Review

Not peer-reviewed version

Reappraisal of Duodenal Exclusions and Biliopancreatic Limb Length in Metabolic Surgery for Nonobese Patients with Type 2 Diabetes

Kyung Yul Hur *

Posted Date: 19 September 2023

doi: 10.20944/preprints202309.1188.v1

Keywords: metabolic surgery; type 2 diabetes; postoperative hyperglycemia; duodenal exclusion; biliopancreatic limb length; altered epithelial identity; GIP

Review

Reappraisal of Duodenal Exclusions and Biliopancreatic Limb Length in Metabolic Surgery for Nonobese Patients with Type 2 Diabetes

Kyung Yul Hur

Soonchunhyang University Hospital, 59- Daesagwan-ro, Yongsan-gu, Seoul 04401, Republic of Korea; hurusa@naver.com

Abstract: Metabolic surgery can promote comprehensive physiological improvements to alleviate metabolic disorders, particularly for patients with type 2 diabetes. Nevertheless, the therapeutic scope is limited owing to unexpectedly inconsistent surgical outcomes. This study aimed to overcome these obstacles by determining the fundamental mechanism underlying the conflicting outcomes. The surgical anatomy, clinical course, and outcomes of various metabolic surgeries, including modified duodenal–jejunal bypass (DJB) procedures, were compared to understand the specific surgical patterns from different perspectives. Patients from a nonobese group were included to prevent confounding effects from overweight patients with type 2 diabetes. Following an intestinal anastomosis, the epithelial identity of the succeeding intestine was replaced by that of the proximal epithelium owing to altered crosstalk between the epithelium and opposing mesenchymal cells. Subsequent intestinal compensatory proliferation and a rapid turnover rate accelerated the propagation of the replaced epithelium. The main factors contributing to inconsistent outcomes of metabolic surgery are inadequate duodenal exclusions and an inappropriate biliopancreatic limb length.

Keywords: metabolic surgery; type 2 diabetes; postoperative hyperglycemia; duodenal exclusion; biliopancreatic limb length; altered epithelial identity; GIP

1. Introduction

Metabolic surgery is a powerful treatment option for patients with type 2 diabetes. However, the therapeutic scope is limited because the underlying mechanism for inconsistent operational outcomes is yet to be determined. Two distinct factors are associated with the development of type 2 diabetes. These factors include toxicity from excessive adipose tissue in overweight individuals and an imbalanced release of gut hormones such as incretins. The main challenge lies in understanding the mechanism behind the altered hormonal release from the gastrointestinal tract rather than the issue of being overweight. Treating imbalances in gut hormones involves rerouting the intestines and identifying the major target hormones responsible for metabolic changes.

It is crucial to determine the mechanism contributing to the recurrence of symptoms several months after surgery [1]. A study examining the density and hormonal gene expression of small intestinal enteroendocrine cells revealed several changes in the distribution of these cells following a Roux-en-Y gastric bypass (RYGB) [2]. These findings suggest a link between the development of postoperative hyperglycemia and the altered distribution of enteroendocrine cells following surgery. Therefore, we investigated the mechanism that maintains the spatiotemporal identity of the intestinal epithelium and the factors contributing to alterations in the distribution of enteroendocrine cells and the expression of hormonal genes. Various metabolic surgeries, including modified DJB procedures, were compared based on the surgical anatomy, clinical course, and outcomes to understand the specific surgical patterns that lead to conflicting results. Nonobese patients were included to avoid confounding weight-loss variables from overweight individuals.

 doi:10.20944/preprints202309.1188.v1

2. Physiology of Intestinal Epithelial Regeneration and Identity Alteration

The intestinal epithelium is continuously replaced at high rates [3]. Different structures of epithelial tissue and unique types of epithelial cells within each site enable the distinct digestive functions necessary for efficient nutritional assimilation [4]. The modeling of the intestinal epithelium depends on two-way communication between the epithelial and mesenchymal cells, which is mediated by signaling pathways [3]. Following the loss of the functional epithelial area through resections or bypasses, the remaining intestine undergoes morphological and functional adaptive compensatory responses. The distribution of enteroendocrine cells and their transcriptional activity in the remaining intestine changes [2]. The proximal intestinal epithelial lineage is transferred to the distal intestine. Recent advances in single-cell RNA sequencing have revealed that the distal small-intestinal epithelium undergoes regional reprogramming to acquire a proximal identity after proximal small-bowel resections [5]. Thus, the general appearance of the Roux limb in a pylorus-preserving DJB resembles the duodenum [6].

