

Review

Gastrointestinal Hormone in Dumping Syndrome and Reflux Esophagitis after Gastric Surgery

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Abstract

Several problems are associated with gastric resection, including the dumping syndrome, reflux esophagitis, and malabsorption. A better understanding of the pathophysiological changes will shed light on new and improved therapy. Serum levels of seven circulating gastrointestinal hormones following a standardized solid meal and a brief score of symptoms were evaluated in 10 patients after partial distal gastrectomy and 12 patients after total gastrectomy, both groups reconstructed by Billroth II anastomosis, and 9 age-matched healthy controls. Patients underwent resection for gastric cancer and were studied 45 ± 10 months after surgery. At the time of study, the patients had adapted well to surgery and no longer exhibited the severe symptoms of dumping seen immediately post-operatively. In contrast, the total gastrectomy patients exhibited the symptoms of reflux esophagitis. The gastrointestinal hormone changes could be divided into three patterns; obtunded responses (gastrin, PP), normal release (motilin, GIP) and increased secretion (CCK, neurotensin, PYY). In these, the early reaction of neurotensin correlated with the scores of late dumping syndrome and reflux esophagitis. In the literature, many gastrointestinal hormones have been shown to respond as an enhancement rather than adaptation. In other gastrointestinal hormones, secretin belonged to the obtunded type and enteroglucagon were classified in the increased type. However, pathophysiological significance of these hormonal changes remained uncertain. The late adaptive changes in gastrointestinal hormone secretion may help to compensate for loss of gastric motor function which accompanies gastric resection. On the other hand, these hormonal changes may exacerbate the esophageal reflux following gastrectomy.

Key words: gastrointestinal hormone, gastrectomy, dumping syndrome, reflux esophagitis

1. Postoperative complications late after gastric resection

It has been reported that several problems are associated with gastric resection, including the dumping syndrome, reflux esophagitis, and malabsorption, late after distal partial and total gastrectomy¹⁾. A large proportion of post-gastrectomy patients suffer from these symptoms,

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and treatment is not always effective. Poor nutritional status can be anticipated following gastric resection²⁾. Iron deficiency anemia, vitamin B₁₂ deficiency anemia with megaloblastic anemia, and vitamin D deficiency are wellknown results by the malabsorption after gastric resection³⁾. Low levels of these substances in the body reflect malabsorption and decreased protein synthesis following gastrectomy.

A better understanding of the pathophysiological changes associated with gastrectomy may shed light on new and improved therapy especially for dumping syndrome and reflux esophagitis. Marked gastrointestinal hormone changes have been described in patients with post-gastrectomy dumping, however, the general pattern of secretion of gastrointestinal hormone late after gastric resection is unknown⁴⁻⁷⁾.

Dumping syndrome and reflux esophagitis are important problems encountered during followup of post-gastrectomy patients in the outpatient clinic. Severe reflux esophagitis may contribute to the development of malnutrition and poor quality of life (QOL) in the patients after total gastrectomy. It is important to treat both dumping syndrome and reflux esophagitis in order to improve the QOL after gastric resection. Following data show postoperative conditions of the patients about dumping syndrome and reflux esophagitis long after gastric surgery.

a. Dumping syndrome

Gastric cancer patients usually undergo one of two types of gastric resection in our hospital. Twelve patients underwent distal partial gastrectomy, where the retrocolic jejunum was anastomosed with the remnant stomach using the Billroth II method. The other ten patients underwent total gastrectomy, where the retrocolic jejunum was anastomosed with the esophagus also by the Billroth II technique. These patients who underwent resection for

Table 1.

Scoring system for dumping syndrome and reflux esophagitis symptoms.

Early dumping symptoms within 30 min after meal		Late hypoglycemic symptoms 2-3 hours after meal	Reflux esophagitis
<i>cardiovascular</i>	<i>gastrointestinal</i>		
feverish sweating palpitations flushing	borborygmus diarrhea abdominal cramps abdominal fullness	general fatigue weakness hunger finger tremor sweating syncope	heartburn chest pain swallowing pain reflux sensation dysphagia

Strength and frequency of symptoms.

