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

Hengliang Zhu1,2, Huaiming Wang3, Zhihai Zheng4, Bailiang Ye4, Xiaojiao Ruan4, Xiaofeng Zheng4 and Guoxin Li1,*

1Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China, 2Department of Gastrointestinal Surgery, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong, China, 3Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, China and 4Department of Gastrointestinal Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China

*Corresponding author. Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, China. Tel: +86-20-61648369; Email: gzliguoxin@163.com

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

Submitted: 10 January 2018; Revised: 4 March 2018; Accepted: 26 June 2018

© The Author(s) 2018. Published by Oxford University Press and Sixth Affiliated Hospital of Sun Yat-Sen University

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
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 Zucker 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 duodenal-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 × 0.5 + BG1h × 0.75 + BG2h × 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 jejenum 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...
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 ratspecific 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 \( P > 0.05 \)).

**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, \( P < 0.05 \).
In comparison with the baseline, F-ins significantly decreased at 8, 16 and 24 weeks post-operatively in the IT group ($P < 0.05$, $P < 0.01$, 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 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).
Recent studies have suggested that increased energy expenditure is accompanied by a beneficial effect on bodyweight [8, 28]. Insulin sensitivity after ileal transposition was also not necessarily present in the current study, the reported improvement of glucose homeostasis. As with the improvement in weight-independent mechanisms might play a role in the improvement of glycemia, marked glucose intolerance, insulin resistance and impaired glucose-induced insulin secretion [29]. When we determined GLP-1 levels 30 minutes after the OGTTs. In our study, 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 fasting 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 insulin 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 in different time points after surgery. 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 postoperatively, 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.

