J Metab Bariatr Surg. 2024 Jun;13(1):1-7
https://doi.org/10.17476/jmbs.2024.13.1.1
pISSN 2287-2930·eISSN 2508-5956

Journal of Metabolic and Bariatric Surgery JMBS

Review Article

Check for updates

Enteroendocrine Reprogramming by Altered Epithelial-Mesenchymal Crosstalk in Metabolic Surgery

Kyung Yul Hur

Department of Surgery, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea

OPEN ACCESS

Received: May 17, 2024
Revised: May 25, 2024
Accepted: May 30, 2024
Published online: Jun 10, 2024

Corresponding author:
Kyung Yul Hur
Department of Surgery, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, 59 Daesagwan-ro, Yongsan-gu, Seoul 04401, Korea.
Tel: +82-2-709-9476
Fax: +82-2-710-3140
Email: surgery@schmc.ac.kr
hurusa@hanmail.net

ORCID iDs
Kyung Yul Hur
https://orcid.org/0000-0003-0560-6434

Data Availability
The data used in this review does not require any special datasets or additional information.

Funding
No funding was obtained for this study.

Conflict of Interest
None of the authors have any conflict of interest.

ABSTRACT

Metabolic surgery is an effective treatment option for type 2 diabetes. However, the therapeutic scope has been limited by unexpected inconsistent outcomes. This study aims to overcome these obstacles by determining fundamental mechanisms from a novel perspective by analyzing and comparing the surgical anatomy, clinical characteristics, and outcomes of metabolic surgery, including duodenal-jejunal bypass, Roux-en-Y gastric bypass, biliopancreatic diversion, one anastomosis gastric bypass, and their modified procedures, predominantly focusing on nonobese patients to mitigate confounding effects from overweighted type 2 diabetes. Regional epithelial cell growth and unique villus formation along the anterior-posterior axis of the small intestine depend on crosstalk between the epithelium and the underlying mesenchyme. Due to altered crosstalk between the epithelium and the opposite mesenchyme at the anastomotic site, the enteroendocrine lineage of the distal intestine is replaced by the proximal epithelium after the bypass procedure. Subsequent intestinal compensatory proliferation accelerates the expansion of the replaced epithelium, including enteroendocrine cells. The primary reasons for unsatisfactory results are incomplete duodenal exclusion and insufficient biliopancreatic limb length. We anticipate that this novel mechanism will have a significant impact on metabolic surgery outcomes and provide valuable insight into optimizing its effectiveness in type 2 diabetes.

Keywords: Metabolic surgery; Enteroendocrine cells; Epithelial-mesenchymal interactions; Epithelial reprogramming; GIP

INTRODUCTION

Metabolic surgery is highly effective treatment option for the patients with type 2 diabetes. Nevertheless, the therapeutic scope has been restricted due to the unexpectedly inconsistent outcomes. This study aims to overcome these obstacles by determining fundamental mechanisms from a novel perspective.

Two independent factors are associated with the pathogenesis of surgical type 2 diabetes. These factors include excessive adipose tissue in overweight individuals and an imbalanced release of gut hormones such as incretins. Improving altered gut hormone secretion entails identifying the major target hormones responsible for metabolic changes and proper

Journal of Metabolic and Bariatric Surgery JMBS

rerouting of nutrients. However, the main challenge lies in elucidating the underlying mechanisms of altered hormonal release from the gastrointestinal tract.

A previous study examining the density and hormonal gene expression of small intestinal enteroendocrine cells revealed several changes in their distribution following a Roux-en-Y gastric bypass (RYGB) [1]. These findings suggest a critical 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 regulation of regionalized epithelial identity, as well as the factors that contribute to alterations in the distribution of enteroendocrine cells and the expression of hormonal genes. We analyzed and compared various metabolic surgeries, such as duodenal-jejunal bypass (DJB), RYGB, biliopancreatic diversion (BPD), and one anastomosis gastric bypass (OAGB), as well as their modified procedures, based on their surgical anatomy, clinical characteristics, and outcomes. This analysis aimed to clarify specific surgical patterns that may lead to conflicting results. We exclusively included nonobese patients to mitigate compounding variables from overweight individuals.