Strength	Frequency	Full (worst) score : 6 × number of symptoms
0 : none	0 : none or rare	early dumping syndrome : 48
1 : minimum	1 : once per couple of days	late dumping syndrome : 36
2 : medical problem	2 : once per day	reflux esophagitis : 30
3 : constant disability	3 : several times per day	

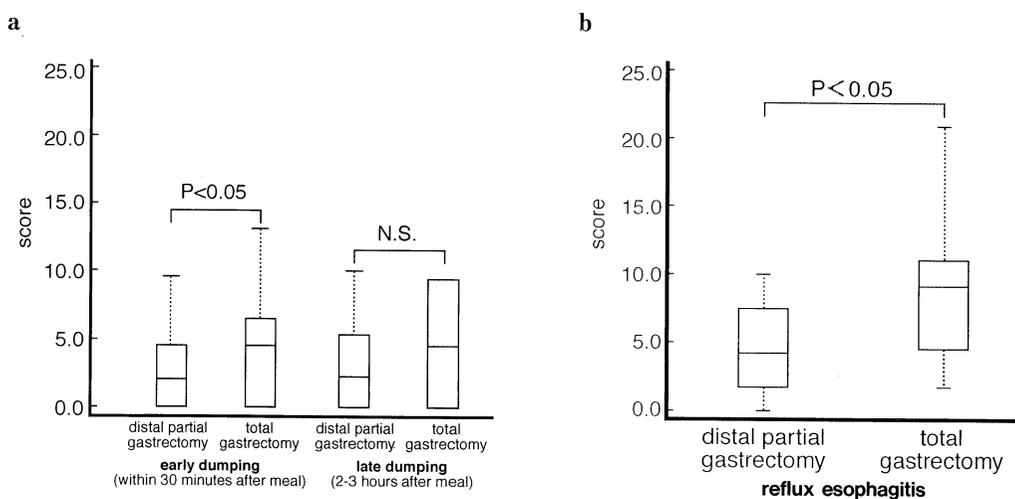


Fig. 1. Box-plot comparison of the dumping score [a], and reflux score [b] between patients following distal partial gastrectomy or total gastrectomy.

gastric cancer were studied 45 ± 10 months after surgery. They were studied at least five months after the surgery and none had other digestive diseases. Full informed consent for the study was obtained from each subject. Each patient was asked to answer a questionnaire regarding the incidence of symptoms. The form consisted of three sections of early and late symptoms of dumping and reflux esophagitis, in which the highest obstacle score would be 48, 36, and 30, respectively (Table 1).

Patients in both gastrectomy groups exhibited few symptoms of the dumping syndrome (Fig. 1a). The median score of early dumping symptoms in the partial gastrectomy group was 2.0, which was significantly lower than that of 4.0 in total gastrectomy group ($P < 0.05$). Median score for late dumping symptoms was 2.0 and 4.0 for partial and total gastrectomy, respectively, which was not statistically significant.

b. Reflux esophagitis

Gastroesophageal reflux score was significantly higher in the total gastrectomy group compared with the partial gastrectomy patients (median score 8.5 vs. 4.5, $P < 0.05$) (Fig. 1b). Therefore, reflux score was more prominent, comparing dumping score in each group. At the time of study, the patients had adapted well to surgery and no longer exhibited the symptoms of dumping seen immediately post-operatively. In contrast, the total gastrectomy patients exhibited severe symptoms of reflux esophagitis. However, reflux esophagitis can not be ignored even after distal partial gastrectomy.

In general, both early and late dumping symptoms are overcome or disappear within approximately half a year because of adaptation to the surgical procedure. Reflux esophagitis is the most important problem that surgeons should overcome to improve patients' QOL. It is also noted that a minor degree of alkaline gastritis is found in most patients after Billroth II partial gastrectomy due to duodeno-gastric reflux (DGR). DGR also brings alkaline esophagitis as well as gastritis. Moreover, alkaline esophagitis may be responsible to provide

Barrette's esophagus and then adenocarcinoma⁹⁾. Alkaline refluxate also induced squamous cell carcinoma of the esophagus in rat models of total gastrectomy^{9,10)}.

2. Serum gastrointestinal hormone levels

There have been several previous reports regarding the secretion of some gastrointestinal hormones following partial or total gastric resection. Some gastrointestinal regulatory peptides, such as vasoactive intestinal polypeptide (VIP) and neurotensin, have been implicated in the pathophysiology of dumping syndrome^{4,5)}.

Serum gastrointestinal hormone responses to a standardized Japanese breakfast (solid meal) were evaluated for the same subjects. They were measured by the sensitive radioimmunoassay which has been previously described in detail¹¹⁻¹⁴⁾. Several of the previous publications have used liquid meals, instilled into the stomach or duodenum¹⁵⁻²¹⁾. In the present study a standardized balanced solid meal was used as the stimulus for hormone release just like daily life of the patients. The test meal consisted of 25.4 g protein, 18.3 g fat and 79.1 g carbohydrate, with 603 total Calories.