The crosstalk between epithelial and opposing subepithelial mesenchymal cells in the anastomosis area facilitates reprogramming the epithelial cellular identity [7]. An intestinal anastomosis performed to maintain continuity after a bypass or resection modifies the site-specific epithelial identity. It can be a causal factor for inconsistent outcomes in metabolic surgery.

The rapid turnover rate of the intestinal epithelium and compensatory proliferation facilitate the spread of an altered identity to the distal intestinal epithelium. However, the clinical effect of epithelial replacement remains unclear. The region-specific functions of enteroendocrine cells in different parts of the intestine lead to metabolic changes over time after sufficient proliferation. The type and density of enteroendocrine cells distributed at the distal end of the preceding bowel modify the epithelial identity of the subsequent section of the digestive tract.

3. Altered Identity of the Roux Limb and Common Channel in the Alimentary Tract

As the duodenum is located immediately after the pyloric sphincter, a small portion of the duodenum connected to the stomach is always exposed to the nutrients of patients who have undergone a pylorus-preserving DJB. The pylorus-preserving procedure ensures direct nutrient contact with the remaining duodenal tissue at the anastomotic site. The counterparts of an alimentary Roux-limb anastomosis in a DJB are either the pyloric portion of the stomach or the first duodenal portion. These represent the gastrojejunal and duodenal–jejunal anastomoses, respectively. A duodenal–jejunal anastomosis is designed to preserve the pyloric sphincter function, although the postoperative clinical courses of the two procedures differ. In a pylorus-preserving DJB surgery group, there was a tendency toward high blood glucose concentrations, which led to unsatisfactory outcomes [6,8–14]. In contrast, recurrent hyperglycemia was rarely detected in a gastrojejunostomy group, which yielded favorable outcomes [15–19].

These results suggest that the remaining duodenal epithelium attached to the pyloric sphincter may trigger recurrent hyperglycemia. The question remains whether the exposed area of the duodenal epithelium is too small to induce hyperglycemia. A possible mechanism could be demonstrated by comparing the different modified forms of DJBs. Commonly modified DJBs include pylorus-preserving DJBs, conventional (pylorus exclusion) DJBs, and endoscopic DJB liners (DJBLs); each method exhibits unique characteristics. Distinct changes in blood glucose levels are observed in pylorus-preserving DJBs. In most cases, blood glucose levels decrease 2–3 months after surgery; an increase follows this. DJBLs scarcely increase blood glucose values if a liner is in place, despite exposure to nutrients such as those from pylorus-preserving DJBs. As exposure to the first portion of the duodenal epithelium influences inconsistent outcomes, another factor may be responsible for the recurrence of DJBLs. Different from DJBLs, surgical DJBs involve an anastomosis procedure. When considering whether an anastomosis is a determinant of recurrence, another factor may contribute to recurrent hyperglycemia in conventional DJBs. Based on these results, it can be concluded that hyperglycemia is associated with the simultaneous nutritional exposure of the first portion of the duodenal epithelium and the accompanying anastomosis procedure.

 doi:10.20944/preprints202309.1188.v1

Studies on the outcomes of transpositions elsewhere in the intestine—such as the transposition of the ileal segment to the jejunal area, jejunal segment to the ileal site, duodenal segment to the ileal area, and vice versa—have been conducted to evaluate the epithelial changes in the intestine. The common features of the adaptations are as follows: when the ileal segment is transposed to the jejunal area, the sizes of the villi increase to a similar extent as the jejunal villi; when the jejunal segment is transposed to the ileal site, the villi shrink to a length likely to be similar to the ileal villi; and when the duodenal segment is anastomosed with the ileum, the villus of the ileum increases in size to the extent of the duodenum [20]. There is no mobile mesentery with duodenal fixations in the retroperitoneum; the distal ileum is brought into the right upper abdominal cavity, ensuring that the duodenum remains in place before creating the anastomosis. Incidentally, the final configuration may resemble that of a pylorus-preserving DJB. Based on these findings, it is evident that the proximal intestinal epithelium migrates to the opposing distal intestinal area via the anastomotic site. The underlying mechanisms for these outcomes likely occur through altered crosstalk between the opposing epithelial and mesenchymal cells exposed to the cutting edge. A subsequent identity alteration of the intestinal epithelium is a plausible assumption, although no definite supporting evidence exists.

