

## Original Article



# Postprandial Changes in Gastrointestinal Hormones and Hemodynamics after Gastrectomy in Terms of Early Dumping Syndrome

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Received: May 27, 2020

Revised: Jul 9, 2020

Accepted: Jul 17, 2020

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## ABSTRACT

**Purpose:** This study aimed to examine the early postprandial changes in gastrointestinal (GI) hormones and hemodynamics in terms of early dumping syndrome after gastrectomy for gastric cancer.

**Materials and Methods:** Forty patients who underwent gastrectomy for gastric cancer and 18 controls without previous abdominal surgery were enrolled. Before and 20 minutes after liquid meal ingestion, blood glucose, glucagon-like peptide-1 (GLP-1), and GLP-2 concentrations and superior mesenteric artery (SMA) and renal blood flow were measured. The patients' heart rates were recorded at 5-minute intervals. All subjects were examined for dumping syndrome using a questionnaire based on Sigstad's clinical diagnostic index.

**Results:** The postprandial increases in blood glucose, GLP-1, and GLP-2 levels as well as SMA blood flow and heart rate were greater in patients who underwent gastrectomy than in controls (all  $P < 0.010$ ). Patients who underwent gastrectomy showed a significantly decreased renal blood flow ( $P < 0.001$ ). Among patients who underwent gastrectomy, distal gastrectomy was a significant clinical factor associated with a lower risk of early dumping syndrome than total gastrectomy (hazard ratio, 0.092; 95% confidence interval, 0.013–0.649;  $P = 0.017$ ). Patients who underwent total gastrectomy showed a greater postprandial increase in blood glucose ( $P < 0.001$ ), GLP-1 ( $P = 0.030$ ), and GLP-2 ( $P = 0.002$ ) levels as well as and heart rate ( $P = 0.013$ ) compared to those who underwent 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 play a crucial role in the pathophysiology of early dumping syndrome.

**Keywords:** Gastrectomy; Dumping syndrome; Glucose; Gastrointestinal hormones; Splanchnic circulation

## INTRODUCTION

The oncological outcomes of gastrectomy for gastric cancer have considerably improved in recent decades due to developments in early diagnosis, surgical technique, perioperative

**Author Contributions**

Conceptualization: Y.J.Y., L.H.J.; Data curation: Y.J.Y., L.W.K.; Formal analysis: K.S.H., P.D.J., Y.H.K.; Investigation: C.S.J.; Methodology: Y.H.K.; Validation: L.H.J., A.F.; Writing - original draft: Y.J.Y.; Writing - review & editing: L.H.J.

**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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 and nutrient absorption [4-6], resulting in various “postgastrectomy syndromes,” among which early dumping syndrome is manifested by GI symptoms such as bloating, borborygmi, diarrhea, and systemic vasomotor symptoms such as diaphoresis, palpitation, and hypotension [4]. These symptoms develop within 10–30 minutes after food ingestion and, therefore, influence oral intake and may lead to poor nutritional status [5].

Although the mechanism of early dumping syndrome is not completely understood, many studies have attempted to elucidate its pathophysiology. Recently, as the number of cases of bariatric surgery has increased, studies have reported on the postoperative changes in GI hormone secretion [7-10]. The results of these studies suggested that altered GI hormone profiles induce postprandial symptoms such as bloating, nausea, and anxiety, which result in reduced food intake and weight loss. While these postprandial symptoms could be considered to have a “therapeutic effect” after bariatric surgery, they are, rather, the main constituents of troublesome early dumping syndrome [8]. Meanwhile, some authors suggested that increased splanchnic blood flow upon food ingestion influences systemic hemodynamics, which is exaggerated in patients who undergo gastrectomy, as manifested by the vasomotor symptoms of early dumping syndrome [11,12].