PHYSIOLOGY OF INTESTINAL EPITHELIAL REGENERATION AND IDENTITY ALTERATION

Each part of the small intestine has its unique structure of epithelial tissue and type of cells, which allows the distinctive functions necessary for efficient nutritional assimilation [2]. The modeling of the intestinal epithelium and villus formation depends on the 2-way communication between the epithelium and underlying mesenchyme, which is mediated by signaling pathways [3,4]. When the functional epithelial area is lost through resections or bypasses, the remaining intestine goes through morphological and functional adaptive compensatory responses. These include changes in the distribution of enteroendocrine cells and transcriptional activities [1]. New developments in single-cell RNA sequencing have shown that following proximal small bowel resections, the epithelium of the distal small intestine undergoes regional reprogramming to acquire a proximal identity [4].

The epithelial-mesenchymal crosstalk impacts epithelial cell growth and regional villus formation along the anterior-posterior axis (regionalization) of the small intestine [5]. Therefore, intestinal anastomosis after a bypass or resection might promote alteration of epithelial identity by the crosstalk between opposite epithelium or mesenchyme exposed at the anastomotic site. In addition, the mechanism is partly based on postoperative proliferation, which takes time; noticeable discrepancies become evident a few months after surgery in humans [6]. Ileal transposition, a procedure consisting of transposing an isolated segment of the ileum to the jejunum, which results in an alteration of the normal distribution of endocrine cells along the gut without changes in the total length of the intestine, is associated with a net increase in insulin sensitivity. Interestingly, these results were observed in rats 45 days after the operation and were likely ascribed to the time to proliferation of reprogrammed epithelium [7]. However, the clinical implication of epithelial identity alteration remains unclear. Nevertheless, the region-specific function of enteroendocrine cells in different parts of the small intestine leads to significant metabolic changes. Additionally, rapid turnover rate of the intestinal epithelium and compensatory proliferation facilitate the propagation and spreading of the altered identity to the distal intestine. Such as the striking resemblance of the alimentary Roux limb of jejunum to duodenum in a pylorus-preserving DJB [8].

https://doi.org/10.17476/jmbs.2024.13.1.1

Journal of Metabolic and Bariatric Surgery JMBS

ALTERED IDENTITY OF THE ROUX LIMB AND COMMON CHANNEL

The surgical DJB procedure has 2 modifications: pylorus-preserving (duodenal-jejunal anastomosis) and conventional (gastro-jejunal anastomosis) types. A duodenal-jejunal anastomosis was developed to preserve pyloric sphincter function but revealed differences in glycemic control. In the pylorus-preserving DJB group, there was a tendency toward high blood glucose concentrations, which led to unsatisfactory outcomes [9-14]. In contrast, recurrent hyperglycemia was rarely detected in the gastro-jejunostomy DJB group, which yielded favorable outcomes [15-19].

These findings imply that the duodenal epithelium, attached to the pyloric sphincter could potentially cause recurrent hyperglycemia. However, the area of the exposed duodenum was considered too small to induce hyperglycemia.

A comparison of surgical DJBs and endoscopic DJB liners (DJBLs) could demonstrate a possible mechanism. Unlike pylorus-preserving DJB, conventional DJB and DJBL demonstrate minimal blood glucose elevation. Comparing pylorus-preserving DJB with conventional DJB and DJBL (recurrent vs. non-recurrent), individually, suggests that duodenal exposure and anastomosis procedure are the possible factors that predispose to recurrence, respectively. Nevertheless, they do not cause recurrence, exclusively. These findings suggest that hyperglycemia may be associated with coexistence of nutritional exposure of the duodenal epithelium and combined anastomosis procedure.

Studies on the impact of transpositions elsewhere in the intestine, such as the transposition of the ileal segment to the jejunal area, the jejunal segment to the ileal site, the 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]. Based on these findings, it is more plausible that the proximal intestinal epithelium migrates to the opposing intestine.