4. The Diabetogenic Role of Glucose-Dependent Insulinotropic Peptide (GIP) Compared with the Length of the Biliopancreatic (BP) Limb

Jejunojejunostomy, another surgical anastomosis used in the DJB procedure, is not exempt from identity changes. Similar to the mechanism above, the epithelial identity of the common limb is affected by that of the distal end of the BP limb. The density of GIP-releasing K cells decreases from the duodenum to the terminal ileum [21]. Therefore, the shorter the BP limb, the higher the density of K-cells at the cutting end of the BP limb should expected. A recent investigation of GIP protein contents within the intestine's separated anatomical segments, mediated by gastrointestinal surgery, characterized significantly increased GIP protein contents in the mid-jejunum [13]. This was possibly induced by an insufficient length of the BP limb, which provoked K-cell proliferation.

Although there is ongoing debate regarding the role of GIP in diabetes, an increase in GIP concentration after surgery is inversely correlated with diabetes remission [22]. The upregulation of Glucagon-like peptide-1(GLP-1) and downregulation of GIP are typical features of the biliopancreatic diversion (BPD) procedure, which is most effective in improving type 2 diabetes. Notably, the surgical aspect of the BPD procedure is characterized by the complete exclusion of the duodenum and the long BP limb [23]. Although the primary function of the long BP limb is to separate nutrients from the BP limb to the high-density K-cell area, another function is to reduce K-cell proliferation in the subsequent common-channel limb. According to recent reports on the importance of the BP limb in metabolic surgery, the beneficial effects of DJBs disappeared after BP limb excisions in rats with improved hyperglycemia that underwent DJBs with a long BP limb [24], suggesting additional function of the long BP limb.

5. Inconsistent Postoperative GIP Values after RYGB [12]

Even though there are a lot of debates regarding the factors that may affect changing GIP values after RYGB, there appear to be correlations between metabolic outcomes, BP limb length, and postoperative GIP changes. Unlike GLP-1, GIP is considered a hormone targeted by the foregut hypothesis, as it leads to hyperglycemia instead of insulin secretion. Evidence continues to be discovered supporting the hypothesis that a sufficient length of the BP limb enhances the effects of surgery. The mechanism underlying this hypothesis is concomitantly associated with changes in GIP concentration and the enteroendocrine cells responsible for GIP secretion. Ultimately, lengthening the BP limb reduces the number of K cells in contact with nutrients, resulting in decreased GIP secretion and improved outcomes. It can be inferred that the postoperative decreased secretion of GIP and the BP limb length are proportional. However, the comparison would only be accepted by excluding other factors that impact GIP alterations, such as the incomplete exclusion of the duodenum from nutritional exposure and weight fluctuations in overweight subjects. Table 1 [23,25–

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 September 2023 doi:10.20944/preprints202309.1188.v1

28] demonstrates the propensity for an inverse correlation between postoperative GIP changes and the BP limb length ratio. Surgical patients without obesity were eligible; pylorus exclusions were performed in every case, including RYGBs, classic BPDs, and one anastomosis gastric bypass (OAGB).

One of the major determinants of inconsistent GIP values after RYGB is the length of the BP limb. A shorter BP limb has been associated with an increased GIP concentration compared with the preoperative level, whereas a longer BP limb has been associated with a decreased concentration. The presumed inflection point was 100 cm from Treitz's ligament [29].

Table 1. Postoperative GIP alterations and length of BP limb in patients who underwent bypass surgery with total duodenal exclusions.