To our knowledge, no report has investigated GI hormone level and splanchnic blood flow concomitantly in patients who underwent gastrectomy for gastric cancer. Thus, this study examined the early postprandial changes in blood glucose level, GI hormone levels, and hemodynamics including splanchnic blood flow in terms of early dumping syndrome after gastrectomy for gastric cancer.

## MATERIALS AND METHODS

### Subjects

Forty patients who had undergone gastrectomy for gastric cancer and 18 controls who had undergone operations other than gastrectomy (inguinal hernia repair [n=14] and subcutaneous mass excision [n=4]) in the past 12 months at a single institution (Gachon University Gil Medical Center) were enrolled. None of the patients or controls had a history of abdominal surgery, except for gastrectomy, diabetes, chronic renal disease, or ongoing adjuvant chemotherapy. Clinical factors including age, sex, type of operation, complications, 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 was conducted in accordance with the Helsinki Declaration of 1964 and later versions. All subjects provided written informed consent before enrollment.

### Protocol

In all subjects, after 8 hours of fasting, baseline venous blood samples were taken for measurements of glucose and GI hormone levels. After blood sampling, baseline Doppler measurements of the superior mesenteric artery (SMA) and intrarenal artery were performed with the subjects in a supine position. After the baseline examinations, the subjects ingested a 400-kcal liquid meal (New Care, DaeSang, Seoul, South Korea; 60 g carbohydrate, 14 g protein, and 12 g lipid) within 5 minutes while in a sitting position, followed by bed rest. Twenty minutes after starting meal ingestion, blood sampling and Doppler examination were

repeated. During the study, the subjects' heart rates were recorded at baseline and at 5-minute intervals from the start of meal ingestion. After post-meal measurements, all subjects were examined directly by the investigator (JYY) using a questionnaire on the syndrome (**Supplementary Table 1**) based on Sigstad's clinical diagnostic index [13]. According to his original report, subjects with scores of 7 or above were considered "dumpers," while those with scores of 4 or below were considered "non-dumpers" [13].

## Measurements

### *Biochemical measurements*

Serum glucose concentrations were measured by photometric assay using a hexokinase, as per usual clinical practice in our institution (Gachon University Gil Medical Center). Blood samples for glucagon-like peptide 1 (GLP-1) and GLP-2 measurements were collected in ethylenediaminetetraacetic acid tubes, centrifuged at 3,000 rpm for 10 minutes, and stored at  $-70^{\circ}\text{C}$  until analysis. Plasma GLP-1 and GLP-2 concentrations were measured with an enzyme-linked immunosorbent assay kit according to the manufacturer's instructions (YK160, YANAIHARA, Fujinomiya, Japan; and EZGLP2-37K, Millipore, St. Charles, MO, USA, respectively).

### *Doppler measurements*

SMA and renal blood flow were measured by duplex ultrasonography (LOGIQ E10, GE Medical Systems, Wauwatosa, WI, USA; and EPIQ7, PHILIPS, Bothell, WA, USA) with a 5.0-MHz convex probe. All Doppler measurements were performed by one experienced radiologist (SJC) blinded to the subjects' groups. SMA blood flow was measured 2–3 cm from the origin as scanned longitudinally (**Supplementary Fig. 1**). Renal blood flow was measured from the right interlobar artery along the borders of the medullary pyramid (**Supplementary Fig. 2**). Among various Doppler parameters to quantify blood flow, we used the resistive index (RI), which is calculated as (peak systolic velocity–end-diastolic velocity)/peak systolic velocity and is inversely related to blood flow.

## Statistics

Values are presented as means $\pm$ standard deviation. Differences in clinical variables between the subject groups were compared using Student's *t*- or Mann-Whitney U tests for continuous data and  $\chi^2$  tests for categorical data. The meal-induced changes in biochemical and hemodynamic variables within each subject group were analyzed using paired Student's *t*-tests. The degrees of meal-induced changes in biochemical and hemodynamic variables between the subject groups were compared by repeated-measures analysis of variance. Multivariable analysis was performed using multiple logistic regression. All analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA), and *P*-values  $<0.05$  were considered significant.

