의학박사 학위논문

Postprandial changes in gastrointestinal hormones and hemodynamics have a role in the development of early dumping syndrome in gastrectomized patients

위절제술 환자에서 식후 위장관 호르몬 분비 및 혈역학적 변화가 조기 덤핑 증후군의 발생에 미치는 영향

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서울대학교 대학원

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지도 교수 이 혁 준

이 논문을 의학박사 학위논문으로 제출함

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Abstract

Postprandial changes in gastrointestinal hormones and hemodynamics have a role in the development of early dumping syndrome in gastrectomized patients

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Introduction

Early dumping syndrome after gastrectomy has a negative impact on patients' quality of life, of which mechanism, however, is not completely understood. The aim of this study was to examine early postprandial changes in gastrointestinal (GI) hormones and hemodynamics after gastrectomy in terms of the early dumping syndrome.

Methods

Forty-two patients who underwent gastrectomy for gastric cancer and 18 controls who had no previous abdominal surgery were enrolled. Before and 20 mins after liquid meal (400 kcal) ingestion, blood glucose, insulin, glucagon-like peptide-1 (GLP-1), GLP-2, and vasoactive intestinal peptide (VIP) concentrations and superior mesenteric artery (SMA) and renal blood flow were measured. Heart rate were recorded at 5-min intervals. All subjects were examined for dumping syndrome using a questionnaire based on Sigstad's clinical diagnostic index.

Results

Blood glucose, insulin, GLP-1, and GLP-2 levels, SMA blood flow, renal resistive index and heart rate were increased significantly greater in patients who underwent gastrectomy than in controls (all p<0.010). Within patients who underwent gastrectomy, distal gastrectomy was a significant clinical factor associated with a lower risk for early dumping syndrome than total gastrectomy (hazard ratio 0.076, 95% confidence interval 0.011–0.531; p=0.009). Patients after total gastrectomy demonstrated greater postprandial increase in blood glucose (p<0.001), GLP-1 (p=0.025), GLP-2 (p=0.001), and heart rate (p=0.016) than those after distal gastrectomy.

Conclusions

Early postprandial changes in GI hormones and hemodynamics were greater in patients who underwent gastrectomy than in controls, especially after total gastrectomy, suggesting that these changes have a role in the development of early dumping syndrome.

Keywords : Gastrectomy, Early dumping syndrome, Gastrointestinal hormones, Splanchnic blood flow, Hemodynamics

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Introduction

In the past few decades, the oncological outcomes of gastrectomy for gastric cancer have considerably improved due to the developments in early diagnosis, surgical technique, perioperative care, and adjuvant chemotherapy (1-3). However, gastrectomy itself is inevitably followed by structural changes in the gastrointestinal (GI) tract anatomy and disturbances in food passage, digestion, and absorption of nutrients (4-6). This results in various "postgastrectomy syndromes," among which early dumping syndrome is manifested by GI symptoms such as bloating, borborygmi, and diarrhea, and systemic vasomotor symptoms such as diaphoresis, desire to lie down, palpitation, hypotension, and syncope (4, 5). These symptoms develop within 10–30 min upon food ingestion and therefore considerably influence oral intake and poor nutritional status (1, 4, 6).

Although the mechanism of early dumping syndrome is not completely understood, accelerated delivery of chyme into the small intestine has been considered as a critical step in most previous studies (4, 5, 7-9). According to the conventional explanation, accelerated delivery of chyme into the small intestine leads to fluid shifts from the intravascular compartment into the intestinal lumen, for helping digestion of chyme and absorption of nutrients (4, 5). This is followed by small intestine distention which has been considered to be responsible for GI symptoms such as bloating, borborygmi, and diarrhea. Concurrent intravascular plasma volume contraction has been considered to be responsible for vasomotor symptoms such as diaphoresis, palpitation, and hypotension. Sigstad H demonstrated that the degree of postprandial plasma volume contraction calculated by the indirect method of Evans blue and hematocrit concentrations was positively correlated with the severity of dumping syndrome based on his clinical diagnostic index (10).

Recently, as the number of cases of bariatric surgery has increased, many studies have reported on the postoperative alterations of GI hormone profiles after meal ingestion (8, 9, 11-18). Among these GI hormones, glucagon-like peptide-1 (GLP-1) is known to slow down gastric emptying and intestinal motility (8, 9, 13). GLP-2 is known to stimulate nutrient absorption and splanchnic blood flow upon food ingestion (11, 12). Vasoactive intestinal peptide (VIP) is also known to be related with splanchnic vasodilation and massive diarrhea (17, 18). The alterations of these GI hormone profiles after bariatric surgery could lead to various postprandial symptoms such as bloating, nausea, and anxiety, which result in reduced food intake and weight loss. These postprandial symptoms could be considered to have a “therapeutic effect” after bariatric surgery; however, are actually the main constituents of troublesome early dumping syndrome (8, 9). Meanwhile, one study reported that the postprandial splanchnic blood flow response became significantly enhanced after bariatric surgery (19). Actually, postprandial increase in splanchnic blood flow have been frequently suggested as a hemodynamic mechanism of early dumping syndrome even before the era of bariatric surgery (20-23). It has been suggested that meal-induced splanchnic blood pooling could introduce systemic hypotensive stress ensued by tachycardia, hypotension, drowsiness, and restlessness, which are the main vasomotor symptoms of early dumping syndrome.

To our knowledge, there has been no report investigating GI hormone level and splanchnic blood flow concomitantly in patients who underwent gastrectomy for gastric cancer. The aim of this study, therefore, was to examine the early postprandial changes in GI hormones and hemodynamics including splanchnic blood flow after gastrectomy for gastric cancer and to analyze the degree of these changes in terms of the early dumping syndrome. We hypothesized that the postprandial changes in GI hormones including GLP-2 which is known to mediate the splanchnic blood flow and hemodynamics would be greater in patients who underwent gastrectomy than in controls.

Materials and Methods

Subjects

Forty-two patients who had undergone gastrectomy for gastric cancer and 18 controls who had undergone operations other than gastrectomy (inguinal hernia repair in 14 controls and subcutaneous mass excision in 4) were enrolled. None of the patients or controls had a history of abdominal surgery, except gastrectomy, diabetes, chronic renal disease, or ongoing adjuvant chemotherapy. Clinical factors including age, sex, type of operation, complication, pathologic stage, and preoperative body weight were examined by medical record review. This study was approved by the Institutional Review Board of Gachon University Gil Medical Center (IRB No.: GAIRB2018-284) and conducted in accordance with the Helsinki Declaration of 1964 and later versions. All subjects provided written informed consent before enrollment.

Questionnaire (direct interview)

All patients were examined directly by the investigator in out-patient clinic. They were asked specifically about the diagnostic symptoms of the dumping syndrome which occurred after meals at home using a questionnaire based on Sigstad's clinical diagnostic index (Table 1) (10). In this form, systemic vasomotor symptoms such as desire to lie down, palpitation, restlessness, feeling of warmth, and sweating were given high weighting factors, however, GI symptoms such as nausea, bloating, and borborygmi were given low weighting factors. According to his original report, the subjects whose score of 7 or above were considered as "dumper," and those of 4 or below as "non-dumper" (10). Therefore, the subjects who have GI symptoms only cannot be determined as "dumper".

Table 1 Dumping symptoms in patients who underwent gastrectomy according to Sigstad's clinical diagnostic index

Symptoms	Score	Patients (n=42)
Pre-shock, shock	+5	0 (0.0%)
"Almost fainting," syncope, unconsciousness	+4	0 (0.0%)
Desire to lie or sit down	+4	6 (14.3%)
Breathlessness, dyspnea	+3	0 (0.0%)
Weakness, exhaustion	+3	5 (11.9%)
Sleepiness, drowsiness, yawning, apathy, falling asleep	+3	7 (16.7%)
Palpitation	+3	1 (2.4%)
Restlessness	+2	15 (35.7%)
Dizziness	+2	6 (14.3%)
Headache	+1	0 (0.0%)
Feeling of warmth, sweating, pallor, clammy skin	+1	19 (45.2%)
Nausea	+1	7 (16.7%)
Fullness in the abdomen, bloating	+1	27 (64.3%)
Borborygmi	+1	31 (73.8%)
Eructation	-1	0 (0.0%)
Vomiting	-4	0 (0.0%)

Table 1-1 Translated into Korean language

증상	점수	환자 (n=42)
쇼크 상태 (병원에 실려갈 정도의 심각한 저혈압)	+5	0 (0.0%)
실신, 의식혼미	+4	0 (0.0%)
눕거나 주저 앉고 싶음	+4	6 (14.3%)
호흡곤란	+3	0 (0.0%)
전신 쇠약감, 무력감	+3	5 (11.9%)
졸림, 하품	+3	7 (16.7%)
가슴 두근거림	+3	1 (2.4%)
안절부절 못함	+2	15 (35.7%)
어지러움	+2	6 (14.3%)
두통	+1	0 (0.0%)
얼굴이 창백해짐, 식은땀, 열감	+1	19 (45.2%)
메스꺼움	+1	7 (16.7%)
복부팽만감	+1	27 (64.3%)
배에서 꾸르륵 소리	+1	31 (73.8%)
트림	-1	0 (0.0%)
구토	-4	0 (0.0%)

Study meal

After 8 h of fasting, all subjects ingested two cans (400 kcal / 400 mL) of liquid meal (New Care, DaeSang, Seoul, South Korea) within 5 min in sitting position. One can (200 kcal / 200 mL) of this meal was composed of 30 g carbohydrate, 7 g protein, and 6 g lipid. The calorie distribution was as follows: 59% from protein, 14% from fat, and 27% from carbohydrates.