Jejunojejunostomy, another surgical anastomosis used in the DJB procedure, is not exempted from identity changes. The distal bilio-pancreatic (BP) limb affects the epithelial identity of the common limb in accordance with the same mechanism as previously mentioned. Although the primary role of the long BP limb is to separate nutrients from the duodenum and upper jejunum, another role is to provide more distal jejunum for common channel anastomosis to mitigate the proliferation of proximal epithelium to the subsequent common channel which promotes recurrence. In a recent report on the importance of the BP limb in metabolic surgery, the beneficial effects of the surgery disappeared after BP limb excisions in rats with improved hyperglycemia that underwent DJBs with a long BP limb [21], suggesting the presence of additional functions of the long BP limb beyond keeping nutrients away from the duodenum and upper jejunum. The cancellation of beneficial effects is likely induced by the migration and proliferation of the preceding duodenal or upper jejunal epithelium to the common channel.

https://doi.org/10.17476/jmbs.2024.13.1.1

Journal of Metabolic and Bariatric Surgery JMBS

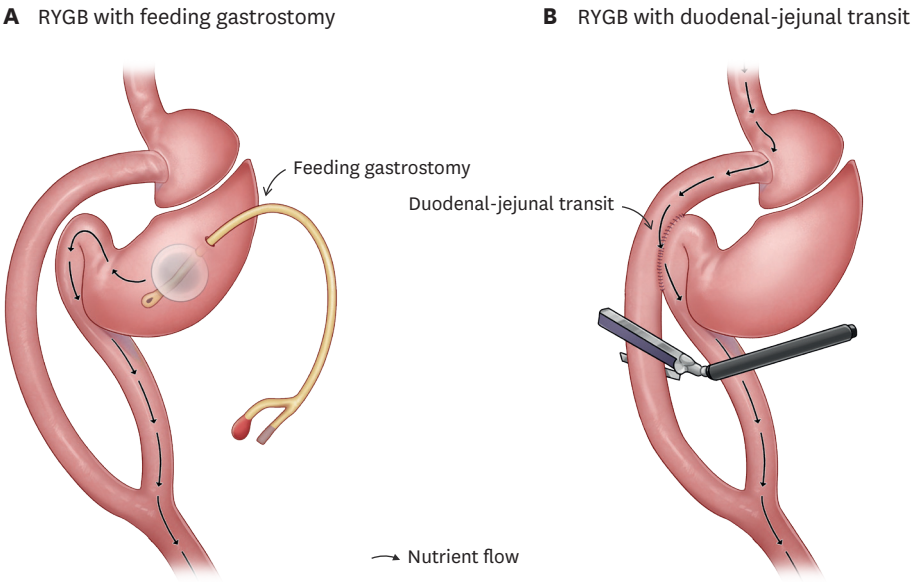

Fig. 1. Different outcomes of RYGB with duodenal-jejunal transit and feeding gastrostomy tube. The beneficial effect of RYGB is canceled after gastrostomy feeding through the bypassed segment (A). Surprisingly, the glucose tolerance dose was not impaired with the duodenal-jejunal transit procedure following RYGB (B).
RYGB = Roux-en-Y gastric bypass.

Usually, gastrostomy feeding to the bypassed segment cancels the beneficial effect of RYGB (**Fig. 1A**). But surprisingly, the glucose tolerance dose was not impaired with the duodenal-jejunal transit procedure following RYGB (**Fig. 1B**). The preservation of the metabolic effect despite nutrients passing through the duodenum and upper jejunum has been mysterious [22].

However, it would be acceptable with applying the hypothesis that the epithelial lineage spreads from the proximal intestine to the distal intestine across the anastomosis. This implies that most of the characteristics of the duodenal epithelium are lost when the jejunal epithelium replaces the duodenal epithelial lineage.