## RESULTS

### **Subject characteristics**

The clinical characteristics of the patients who underwent gastrectomy and controls are summarized in **Table 1**. No significant differences were observed in age, sex, preoperative body weight, and body mass index between the patients and controls. The number of postoperative days at the time of examination was higher in gastrectomy patients than that in the controls who underwent inguinal hernia repair or subcutaneous mass excision and

**Table 1.** Subject characteristics

| Characteristics                       | Patients who underwent gastrectomy (n=40) | Controls (n=18) | P-value |
|---------------------------------------|---|-----------------|---------|
| Age (yr)                              | 59.1±12.7                                 | 56.3±15.6       | 0.462   |
| Sex (male/female)                     | 27:13                                     | 16:2            | 0.112   |
| Postoperative days                    | 150.8±118.6                               | 24.9±9.7        | <0.001  |
| Body mass index (kg/m <sup>2</sup> )* | 24.2±3.3                                  | 23.6±1.8        | 0.410   |
| Body weight (preoperative; kg)        | 65.5±12.3                                 | 65.6±8.6        | 0.979   |
| Body weight (postoperative; kg)       | 60.9±12.4                                 | 65.0±8.9        | 0.213   |
| Body weight change (%) <sup>†</sup>   | 93.0±6.5                                  | 99.1±1.8        | <0.001  |
| Dumping score <sup>‡</sup>            | 4.2±3.9                                   | 0.0±0.0         | <0.001  |

Values are means±standard deviation.

\*Postoperative values; <sup>†</sup>Postoperative body weight/preoperative body weight × 100; <sup>‡</sup>According to Sigstad's clinical diagnostic index.

had relatively short postoperative recovery periods. The postoperative body weight loss and the severity of dumping syndrome according to Sigstad's clinical diagnostic index [13] were greater in patients than those in the controls (both  $P < 0.001$ ). Among patients who underwent gastrectomy, the most common dumping symptom was borborygmi (72.5%), followed by bloating (65.0%), feeling of warmth or sweating (42.5%), restlessness (35.0%), and drowsiness (12.5%) (**Supplementary Table 1**).

