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MINI REVIEW

Contribution of the distal small intestine to metabolic improvement after bariatric/metabolic surgery: Lessons from ileal transposition surgery

Tae Jung Oh[1,2], Chang Ho Ahn[2], Young Min Cho[2]*

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, and [2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

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***Correspondence**
Young Min Cho
Tel.: +82-2-2072-1965
Fax: +82-2-762-9662
E-mail address: ymchomd@snu.ac.kr

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ABSTRACT

Roux-en Y gastric bypass is a highly effective bariatric/metabolic surgical procedure that can induce robust weight loss and even remission of type 2 diabetes. One of the characteristic consequences of Roux-en Y gastric bypass is the expedited nutrient delivery to the distal small intestine, where L-cells are abundant and bile acid reabsorption occurs. To examine the role of the distal small intestine in isolation from other components of Roux-en Y gastric bypass, the ileal transposition (IT) surgery has been used in various rat models. IT relocates the distal ileal segment to the upper jejunum distal to the ligament of Treitz without any other alterations in the gastrointestinal anatomy. Therefore, IT exposes the distal ileal tissue to ingested nutrients after a meal faster than the normal condition. Although there is some inconsistency in the effect of IT according to different types of rat models and different types of surgical protocols, IT typically improved glucose tolerance, increased insulin sensitivity and induced weight loss, and the findings were more prominent in obese diabetic rats. Suggested mechanisms for the metabolic improvements after IT include increased L-cell secretion (e.g., glucagon-like peptides and peptide YY), altered bile acid metabolism, altered host–microbial interaction, attenuated metabolic endotoxemia and many others. Based on the effect of IT, we can conclude that the contribution of the distal small intestine to the metabolic benefits of bariatric/metabolic surgery is quite considerable. By unveiling the mechanism of action of IT, we might revolutionize the treatment for obesity and type 2 diabetes.

INTRODUCTION

The prevalence of type 2 diabetes has increased to an unforeseen level in accordance with rapid lifestyle changes including excessive calorie intake and decreased physical activity. According to 2010 statistics, 285 million people worldwide have diabetes, and the number is expected to increase up to 439 million by 2030[1]. Unfortunately, there is no cure for type 2 diabetes, and therefore patients with type 2 diabetes have to take antidiabetes medications for their lifetime. However, bariatric/metabolic surgery has been shown to induce remission (but not cure) of type 2 diabetes in addition to excellent weight reduction[2]. Intriguingly, diabetes remission often takes place well before significant weight loss occurs after bariatric surgery, from which the concept of metabolic surgery has emerged[3]. Although bariatric/metabolic surgery is the most effective treatment for obesity and diabetes, its invasive and irreversible nature prevents widespread clinical application. If the mechanism of diabetes remission after bariatric/metabolic surgery is unveiled, medical therapy might replace the surgery. In the present article, we reviewed the role of the distal small intestine in metabolic improvement after bariatric/metabolic surgery based on the results of experimental ileal transposition (IT) surgery.

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DISTAL SMALL INTESTINE HYPOTHESIS

Roux-en Y gastric bypass (RYGB) is the standard bariatric/metabolic surgical procedure at present. RYGB is characterized by restricted stomach volume; bypass of most of the stomach, entire duodenum and upper jejunum; and expedited delivery of unabsorbed nutrients to the distal small intestine[3,4]. Because L-cells

