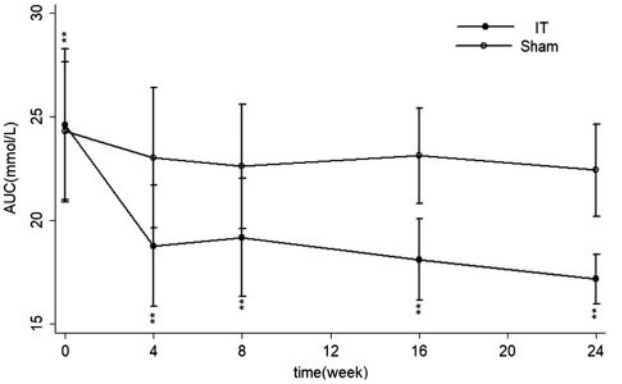

Figure 8. Changes in the area under the curve (AUC) of oral glucose tolerance tests (OGTTs) after ileal transposition. *$P < 0.05$ and **$P < 0.01$, respectively, by paired samples t-test between the post-operative time point and baseline.

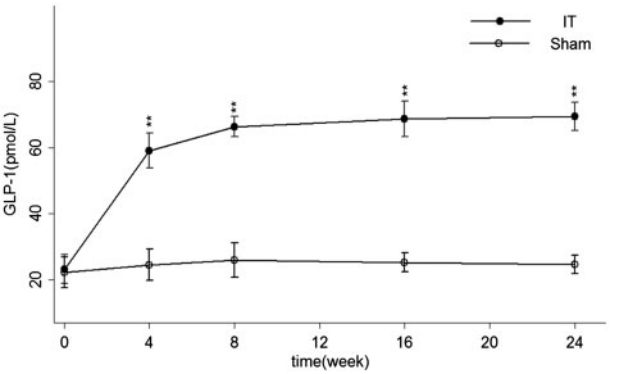

Figure 9. Changes in glucagon-like peptide-1 (GLP-1) after ileal transposition. *$P < 0.05$ and **$P < 0.01$, respectively, by paired samples t-test between the post-operative time point and baseline.

no significant changes in the Sham group at each post-operative time point (Figure 9).

Histological determination on GLP-1R

In comparison with Sham group, GLP-1R expression in the IT group was significantly higher in both the pancreas ($P < 0.01$) and the ileum ($P < 0.05$) 24 weeks post-operatively, regarding mRNA and protein expression (Figure 10).

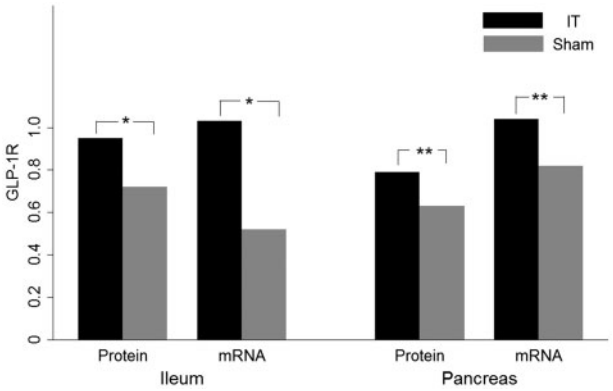

Figure 10. The expression of glucagon-like peptide-1 receptor (GLP-1R) in the ileum and pancreas 24 weeks after ileal transposition. A *P*-value indicated the differences by independent samples *t*-test between the IT and Sham groups. $^{*}P < 0.05$; $^{**}P < 0.01$.

Discussion

Alimentary tract surgery for T2DM has been referred to as either metabolic surgery [25, 26] or diabetes surgery [27]. The hindgut effect has been explored with ileal transposition, a simplified surgery model [8], which revealed improved insulin sensitivity [28], decreased endoplasmic reticulum stress in the fat, muscle, liver and pancreas [29], increased L-cell hormone secretion [19, 20], increased bile acid pool [20] and altered gut microbiota [29] as possible mechanisms of metabolic improvement. Many of these mechanisms could be linked to the effect of GLP-1 action [30]. The active form of GLP-1 potentiates oral glucose-induced insulin secretion [19, 20], inhibits glucagon secretion, decreases food intake, improves insulin sensitivity [29], promotes β-cell proliferation and prevents β-cell apoptosis [30, 31]. Oral, but not intravenous, glucose administration stimulates GLP-1 secretion [32]. Fasting plasma GLP-1 levels are low and increase approximately 2- to 3-fold after a meal [33] via an early (within 10–15 minutes) phase followed by a longer (30–60 minutes) second phase [32]. To the best of our knowledge, changes in plasma GLP-1 levels following IT are probably related to the second phase of oral glucose-stimulated GLP-1 secretion [34]; therefore, we determined GLP-1 levels 30 minutes after the OGTTs. In our study, compared with the Sham group, the IT group showed an over 2-fold increase in plasma GLP-1 about 30 minutes in the OGTT, similar to findings in other studies [19, 20, 30, 35].