Fig. 2 shows summary of the hormone responses. The hormone level changes could be divided into three patterns; obtunded responses (gastrin, pancreatic polypeptide: PP), normal release (motilin, glucose-dependent insulinotropic peptide: GIP) and increased secretion (cholecystokinin: CCK, neurotensin, peptide YY: PYY). Table 2 is summary of three types of gastrointestinal hormone responses to meal after gastric resection in the literature.

a. Obtunded group

Post-prandial responses of both gastrin and PP in plasma were completely abolished following partial gastrectomy (gastrin: $P < 0.02$, PP: $P < 0.01$) and total gastrectomy (both: $P < 0.002$) as shown in Fig. 2a and 2b. Basal (fasting) levels of both hormones were reduced after total gastrectomy (gastrin: $P < 0.02$, PP: $P < 0.05$).

The absence of gastrin responses was expected after antrectomy, and reduced gastrin

Table 2. Three type responses of gastrointestinal hormone after distal partial and total gastrectomy in the literature

Type	Hormones	References
Obtunded	gastrin	22, 23, 24, 29, 30
	pancreatic polypeptide (PP)	23, 25, 26, 27, 28, 29, 30
	secretin	31, 32
Normal	motilin	33, 34
	glucose-dependent insulinotropic peptide (GIP)	34, 35, 36
Increased	cholecystokinin (CCK)	15, 16, 17, 28, 37, 38, 39, 40
	neurotensin	6, 46, 47, 48, 49, 50, 57
	peptide YY (PYY)	7, 51, 52, 53, 55, 56
	enteroglucagon (GLI)	4, 43, 44, 45, 52, 53
	vasoactive intestinal peptide (VIP)	5, 43, 46, 57

responses after partial or total gastrectomy have been reported previously^{22,23}. However, it is reported that gastrin response after meal was seen in Billroth I procedure after distal partial gastrectomy due to possible passage of food through duodenum²⁴. Therefore, duodenum is also considered to be important organ to secrete gastrin in respect to physiological pathway of alimentary tract.

The PP response was abolished, undoubtedly reflecting the sectioning of pancreatic vagal fibers by duodenal transection^{25,26}. Previous studies have revealed a blunted PP response after total gastrectomy^{23,27} and partial gastrectomy with a Billroth II anastomosis^{27,28}. Since both gastrin and PP have been shown to contract the lower esophageal sphincter (LES), it is possible that the absence of gastrin and PP may contribute to gastro-esophageal reflux after distal partial gastrectomy^{29,30}.

The release of another hormone from the upper small intestine, secretin, has been reported to be reduced following gastrectomy^{31,32}. Since secretin is responsible for stimulating pancreatic and hepatic bicarbonate to neutralize the acid component of chyme, and is released by low pH in the duodenum, this reduction in secretin release is entirely appropriate following gastrectomy.

b. Normal group

Plasma GIP and motilin levels were not remarkably different between the controls and two groups of gastrectomy patients as shown in Fig. 2c and 2d.