are abundant in the distal small intestine, and L-cell hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) have beneficial roles for glucose homeostasis and weight loss[5], the effect of bariatric/metabolic surgery could be explained by increased stimulation of L-cells. Formerly, the hindgut hypothesis was suggested as a mechanism of diabetes remission after bariatric/metabolic surgery, emphasizing the role of L-cell hormones[6]. Because the role of the colon and rectum, which constitute the embryologically-defined hindgut, in diabetes remission is unclear, and the distal small intestine hypothesis would be a more correct term than the hindgut hypothesis. Among L-cell hormones, GLP-1 was regarded as the key hormone explaining diabetes remission after bariatric/metabolic surgery. Indeed, hypersecretion of GLP-1 has been consistently observed after bariatric/metabolic surgery, except for purely restrictive procedures (e.g., adjustable gastric banding)[7]. However, GLP-1 receptor agonists, which provide pharmacological stimulation of the GLP-1 receptor, typically do not induce diabetes remission or dramatic weight loss in patients with type 2 diabetes. In addition, the amount of GLP-1 secretion in obese type 2 diabetes patients who showed diabetes remission after RYGB was similar to that found in such patients who did not reach diabetes remission[8]. In addition, GLP-1 receptor signaling is not required for weight loss[9] or diabetes remission[10] after RYGB in rodents. Therefore, factors other than GLP-1 might be responsible for diabetes remission and weight loss after RYGB.

ILEAL TRANSPOSITION

IT is an experimental surgical procedure to investigate the role of the distal ileum in weight loss and diabetes remission after RYGB[11]. IT translocates the distal ileal segment with intact mesentery to the upper jejunum distal to the ligament of Treitz (Figure 1), which enables ingested nutrients to rapidly reach the distal ileal tissue. There is no other alteration in the gastrointestinal anatomy, except the translocated distal ileum. Interestingly, the length of the transposed ileal segment and the observation duration after surgery might have an influence on the surgical outcomes, which need to be taken into account when interpreting the results of IT surgery. For example, in Sprague–Dawley (SD) rats, a non-obese non-diabetic rodent model, IT surgery with a longer segment (20 cm) and a longer follow up (8 weeks)[12] showed a significant improvement in glucose tolerance, whereas IT surgery with a shorter segment (10 cm) and a shorter follow up (4 weeks) did not improve glucose tolerance[13]. IT surgery has been carried out in various animal models encompassing normal glucose tolerance to overt diabetes and normal bodyweight to obesity. Table 1 summarizes major findings of each animal study carried out with IT.

EFFECT OF ILEAL TRANSPOSITION

Food Intake and Bodyweight

In our study with non-obese non-diabetic SD rats[13], IT decreased food intake for 2 weeks after surgery compared with sham surgery. After 2 weeks, food intake of IT-operated rats was gradually recovered to a similar degree to that of sham-operated rats. The biphasic response in food intake after IT was also reported by other researchers[12,14]. It is conceivable that the anorexigenic effect of IT might be compensated by other factors soon after the surgery. Of note, in obese diabetic rats, food intake was not changed after IT surgery (Table 1), which suggests that obese diabetic rats are resistant to the anorexigenic

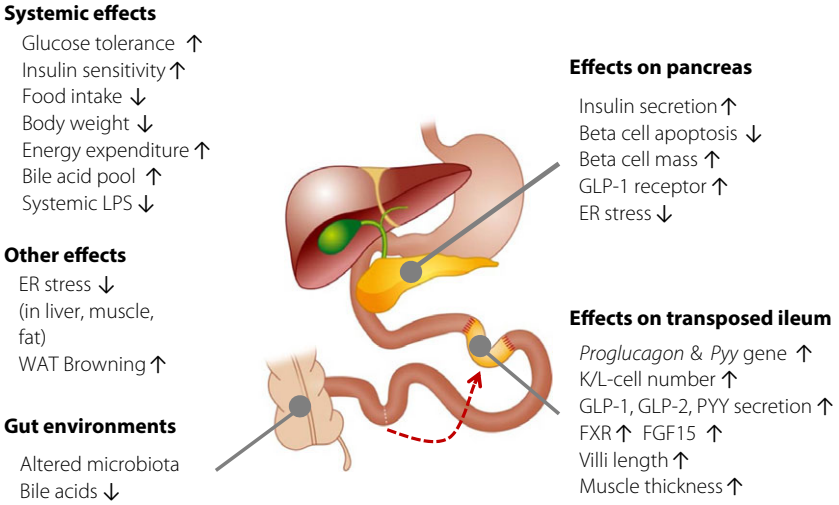

Figure 1 | Schematic illustration of the ileal transposition surgery and summary of its effects. A distal ileal segment is repositioned in the upper jejunum by the surgery (arrow). Some effects shown in this figure were inconsistent among studies. Please refer to the text for details. ER, endoplasmic reticulum; FGF15, fibroblast growth factor 15; FXR, farnesoid X receptor; GLP, glucagon-like peptide; LPS, lipopolysaccharide; PYY, peptide YY; WAT, white adipose tissue.