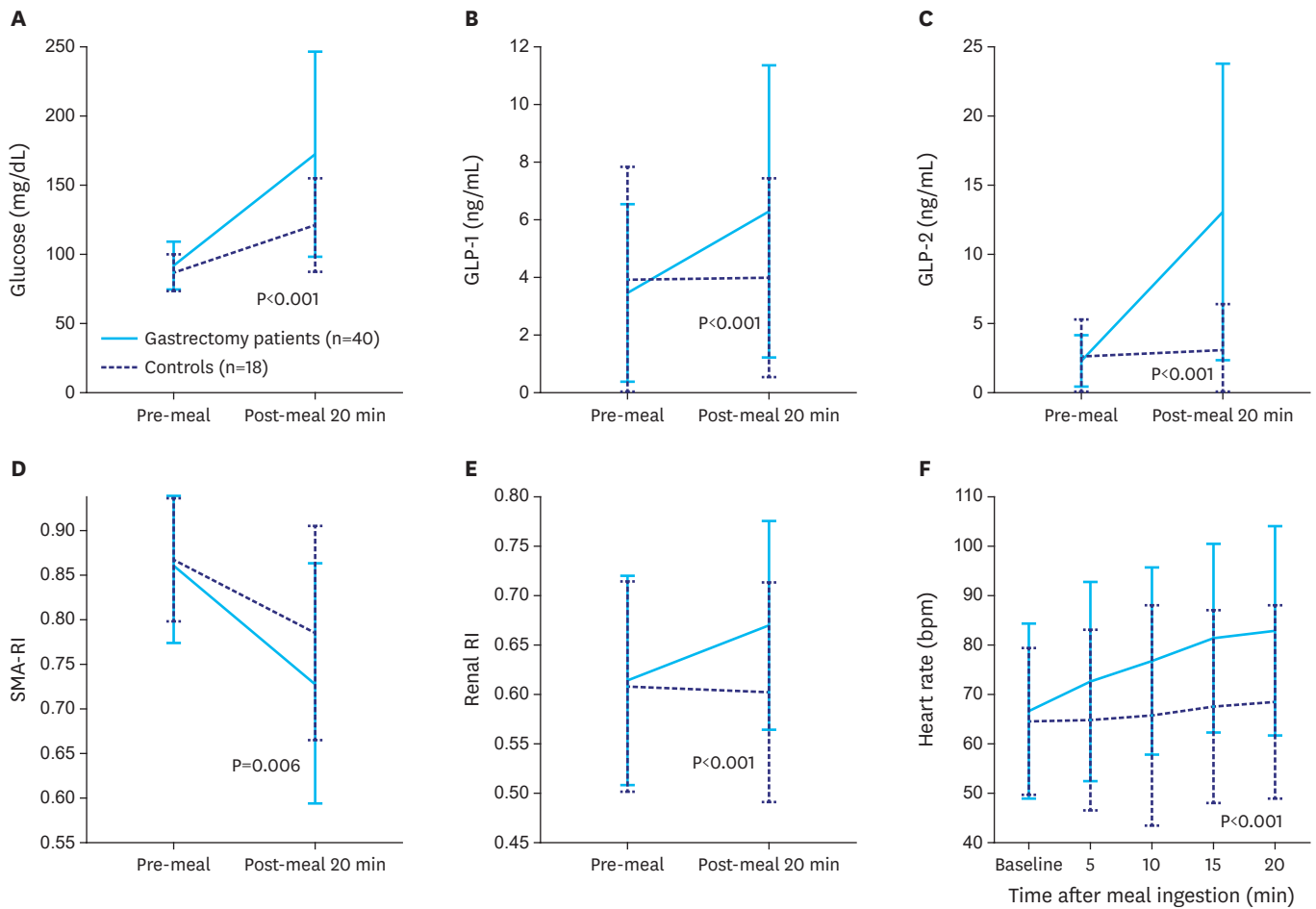
### Meal-induced changes in blood glucose and GI hormone levels and hemodynamics

After meal ingestion, the degree of increase in serum glucose concentration was significantly greater in patients who underwent gastrectomy than that in controls ( $P < 0.001$ ) (**Fig. 1A**). The plasma GLP-1 concentration increased only in patients who underwent gastrectomy ( $P < 0.001$ ) (**Fig. 1B**). The degree of increase in plasma GLP-2 concentration was significantly greater in patients who underwent gastrectomy than that in controls ( $P < 0.001$ ) (**Fig. 1C**). The degree of decrease in SMA RI was significantly greater in patients who underwent gastrectomy than that in controls ( $P = 0.006$ ) (**Fig. 1D**). The renal RI increased only in patients who underwent gastrectomy ( $P < 0.001$ ) (**Fig. 1E**). The degree of heart rate increase was significantly greater in patients who underwent gastrectomy than that in controls ( $P < 0.001$ ) (**Fig. 1F**).

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

Among the patient clinical factors, 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 factors associated with “non-dumper” (dumping score of 4 or below) in multivariable analysis (**Table 2**). The degree of meal-induced changes in blood glucose and GI hormone levels and hemodynamics did not differ significantly between patients aged <65 years who underwent gastrectomy and those aged ≥65 years (**Fig. 2**). However, in terms of operation type, the patients who underwent total gastrectomy showed a greater postprandial increase in blood glucose ( $P < 0.001$ ), GLP-1 ( $P = 0.030$ ), and GLP-2 ( $P = 0.002$ ) levels compared to those in patients who underwent distal gastrectomy (**Fig. 3A-C**). The degree of postprandial changes in the SMA and renal RI did not differ significantly between these 2 gastrectomy groups. (**Fig. 3D and E**). However, the postprandial increase in heart rate was significantly greater in patients who underwent total gastrectomy than that in those who underwent distal gastrectomy ( $P = 0.013$ ) (**Fig. 3F**).