DIABETOGENIC ROLE OF GLUCOSE-DEPENDENT INSULINOTROPIC POLYPEPTIDE (GIP)

Recently, synthetic dual-acting peptides targeting GIP and glucagon-like peptide-1 (GLP-1) receptors have significantly affected type 2 diabetes patients, highlighting their potential therapeutic benefits [23]. However, clinical studies regarding GIP administration remain inconclusive. Unlike GLP-1, GIP is considered a hormone targeted by the foregut hypothesis, as it induces hyperglycemia instead of insulin secretion. Researchers continue to discover new evidence supporting the hypothesis that a sufficient length of the BP limb enhances the effects of surgery [24]. Furthermore, the upregulation of GLP-1 and the downregulation of GIP are typical features of the BPD procedure, which is most effective in improving type 2 diabetes. Notably, the surgical characteristics of the BPD procedure is the complete exclusion of the duodenum and the long BP limb [7].

https://doi.org/10.17476/jmbs.2024.13.1.1

Table 1. Demonstration of the propensity for an inverse correlation between postoperative GIP changes and the BP limb length ratio

Operation	AUC GIP		GIP alteration[a] (%)	BP limb (cm)	Reference
	Before operation	After operation			
BPD	3,297.0 pmol/L	1,874.0 pmol/L	56	≥250[b]	Guidone et al. [7]
RYGB	48.67 ng/L^{-1}·min^{-1}	51.56 ng/L^{-1}·min^{-1}	105	30	Laferrère et al. [27]
RYGB	50.96 pmol^{-1}·L^{-1}·min^{-1}	52.66 pmol^{-1}·L^{-1}·min^{-1}	103	40	Laferrère et al. [28]
RYGB	30.2 ng/dL·10 min	27.0 ng/dL·10 min	90	100	Fellici et al. [29]
OAGB	184.0 pg/mL·min^{-1}	98.0 pg/mL·min^{-1}	53	200	Kim et al. [30]

GIP = glucose-dependent insulinotropic polypeptide, BP limb = bilio-pancreatic limb, AUC = area under the curve, BPD = biliopancreatic diversion, RYGB = Roux-en-Y gastric bypass, OAGB = one anastomosis gastric bypass.
[a]GIP Alteration (%) = $\frac{\text{PostOp AUC}}{\text{PreOp AUC}} \times 100$; [b]Or above.

The surgical outcome of modified BPDs compared to classic BPD, demonstrates the importance of complete duodenal exclusion from nutrients and sufficient biliopancreatic limb length. The results of pylorus-preserving BPDs with a duodenal switch were not comparable to those of classic BPDs, even though bypassed BP limb length was the same as a classic BPD [25]. The remaining duodenal epithelium at the anastomosis site may have been responsible for the unsatisfactory outcomes. In addition, the metabolic outcomes of revisional surgery following classic BPD, where the gastric pouch is reduced in size, the common-channel limb is lengthened, and total duodenal exclusion is maintained with an undiversified BP limb length, were comparable to a classic BPD [26].

Ultimately, lengthening the BP limb reduces the number of K-cells exposed to nutrients, resulting in decreased GIP secretion and improved outcomes. Therefore, we can deduce that the length of the BP limb directly correlates with the postoperative decrease in GIP secretion. However, we can only accept the comparison by excluding other factors that impact GIP alterations, such as incomplete exclusion of the duodenum from nutrients and weight fluctuations in overweight subjects. **Table 1** [7,27-30] demonstrates the propensity for an inverse correlation between postoperative GIP changes and the BP limb length ratio. Surgical patients with minimal obesity were eligible, and the applied procedures were those that do not allow nutrient exposure to the duodenum and upper jejunum, such as RYGBs, classic BPDs, and OAGB.

As a result, the length of the BP limb is the major determinant of the inconsistency of GIP values after bypass surgery; specifically, the length of the BP limb is inversely proportional to the GIP concentration. However, despite separating the high K-cell density area from nutrients, there is an increased GIP value of RYGB with a short BP limb [27,28]. Since the density of GIP-releasing K-cells gradually decreases from the duodenum to the terminal ileum [31], the high K-cell density at the end of the short BP limb may stimulate the proliferation of K-cells in the common channel. The presumed GIP decline inflection point is around 100 cm in length distal to the ligament of Treitz [32].