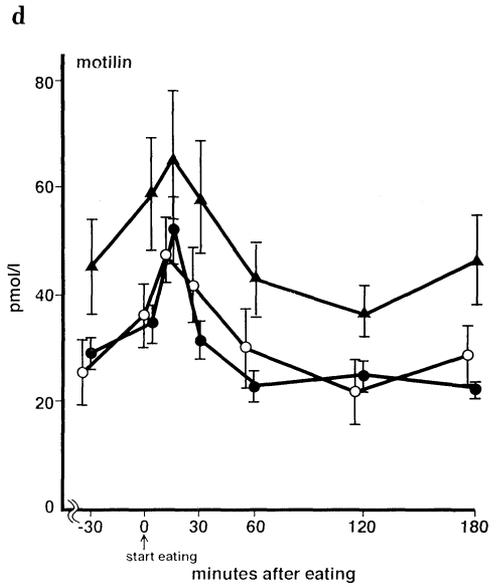
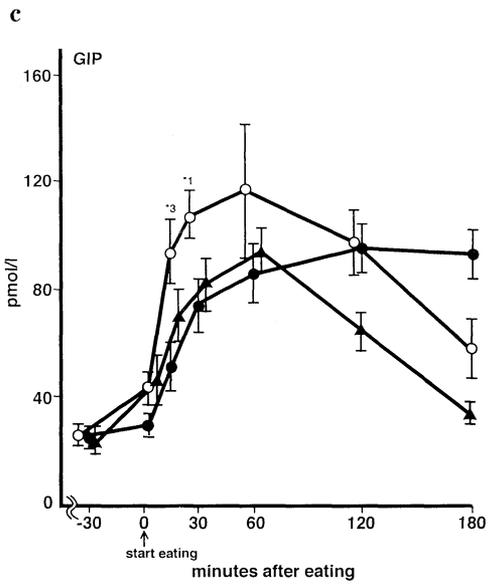
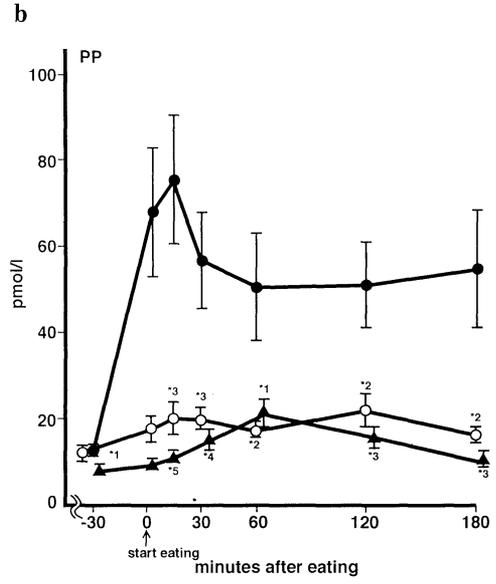
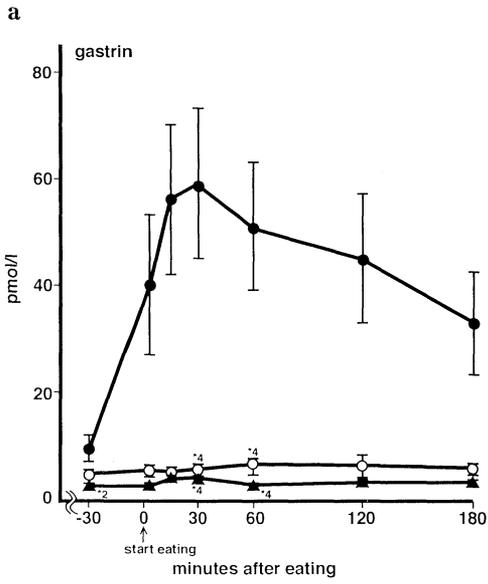
Motilin secretion was reported to be almost normal or slightly reduced after gastric resection³³. Motilin concentration was normal following gastrectomy in the present study. It is interesting that the normal interdigestive migrating motor complexes are seen in these patients, even though postprandial small bowel transit is accelerated²⁴.

The increased early response of GIP in distal gastrectomy patients may also reflect the rapid passage of gastric contents into the upper small intestine. Since GIP appears to be a major incretin in man, an increased response may be anticipated to precede the hyperinsulinemia associated with dumping^{24,34}. A previous study reported an increased GIP secretion in association with symptomatic postprandial hypoglycemia³⁵. However, in the present study the increase in GIP secretion was minor, in keeping with the lack of dumping symptoms in the two patient groups.

c. Increased group

In contrast, CCK, neurotensin and PYY levels went up shortly after meal in patients with gastric resection as shown in Fig. 2e, 2f, and 2g. CCK response was increased 2-fold after partial gastrectomy ($P < 0.02$) and 3-fold after total gastrectomy ($P < 0.001$). Basal levels of CCK were similar in all three groups. Postprandially, an 8-fold increase in neurotensin level and a 2-fold increase in PYY level were observed in both partial and total gastrectomy ($P < 0.02$). Furthermore, basal PYY levels were increased after total gastrectomy ($P < 0.05$).