Operation	AUC GIP Before Operation	AUC GIP After Operation	GIP Alteration * (%)	BP Limb (cm)	Reference
BPD	3297.0 pmol/L	1874.0 pmol/L	56	≥ 250**	Guidone et al. [23]
RYGB	48.67 ng/L^{-1}·min^{-1}	51.56 ng/L^{-1}·min^{-1}	105	30	Laferrère et al. [25]
RYGB	50.96 pmol^{-1}·L^{-1}·min^{-1}	52.66 pmol^{-1}·L^{-1}·min^{-1}	103	40	Laferrère et al. [26]
RYGB	30.2 ng/dL·10 min	27.0 ng/dL·10 min	90	100	Fellici et al. [27]
OAGB	184.0 pg/mL·min^{-1}	98.0 pg/mL·min^{-1}	53	200	Kim et al. [28]

RYGB: Roux-en-Y gastric bypass; OAGB: one anastomosis gastric bypass; BPD: biliopancreatic diversion; BP limb: biliopancreatic limb; GIP: glucose-dependent insulinotropic polypeptide; AUC: area under the curve; * GIP alteration (%) = $\frac{\text{PostOp AUC GIP}}{\text{PreOp AUC GIP}}$ 100.; **: or above.

6. Supporting Evidence for This Hypothesis

The most effective surgical procedure at present is a classic BPD. Outcomes of pylorus-preserving BPDs with a duodenal switch (DS) could not be compared with those of classic BPDs, even though the bypassed intestinal length was the same as a classic BPD [30]. The remaining duodenal epithelium at the anastomosis site may have been responsible for the unsatisfactory outcomes. The metabolic outcomes of revisional surgery—where the gastric pouch is reduced in size, the common-channel limb is lengthened, and the total duodenal exclusion is maintained with an undiversified BP limb length—are comparable with those of a classic BPD [31].

When comparing the efficacy of a laparoscopic DJB(LDJB) and laparoscopic RYGB in controlling type 2 diabetes over a three-year follow-up, an LDJB group experienced a significant increase in mean weight by the third postoperative month and a considerable increase in HbA1c from the baseline at six months and two years after surgery. However, these outcomes were characterized by incomplete duodenal exclusions. The alimentary Roux limb was anastomosed with the duodenum, 3~4 cm distal to the pyloric sphincter in this study. Thus, the inadequate exclusion of the duodenum may have been responsible for the poor outcomes of the LDJB [1].

Usually, the beneficial effect of RYGB disappeared after gastrostomy feeding to the bypassed segment, including the BP limb (Figure 1a). Surprisingly, glucose tolerance dose was not impaired with the duodenal-jejunal transit procedure following RYGB(Figure 1b). The surgical structure of duodenal-jejunal transit with gastric bypass is as follows; concomitant RYGB with side-to-side anastomosis between the alimentary Roux limb and the anterior portion of the proximal duodenum and stapling 2 cm distal to duodenal-jejunal anastomosis without cutting for divert food passage[32]. The preservation of the metabolic effect despite nutrients passing through the duodenum and upper jejunum has been mysterious. However, the assumption of mechanism could be illustrated by understanding the propagation of epithelial lineage to the distal intestine at the anastomosis site. The replaced intestinal identity of the duodenum and upper jejunum to that of the distal jejunum may be an acceptable consequence.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 19 September 2023 doi:10.20944/preprints202309.1188.v1

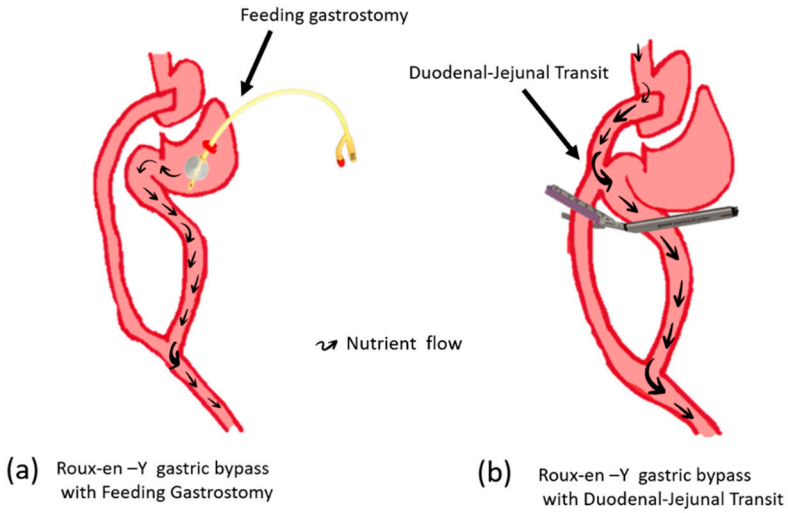

Figure 1. Different outcomes of food transit to the bypassed duodenal-jejunal segment following RYGB, preservation of the metabolic effect despite nutrients passing through the duodenum and upper jejunum suggesting another mechanism is responsible for bypass surgery. The hypothesis of migration of epithelial identity could illustrate possible mechanisms of conflict outcomes.