Table 1 | Summary of the effect of ileal transposition

Reference	Animal	Length/ duration†	Bodyweight‡	Food intake‡	Glucose/insulin secretion§/ insulin sensitivity¶	GLP-1/GIP/PYY	Comments
I. Non-obese, non-diabetes model							
Am J Physiol Endocrinol Metab 2005[11]	Long-Evans rat on a high-fat	10 cm/6 weeks	Reduced	Reduced	→/→/↑	↑/NR/↑	↑ Proglucagon and *PYY* gene expression in the transposed ileum
Surgery 2007[21]	SD rat	10 cm/5 months	No change	No change	↓/↑/↑	→/NR/NR	
Obes Surg 2009[42]	Long-Evans rat	10 cm/12 weeks	No change	NR	↓/↑/NR	↑/→/↑	↑ Plasma bile acid ↑ Plasma glucagon levels
Am J Physiol Endocrinol Metab 2013[12]	SD rat	20 cm/7 weeks	Reduced	Reduced	↓/→/↑	↑/↓/↑	↑ *PYY* gene expression in the transposed ileum with ↑ GLP-1 or PYY positive cells
Diabetes 2013[25]	Wistar rat	10 cm/7 months	No change	No change	→/↑/NR	↑/NR/NR	↑ Plasma bile acid ↑ Proglucagon and *FXR* gene expression in the transposed ileum
Int J Obes 2014[20]	SD rat	5, 10, 20 cm/4 weeks	Reduced	Reduced	↓/→/NR	↑/NR/↑	↑ Proglucagon and *PYY* gene expression in the transposed ileum with ↑ GLP-1 or PYY positive cells ↓ Plasma leptin levels
Obes Surg 2015[13]	SD rat	10 cm/4 weeks	Reduced	Reduced	↓/↑/↑	↑/→/↑	↓ Plasma lipopolysaccharide levels
II. Non-obese, diabetes model							
Surgery 2007[21]	GK rat	10 cm/5 months	No change	No change	↓/↑/↑	→/NR/NR	↑ Proglucagon gene expression in the transposed ileum
Ann Surg 2008[43]	GK rat	8 cm/24 weeks	Reduced	NR	↓/↑/↑	↑/NR/NR	
Obes Surg 2009[42]	STZ treated Long-Evans rat	10 cm/12 weeks	No change	NR	↓/→/→	NR/NR/NR	
Exp Ther Med 2013[16]	GK rat	10 cm/ 4 weeks	Reduced	Reduced	↓/↑/↑	NR/NR/NR	↑ *TCF7L2* gene expression in the pancreas
Int J Clin Exp Pathol 2014[15]	GK rat	10 cm/4 weeks	Reduced	Reduced	↓/↑/↑	↑/NR/NR	↑ *GLP-1R* expression in the pancreas and ↓ pancreatic beta cell apoptosis
III. Obese, diabetes model							
Surgery 2012[18]	OLETF rat	15 cm/10 weeks	No change	No change	↓/→/↑	→/→/↑	↑ UCP-1 expression in the brown adipose tissue
Am J Physiol Gastrointest Liver Physiol 2010[44]	Zucker rat	10 cm/8 weeks	Reduced	No change	↓/→/↑	↑/↓/NR	↑ Plasma bile acid levels and improved muscle glucose uptake

Table 1 (*Continued*)