While there is general agreement about the changes observed, the pattern of CCK release after gastrectomy, is controversial^{15-17,28,36-38}. It is not clear why obtunded^{15,28} or normal¹⁶ CCK response has been found in some previous studies of gastrectomized patients. However,



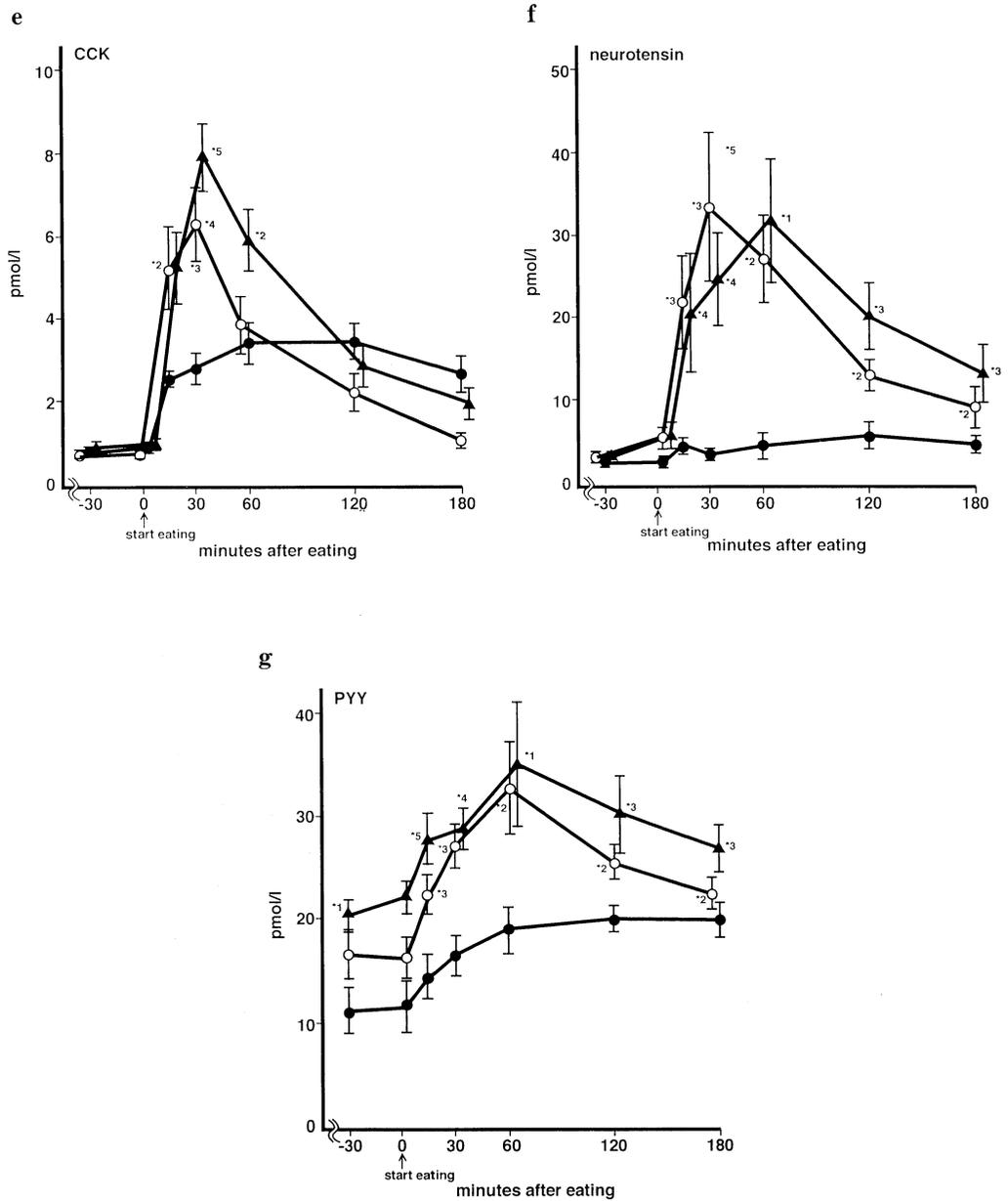


Fig. 2. Plasma gastrin [a], pancreatic polypeptide (PP) [b], glucose-dependent insulintropic polypeptide (GIP) [c], motilin [d], cholecystokinin (CCK) [e], neurotensin [f], and peptide YY (PYY) [g], responses to a standardized meal in healthy controls ●---●, and patients following distal partial gastrectomy ○---○ or total gastrectomy ▲---▲ (mean ± SEM). Asterisks with a number show statistical differences (*1: $P < 0.05$, *2: $P < 0.02$, *3: $P < 0.01$, *4: $P < 0.002$, *5: $P < 0.001$ all vs. healthy controls).

the general consensus suggests an increase in CCK secretion after total or partial distal gastric resection^{17,36-38}. The differences may be due, at least in part, to different methods of stimulation. In the present study the early release of CCK was increased in patients who had undergone distal gastrectomy and early and late responses were greatly increased in total gastrectomy patients. It is likely that this increased secretion is a response to rapid gastric emptying as it was previously seen in patients with primary duodenogastric reflux³⁹. Furthermore, the increased early CCK response seen after gastrectomy may help to compensate for vagal denervation of the gallbladder and to promote contraction of the organ³⁷.