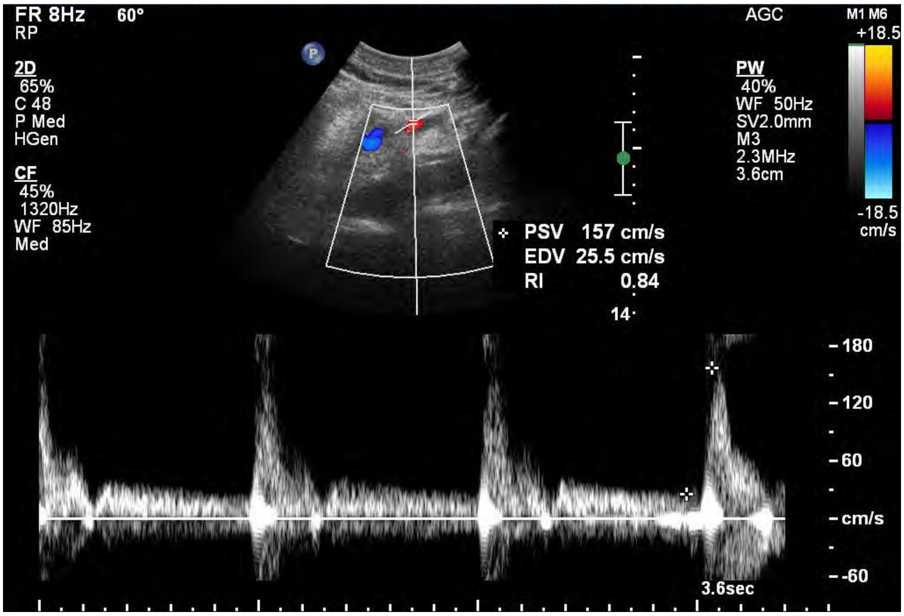
Biochemical measurements

Serum glucose and insulin concentrations were measured by the photometric assay and the chemiluminescent immunoassay (CLIA), respectively, as a usual clinical practice. Three milliliters of venous blood samples for GLP-1, GLP-2, and VIP measurements was collected into ethylenediaminetetraacetic acid (EDTA) tubes. After 30 min of clotting at room temperature, they were centrifuged at 3,000 rpm for 10 min. The supernatant (plasma) after centrifugation was separated from whole blood, collected into microtube, and stored at -70°C until analysis. Plasma GLP-1 concentration was measured with an enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions (YK160, YANAIHARA, Japan). Plasma GLP-2 concentration was also measured with ELISA kit according to the manufacturer's instructions (EZGLP2-37K, Millipore, USA). These two GI hormones were analyzed using duplicate samples for quality assessment on all 60 subjects (42 patients who underwent gastrectomy and 18 controls). Plasma VIP concentration was measured with ELISA kit according to the manufacturer's instructions (EIA-VIP-1, RayBiotech, USA) and analyzed using single samples on 40 subjects (24 patients who underwent gastrectomy and 16 controls).

Doppler measurements

SMA and renal blood flow were measured using duplex ultrasonography (DU) (LOGIQ E10, GE Medical Systems, USA, and EPIQ7 by PHILIPS, USA) with a 5.0-MHz convex probe. All Doppler measurements were performed by one experienced radiologist who was not aware of the subjects' group. For physical and psychological stability, the room temperature was maintained at 20~25°C by a thermal feedback device. After 10~20 min of bed rest, under dim light and calm atmosphere, subjects were made to lie in supine position with slight head elevation which could induce relaxation of the abdominal muscles (24-29). For SMA exam, the probe is placed just below the xiphoid process and directed slightly to the left to visualize the upper abdominal aorta. Then, scanning downwards display the celiac trunk and SMA which are usually separated by 1-1.5 cm. Sample volume cursor is located on 1-2 cm downstream from the aortic origin of the SMA and the Doppler beam is discharged (Figure 1a). The recommended angle of insonation during Doppler sampling is 60° or less, as higher angles increase the risks of significant imprecision. Sample volume should encompass the whole diameter of the vessel to cover all detectable velocities along the entire cross-section of the vessel (24, 29). For renal blood flow exam, the probe is placed below the costal margin in the dorsal and lateral areas of the right flank (flank coronal scanning) (25, 26). Color Doppler imaging is used to access easily the intrarenal arteries such as interlobar, interlobular, or arcuate arteries. The sample volume cursor is located to an intrarenal interlobar artery along the borders of the medullary pyramid and the Doppler beam is discharged for blood flow measurement (Figure 1b).

(a)



(b)

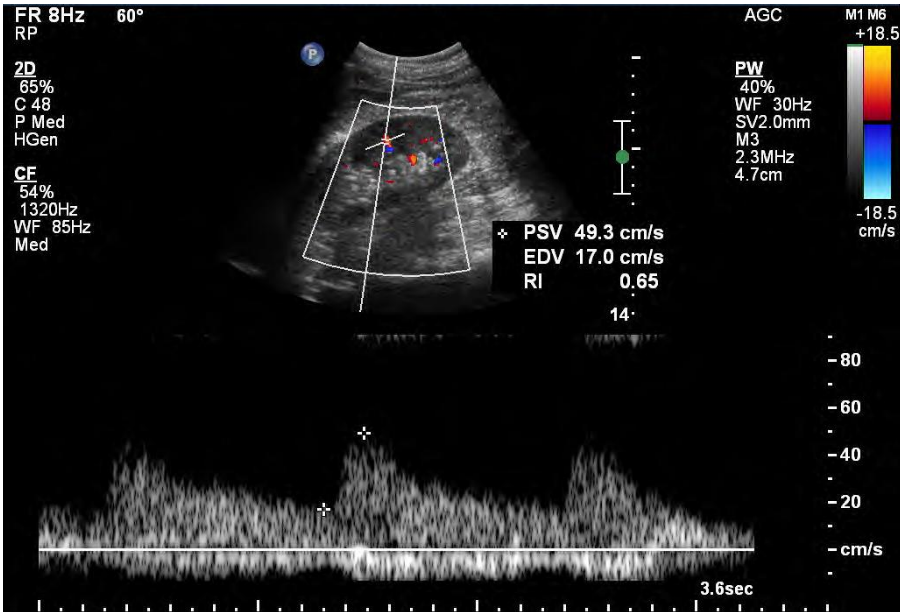


Figure 1 Doppler US image of (a) SMA and (b) intrarenal artery at fasting state in a 44-year-old man who underwent total gastrectomy 49 days ago.

Postprandial features of various SMA Doppler parameters at 10 min intervals

We performed Doppler exams for evaluation of various SMA parameters including peak systolic velocity (PSV), end diastolic velocity (EDV), resistive index (RI), time averaged mean velocity (TAMV), diameter (D) and calculated volume flow on 9 gastrectomy patients and 2 controls. RI is calculated as (PSV – EDV) / PSV and is known to have an inverse relationship with blood flow (27, 28). TAMV represents a mean Doppler shift on full range spectrum along the cardiac cycle (a continuous pink line delineating the mean values gathered from all detectable velocities in Figure 2) and is calculated automatically from innate DU software (29). Volume flow (mL/min) is calculated as $\pi \times (D/2)^2 \times TAMV \times 60$ (29). During 50 min after 400-kcal liquid meal ingestion, the degree of changes in Doppler parameters except diameter were most prominent in 10-30 min (Figure 3). Previous studies also reported that the signs and symptoms of early dumping syndrome are most prominent within 10-30 min (4, 9, 16, 21). After 40 min, the values of those parameters spontaneously returned to pre-meal levels. Among the various parameters, RI values showed most regular and concentrated features in which the greatest changes were presented at 20 min. Therefore, on followed protocol, we chose RI as a parameter to quantify blood flow and performed postprandial blood samples and Doppler exams at 20 min after meal ingestion.

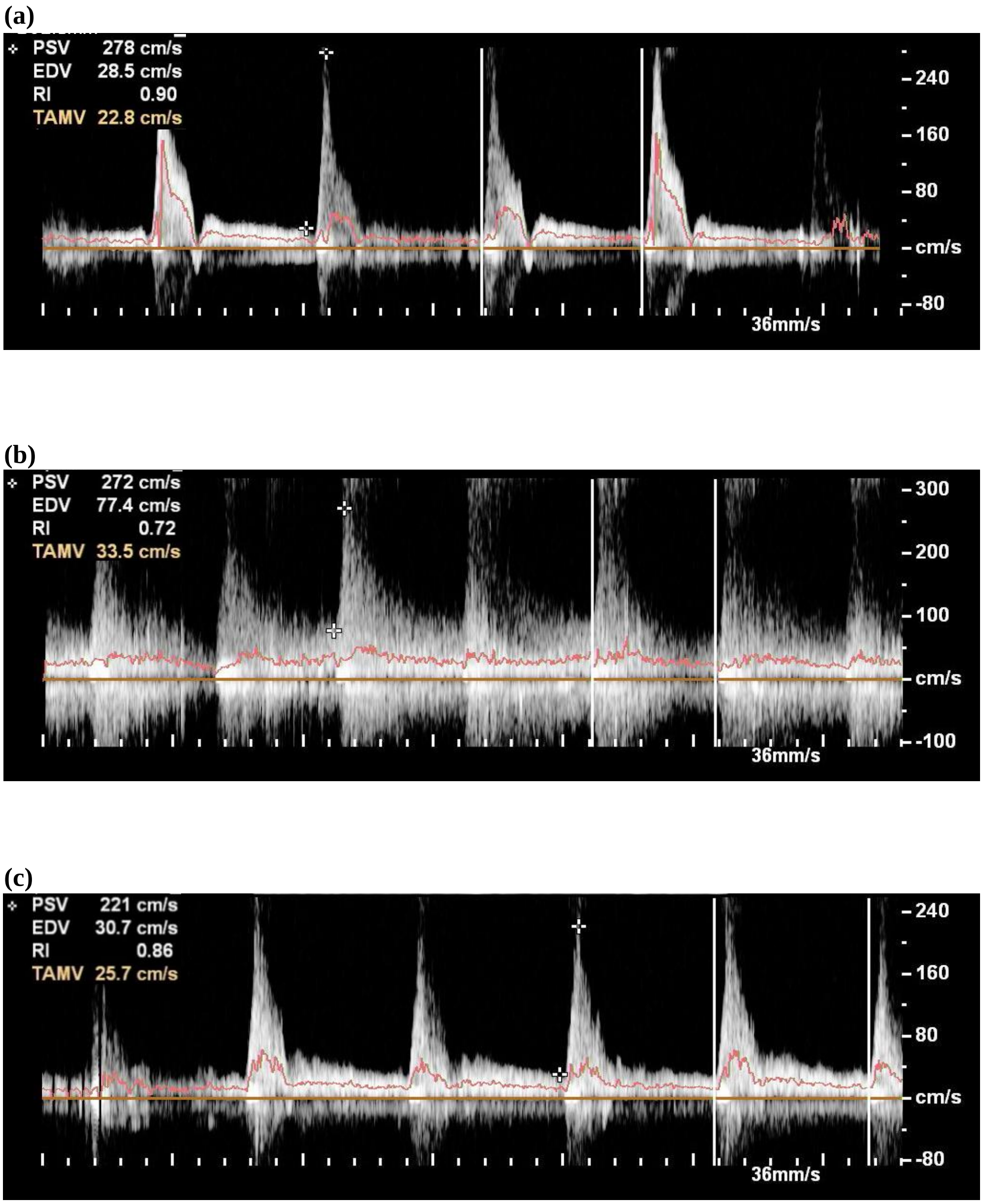


Figure 2 SMA Doppler US image at (a) fasting state, (b) 20 min, and (c) 50 min after meal ingestion in a 59-year-old man who underwent distal gastrectomy 30 months ago.