References
1. Schauer PR, Kashyap SR, Wolksi K. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012;366:1567–76.
2. Mingrone G, Panunzi S, De Gaetano A et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med 2012;366:1577–85.
3. Dixon JB, Le Roux CW, Rubino F et al. Bariatric surgery for type 2 diabetes. Lancet 2012;379:2300–11.
4. Cho YM. A gut feeling to cure diabetes: potential mechanisms of diabetes remission after bariatric surgery. Diabetes Metab J 2014;38:406–15.
5. Seeley RJ, Chambers AP, Sandoval DA. The role of gut adaptation in the potent effects of multiple bariatric surgeries on obesity and diabetes. Cell Metab 2015;21:369–78.
6. Sun X, Li F, Yang X et al. From genetics and epigenetics to the future of precision treatment for obesity. Gastroenterol Rep (Oxf) 2017;5:266–70.
7. Madsbad S, Dirksen C, Holst JJ. Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. Lancet Diabetes Endocrinol 2014;2:152–64.
8. Oh TJ, Lee HJ, Cho YM. Ileal transposition decreases plasma lipopolysaccharide levels in association with increased L cell secretion in non-obese non-diabetic rats. Obes Surg 2016;26:1287–95.
9. Tomasz S, Dominika S, Iwona KS et al. Long-term effect of ileal transposition on adipokine serum level in Zucker (orl)-lepr(fa) fatty rats. Obes Surg 2015;25:1848–57.
10. Cho YM, Fujita Y, Kieffer TJ. Glucagon-like peptide-1: glucose homeostasis and beyond. Annu Rev Physiol 2014;76:535–59.
11. Jimenez A, Casamitjana R, Viaplana-Masclans J et al. GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. Diabetes Care 2013;36:2062–9.
12. Jiménez A, Mari A, Casamitjana R et al. GLP-1 and glucose tolerance after sleeve gastrectomy in morbidly obese subjects with type 2 diabetes. Diabetes 2014;63:3372–7.
13. Salehi M, Gastaldelli A, D’Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. Gastroenterology 2014;146:669–80, e2.
14. Jiménez A, Casamitjana R, Flores L et al. GLP-1 and the long-term outcome of type 2 diabetes mellitus after Rouxen-Y gastric bypass surgery in morbidly obese subjects. Ann Surg 2013;257:894–9.
15. Mokadem M, Zechner HF, Margolseke RF et al. Effects of Rouxen-Y gastric bypass on energy and glucose homeostasis are preserved in two mouse models of functional glucagon-like peptide-1 deficiency. Mol Metab 2014;3:191–201.
16. Wilson-Perez HE, Chambers AP, Ryan KK et al. Vertical sleeve gastrectomy is effective in two genetic mouse models of glucagonlike Peptide 1 receptor deficiency. Diabetes 2013;62:2380–5.
17. Kota SK, Ugale S, Gupta N et al. Laparoscopic ileal interposition with diverted sleeve gastrectomy for treatment of type 2 diabetes. Diabetes Metabol Syndr 2012;6:125–31.
18. Ikezawa F, Shibata C, Kikuchi D et al. Effects of ileal interposition on glucose metabolism in obese rats with diabetes. Surgery 2012;151:822–30.
19. Strader AD, Vahl TP, Jandacek RJ et al. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab 2005;288:E447–53.
20. Kohli R, Kirby M, Sitchell KD et al. Intestinal adaptation after ileal interposition surgery increases bile acid recycling and protects against obesity-related comorbidities. Am J Physiol Gastrointest Liver Physiol 2010;299:G652–60.
21. Grueneberger JM, Karcz-Socha I, Sawczyn T et al. Systematic ileal transposition in Zucker rats shows advantage for long segment distal transposition. Surgery 2014;155:165–72.
22. DiGiorgi M, Rosen DJ, Choi JJ et al. Re-emergence of diabetes after gastric bypass in patients with mid- to long-term follow-up. Surg Obes Relat Dis 2010;6:249–53.
23. Jiang F, Zhu H, Zheng X et al. Duodenal-jejunal bypass for the treatment of type 2 diabetes in Chinese patients with an average body mass index < 24 kg/m². Surg Obes Relat Dis 2014;10:641–6.
24. Ruan X, Zhang W, Cai H et al. Sleeve gastrectomy with duode-nojejunal end-to-side anastomosis in the treatment of type 2 diabetes mellitus: the initial experiences in a Chinese population with a more than 4-year follow-up. Surg Obes Relat Dis 2017;13:1683–91.
25. Rubino F, Gagner M, Marescaux J. Surgical treatment of type 2 diabetes mellitus. Lancet 2001;358:668–9.
26. Patriti A, Facchiano E, Sanna A et al. The enteroinsular axis and the recovery from type 2 diabetes after bariatric surgery. Obes Surg 2004;14:840–8.
27. Rubino F. Is type 2 diabetes an operable intestinal disease? A provocative yet reasonable hypothesis. Diabetes Care 2008;31:829–6.
28. Culian DM, Albaugh V, Sun M et al. Ileal interposition improves glucose tolerance and insulin sensitivity in the obese Zucker rat. Am J Physiol Gastrointest Liver Physiol 2010;299:G751–60.
29. Cummings BP, Bettaieb A, Graham JL et al. Bile-acid-mediated decrease in endoplasmic reticulum stress: a potential contributor to the metabolic benefits of ileal interposition surgery in UCD-T2DM rats. Dis Model Mech 2013;6:443–56.
30. Oh TJ, Ahn CH, Cho YM. Contribution of the distal small intestine to metabolic improvement after bariatric/metabolic surgery: lessons from ileal transposition surgery. J Diabetes Investig 2016;7:94–101.
31. Abu-Hamadah R, Rabiee A, Meneilly GS et al. Clinical review: the extrapancreatic effects of glucagon-like peptide-1 and related peptides. J Clin Endocrinol Metab 2009;94:1843–52.
32. Herrmann C, Göke R, Richter G et al. Glucagon-like peptide-1 and glucagon-dependent insulin-releasing polypeptide plasma levels in response to nutrients. Digestion 1995;56:117–26.
33. Vilabol T, Krarup T, Deacon CF et al. Reduced postprandial concentrations of intact biologically active glucagon-like peptide-1 in type 2 diabetic patients. Diabetes 2001;50:609–13.
34. Roberge JN, Brubaker PL. Secretion of proglucagon-derived peptides in response to intestinal luminal nutrients. Endocrinology 1991;128:3169–74.
35. Strader AD, Clausen TR, Goodin SZ et al. Ileal interposition improves glucose tolerance in low dose streptozotocin-treated diabetic and euglycemic rats. Obes Surg 2009;19:96–104.
36. Yan Z, Chen W, Liu S et al. Myocardial insulin signaling and glucose transport are up-regulated in Goto-Kakizaki type 2 diabetic rats after ileal transposition. *Obes Surg* 2012;22:493–501.
37. Chen W, Xu Q, Xiao Y et al. Blockade of central GLP-1 receptors deteriorates the improvement of diabetes after ileal transposition. *Int J Med Sci* 2016;13:955–62.
38. Celik A, Cagiltay E, Ugale S et al. Diverted sleeve gastrectomy with ileal transposition in overweight, obese, and morbidly obese patients with type 2 diabetes: results of 1-year follow-up. *Surg Obes Relat Dis* 2016;12:541–9.
39. Nausheen S, Shah IH, Pezeshki A et al. Effects of sleeve gastrectomy and ileal transposition, alone and in combination, on food intake, body weight, gut hormones, and glucose metabolism in rats. *Am J Physiol Endocrinol Metab* 2013;305:E507–18.
40. Meier JJ, Gallwitz B, Salmen S et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2003;88:2719–25.
41. Miras AD, Le Roux CW. Mechanisms underlying weight loss after bariatric surgery. *Nat Rev Gastroenterol Hepatol* 2013;10:575–84.
42. Chamberlain JJ, Rhinehart AS, Shaefer CF et al. Diagnosis and management of diabetes: synopsis of the 2016 American Diabetes Association Standards of Medical Care in Diabetes. *Ann Intern Med* 2016;164:542–52.
43. Sun X, Zheng M, Song M et al. Ileal interposition reduces blood glucose levels and decreases insulin resistance in a type 2 diabetes mellitus animal model by up-regulating glucagon-like peptide 1 and its receptor. *Int J Clin Exp Pathol* 2014;7:4136–42.
44. Jorgensen NB, Dirksen C, Bojsen MKN et al. Exaggerated glucagon-like peptide 1 response is important for improved beta-cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. *Diabetes* 2013;62:3044–52.
45. Ramzy AR, Nausheen S, Chelikani PK. Ileal transposition surgery produces ileal length-dependent changes in food intake, body weight, gut hormones and glucose metabolism in rats. *Int J Obes* 2014;38:379–87.