Finally, the hypothesis regarding the inconsistent outcomes of metabolic surgeries is partly based on epithelial regeneration and proliferation, which take time; noticeable discrepancies become evident a few months after surgery. The similarity between the interval and clinical recurrence after surgery—including weight gain and increased blood glucose—suggests a direct relationship between GIP alterations and recurrent hyperglycemia.

7. Simultaneous Preservation of the Pyloric Sphincter Function and Complete Exclusion of the Duodenum

The ideal surgical technique for DJBs should preserve the gastrointestinal capacity while ensuring the effectiveness of diabetes improvement. A duodenal epithelium attached to a pyloric sphincter should be completely removed from the visible border using surgical excision or cauterization, followed by interrupted stitching between the pyloric sphincter muscle and alimentary Roux limb to preserve the sphincter function.

8. Conclusions

The core mechanisms of diabetic improvements include separating the high-density K-cell area from the nutrient contact and modulating epithelial identity alteration from crosstalk with opposite mesenchymal cells and epithelium at the anastomosis site. The compensatory proliferation of the remaining intestinal epithelium intensifies the spreading of altered identity, specifically the length of the BP limb and exposure of the duodenal epithelium. These findings offer valuable insight for optimizing metabolic surgery's effectiveness in managing type 2 diabetes.

Funding: This research received no external funding.

Informed Consent Statement: Not applicable

Acknowledgments: The author would like to thank all the colleagues who assisted with writing the dissertation.

Conflicts of Interest: The author declares no conflicts of interest.