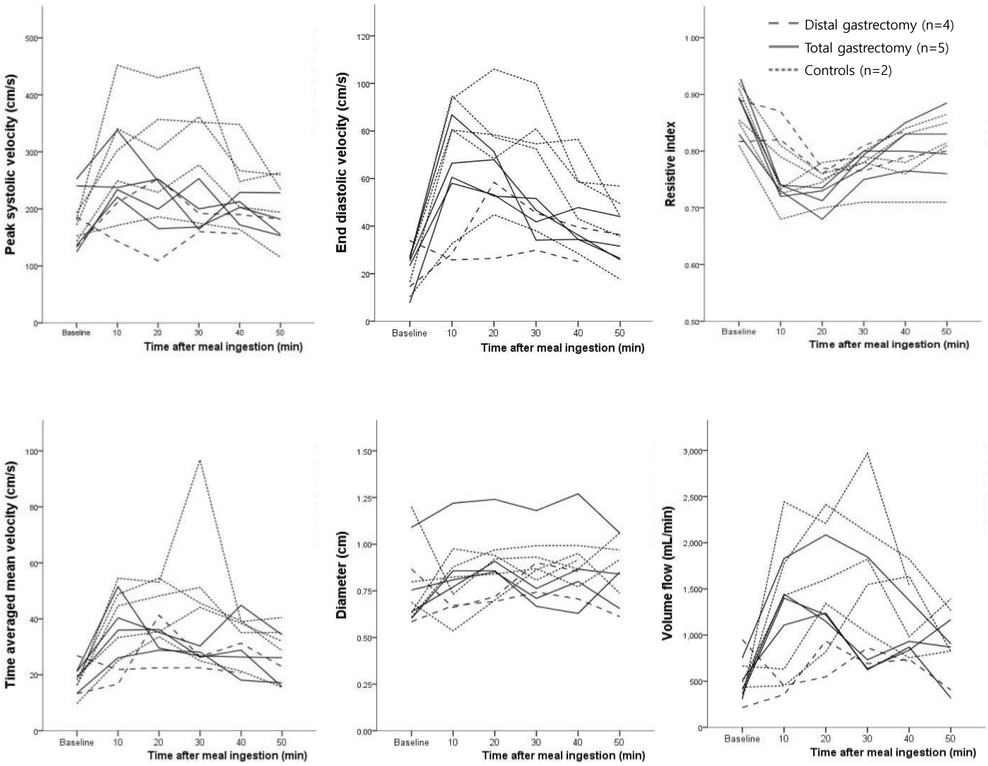


Figure 3 Postprandial features of various SMA Doppler parameters at 10 min intervals.

Protocol

In all subjects, after 8 h of fasting, baseline venous blood samples were taken for measurements of glucose, insulin, and GI hormone level. After blood sampling, baseline Doppler measurements of the SMA and intrarenal artery were performed in supine position. After baseline examinations, subjects ingested a 400-kcal liquid meal within 5 min in sitting position and took a bed rest. After 20 min elapsed from the time point when subjects started meal ingestion, blood sampling and Doppler examination were repeated once more. During the study, the subject's heart rate was recorded at baseline and 5-min intervals elapsed from the time point when subjects started meal ingestion.

Statistics

Our null hypothesis for the sample size calculation was that the postprandial changes of plasma GLP-2 level (our primary end point) would not be different between gastrectomy patients and controls. The effect size was estimated based on our own data of plasma GLP-2 levels in patient and control groups because these were the only data available. From the mean values of 6.90 ± 4.76 for patients and 1.28 ± 4.76 for controls, the sample size was calculated to n=17 in each group at the 5% level of significance with 90% power using PASS Software (Power Analysis and sample size software : http://www.ncss.com). This calculation was performed through consultation with Medical Research Collaborating Center (MRCC), Seoul National University Hospital.

Values are presented as mean ± standard deviation. Differences in clinical variables between the subject groups were compared using Student's t-test or Mann-Whitney

U test for continuous data and the χ^2 test for categorical data. The meal-induced change in biochemical and hemodynamic variables within each subject group was analyzed using paired Student's t-test. The degree of the meal-induced change in biochemical and hemodynamic variables between the subject groups was compared by repeated-measures analysis of variance. Multivariable analysis was performed using multiple logistic regression. All analyses were performed using SPSS version 20 (SPSS, Chicago, IL), and a p-value of <0.05 was considered significant.

Results

Characteristics of the subjects

The clinical characteristics of the patients who underwent gastrectomy and controls are summarized in Table 2. There were no significant differences between patients and controls in terms of age, sex, preoperative body weight, and body mass index. The postoperative body weight loss and the severity of dumping syndrome according to Sigstad's clinical diagnostic index [13] were greater in patients than in controls (both $p<0.001$). The characteristics of the patients who underwent gastrectomy are summarized in Table 3. In patients who underwent gastrectomy, the most common dumping symptom was borborygmi (73.8%), followed by bloating (64.3%), feeling of warmth or sweating (45.2%), restlessness (35.7%), and drowsiness (16.7%) (Table 1). The characteristics of the patients who underwent gastrectomy are summarized in Table 3. Postoperative complications (Clavien-Dindo classification II or higher) occurred more frequently in total gastrectomy group than in distal gastrectomy group ($p=0.003$). Pathological stages (according to the AJCC 8th classification) were more advanced in total gastrectomy group than in distal gastrectomy group ($p = 0.008$). Adjuvant chemotherapy was performed more frequently in total gastrectomy group than in distal gastrectomy group ($p = 0.031$).

Table 2 Characteristics of subjects

	Patients (n=42)	Controls (n=18)	p value
Age (years)	59.5 ± 12.7	56.3 ± 15.6	0.411
Sex (male/female)	29:13	16:2	0.192
Body mass index (kg/m^2)*	24.0 ± 3.3	23.6 ± 1.8	0.535
Body weight (kg), preoperative	65.3 ± 12.0	65.6 ± 8.6	0.930
Body weight (kg), postoperative	61.0 ± 12.1	65.0 ± 8.9	0.208
Body weight change (%)†	93.3 ± 6.6	99.1 ± 1.8	<0.001
Dumping score‡	4.7 ± 4.4	0.0 ± 0.0	<0.001

Values are mean ± SD *postoperative values †Postoperative body weight/preoperative body weight × 100

‡According to Sigstad's clinical diagnostic index

Table 3 Characteristics of gastrectomy patients

	Distal gastrectomy * (n=24)	Total gastrectomy (n=18)	p value
Age (years)	58.3 ± 14.1	61.1 ± 10.7	0.485
Sex (male/female)	14:10	15:3	0.083
ASA score			
I	3 (12.5%)	4 (22.2%)	0.438
II	21 (87.5%)	14 (77.8%)	
Postoperative days			
≤ 180	13 (54.2%)	10 (55.6%)	0.929
> 180	11 (45.8%)	8 (44.4%)	
Complication†			
No	21 (87.5%)	13 (72.2%)	0.003
Yes	3 (12.5%)	5 (27.8%)	
Stage (AJCC 8th)			
I	21 (87.5%)	9 (50.0%)	0.008
II	2 (8.3%)	2 (11.1%)	
III	1 (4.2%)	7 (38.9%)	
Chemotherapy			
No	23 (95.8%)	12 (66.7%)	0.031
Yes	1 (4.2%)	6 (33.3%)	

ASA American society of anesthesiologist AJCC American Joint Committee on Cancer

*Including one patient with pylorus preserving gastrectomy †In cases of the Clavien-Dindo classification II or higher

Meal-induced changes in blood glucose, GI hormones, and hemodynamics

After meal ingestion, serum glucose concentration was increased in both patients who underwent gastrectomy and controls (both $p<0.001$) (Figure 4a). However, the degree of increase was significantly greater in patients who underwent gastrectomy than in controls ($p<0.001$). Serum insulin concentration was also increased in both gastrectomy patients and controls (both $p<0.001$), however, the degree of increase was significantly greater in gastrectomy patients than in controls ($p<0.001$) (Figure 4b). Plasma GLP-1 concentration was increased only in patients who underwent gastrectomy ($p<0.001$) (Figure 4c). Plasma GLP-2 concentration was increased in both patients who underwent gastrectomy and controls ($p<0.001$ and $p=0.030$, respectively) (Figure 4d). However, the degree of increase was significantly greater in patients who underwent gastrectomy than in controls ($p<0.001$). Plasma VIP concentration was not significantly increased in either patients who underwent gastrectomy or controls (Figure 4e). SMA RI was decreased in both patients who underwent gastrectomy and controls (both $p<0.001$) (Figure 4f). However, the degree of decrease was significantly greater in patients who underwent gastrectomy than in controls ($p=0.011$). The renal RI increased only in patients who underwent gastrectomy ($p<0.001$) (Figure 4g). Heart rate was increased in both patients who underwent gastrectomy and controls ($p<0.001$ and $p=0.008$, respectively) (Figure 4h). However, the degree of increase was significantly greater in patients who underwent gastrectomy than in controls ($p<0.001$).