Reference	Animal	Length/ duration†	Bodyweight‡	Food intake‡	Glucose/insulin secretion§/ insulin sensitivity¶	GLP-1/GIP/PYY	Comments
Am J Physiol Gastrointest Liver Physiol 2010[14]	DIO rat	10 cm/6 weeks	Reduced fat mass	No change	↓/NR/NR	NR/NR/NR	↑ Plasma bile acid, Jejunization of the transposed ileum with increased GLP-1 positive cells
Gastroenterology 2010[45]	UCD-T2DM rat	10 cm/8 weeks	No change	No change	↓/↑/↑	↑/→/↑	↑ Plasma bile acid
J Surg Res 2012[22]	DIO rat	10 cm/6 weeks	No change	No change	↓/NR/NR	NR/NR/NR	
Dis Model Mech 2013[17]	UCD-T2DM rat	10 cm/4 months	No change	No change	↓/↑/↑	↑/→/↑	↑ Plasma bile acid ↑ Cecal *Gammaproteobacteria* ↓ ER stress in liver, fat, muscle, and pancreas
Videosurgery 2013[46]	Zucker rat	15 cm/3 weeks	Reduced	NR	↓/↑/NR	↑/NR/↑	
Surgery 2014[47]	Zucker rat	10, 20 cm/6 months	Reduced	NR	↓/→/NR	↑/NR/NR	Ileal transposition with a longer and more distal segment induced more metabolic improvement

†Length of the transposed ileum and the duration of postoperative observation. ‡Bodyweight and food intake compared to the sham operation group. §Insulin secretion estimated by the oral or intraperitoneal glucose tolerance test. ¶Insulin sensitivity estimated by the insulin tolerance test, homeostatic model assessment for insulin resistance or Matsuda index. DIO, diet-induced obesity; GIP, glucose-dependent insulinotropic polypeptide; GK, Goto-Kakizaki; GLP-1, glucagon-like peptide-1; NR, not reported; OLETF, Otsuka Long-Evans Tokushima Fatty; PYY, peptide YY; SD, Sprague–Dawley; STZ, streptozotocin; UCD-T2DM, University of California at Davis type 2 diabetes mellitus.

effect of IT surgery seen in non-obese non-diabetic or obese non-diabetic rats.

The bodyweight of rats that underwent IT was lower than or similar to sham controls regardless of metabolic status (Table 1). However, most studies carried out with obese rats reported lower bodyweight in the IT group than in the sham group (Table 1), which might contribute to improved glucose homeostasis and insulin sensitivity in these animals. However, in some obese diabetic rats, IT surgery resulted in a lower bodyweight than sham surgery (Table 1), which indicates a possible increase in energy expenditure or decrease in energy acquisition.

Glucose Tolerance

As shown in Table 1, IT surgery improved glucose tolerance in obese or non-obese diabetic rats. Interestingly, in non-obese diabetic rats (mostly in Goto–Kakizaki [GK] rats), IT decreased blood glucose levels even without any significant effect on bodyweight, which suggests that some weight-independent mechanisms might play a role in the improvement of glucose homeostasis. Furthermore, in some studies with non-obese non-diabetic rats, IT decreased glucose levels, which underpins the important role of the distal small intestine in glucose homeostasis.

Insulin Secretion and Insulin Sensitivity

In our study with non-obese non-diabetic SD rats, the incremental area under the curve of the plasma insulin level during the oral glucose tolerance test was higher in the IT group than the sham group[13]. Most studies shown in Table 1 reported increased insulin secretion after IT surgery regardless of the metabolic status of the rats. Increased GLP-1 might explain the improved β-cell function after IT surgery. Intriguingly, in GK rats, IT surgery increased GLP-1 receptor[15] and TCF7L2[16] expression in the pancreas, and decreased β-cell apoptosis[15], which could be additional mechanisms of improved β-cell function after IT surgery.

Despite modest discrepancies among studies, improved insulin sensitivity was reported in non-obese non-diabetic rats, non-obese diabetic rats and obese diabetic rats (Table 1). Furthermore, improved insulin sensitivity after IT surgery was not necessarily accompanied by a beneficial effect on bodyweight.

Therefore, some weight-independent mechanisms might contribute to the improved insulin sensitivity. Although the exact mechanisms are still elusive, recent studies suggested that increased energy expenditure[17], browning of white adipose tissue[18], alleviated endoplasmic reticulum stress[17] and decreased circulating endotoxin levels[13] might be related to the improved insulin sensitivity.

