Review

Inconsistent Outcomes of Metabolic Surgery for Nonobese Patients with Type 2 Diabetes

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Inconsistent Outcomes of Metabolic Surgery for Nonobese Patients with Type 2 Diabetes

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Abstract: Purpose: Metabolic surgery can promote integrated physiologic improvement to ameliorate metabolic illness, particularly type 2 diabetes. Nevertheless, the therapeutic scope has been limited by unexpectedly inconsistent surgical outcomes. Therefore, the purpose of this study is to overcome the obstacles by determining the core mechanism of conflicting results. Methods: The surgical anatomy, clinical course, and outcomes of various metabolic surgeries, including modified types of duodenal-jejunal bypass procedures, were compared to comprehend specific surgical patterns from distinctive perspectives. Patients in exclusively nonobese groups are subjected to avoid compounding by weight fluctuations. Results: During intestinal anastomosis, the epithelial identity of the succeeding intestine is replaced by that of the proximal epithelium through altered crosstalk between the epithelium and opposing mesenchymal cells. The rapid turnover rate and compensatory proliferation of the succeeding intestine accelerate the propagation of the replaced epithelium. Propagation of replaced epithelium could provoke inconsistent outcomes of metabolic surgery.Conclusion: The major determinants of the conflicting results of metabolic surgery are inadequate duodenal exclusion and inappropriate length of the biliopancreatic limbs. The replaced enteroendocrine cells during regeneration provoke inconsistent outcomes of metabolic surgery. The critical factors are the type and density of enteroendocrine cells distributed at the terminal end of the preceding proximal intestine.

Keywords: inconsistent outcomes; epithelial-mesenchymal crosstalk; altered identity; duodenal-jejunal bypass; biliopancreatic limb; GIP

1. Introduction

Metabolic surgery is a potent therapeutic modality for type 2 diabetes. However, the therapeutic scope is limited because the underlying mechanism for the inconsistent outcomes of metabolic surgery has yet to be determined. Various metabolic surgeries, including modified types of duodenal-jejunal bypass procedures, were compared with their surgical anatomy, clinical course, and outcomes to understand the specific surgical patterns causing conflicting results. Nonobese groups of patients were subjected to avoid compounding variable impact from weight fluctuation.

2. Physiology of Intestinal Epithelial Regeneration and Identity Alteration

The intestinal epithelium is replaced continuously at great rates [1]. Epithelial-mesenchymal crosstalk regulates the organized spatiotemporal regeneration process to maintain the site and time-specific epithelial identity [2]. Following the loss of functional epithelial area via resection or bypass, the residual intestine undergoes morphologic and functional adaptive compensatory response [2]. In addition, intestinal anastomosis, performed to maintain continuity after bypass or resection, modifies site-specific epithelial identity and can be a causal factor for inconsistent outcomes in metabolic surgery.

Although we do not fully understand how it works, recent improvements in single-cell RNA resolution analysis have helped show that proximal epithelial cells are interspersed in the distal intestinal epithelial area following intestinal anastomosis [3]. The crosstalk between the epithelial and opposing subepithelial mesenchymal cells at the anastomosis area promotes altered epithelial identity. The exceptionally rapid turnover rate of the intestinal epithelium and compensatory proliferation intensify the propagation of the altered identity to the distal intestinal epithelium.

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Therefore, the general appearance of the alimentary Roux limb of the pylorus-preserving DJB looks similar to that of the duodenum [4]. However, the replacement of epithelial cells has less clinical importance. Nevertheless, the region-specific function of enteroendocrine cells from elsewhere in the intestine induces metabolic alterations over time following adequate proliferation. The type and density of enteroendocrine cell distribution in the distal end of the preceding proximal bowel are critical determinants for the following distal intestinal epithelial identity.

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

Since the duodenum comes immediately after the pyloric sphincter, a small area of duodenum attached to the stomach will always be exposed to the nutrients of the patient who underwent the pylorus-preserving DJB. Therefore, a pylorus-preserving procedure leads to automatic nutrient contact with the small residual duodenal tissue left at the anastomotic site. The counterpart of the alimentary Roux limb anastomosis in DJB is either the pyloric portion of the stomach or the first duodenal portion, representing the gastrojejunal and duodenal-jejunal anastomoses, respectively. The latter is designed for pyloric sphincter preservation. Intriguingly, the postoperative clinical courses of the two procedures are different. In the pylorus-preserving DJB group, a tendency toward high blood glucose concentrations was evident, resulting in an unsatisfactory outcome [4–11]. In contrast, recurrent hyperglycemia was scarcely detectable in the gastrojejunostomy group, which had a favorable result [12–16].