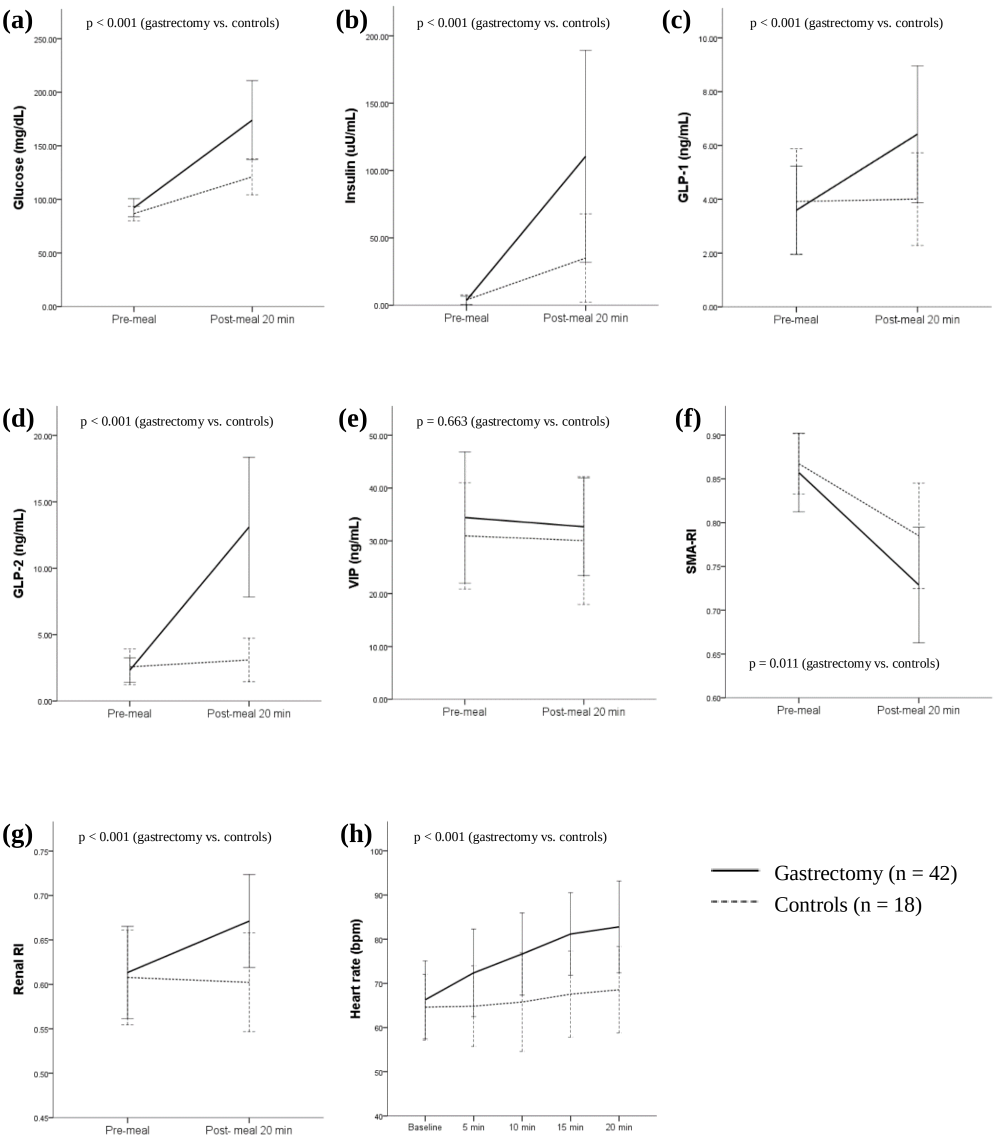


Figure 4 Meal-induced changes in **(a)** glucose, **(b)** insulin **(c)** GLP-1, **(d)** GLP-2, **(e)** VIP, **(f)** superior mesenteric artery resistive index (RI), **(g)** renal RI, **(h)** heart rate in patients who underwent gastrectomy (solid line) and controls (dotted line). Values are mean ± SD.

Meal-induced changes in blood glucose, GI hormones, and hemodynamics according to the presence of dumping syndrome (dumping score ≥ 7)

Within 42 patients who underwent gastrectomy, 9 patients were considered as "dumper" who had dumping score ≥ 7 based on Sigstad's clinical diagnostic index. The degree of meal-induced changes in blood glucose, insulin, GLP-1, and GLP-2 concentrations did not differ significantly between the patients with dumping score ≥ 7 and those with dumping score <7, although these changes in both patient groups were greater than in controls (all $p<0.001$) (Figure 5a, b, c, d). VIP concentration was not significantly changed in either patients or controls (Figure 5e). The degree of postprandial change in SMA RI did not differ significantly between the patients with dumping score ≥ 7 and those with dumping score <7, although these changes in both patient groups were greater than in controls ($p=0.068$ and $p=0.007$, respectively) (Figure 5f). The degree of postprandial changes in renal RI and heart rate were greater in the patients with dumping score ≥ 7 than in those with dumping score <7 ($p=0.041$ and $p=0.059$, respectively) and these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 5g, h)

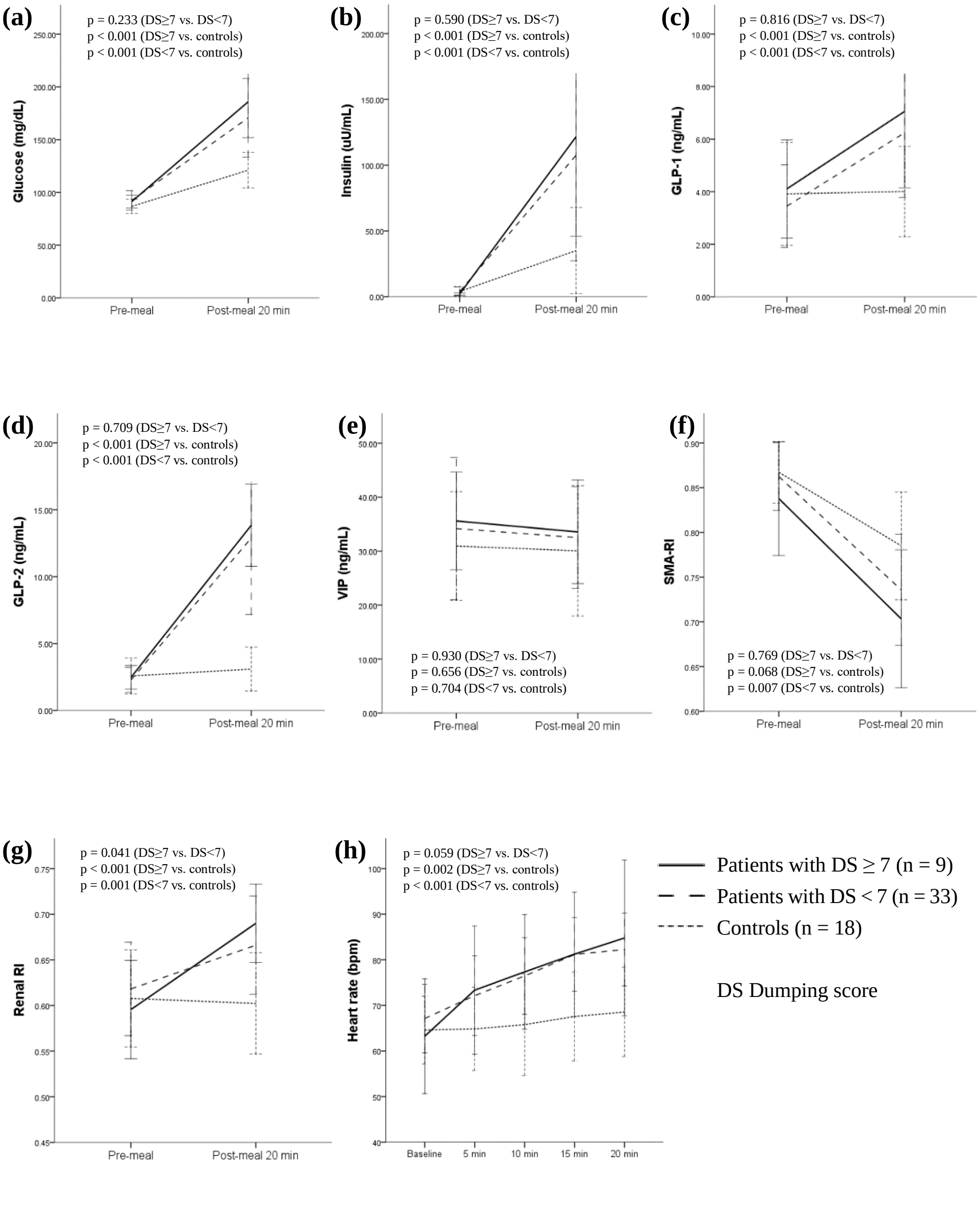


Figure 5 Meal-induced changes in **(a)** glucose, **(b)** insulin **(c)** GLP-1, **(d)** GLP-2, **(e)** VIP, **(f)** superior mesenteric artery resistive index (RI), **(g)** renal RI, **(h)** heart rate in patients with dumping score ≥ 7 ("dumper") (solid line), those with dumping score < 7 (dashed line) and controls (dotted line). Values are mean ± SD.

Meal-induced changes in blood glucose, GI hormones, and hemodynamics in the patients with dumping score ≥ 7 and those with dumping score ≤ 4

According to Sigstad's original report, the subjects who had dumping score of 4 or below were considered as “non-dumper". Therefore we compared the patients with dumping score ≥ 7 (dumper) and those with dumping score ≤ 4 (non-dumper). The degree of meal-induced changes in blood glucose had a tendency to be greater in patients with dumping score ≥ 7 than in those with dumping score ≤ 4 ($p=0.154$) and these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 6a). The degree of meal-induced changes in insulin, GLP-1, and GLP-2 concentrations did not differ significantly between the patients with dumping score ≥ 7 and those with dumping score ≤ 4, although these changes in both patient groups were greater than in controls (all $p<0.001$) (Figure 6b, c, d). VIP concentration was not significantly changed in either patients or controls (Figure 6e). The degree of postprandial change in SMA RI did not differ significantly between the patients with dumping score ≥ 7 and those with dumping score ≤ 4, although these changes in both patient groups were greater than in controls ($p=0.068$ and $p=0.025$, respectively) (Figure 6f). The degree of postprandial changes in renal RI and heart rate were greater in the patients with dumping score ≥ 7 than in those with dumping score ≤ 4 ($p=0.019$ and $p=0.125$, respectively) and these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 6g, h)