Gut Hormones and Glucagon

L-cells, which produce GLP-1, GLP-2 and PYY, are predominantly expressed in the distal ileum[5]. With IT surgery, L-cells located in the transposed ileum are stimulated by ingested nutrients in a very rapid manner. Therefore, L-cell hormones robustly increased after nutrient ingestion in the IT surgery group compared with the sham surgery group (Table 1). In addition, gene expression of L-cell hormones[11,12,19–21] and the L-cell number were increased in the transposed ileum[14].

As we discussed earlier in the present review, the role of GLP-1 receptor signaling is not indispensable for diabetes remission after RYGB. With IT models, the role of GLP-1 receptor signaling was investigated by using exendin$_{9\text{-}39}$, a GLP-1 receptor antagonist. In diet-induced obese rats, exendin$_{9\text{-}39}$, abolished the improvements in glucose tolerance created by IT surgery[22]. However, in our study with non-obese non-diabetic rats, exendin$_{9\text{-}39}$ deteriorated glucose tolerance in the sham group, but not in the IT group[13], which suggests that non-GLP-1-mediated mechanisms might play a role in maintaining glucose homeostasis after IT surgery. Further studies are required to examine the role of GLP-1 in glucose metabolism after IT surgery.

K-cells, which produce glucose-dependent insulinotropic polypeptide (GIP), are mainly located in the duodenum and upper jejunum[23]. After IT surgery, nutrient exposure to some part of the K-cell-rich upper jejunum is delayed because of the intervening ileal segment. As such, we observed that the plasma total GIP level early after oral glucose administration was more decreased in the IT group than in the sham group, whereas the area under the curve of plasma total GIP levels during the oral glucose tolerance test was comparable between the two groups[13]. A small delay in GIP secretion after IT surgery appears to have little to do with glucose metabolism.

After RYGB, glucagon secretion is paradoxically increased, despite marked improvement of glucose tolerance and robust increase in GLP-1, a glucagonostatic hormone[5]. However, the mechanism and source of hyperglucagonemia after RYGB are still unclear. As hyperglucagonemia is clearly seen after IT surgery[13], the distal ileum stimulated by nutrients must have critical roles in hypersecretion of glucagon after RYGB.

Bile Acids

Circulating bile acid pool increases after RYGB[24], which denotes the possible role of bile acids in metabolic improvements after RYGB. As the distal small intestine, which is equipped with bile acid transporters, is the major site of intestinal bile acid reabsorption, IT surgery would be a good model to examine the role of the distal ileum in altered bile acid metabolism after RYGB. In rats with IT surgery, the intraluminal bile acid content is remarkably decreased starting from the transposed ileal segment all the way down to the colon, whereas fasting and postprandial serum bile acid pool is increased[14]. In this experiment, the expression of hepatic Cyp27A1, the key regulator of the alternative pathway of the bile acid production, decreased in the IT group, whereas the hepatic expression of Cyp7A1, the key regulator of the classical pathway of bile acid synthesis, did not change[14], which suggests that the increased bile acid reabsorption is the principal mechanism of increased serum bile acid pool after IT surgery. Farnesoid X receptor (FXR), a nuclear receptor that is activated by bile acids, regulates bile acid and fuel metabolism. Expression of FXR increased in the intestine, but not in the liver, in male Wistar rats that underwent IT surgery[25]. In the intestine, FXR induces fibroblast growth factor 15 (19 for the human ortholog)[25], which inhibits hepatic gluconeogenesis[26]. In addition, FXR signaling is critical in conveying the metabolic and weight loss effect of vertical sleeve gastrectomy (VSG), another highly effective bariatric/metabolic surgery, in mice[27]. However, it needs to be elucidated if FXR signaling is required for the metabolic and weight benefit of IT surgery.