References

1. Kim, D.J.; Paik, K.Y.; Kim, M.K.; Kim, E.; Kim, W. Three-year result of efficacy for type 2 diabetes mellitus control between laparoscopic duodenojejunal bypass compared with laparoscopic Roux-en-Y gastric bypass. *Ann. Surg. Treat. Res.* **2017**, *93*, 260–265.
2. Rhee, N.A.; Wahlgren, C.D.; Pedersen, J.; Mortensen, B.; Langholz, E.; Wandall, E.P.; Friis, S.U.; Villman, P.; Paulsen, S.J.; Knop, F.K. Effect of Roux-en-Y gastric bypass on the distribution and hormone expression of small-intestinal enteroendocrine cells in obese patients with type 2 diabetes. *Diabetologia* **2015**, *58*, 2254–2258.
3. Crosnier, C.; Stamataki, D.; Lewis, J. Organizing cell renewal in the intestine: Stem cells signals, and combinatorial control. *Nat. Rev. Genet.* **2006**, *7*, 349–359.
4. Thompson, C.A.; DeLaForest, A.; Battle, M.A. Patterning the gastrointestinal epithelium to confer regional-specific functions. *Dev. Biol.* **2018**, *435*, 97–108.
5. Seiler, K.M.; Waye, S.E.; Kong, W.; Kamimoto, K.; Bajinting, A.; Goo, W.H.; Onufer, E.J.; Courtney, C.; Guo, J.; Warner, B.W.; et al. Single-cell analysis reveals regional reprogramming during adaptation to massive small bowel resection in mice. *Cell. Mol. Gastroenterol. Hepatol.* **2019**, *8*, 407–426.
6. Li, B.; Lu, Y.; Srikant, C.B.; Gao, Z.H.; Liu, J.L. Intestinal adaptation and Reg gene expression induced by antidiabetic duodenal-jejunal bypass surgery in Zucker fatty rats. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2013**, *304*, G635–G645.
7. Larsen, H.L.; Jensen, K.B. Reprogramming cellular identity during intestinal regeneration. *Curr. Opin. Genet. Dev.* **2021**, *70*, 40–47.
8. Kindel, T.L.; Martins, P.J.; Yoder, S.M.; Jandacek, R.J.; Seeley, R.J.; D'Alessio, D.A.; Obici, S.; Tso, P. Bypassing the duodenum does not improve insulin resistance associated with diet-induced obesity in rodents. *Obesity* **2011**, *19*, 380–387.
9. Lee, H.C.; Kim, M.K.; Kwon, H.S.; Kim, E.; Song, K.H. Early changes in incretin secretion after laparoscopic duodenal-jejunal bypass surgery in type 2 diabetic patients. *Obes. Surg.* **2010**, *20*, 1530–1535.
10. Petry, T.Z.; Fabbrini, E.; Otoch, J.P.; Carmona, M.A.; Caravatto, P.P.; Salles, J.E.; Sarian, T.; Correa, J.L.; Schiavon, C.A.; Patterson, B.W.; et al. Effect of duodenal-jejunal bypass surgery on glycemic control in type 2 diabetes: A randomized controlled trial. *Obesity* **2015**, *23*, 1973–1979.
11. Klein, S.; Fabbrini, E.; Patterson, B.W.; Polonsky, K.S.; Schiavon, C.A.; Correa, J.L.; Salle, J.E.; Wajchenberg, B.L.; Cohen, R. Moderate effect of duodenal-jejunal bypass surgery on glucose homeostasis in patients with type 2 diabetes. *Obesity* **2012**, *20*, 1266–1272.
12. Kindel, T.L.; Yoder, S.M.; D'Alessio, D.A.; Tso, P. The effect of the duodenal-jejunal bypass on glucose-dependent insulinotropic polypeptide secretion in Wistar rats. *Obes. Surg.* **2010**, *20*, 768–775.
13. Heo, Y.; Ahn, J.H.; Shin, S.H.; Lee, Y.J. The effect of duodenojejunal bypass for type 2 diabetes mellitus patients below body mass index 25 kg/m^2: One-year follow-up. *J. Korean Surg. Soc.* **2013**, *85*, 109–115.
14. Grong, E.; Arbo, I.B.; Thu, O.K.; Kuhry, E.; Kulseng, B.; Marvik, R. The effect of duodenojejunostomy and sleeve gastrectomy on type 2 diabetes mellitus and gastrin secretion in Goto-Kakizaki rats. *Surg. Endosc.* **2015**, *29*, 723–733.
15. Hu, C.; Zhang, G.; Sun, D.; Han, H.; Hu, S. Duodenal-jejunal bypass improves glucose metabolism and adipokine expression independently of weight loss in a diabetic rat model. *Obes. Surg.* **2013**, *23*, 1436–1444.
16. Sun, D.; Wang, K.; Yan, Z.; Zhang, G.; Liu, S.; Liu, F.; Hu, C.; Hu, S. Duodenal-jejunal bypass surgery upregulates the expression of the hepatic insulin signal in proteins and the key regulatory enzymes of intestinal gluconeogenesis in diabetic Goto-Kakizaki rats. *Obes. Surg.* **2013**, *23*, 1734–1742.
17. Speck, M.; Cho, Y.M.; Asadi, A.; Rubino, F.; Kieffer, T.J. Duodenal-jejunal bypass protects GK rats from β-cell loss and aggravation of hyperglycemia and increases enteroendocrine cells coexpressing GIP and GLP-1. *Am. J. Physiol. Endocrinol. Metab.* **2011**, *300*, E923–E932.
18. Geloneze, B.; Geloneze, S.R.; Chaim, E.; Hirsch, F.F.; Felici, A.C.; Lambert, G.; Tambascia, M.A.; Pareja, J.C. Metabolic surgery for nonobese type 2 diabetes: Incretins, adipocytokines, and insulin secretion/resistance changes in a 1-year interventional clinical controlled study. *Ann. Surg.* **2012**, *256*, 72–78.
19. Geloneze, B.; Geloneze, S.R.; Fiori, C.; Stabe, C.; Tambascia, M.A.; Chaim, E.A.; Brenno, D.; Pareja, A.J. Surgery for nonobese type 2 diabetic patients: An interventional study with duodenal-jejunal exclusion. *Obes. Surg.* **2009**, *19*, 1077–1083.
20. Altmann, G.G.; Leblond, C.P. Factors influencing villus size in the small intestine of adult rats as revealed by transposition of intestinal segments. *Am. J. Anat.* **1970**, *127*, 15–36.