These results suggest that the remaining duodenal epithelium attached to the pyloric sphincter may trigger recurrent hyperglycemia. Nevertheless, the question is whether the exposed area of the duodenal epithelium is too small to induce hyperglycemia. A possible mechanism could be demonstrated by comparing modified forms of DJBs with one another.

The commonly modified DJBs are pylorus-preserving DJBs, conventional (pylorus exclusion) DJBs, and endoscopic DJB liners (DJBLs). Each method has unique characteristics. Recurrent hyperglycemia, which leads to a propensity for increased blood glucose values about several months after surgery, exceptionally exists in the pylorus-preserving DJB.

The DJBL scarcely increases blood glucose values as long as the liner is in place, despite exposure to nutrients similar to the pylorus-preserving DJB. Considering whether exposure to the first portion of the duodenal epithelium determines inconsistent outcomes, another factor could be responsible for the recurrence of the DJBL approach. In contrast to surgical DJBs, the DJBL technique does not involve an anastomosis. Similarly, considering whether the anastomosis is a determinant for recurrence, another factor must contribute to recurrent hyperglycemia in conventional DJB. Based on these results, hyperglycemia can be associated with simultaneous nutritional exposure of the first portion of the duodenal epithelium and the accompanying anastomosis.

Literature on the outcomes of transposition elsewhere in the intestine, such as 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, has been conducted to evaluate epithelial changes of the intestine. The common features of the adaptations are as follows: with transposition of the ileal segment to the jejunal area, the villus increased in size as much as the jejunal villi; with transposition of the jejunal segment to the ileal site, the villi shrunk likely to the length of the ileal villi; and when the duodenal segment was anastomosed with the ileum, the villus of ileum increased in size as much as the duodenum [17]. In this context, there is no mobile mesentery with the fixation of the duodenum in the retroperitoneum; the distal ileum was brought up to the right upper abdominal cavity, keeping the duodenum in place before the anastomosis was created. Incidentally, the final configuration may be similar to that of a pylorus-preserving DJB. Based on these findings, the hypothesis that the proximal intestinal epithelium migrates to the opposing distal intestinal epithelial area via the anastomosis site is becoming more evident. The underlying mechanisms for these outcomes likely occur via the altered crosstalk between the opposing epithelium and mesenchymal cells, which are exposed to the cutting edge. The identity alteration of the subsequent intestinal epithelium would be the plausible assumption, although definite supporting evidence is lacking.

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4. Diabetogenic Role of GIP Compared to the Length of the BP Limb

The jejunojejunostomy, another surgical anastomosis utilized in the DJB procedure, is not exempt from identity modification. Similar to the previous mechanism, the common limb's epithelial identity depends on the BP limb's distal edge [18]. The density of K cells that release glucose-dependent insulinotropic peptide (GIP) declines from the first portion of the duodenum to the terminal ileum [19]. Therefore, depending on the length of the BP limb, the K cell density at the terminal BP limb should be varied. The longer the BP limb, the lower the K-cell density at the terminal BP limb may be expected. A recent investigation of GIP protein contents within the separate anatomical segments of the intestine mediated by gastrointestinal surgery characterized significantly increased GIP protein contents in the mid-jejunum, the common channel for nutrients and biliopancreatic secretions [20], possibly induced by the insufficient length of the BP limb.

Despite the fact that an ongoing debate about the diabetogenic role of GIP, a postoperative increase in GIP concentration is inversely correlated with diabetic remission. Although the primary function of a long BP limb is nutrient separation from the high-density K-cell area, another function is reducing the K-cell density at the end of the BP limb to minimize K-cell proliferation in the following common limb. According to a recent report on the importance of the BP limb in metabolic surgery, in rats with improved hyperglycemia that underwent DJB with a long BP limb, the favorable impact of DJB disappeared following BP limb excision [21]. These outcomes suggest another critical role for long BP limbs in preventing nutrient contact with the K-cell-rich area.

5. Inconsistent Postoperative GIP Value after Roux-en-Y Gastric Bypass [9]

Better surgical outcomes of metabolic surgery are positively correlated with long BP limbs but negatively correlated with postoperative increased GIP changes, which are widely accepted assumptions. If these are correct, the length of the BP limb and postoperative GIP changes should be inversely proportionated. However, the comparison would only be accepted by excluding other impact factors to the GIP alterations, such as the incomplete exclusion of the duodenum from nutritional exposure and weight fluctuation from surgery. Table 1 [22–26] demonstrates an inverse correlation between the postoperative GIP value and BP limb length in nonobese patients who underwent operations that cannot be permitted incomplete duodenal exclusion, such as Roux-en-Y gastric bypass, classic biliopancreatic diversion (BPD), and single anastomosis gastric bypass. With these results, one of the major determinants of inconsistent GIP values after Roux-en-Y gastric bypass is the length of the BP limb.