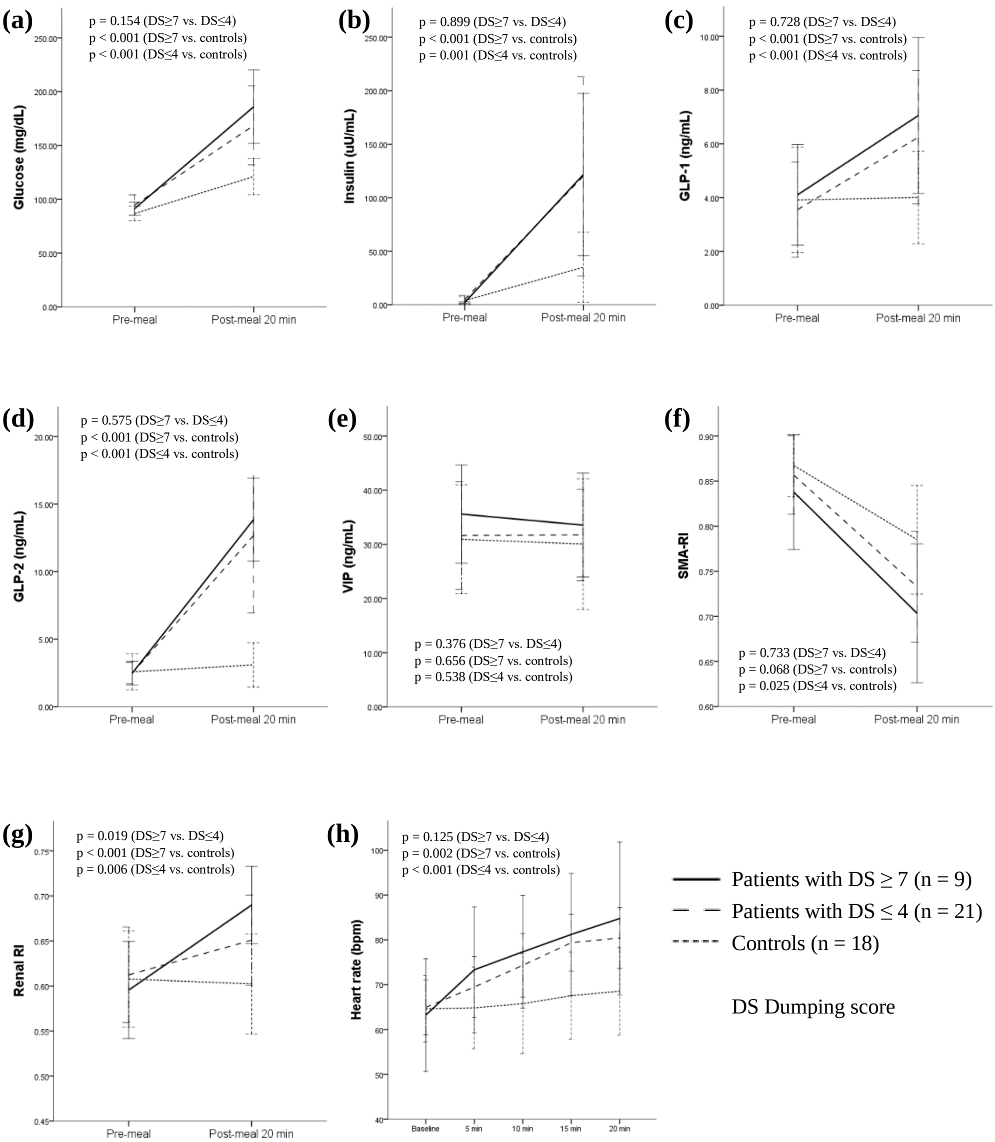


Figure 6 Meal-induced changes in **(a)** glucose, **(b)** insulin **(c)** GLP-1, **(d)** GLP-2, **(e)** VIP, **(f)** superior mesenteric artery resistive index (RI), **(g)** renal RI, **(h)** heart rate in patients with dumping score ≥ 7 ("dumper") (solid line), those with dumping score ≤ 4 ("non-dumper") (dashed line) and controls (dotted line). Values are mean ± SD.

Meal-induced changes in blood glucose, GI hormones, and hemodynamics in the patients with dumping score ≥ 10 and those with dumping score ≤ 2

Considering the subjective nature of patients' symptoms and the broad spectrum of dumping score, we compared the patients with dumping score ≥ 10 and those with dumping score ≤ 2 in addition to a cut-off point of 4 or 7. In our study, the patients with dumping score ≥ 10 had at least one of serious systemic symptoms including exhaustion or desire to lie down, and those with dumping score ≤ 2 had only one or two abdominal symptoms (Figure 7). The degree of meal-induced changes in blood glucose had a tendency to be greater in patients with dumping score ≥ 10 than in those with dumping score ≤ 2 (p=0.139) and these changes in both patient groups were greater than in controls (all p<0.010) (Figure 8a). The degree of meal-induced changes in insulin, GLP-1, and GLP-2 concentrations did not differ significantly between the patients with dumping score ≥ 10 and those with dumping score ≤ 2, although these changes in both patient groups were greater than in controls (all p<0.001) (Figure 8b, c, d). VIP concentration was not significantly changed in either patients or controls (Figure 8e). The degree of postprandial change in SMA RI, renal RI and heart rate were greater in patients with dumping score ≥ 10 than in those with dumping score ≤ 2 (p=0.101, p=0.039 and p=0.114, respectively) (Figure 8f, g, h).

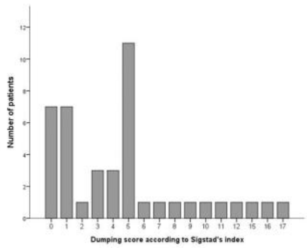


Figure 7 Distribution of gastrectomy patients according to the dumping score based on Sigstad's clinical diagnostic index

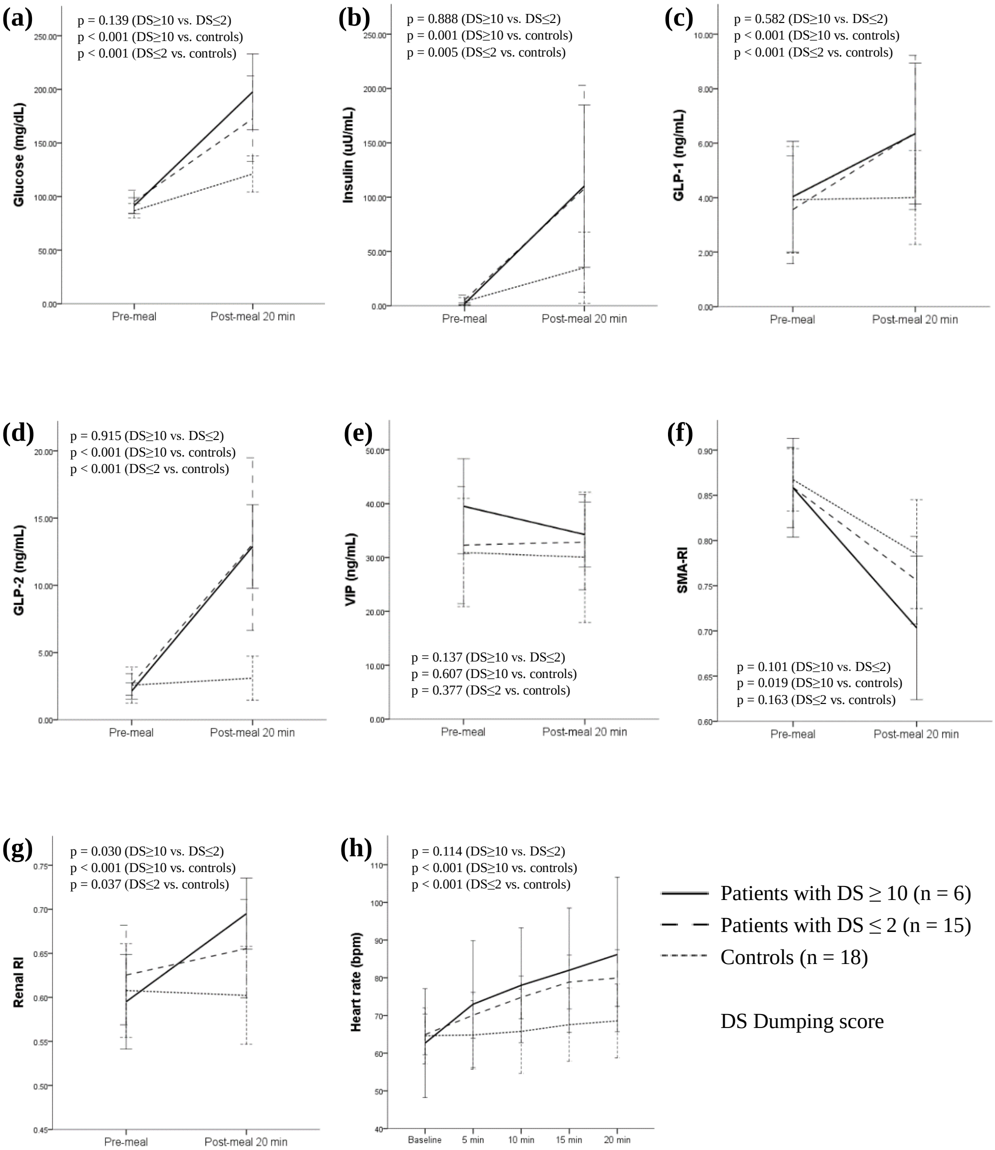


Figure 8 Meal-induced changes in **(a)** glucose, **(b)** insulin **(c)** GLP-1, **(d)** GLP-2, **(e)** VIP, **(f)** superior mesenteric artery resistive index (RI), **(g)** renal RI, **(h)** heart rate in patients with dumping score ≥ 10 (solid line), those with dumping score ≤ 2 (dashed line) and controls (dotted line). Values are mean ± SD.

Associations between clinical factors and dumping score in patients who underwent gastrectomy

Within patients who underwent gastrectomy, no clinical factor was significantly associated with the "dumper" who had dumping score of 7 or above (Table 4). According to Sigstad's original report, the subjects who had dumping score of 4 or below were considered as “non-dumper". Therefore we evaluated the association between clinical factors and "non-dumper" who had dumping score ≤ 4 (Table 5). Among the clinical factors, the age younger than 65 years was significantly associated with "non-dumper" (p=0.011). Regarding the type of operation, the proportion of patients who received distal gastrectomy relative to total gastrectomy was significantly higher in "non-dumper" group (p=0.002). The postoperative weight loss less than 10% (p=0.026) was also significantly associated with "non-dumper" (p=0.050). Multivariable analysis revealed that age <65 years (hazard ratio [HR] 0.099; 95% confidence interval [CI], 0.016–0.630; p=0.014) and distal gastrectomy (HR 0.092; 95% CI 0.013–0.649; p=0.017) were independent clinical factors associated with “non-dumper”. We evaluated the meal-induced changes in blood glucose, GI hormones, and hemodynamics according to these two clinical factors in followed analysis.