21. Jorsal, T.; Rhee, N.A.; Pedersen, J.; Wahlgren, C.D.; Mortensen, B.; Jepsen, S.L.; Dalbøge, L.; Vilmann, P.; Hassan, H.; Hendel, J.W.; et al. Enteroendocrine K and L cells in healthy and type 2 diabetic individuals. *Diabetologia* **2018**, *61*, 284–294.
22. Rao, R.S.; Kini, S. GIP and bariatric surgery. *Obes. Surg.* **2010**, *21*, 244–252.
23. Guidone, C.; Manco, M.; Valera-Mora, E.; Iaconelli, A.; Gniuli, D.; Mari, A.; Nanni, G.; Castagneto, M.; Calvani, M.; Mingrone, G. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. *Diabetes* **2006**, *55*, 2025–2031.
24. Miyachi, T.; Nagao, M.; Shibata, C.; Kitahar, Y.; Tanaka, N.; Watanabe, K.; Tsuchiya, T.; Motoi, F.; Naitoh, T.; Unno, M. Biliopancreatic limb plays an important role in metabolic improvement after duodenal-jejunal bypass in a rat model of diabetes. *Surgery* **2016**, *159*, 1360–1371.
25. Laferrere, B.; Teixeira, J.; McGinty, J.; Tran, H.; Egger, J.R.; Colarusso, A.; Kovack, B.; Bawa, B.; Koshy, N.; Lee, H.; et al. Effect of weight loss by gastric bypass surgery versus hypocaloric diet on glucose and incretin levels in patients with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **2008**, *93*, 2479–2485.
26. Laferrere, B.; Heshka, S.; Wang, K.; Khan, Y.; McGinty, J.; Teixeira, J.; Hart, A.B.; Olivan, B. Incretin levels and effect are markedly enhanced 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. *Diabetes Care* **2007**, *30*, 1709–1716.
27. Fellici, A.C.; Lambert, G.; Lima, M.M.; Pareja, J.C.; Rodovalho, S.; Chaim, E.A.; Geloneze, B. Surgical treatment of type 2 diabetes in subjects with mild obesity: Mechanisms underlying metabolic improvements. *Obes. Surg.* **2015**, *25*, 36–44.
28. Kim, M.J.; Park, H.K.; Byun, D.W.; Suh, K.I.; Hur, K.Y. Incretin levels 1 month after laparoscopic single anastomosis gastric bypass surgery in non-morbid obese type 2 diabetes patients. *Asian J. Surg.* **2014**, *37*, 130–137.
29. Whitson, B.A.; Leslie, D.B.; Kellogg, T.A.; Maddaus, M.A.; Buchwald, H.; Billington, C.J.; Ikramuddin, S. Entero-endocrine changes after gastric bypass in diabetic and nondiabetic patients: A preliminary study. *J. Surg. Res.* **2007**, *141*, 31–39.
30. Cossu, M.L.; Noya, G.; Tonolo, G.C.; Profili, S.; Meloni, G.B.; Ruggiu, M.; Brizzi, P.; Cossu, F.; Pilo, L.; Tilocca, P.L. Duodenal switch without gastric resection: Results and observations after 6 years. *Obes. Surg.* **2004**, *14*, 1354–1359.
31. Ceriani, V.; Cetta, F.; Lodi, T.; Pinna, F.; Pontiroli, A.E. Clinical and metabolic effects of biliopancreatic diversion persist after the reduction of the gastric pouch and elongation of the common alimentary tract. Preliminary report in a series of patients with a 10-year follow-up. *Obes. Surg.* **2017**, *27*, 1493–1500.
32. Dolo, P.R.; Yao, L.; Li, C.; Zhu, X.; Shi, L.; Widjaja, J. Preserving duodenal-jejunal(foregut)transit does not impair glucose tolerance and diabetes remission following gastric bypass in type 2 diabetes Sparague-Dawley rat model. *Obes. Surg*. 2018;28, 1313-1320.