CONCLUSIONS

The core mechanisms of diabetic improvements include separating the entire duodenum and upper jejunum from the nutrient and modulating epithelial identity alteration, induced by crosstalk between the epithelium and opposite mesenchyme at the anastomosis site. The compensatory proliferation of residual intestines promotes the propagation of altered epithelial lineages to the distal area. The mechanisms uncovered in our study offer valuable insights into optimizing the effectiveness of metabolic surgery in type 2 diabetes.

https://doi.org/10.17476/jmbs.2024.13.1.1

ACKNOWLEDGMENTS

I am writing to express my sincere gratitude to all the members of our surgery department for their contributions that have led to the completion of the dissertation.

REFERENCES

1. Rhee NA, Wahlgren CD, Pedersen J, Mortensen B, Langholz E, Wandall EP, et al. 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;58:2254-8. PUBMED | CROSSREF
2. Thompson CA, DeLaForest A, Battle MA. Patterning the gastrointestinal epithelium to confer regional-specific functions. Dev Biol 2018;435:97-108. PUBMED | CROSSREF
3. Crosnier C, Stamataki D, Lewis J. Organizing cell renewal in the intestine: stem cells, signals and combinatorial control. Nat Rev Genet 2006;7:349-59. PUBMED | CROSSREF
4. Seiler KM, Waye SE, Kong W, Kamimoto K, Bajinting A, Goo WH, et al. Single-cell analysis reveals regional reprogramming during adaptation to massive, small bowel resection in mice. Cell Mol Gastroenterol Hepatol 2019;8:407-26. PUBMED | CROSSREF
5. Maimets M, Pedersen MT, Guiu J, Dreier J, Thodberg M, Antoku Y, et al. Mesenchymal-epithelial crosstalk shapes intestinal regionalisation via Wnt and Shh signalling. Nat Commun 2022;13:715. PUBMED | CROSSREF
6. Wu Q, Xiao Z, Cheng Z, Tian H. Changes of blood glucose and gastrointestinal hormones 4 months after Roux-en-Y gastric bypass surgery in Chinese obese type 2 diabetes patients with lower body mass index. J Diabetes Investig 2013;4:214-21. PUBMED | CROSSREF
7. Guidone C, Manco M, Valera-Mora E, Iaconelli A, Gniuli D, Mari A, et al. Mechanisms of recovery from type 2 diabetes after malabsorptive bariatric surgery. Diabetes 2006;55:2025-31. PUBMED | CROSSREF
8. Li B, Lu Y, Srikant CB, Gao ZH, Liu JL. 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:G635-45. PUBMED | CROSSREF
9. Kindel TL, Martins PJ, Yoder SM, Jandacek RJ, Seeley RJ, D'Alessio DA, et al. Bypassing the duodenum does not improve insulin resistance associated with diet-induced obesity in rodents. Obesity (Silver Spring) 2011;19:380-7. PUBMED | CROSSREF
10. Lee HC, Kim MK, Kwon HS, Kim E, Song KH. Early changes in incretin secretion after laparoscopic duodenal-jejunal bypass surgery in type 2 diabetic patients. Obes Surg 2010;20:1530-5. PUBMED | CROSSREF
11. Petry TZ, Fabbrini E, Otoch JP, Carmona MA, Caravatto PP, Salles JE, et al. Effect of duodenal-jejunal bypass surgery on glycemic control in type 2 diabetes: a randomized controlled trial. Obesity (Silver Spring) 2015;23:1973-9. PUBMED | CROSSREF
12. Klein S, Fabbrini E, Patterson BW, Polonsky KS, Schiavon CA, Correa JL, et al. Moderate effect of duodenal-jejunal bypass surgery on glucose homeostasis in patients with type 2 diabetes. Obesity (Silver Spring) 2012;20:1266-72. PUBMED | CROSSREF
13. Heo Y, Ahn JH, Shin SH, Lee YJ. 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;85:109-15. PUBMED | CROSSREF
14. Grong E, Arbo IB, Thu OK, Kuhry E, Kulseng B, Mårvik R. The effect of duodenojejunostomy and sleeve gastrectomy on type 2 diabetes mellitus and gastrin secretion in Goto-Kakizaki rats. Surg Endosc 2015;29:723-33. PUBMED | CROSSREF
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;23:1436-44. PUBMED | CROSSREF
16. Sun D, Wang K, Yan Z, Zhang G, Liu S, Liu F, et al. Duodenal-jejunal bypass surgery up-regulates the expression of the hepatic insulin signaling proteins and the key regulatory enzymes of intestinal gluconeogenesis in diabetic Goto-Kakizaki rats. Obes Surg 2013;23:1734-42. PUBMED | CROSSREF
17. Speck M, Cho YM, Asadi A, Rubino F, Kieffer TJ. 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:E923-32. PUBMED | CROSSREF
18. Geloneze B, Geloneze SR, Chaim E, Hirsch FF, Felici AC, Lambert G, et al. Metabolic surgery for non-obese type 2 diabetes: incretins, adipocytokines, and insulin secretion/resistance changes in a 1-year interventional clinical controlled study. Ann Surg 2012;256:72-8. PUBMED | CROSSREF