Table 4 Clinical factors associated with the "dumper" (dumping score > 7*) in patients who underwent gastrectomy (n=42)

	DS < 7	DS ≥ 7	
	n=33	n=9	p value
Age			
<65 yrs	20 (60.6%)	6 (66.7%)	1.000
≥65 yrs	13 (39.4%)	3 (33.3%)	
Sex			
Male	24 (72.7%)	5 (55.6%)	0.422
Female	9 (27.3%)	4 (44.4%)	
Operation			
DG†	21 (63.6%)	3 (33.3%)	0.139
TG	12 (36.4%)	6 (66.7%)	
Complication‡			
No	28 (84.8%)	6 (66.7%)	0.336
Yes	5 (15.2%)	3 (33.3%)	
Stage (AJCC 8th)			
I	24 (72.7%)	6 (66.7%)	0.699
II or III	9 (27.3%)	3 (33.3%)	
POD			
≤180 days	20 (60.6%)	3 (33.3%)	0.257
>180 days	13 (39.4%)	6 (66.7%)	
Weight loss§			
<10 %	23 (69.7%)	5 (55.6%)	0.451
≥10 %	10 (30.3%)	4 (44.4%)	

DG distal gastrectomy, TG total gastrectomy, POD postoperative day

*According to Sigstad's clinical diagnostic index, the subjects whose dumping score ≥7 are considered as "dumper"

†Including one patient who underwent pylorus preserving gastrectomy

‡In cases of the Clavien-Dindo classification II or higher

§(Preoperative body weight – postoperative body weight) / preoperative body weight × 100

Table 5 Clinical factors associated with the "non-dumper" (dumping score ≤ 4*) in patients who underwent gastrectomy (n=42)

	DS ≤ 4	DS > 4		Multivariable analysis	
	n=21	n=21	p value	HR (95% CI)	p value
Age					
<65 yrs	17 (81.0%)	9 (42.9%)	0.011	0.089 (0.014–0.558)	0.010
≥65 yrs	4 (19.0%)	12 (57.1%)		1.000	
Sex					
Male	15 (71.4%)	14 (66.7%)	0.739		
Female	6 (28.6%)	7 (33.3%)			
Operation					
DG†	17 (81.0%)	7 (33.3%)	0.002	0.076 (0.011–0.531)	0.009
TG	4 (19.0%)	14 (66.7%)		1.000	
Complication‡					
No	18 (85.7%)	16 (76.2%)	0.697		
Yes	3 (14.3%)	5 (23.8%)			
Stage					
I	17 (81.0%)	13 (61.9%)	0.172		
II or III	4 (19.0%)	8 (38.1%)			
POD					
≤180 days	13 (61.9%)	10 (47.6%)	0.352		
>180 days	8 (38.1%)	11 (52.4%)			
Weight loss§					
<10 %	17 (81.0%)	11 (52.4%)	0.050	0.680 (0.104–4.432)	0.686
≥10 %	4 (19.0%)	10 (47.6%)		1.000	

DG distal gastrectomy, TG total gastrectomy, POD postoperative day

*According to Sigstad's clinical diagnostic index, the subjects whose dumping score ≤ 4 are considered as "non-dumper"

†Including one patient who underwent pylorus preserving gastrectomy

‡In cases of the Clavien-Dindo classification II or higher

§(Preoperative body weight – postoperative body weight) / preoperative body weight × 100

Meal-induced changes in blood glucose, GI hormones, and hemodynamics according to the age < 65 years in patients who underwent gastrectomy

The degree of meal-induced changes in blood glucose, insulin, GLP-1, and GLP-2 concentrations did not differ significantly between the patients aged <65 years and those aged ≥65 years although these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 9a, b, c, d). VIP concentration was not significantly changed in either patients or controls (Figure 9e). The degree of postprandial change in SMA RI was greater in patients aged <65 years than in those aged ≥65 years ($p=0.057$) (Figure 9f). The degree of postprandial changes in renal RI and heart rate did not differ significantly between patients aged <65 years and those aged ≥65 years although these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 9g, h).

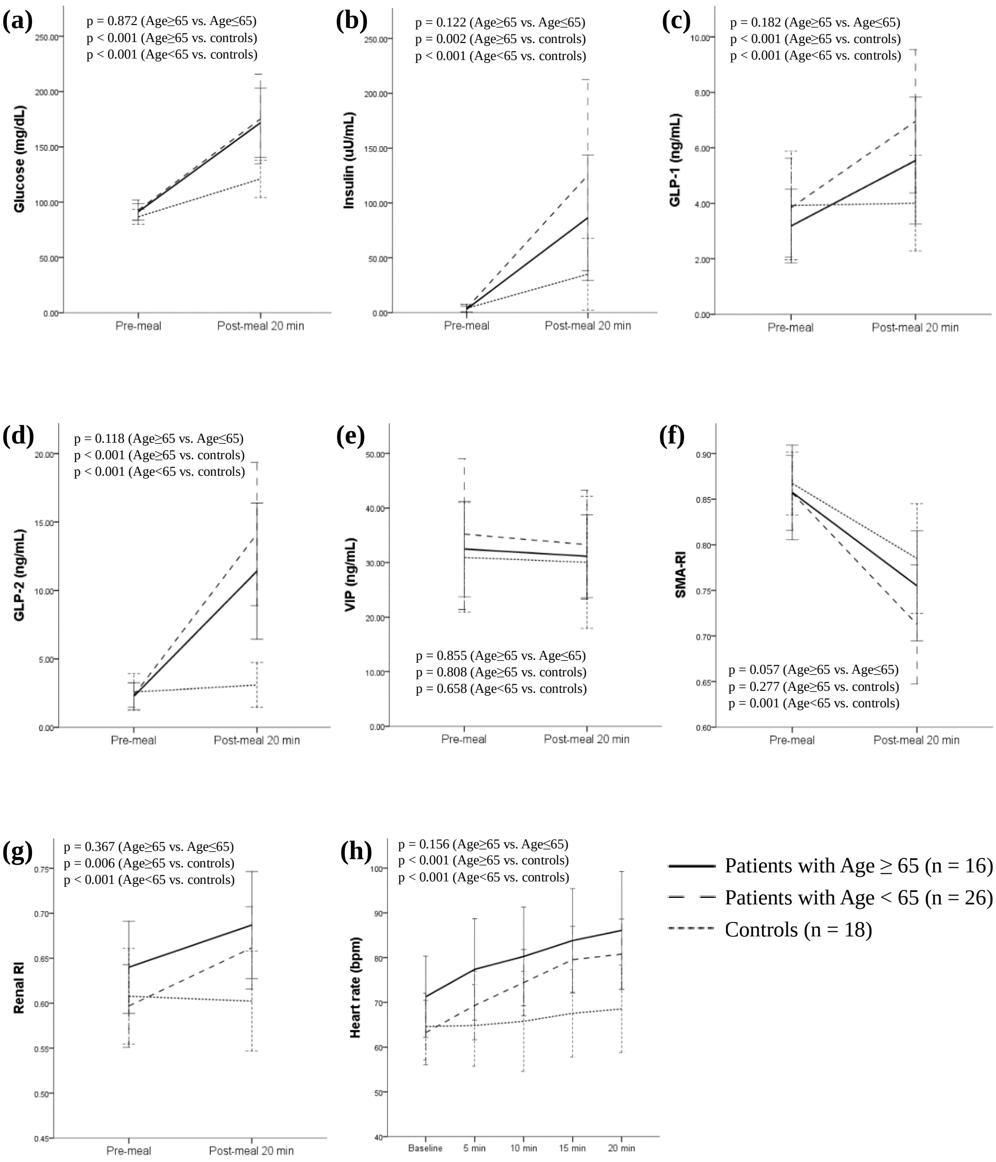


Figure 9 Meal-induced changes in **(a)** glucose, **(b)** insulin **(c)** GLP-1, **(d)** GLP-2, **(e)** VIP, **(f)** superior mesenteric artery resistive index (RI), **(g)** renal RI, **(h)** heart rate in patients with age ≥ 65 (solid line), those with age < 65 (dashed line) and controls (dotted line). Values are mean ± SD.

Meal-induced changes in blood glucose, GI hormones, and hemodynamics according to the type of operation in patients who underwent gastrectomy

The degree of meal-induced changes in blood glucose, GLP-1, and GLP-2 were significantly greater in patients who underwent total gastrectomy than in those who underwent distal gastrectomy ($p<0.001$, $p=0.025$ and $p=0.001$, respectively), and all these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 10a, c, d). The degree of postprandial change in insulin was greater in in patients who underwent distal gastrectomy than in those who underwent total gastrectomy ($p=0.028$) and these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 10b). VIP concentration was not significantly changed in either patients or controls (Figure 10e). The degree of postprandial change in SMA RI did not differ significantly between patients who underwent total gastrectomy and those who underwent distal gastrectomy, although these changes in both patient groups were greater than in controls ($p=0.001$ and $p=0.069$, respectively) (Figure 10f). The degree of postprandial changes in renal RI and heart rate were significantly greater in patients who underwent total gastrectomy than in those who underwent distal gastrectomy ($p<0.094$ and $p=0.016$, respectively) and all these changes in both patient groups were greater than in controls (all $p<0.010$) (Figure 10g, h).

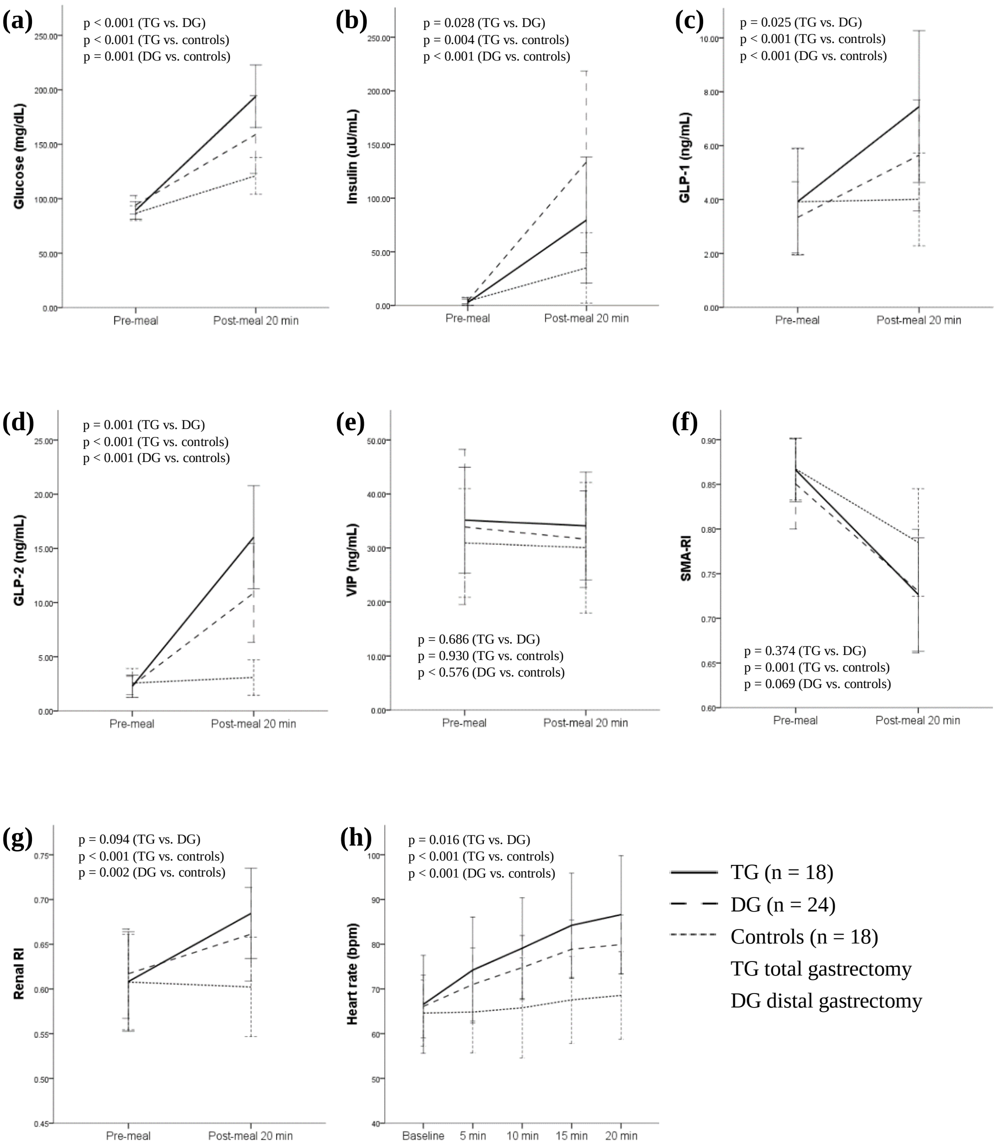


Figure 10 Meal-induced changes in **(a)** glucose, **(b)** insulin **(c)** GLP-1, **(d)** GLP-2, **(e)** VIP, **(f)** superior mesenteric artery resistive index (RI), **(g)** renal RI, **(h)** heart rate in patients who underwent total gastrectomy (solid line) and those who underwent distal gastrectomy (dashed line) and controls (dotted line). Values are mean ± SD.