Spontaneously non-obese diabetic GK rats have been widely used in research on MBS because these rats exhibit stable hyperglycemia, marked glucose intolerance, insulin resistance and impaired glucose-induced insulin secretion [36]. In non-obese diabetic rats (mostly in GK rats), ileal transposition decreased BG levels even without weight loss [9, 30, 37, 38], which was similar to our present findings, suggesting that some weight-independent mechanisms might play a role in the improvement of glucose homeostasis. As with the improvement in HOMA-IR present in the current study, the reported improved insulin sensitivity after ileal transposition was also not necessarily accompanied by a beneficial effect on bodyweight [8, 28]. Recent studies have suggested that increased energy expenditure [29], alleviated endoplasmic reticulum stress [29], browning of white adipose tissue [18] and decreased circulating endotoxin levels [8] might be related to the improved insulin sensitivity.

Most studies reported increased insulin secretion after ileal transposition and the increased GLP-1 might explain the improved β-cell function after ileal transposition [30]. In this possibility, the increased GLP-1 in our study might have promoted insulin secretion [19, 20], instead of the fact that the decreased insulin levels were observed. In addition, intriguingly, our present data showed that the 'delayed improvements' in FPG and HOMA-IR and decreased insulin levels were observed several weeks (>4 weeks) later than the increased GLP-1 and GT improvement, supporting the hypothesis that ileal transposition improves GT independently of insulin action [9]. Furthermore, GT improvement is widely observed after ileal transposition [9, 39], associated with reduced insulin levels as we obtained, rather than increased insulin levels [40], which suggested that it might probably be the GT improvement other than the increased GLP-1 expression that led to the subsequent improvement of insulin resistance.

Recently, the roles of GLP-1/GLP-1R signaling have been questioned. RYGB has exhibited improved glucose homeostasis in GLP-1R knockout mice [15, 16]. More and more evidence showed that signaling is not indispensable for diabetes remission after RYGB [15, 30]. Although hypersecretion of GLP-1 has been consistently observed after MBS [41], the amount of GLP-1 secretion is not correlated with diabetes remission [14]. Functional studies, designed to assess the roles of GLP-1 signaling, have produced mixed results. GLP-1R agonists, which provide pharmacological stimulation of the GLP-1R, recommended by the 2016 ADA in the treatment of poorly controlled T2DM [42], typically do not induce diabetes remission in T2DM patients. In addition, pharmacologic blockade of the GLP-1R after bariatric surgery greatly inhibits prandial insulin release [11–13]; however, the corresponding impairment in glycemia is modest, indicating that the contribution of endogenous GLP-1 to overall β-cell function after surgeries may be relatively minor [5]. Therefore, factors other than GLP-1 might be responsible for diabetic remission after RYGB. Furthermore, with ileal transposition models, in a study with non-obese non-diabetic rats, exendin (9–39), a GLP-1R antagonist, deteriorated GT in the Sham group, but not in the ileal transposition group [8], which suggests that non-GLP-1-mediated mechanisms might play a role in maintaining glucose homeostasis after ileal transposition. In our study on GK rats, ileal transposition increased GLP-1R expression in the pancreas 24 weeks post-operatively, accompanied by the decreased insulin levels, from which it could not be inferred that the increased GLP-1 directly improved the insulin action, namely improving β-cell function and decreasing β-cell apoptosis [43]. Further studies are required to define the role of GLP-1 in glucose metabolism after ileal transposition [30].

With ileal transposition, L-cells located in the transposed ileum are stimulated by ingested nutrients and L-cell hormones robustly increased after nutrient ingestion. Therefore, in our 'long-term' study, the expression of GLP-1R was increased in the transposed ileum as previously reported [20, 40, 44, 45]. Neither the impairing GLP-1-secreting ability ('jejunization') nor the fading effect of glucose homeostasis was observed in the transposed ileum 24 weeks after ileal transposition [21]. The role of GLP-1 in the recurrence of diabetic remission should be re-examined [22–24].

Our study presents several limitations. First, besides OGTTs, intravenous GT tests or insulin-tolerance tests should be performed to evaluate the action of incretin better. However, the excessive blood extractions that rats suffered from may cause more risks of death. Second, GLP-1R on the ileum and pancreas was only determined at 24 weeks post-operatively, not at baseline or other time points after surgery, which was proposed

to enhance the rate of survival for rats, but it may weaken our conclusion to a certain extent.

In summary, ileal transposition ameliorated glucose metabolism without reduction of weight or food intake in GK rats, which may be induced by the increased GLP-1 expression. However, the delayed improvement of insulin resistance, accompanied by decreased plasma insulin levels, might not directly result from the increased GLP-1.

Conflict of interest statement: none declared.

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