Marked increases in the distal gastrointestinal hormones, neurotensin and PYY, were observed after gastrectomy in the present study. Similar increases have been reported in gastrectomized patients with symptoms of dumping^{6,7}. High doses of neurotensin cause vasodilatation. However, current evidence suggests that it is unlikely that this peptide plays a role in the pathophysiology of dumping⁴⁰. There is little evidence to support the role of neurotensin in dumping. Serum concentrations of enteroglucagon, neurotensin and VIP are all increased when dumping symptoms are provoked in susceptible post-gastrectomy patients⁴⁻⁶. As these changes in gastrointestinal regulatory peptides accompany the symptoms of dumping, it has been speculated that they may contribute to the pathophysiology of the condition⁴⁻⁶. On the other hand, the effects of CCK and neurotensin on the lower esophageal sphincter (LES) have been reported as inhibitory; they might exhibit some inhibitory control on the LES^{41,42}.

Enteroglucagon and VIP are also classified as the increased type. Enteroglucagon seems to relate with not only the early dumping but also hypoglycemia^{4,43-45}. It is reported that VIP level increases after meal ingestion in early dumping syndrome^{5,43,46}.

3. Relationship and interaction of serum gastrointestinal hormone changes with symptoms

In our study, correlation between symptom score and increased hormone levels were investigated in increased type of gastrointestinal hormones. Table 3 shows regression coefficient by χ^2 test. Neurotensin has some relationship with both dumping syndrome and reflux esophagitis in distal partial gastrectomy. CCK and PYY also seem to be responsible for these symptoms. However, there is not definite correlation between them.

Some of these hormonal changes may actually be beneficial by slowing gastric emptying and delaying small bowel transit^{6,7}. Indeed, increased secretion of hormones that delay transit could be considered to be appropriate adaptive responses to gastric resection. Since both neurotensin and PYY have inhibitory effects on upper gastrointestinal motility and secretion, these increased responses appear to be adaptive changes which may slow transit and improve absorption⁴⁷⁻⁵². Enteroglucagon is also classified as the increased type as adaptive changes after gastrectomy^{53,54}. Furthermore, recent studies have demonstrated that PYY is physiologically important in the postprandial promotion of small intestinal absorption^{55,56}. Gastrointestinal hormone changes may play an important role in the adaptive responses to gastrectomy, contributing to post-gastrectomy symptoms. Gastrointestinal hormones in both obtunded and increased groups give inhibitory effect to the LES pressure after distal partial

Table 3. Relationship (regression coefficient) between gastrointestinal hormone release and symptoms

	CCK 30	CCK 180	Nt 30	Nt 180	PYY 30	PYY 180	-ΔGIP 180
<i>partial gastrectomy</i>							
early dumping	0.54	—	0.59	—	0.14	—	—
late dumping	—	0.14	—	0.51	—	0.14	0.37
reflux esophagitis	0.03	0.26	0.56	0.58	0.43	0.58	—
<i>total gastrectomy</i>							
early dumping	0.16	—	0.19	—	0.10	—	—
late dumping	—	0.34	—	0.16	—	0.03	0.13
reflux esophagitis	0.21	0.03	0.03	0.03	0.21	0.30	—

ex. Nt 30 : neurotensin secretion 30 minutes after test meal

-ΔGIP 180 : decrease of GIP secretion 180 minutes after test meal

gastrectomy.

The effects of increased secretion of PYY and enteroglucagon would tend to alleviate the symptoms of dumping and these hormonal changes which accompany the syndrome could be considered to be appropriate adaptive responses to the rapid delivery of unabsorbed nutrient into the distal intestine^{6,7}. Long et al reported that somatostatin infusion reduced the symptoms of the dumping syndrome with a corresponding decrease in secretion of peptides such as neurotensin and VIP⁵⁷. More recent reports suggest that long-acting somatostatin analogues offer promise in treating the condition^{58,59}. It is interesting that somatostatin not only slows bowel transit but also stimulates esophageal motor activity⁶⁰. A better understanding of the hormonal changes associated with gastrectomy could provide a more rational and effective therapeutic approach for post-gastrectomy symptoms, including reflux esophagitis as well as the dumping syndrome. Long-acting somatostatin analogues may be useful in this regard.

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