Correlations among the meal induced changes of metabolic parameters in patients who underwent gastrectomy

Among the metabolic parameters, the meal induced change of GLP-1 concentration was positively correlated with that of GLP-2 in patients who underwent distal gastrectomy (r=0.486, p=0.016) (Figure 11b). However other metabolic factors were not significantly correlated with one another in these patients. Also in total gastrectomy patients, the postprandial change of GLP-1 concentration was positively correlated with that of GLP-2 (r=0.711, p=0.001) (Figure 12b). However other metabolic factors were not significantly correlated with one another in these patients, either.

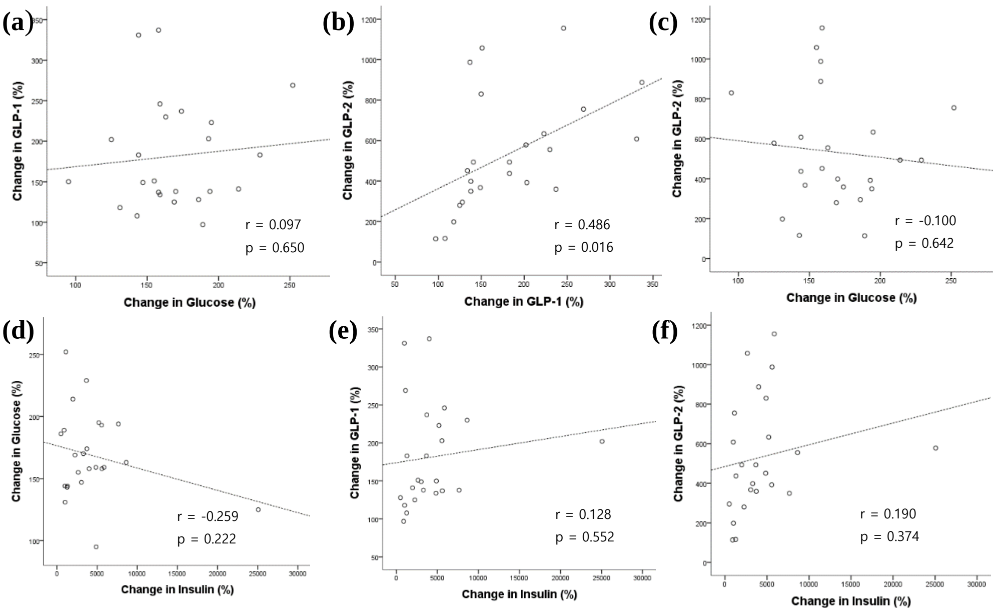


Figure 11 Correlations among the meal induced changes of metabolic parameters in patients who underwent distal gastrectomy (n=24).

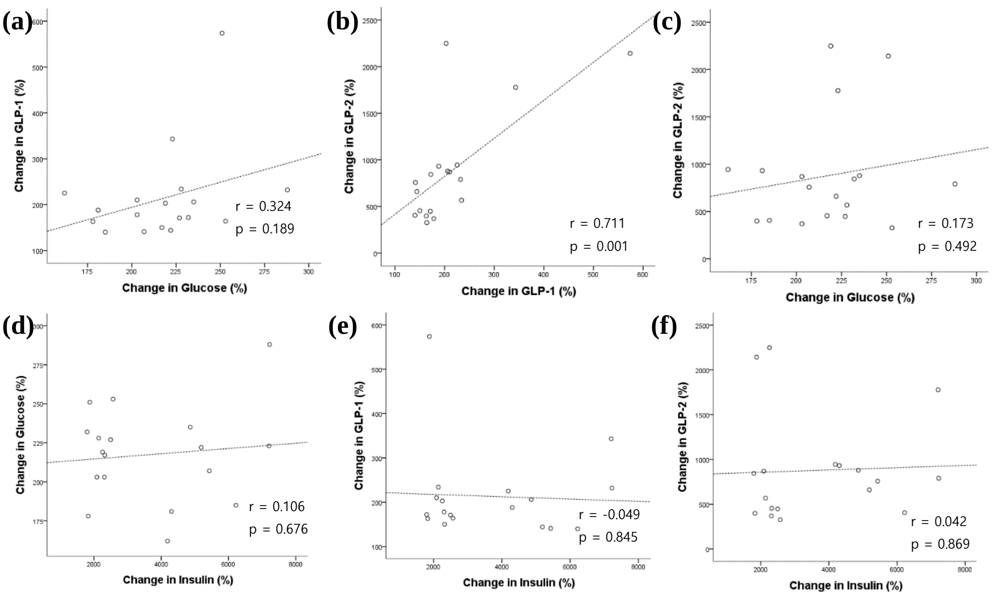


Figure 12 Correlations among the meal induced changes of metabolic parameters in patients who underwent total gastrectomy (n=18).

Dumping score according to BMI and weight loss in gastrectomy patients

The dumping score in patients with preoperative BMI < 25 had a tendency to be higher than that in those with preoperative BMI ≥ 25 (p=0.164) (Figure 13a). The patients with lower postoperative BMI were also related with higher dumping scores (p=0.073) (Figure 13b). Likewise, the dumping score in patient with weight loss ≥ 10% was higher than that in those with weight loss <10% (p=0.067) (Figure 13c).

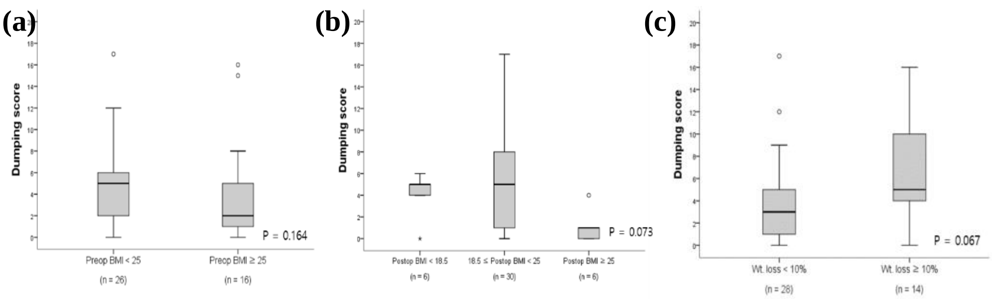


Figure 13 Dumping score according to **(a)** preoperative BMI, **(b)** postoperative BMI and **(c)** weight loss.

Discussion

Our study demonstrated that meal-induced changes in GI hormones including GLP-2 and hemodynamics were significantly greater in patients who underwent gastrectomy for gastric cancer than in controls. Within the patients who underwent gastrectomy, these changes were more prominent after total gastrectomy than after distal gastrectomy. To our knowledge, this is the first study to report the postprandial changes in GI hormones and hemodynamics concomitantly in patients who underwent gastrectomy for gastric cancer.

Although the pathophysiology of early dumping syndrome remains unclear, accelerated delivery of chyme into the small intestine has been considered as a critical step in most previous studies (4, 5, 7-9). This leads to accelerated glucose absorption, which is followed by exaggerated early blood glucose excursion (7, 8, 30, 31). Accelerated delivery of chyme into the small intestine also influence insulin secretion which is regulated by GI hormones as well as blood glucose. In our study, the postprandial increase in blood glucose, insulin, and GLP-1 levels was significantly greater in patients who underwent gastrectomy than in controls. GLP-1 is a GI hormone secreted from the GI tract upon meal ingestion and is known to slow down gastric emptying and intestinal motility and to promote early satiety (13, 14, 16). Therefore, previous studies suggested that this exaggerated early release of GLP-1 could lead to postprandial symptoms such as bloating, nausea, and anxiety, which are the main constituents of early dumping syndrome (8, 9, 16).

Along with GLP-1, GLP-2 is also a GI hormone secreted from the GI tract upon meal ingestion and is known to stimulate the splanchnic blood flow and to facilitate the nutrient absorption (11, 12, 32). GLP-2 is a 33-amino acid peptide secreted from the enteroendocrine L cells and has a low basal level in fasting period (11). However, its level up-rises rapidly upon meal ingestion and acts via G protein-coupled receptor expressed within GI tract (12). GLP-2 is also known to be related with recovery after gut injury via mucosa proliferation and intestinal adaptation after massive small bowel resection (11, 32). Regarding the relationship between GLP-2 and splanchnic blood flow, Hansen et al. suggested that a meal-induced increase in SMA blood flow is metabolically mediated by GLP-2 (12). In our study, the postprandial increase in blood GLP-2 levels and SMA blood flow was significantly greater in patients who underwent gastrectomy than in controls. These results are consistent with those of previous studies based on bariatric surgery (11, 19, 32).