19. Geloneze B, Geloneze SR, Fiori C, Stabe C, Tambascia MA, Chaim EA, et al. Surgery for nonobese type 2 diabetic patients: an interventional study with duodenal-jejunal exclusion. Obes Surg 2009;19:1077-83. PUBMED | CROSSREF

20. Altmann GG, Leblond CP. 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. PUBMED | CROSSREF

21. Miyachi T, Nagao M, Shibata C, Kitahara Y, Tanaka N, Watanabe K, et al. Biliopancreatic limb plays an important role in metabolic improvement after duodenal-jejunal bypass in a rat model of diabetes. Surgery 2016;159:1360-71. PUBMED | CROSSREF

22. Dolo PR, 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;28:1313-20. PUBMED | CROSSREF

23. Nauck MA, D'Alessio DA. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. Cardiovasc Diabetol 2022;21:169. PUBMED | CROSSREF

24. Aleassa EM, Papasavas P, Augustin T, Khorgami Z, Benson-Davies S, Ghiassi S, et al. ASMBS literature review on the effect of Roux-en-Y Gastric bypass limb lengths on outcomes. Surg Obes Relat Dis 2023;19:755-62. PUBMED | CROSSREF

25. Cossu ML, Noya G, Tonolo GC, Profili S, Meloni GB, Ruggiu M, et al. Duodenal switch without gastric resection: results and observations after 6 years. Obes Surg 2004;14:1354-9. PUBMED | CROSSREF

26. Ceriani V, Cetta F, Lodi T, Pinna F, Pontiroli AE. 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;27:1493-500. PUBMED | CROSSREF

27. Laferrère B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, 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;93:2479-85. PUBMED | CROSSREF

28. Laferrère B, Heshka S, Wang K, Khan Y, McGinty J, Teixeira J, et al. 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;30:1709-16. PUBMED | CROSSREF

29. Fellici AC, Lambert G, Lima MM, Pareja JC, Rodovalho S, Chaim EA, et al. Surgical treatment of type 2 diabetes in subjects with mild obesity: mechanisms underlying metabolic improvements. Obes Surg 2015;25:36-44. PUBMED | CROSSREF

30. Kim MJ, Park HK, Byun DW, Suh KI, Hur KY. Incretin levels 1 month after laparoscopic single anastomosis gastric bypass surgery in non-morbid obese type 2 diabetes patients. Asian J Surg 2014;37:130-7. PUBMED | CROSSREF

31. Jorsal T, Rhee NA, Pedersen J, Wahlgren CD, Mortensen B, Jepsen SL, et al. Enteroendocrine K and L cells in healthy and type 2 diabetic individuals. Diabetologia 2018;61:284-94. PUBMED | CROSSREF

32. Whitson BA, Leslie DB, Kellogg TA, Maddaus MA, Buchwald H, Billington CJ, et al. Entero-endocrine changes after gastric bypass in diabetic and nondiabetic patients: a preliminary study. J Surg Res 2007;141:31-9. PUBMED | CROSSREF