Gut Microbiota

A large body of evidence suggests that altered host–microbial interaction has an important role in obesity and diabetes[28]. In mice, RYGB surgery induced a marked change in gut microbiota compared with sham surgery[29]. When cecal content of the RYGB- or sham-operated rats were transferred to germ-free mice, bodyweight and fat mass were lower in the recipients of the RYGB cecal content than the recipients of sham cecal content[29]. Therefore, altered gut microbiota might be causally related to weight loss after RYGB. Both VSG[27] and RYGB[29] were associated with an increase of *Gammaproteobacteria*. Similarly, compared with sham surgery, IT surgery increased the proportion of *Gammaproteobacteria*[17]. Hence, RYGB, VSG and IT seem to induce a similar change in gut microbiota. Alterations in bile acid metabolism[30] and short chain fatty acid composition[29] by different gut microbiota might be related to metabolic changes after bariatric/metabolic surgery. However, further studies are still required.

Intestinal Histology

The intestine is a highly plastic organ, which has an ability to adapt to the internal and external environment[31]. It was reported that some bariatric/metabolic surgery induced histological change in the intestine. For example, duodenal jejunal bypass induced hyperplasia of the jejunum attached to the stomach in Zucker fatty rats[32], but not in non-obese diabetic GK rats[33]. The transposed ileum underwent a so-called jejunization process that is characterized by increased villi length

and muscle thickness in rats[13,14]. In a human study using mucosal biopsy, RYGB brought considerable changes in gene or protein expression of numerous gut hormones in the alimentary limb, biliopancreatic limb and common limb[34]. Duodenal jejunal bypass increased the density of K/L cells that co-express GIP and GLP-1 in the attached jejunum in GK rats[33]. The K/L cell density in the transposed ileum was also increased by IT surgery in SD rats[13]. However, it is unknown whether histological changes brought by IT confer metabolic benefits.

Metabolic Endotoxemia

Lipopolysaccharide (LPS) or endotoxin is a structural molecule constituting the cell wall of Gram-negative bacteria. LPS binds to toll-like receptor 4 and activates innate immunity. LPS can be detected in humans with no apparent bacteremia, and increased LPS levels in the circulation have been reported to be associated with type 2 diabetes[35], metabolic syndrome[36] and cardiovascular disease[36]. Chronic exposure of low-level LPS resulted in glucose intolerance, insulin resistance and increased expression of inflammatory cytokines in mice[37]. This low-level chronic endotoxemia is known as "metabolic endotoxemia" in contrast to a massive increase in circulating LPS levels found in sepsis[37]. Interestingly, plasma LPS levels in obese subjects can be decreased after bariatric surgery[38]. We found that IT surgery decreased fasting plasma LPS levels in non-obese non-diabetic rats[13]. In our study, fasting plasma LPS levels were well correlated with the degree of insulin resistance[13]. In addition, the plasma LPS levels were significantly correlated with both plasma GLP-2 and PYY levels, but not with plasma GLP-1 levels[13]. Because both GLP-2[39,40] and PYY[41] have a tropic effect on the intestinal epithelium, increased secretion of GLP-2 and PYY after IT surgery might prevent LPS translocation from the gut lumen to the circulation, possibly by modulating gut permeability. Taken together, decreased metabolic endotoxemia could be a mechanism explaining the metabolic benefit after IT or other bariatric/metabolic surgery.

SUMMARY AND CONCLUSIONS

The effect of expedited nutrients delivery to the distal small intestine after RYGB has been extensively examined through the IT surgery model in rats. Although heterogeneity exists between different types of rat models and different types of surgical protocols, the common findings of IT encompass improved glucose tolerance, increased insulin sensitivity and weight loss, which are more prominent in obese diabetic rats. The mechanisms for the metabolic improvements might include increased L-cell secretion, altered bile acid metabolism, altered host-microbial interaction, attenuated metabolic endotoxemia and many others, as listed in Figure 1. It is uncertain, however, whether a single factor secreted from or expressed in the distal small intestine might reproduce all the metabolic benefit induced by IT or all the aforementioned mechanisms in concert. Nevertheless, the contribution of the distal small intestine in metabolic benefits of bariatric/metabolic surgery appears to be considerable, which should be the major target of research to revolutionize the treatment for obesity and type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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