Table 1. Postoperative GIP alteration and length of the BP limb in patients who underwent bypass surgery with the total duodenal exclusion.

Operation	PreOp AUC GIP	PostOp AUC GIP	GIP Alteration*(%)	BP Limb (cm)	Reference
RYGBP	48.67 ng/liter^{-1}·min^{-1}	51.56 ng/liter^{-1}·min^{-1}	105	30	Laferrère *et al.* [22]
RYGBP	50.96 Pmol^{-1}·l^{-1}·min^{-1}	52.66 Pmol^{-1}·l^{-1}·min^{-1}	103	40	Laferrère *et al.* [23]
RYGBP	30.2 ng/dl·10 min	27.0 ng/dl·10 min	90	100	Fellici *et al.* [24]
OAGB	184.0 pg/mL·min^{-1}	98.0 pg/mL·min^{-1}	89	200	Kim *et al.* [25]
BPD	3297.0 pmol/l	1874.0 pmol/l	56	250↑	Guidone *et al.* [26]

RYGBP = Roux-en-Y gastric bypass; OAGB = one anastomosis gastric bypass; BPD = BilioPancreatic Diversion; BP limb = BilioPancreatic limb; GIP = glucose-dependent insulinotropic polypeptide;. PreOp = preoperative; PostOp=postoperative; AUC = area under the curve; *GIP alteration (%) = $\frac{\text{PostOp AUC GIP}}{\text{PreOp AUC GIP}} \times 100$.

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6. Supporting Evidence for the Hypothesis

The most effective metabolic surgery is considered to be the conventional BPD. In contrast, the outcomes of pylorus-preserving BPD with a duodenal switch cannot be compared to those of conventional BPD [26]. The residual duodenal epithelium at the anastomosis line may be responsible for the unsatisfactory results. Meanwhile, metabolic outcomes of revisional surgery that reduce the gastric pouch and elongate the common limb while maintaining total duodenal exclusion and an undiversified BP limb length are comparable to those of classic BPD [27]. The conventional BPD is characterized by a specific upregulation of GLP-1 and downregulation of GIP [28].

In a recently published article comparing the efficacy of laparoscopic DJB (LDJB) and laparoscopic Roux-en-Y gastric bypass (LRYGB) in controlling type 2 diabetes for a 3-year follow-up, the LDJB group experienced a significant rise in mean weight by the third postoperative month and a considerable increase in the mean HbA1c values from baseline at six months and two years after surgery. However, these outcomes are characterized by incomplete duodenal exclusion; the opposing side of the alimentary Roux-limb anastomosis was the duodenum, 3~4 cm. distal to the pyloric sphincter [29] in this study. Therefore, the dismal outcomes of LDJB might be evoked by inadequate surgical techniques.

Finally, the hypothesis on the inconsistent outcomes of metabolic surgeries is partly based on epithelial regeneration and proliferation, which takes time, and the noticeable discrepancies become evident a few months after surgery. Therefore, the similarity of the intervals between GIP alterations in laboratory findings and clinical recurrence from surgery, such as weight gain and increased blood glucose, suggests a direct relationship between GIP alteration and recurrent hyperglycemia.

7. Simultaneous Pyloric Sphincter Preservation and Entire Duodenal Exclusion

The ideal surgical technique should guarantee a better gastrointestinal quality of life while maintaining pyloric sphincter function and substantial anti-diabetic impact. The duodenal epithelium attached to the pyloric sphincter should be removed completely from the visible border using surgical excision or electrocautery devitalization to meet above options. The interrupted stitches between the pyloric sphincter muscle and the alimentary Roux-limb are an important technique to preserve pyloric sphincter function.

8. Conclusions

The determinants of the conflicting results for metabolic surgeries are inadequate duodenal exclusion and inappropriate length of the biliopancreatic limbs.

The migration of preceding proximal enteroendocrine cells to the distal intestine at the anastomosis is triggered by altered crosstalk between the epithelial cells and opposite mesenchymal cells. Propagation of the replaced epithelium intensified with compensatory proliferation and rapid turnover of the residual intestine. The types and density of enteroendocrine cells distributed at the terminal end of the preceding intestine are critical determinants.

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