VIP is another GI hormone released by the enteric nervous system, which stimulates the secretion of water and electrolytes into the intestinal lumen and induces splanchnic vasodilation (14, 33). Hypersecretion of VIP is known to induce severe watery diarrhea as in WDHA syndrome known as pancreatic cholera, by a VIP-secreting tumor termed VIPoma (18, 33). Because of these characteristics of VIP, several studies reported this GI hormone as a significant mediator in early dumping syndrome (17, 18). Sagor GR et al. demonstrated the more rapid rise of VIP concentrations after meal ingestion in the dumpers with gastrectomy than in the asymptomatic patients with gastrectomy (18). However, in our study, plasma VIP concentration was not significantly increased after meal ingestion in either patients who underwent gastrectomy or controls. We speculated that there are several differences in subjects and methods between their study and ours. Firstly, in their study, all subjects with dumping syndrome were reported to have watery diarrhea at 30 min after meal ingestion (18). Unlike their subjects, the dumping symptoms of our subjects were not so severe enough to experience watery diarrhea. Secondly, the study meal used in their study was 200 mL 50% glucose solution which was drunken within 2 min. Our study meal was a commercial standard liquid meal which is commonly consumed in gastrectomy patients for nutritional support, therefore, relatively less burdensome for subjects.

As inferred from the coordinated nature of regional and systemic hemodynamics, meal-induced increase in splanchnic blood flow has been considered as an initial event for systemic postprandial hemodynamic changes by some investigators (20-23). In our study, meal-induced SMA vasodilatation (RI decrease) was more exaggerated in patients who underwent gastrectomy, in whom the degree of heart rate increase was greater than that in controls. This relationship between splanchnic circulation and systemic hemodynamics has been extensively investigated on the patients with liver cirrhosis (34-36). In these patients with liver cirrhosis and portal hypertension, splanchnic blood pooling relentlessly occur with progressive vasodilation of mesenteric vascular bed. Besides, followed development of portal-systemic collateral circulation lead to increased splanchnic blood flow, which eventually contributes the systemic hyperdynamic circulation characterized by increased cardiac output and heart rate, and low arterial blood pressure. During hyperdynamic circulation, renal blood flow is known to decrease because of reduced effective circulatory volume caused by splanchnic blood pooling (36-38). Therefore, renal RI in these patients with liver cirrhosis has been known to increase even in the early phase before development of the hepato-renal syndrome. Specifically, some investigators reported that meal-induced splanchnic vasodilatation (RI decrease) was accompanied by renal vasoconstriction (RI increase) as a homeostatic response of the kidney to prevent systemic hypotension in patients with liver cirrhosis (25, 26). In our study, meal-induced SMA vasodilatation (RI decrease) was more exaggerated in patients who underwent gastrectomy than in controls, and only in patients who underwent gastrectomy, renal vasoconstriction (RI increase) significantly occurred.

In our study, we used RI as a Doppler parameter to quantify blood flow. RI represents the magnitude of resistance from downstream vasoconstriction or vasodilation (38, 39). If vasodilation of downstream vascular bed occurred, blood flow of that area would increase and EDV of the vessel proximal to that area would increase more than PSV on Doppler exam (40). Therefore, estimated RI value of that vessel examined by Doppler should be decreased because RI = (PSV – EDV) / PSV. RI has some advantages in comparison with other Doppler parameters, because its measurement is not influenced by insonation angle (angle between the Doppler beam and the long axis of the vessel) or the vessel diameter which are known to be related with intra- and inter-observer variability (27, 28). However, the estimated RI value needs cautious interpretation, because this value is affected not only by circulation status of the corresponding vascular bed, but also by the systemic hemodynamic factors (38, 39). Therefore, postprandial increase of renal RI in gastrectomy patients might represent not only renal vasoconstriction, but also systemic hyperdynamic circulation induced by splanchnic vasodilation.

In our study, the degree of postprandial changes in renal RI and heart rate were greater in the patients with dumping score ≥ 7 than in those with dumping score <7. In addition to these differences in terms of renal RI and heart rate, the degree of postprandial change in blood glucose had a tendency to be greater in patients with dumping score ≥ 7 than in those with dumping score ≤ 4. Furthermore, the degree of postprandial change in the SMA RI was also greater in patients with dumping score ≥ 10 than in those with dumping score ≤ 2. Considering the subjective nature of patients' symptoms and the broad spectrum of dumping score, we suppose that a single cut-off point of 4 or 7 based on clinical score would have a limitation to diagnose the early dumping syndrome.

Among the clinical factors of patients, age younger than 65 years and distal gastrectomy were independent factors associated with the "non-dumper" (dumping score of 4 or below). Regarding age, the degree of postprandial changes in blood glucose, insulin, and GI hormones was not significantly different between the patients aged <65 years and those aged ≥65 years. Furthermore, the degree of postprandial change in the SMA RI was greater in patients aged <65 years than in those aged ≥65 years. Therefore, other mechanisms could be involved for this relationship between age and dumping syndrome, or the younger patients might have a tendency to respond less sensitively to the questionnaire of dumping symptoms.

Regarding the type of operation, however, the degree of postprandial increases in blood glucose, GLP-1, and GLP-2 were significantly more prominent in the patients with total gastrectomy than those with distal gastrectomy. The degree of postprandial SMA vasodilatation (RI decrease) or renal vasoconstriction (RI increase) was not significantly different between these two gastrectomy groups. Regarding this, we suppose that the regional hemodynamic changes such as SMA vasodilatation and renal vasoconstriction might already had occurred fully enough in distal gastrectomy group. However, the postprandial increase in hear rate representing systemic hemodynamic changes was significantly more prominent in the patients with total gastrectomy than those with distal gastrectomy. Previous studies reported that the patients who underwent total gastrectomy showed higher incidences of early dumping syndrome than those who underwent distal gastrectomy due to more accelerated nutrient delivery into the small intestine (1, 41, 42). To our knowledge, this is the first study to reveal a significant difference in the degree of postprandial changes in GI hormones and hemodynamics between patients who underwent distal and total gastrectomy. Considering that early dumping syndrome is clinically featured by gastrointestinal and vasomotor symptoms related with accelerated nutrient delivery into the small intestine, the accelerated postprandial changes in GI hormones and hemodynamics after gastrectomy, especially for total gastrectomy, might be an underlying pathophysiology.

Our study has several limitations. Among the patients who underwent gastrectomy, four patients had SMA stenosis less than 30% in preoperative computed tomography (CT). There have been several studies in which the relationships between arterial stenosis and Doppler waveform were analyzed (43-45). Regarding internal carotid artery (ICA), a consensus conference proposed velocity criteria for carotid artery stenosis (46). In these criteria, the severity of ICA stenosis are categorized as normal, <50%, 50-69%, and ≥70%, for which the cut-off values of Doppler parameters such as PSV and EDV were presented. The cut-off values for significant stenosis (≥50%) are greater than those for normal ICA, however, those for stenosis <50% are same as for normal ICA. Mesenteric arteries are usually deep-seated in abdominal cavity and Doppler exam for these arteries are hindered frequently from bowel gas even in experienced hands. Therefore, the consensus criteria for SMA stenosis have not been determined yet. There are several reports about Doppler parameters for detecting significant SMA stenosis (≥50% and 70%) (44, 45). However, SMA stenosis less than 30% have been regarded as normal category by Doppler exams in most previous studies (43-45). In our study, for 4 patients who showed SMA stenosis less than 30% in preoperative computed tomography (CT), the postprandial changes of Doppler parameters such as PSV, EDV, and RI for SMA in these patients were not significantly different from the other patients who underwent same type of operations, respectively. Secondly, in our study, the meal induced changes in metabolic parameters were not correlated with one another except between GLP-1 and GLP-2. Previous studies for bariatric surgery have reported that the postprandial changes in blood glucose, insulin, and various GI hormones had a similar feature with one another (8, 9, 15). Those studies performed more than one blood samples for evaluation of GI hormones profiles after meal ingestion and the relationships among these GI hormones were analyzed based on these multiple measurements. However, we performed only one post-meal blood samples 20 minutes after ingestion because our main focus was to examine the mechanisms of early dumping syndrome, for which the signs and symptoms are most prominent within this time period (5, 16, 20, 21). We suppose that additional postprandial exams until 1-2 hours after meal ingestion would be more informative for evaluation of the whole nature in these metabolic parameters.

In conclusion, the early postprandial changes in GI hormones and hemodynamics were greater in patients who underwent gastrectomy than in controls. Within patients who underwent gastrectomy, these changes were more prominent after total gastrectomy than after distal gastrectomy, which was associated with a lower risk for early dumping syndrome. Our results suggest that early postprandial changes in GI hormones and hemodynamics have a role in the development of early dumping syndrome.

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요약 (국문 초록)

서론

위절제술 이후 나타나는 조기 덤핑 증후군은 환자들에게 부정적 영향을 주고 있으나, 이에 대한 발생 기전은 아직 완전히 규명되지 않았다. 본 연구의 목적은 위절제술 환자에서의 식후 위장관 호르몬 분비 양상 및 혈역학적 변화를 조기 덤핑 증후군과 관련하여 조사하는 것이다.

방법

위암으로 위절제술을 시행한 42명의 환자군과 복부 수술력이 없는 18명의 대조군이 연구에 참여하였다. 공복 상태와, 400 kcal의 영양 음료를 섭취한 후 20분 지난 시점에서, 각각 혈중 포도당, 인슐린, glucagon-like peptide (GLP-1), GLP-2, vasoactive intestinal peptide (VIP)의 농도와, 상장간막동맥 (superior mesenteric artery) 및 신혈류 (renal blood flow)를 측정하였다. 이 기간 동안, 심박수는 5분 간격으로 체크하였다. 모든 연구 참여자를 대상으로, Sigstad의 임상 진단 지표에 근거한 설문지를 이용하여, 덤핑 증상 유무를 조사하였다.

결과

혈중 포도당, 인슐린, GLP-1, GLP-2 농도와 상장간막동맥 혈류, 신혈류 저항 지수 (renal resistive index), 심박수의 식후 변화는 위절제술 환자군에서 대조군보다 유의하게 더 높은 정도로 증가하였다 ($p<0.010$). 위절제술 환자군 내에서는, 원위부위절제술을 시행 받은 환자들이 위전절제술을 시행 받은 환자들보다 조기 덤핑 증후군의 위험이 낮았다. (위험비 0.076, 95% 신뢰 구간 0.011-0.531; $p=0.009$). 위전절제술을 시행한 환자들은 원위부위절제술을 시행한 환자들보다 혈중 포도당 ($p<0.001$), GLP-1 ($p=0.025$), GLP-2 ($p=0.001$) 농도

및 심박수 (p=0.016)의 증가 정도가 유의하게 더 높은 양상을 보였다.

결론

위절제술 환자에서의 식후 위장관 호르몬 분비 및 혈역학적 변화는 대조군보다 높은 정도로 진행되었고, 특히 위전절제술을 시행 받은 환자에서, 더욱 현저히 관찰되는 바, 이러한 변화들이 조기 덤핑 증후군의 발생에 관여함을 시사한다.

주요어 : 위절제술, 조기 덤핑 증후군, 위장관 호르몬, 상장간막동맥혈류, 혈역학

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