Postprandial Responses after Gastrectomy



**Fig. 1.** Meal-induced changes in (A) glucose, (B) GLP-1, (C) GLP-2, (D) superior mesenteric artery RI, (E) renal RI, and (F) heart rate in patients who underwent gastrectomy (solid line) and controls (dotted line). Values are means±2 standard deviation. GLP = glucagon-like peptide; RI = resistive index; SMA = superior mesenteric artery.

**DISCUSSION**

The results of our study showed significantly greater meal-induced changes in GI hormones and hemodynamics in patients who underwent gastrectomy for gastric cancer than those in controls. Among patients who underwent gastrectomy, these changes were more prominent after total gastrectomy compared to after distal gastrectomy. To our knowledge, this is the first study to report 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, the critical step is accelerated nutrient delivery into the small intestine by gastrectomy [4,14] leading to accelerated glucose absorption followed by exaggerated early blood glucose excursion [15-17]. In our study, the postprandial increases in blood glucose and GLP-1 levels were significantly greater in patients who underwent gastrectomy than those in the controls. GLP-1 is a GI hormone secreted from the GI tract upon meal ingestion and slows gastric emptying and intestinal motility to promote early satiety [18-20]. Previous studies suggested that an 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 [8,21].

## Postprandial Responses after Gastrectomy

**Table 2.** Clinical factors associated with “non-dumpers” (DS $\leq$ 4\*) in patients who underwent gastrectomy (n=40)

| Characteristics              | DS $\leq$ 4 (n=21) | DS >4 (n=19) | P-value | Multivariable analysis |         |
|------------------------------|--------------------|--------------|---------|------------------------|---------|
|                              |                    |              |         | HR (95% CI)            | P-value |
| Age (yr)                     |                    |              | 0.011   |                        |         |
| <65                          | 17 (81.0)          | 8 (42.1)     |         | 0.099 (0.016–0.630)    | 0.014   |
| $\geq$ 65                    | 4 (19.0)           | 11 (57.9)    |         | 1.000                  |         |
| Sex                          |                    |              | 0.577   |                        |         |
| Male                         | 15 (71.4)          | 12 (63.2)    |         |                        |         |
| Female                       | 6 (28.6)           | 7 (36.8)     |         |                        |         |
| Type of operation            |                    |              | 0.002   |                        |         |
| DG                           | 17 (81.0)          | 6 (31.6)     |         | 0.092 (0.013–0.649)    | 0.017   |
| TG                           | 4 (19.0)           | 13 (68.4)    |         | 1.000                  |         |
| Complications <sup>†</sup>   |                    |              | 0.689   |                        |         |
| No                           | 18 (85.7)          | 15 (78.9)    |         |                        |         |
| Yes                          | 3 (14.3)           | 4 (21.1)     |         |                        |         |
| Stage (AJCC 8th)             |                    |              | 0.208   |                        |         |
| I                            | 17 (81.0)          | 12 (63.2)    |         |                        |         |
| II or III                    | 4 (19.0)           | 7 (36.8)     |         |                        |         |
| POD (day)                    |                    |              | 0.554   |                        |         |
| $\leq$ 180                   | 13 (61.9)          | 10 (52.6)    |         |                        |         |
| >180                         | 8 (38.1)           | 9 (47.4)     |         |                        |         |
| Weight loss (%) <sup>‡</sup> |                    |              | 0.026   |                        |         |
| <10                          | 17 (81.0)          | 9 (47.4)     |         | 0.522 (0.078–3.487)    | 0.503   |
| $\geq$ 10                    | 4 (19.0)           | 10 (52.6)    |         | 1.000                  |         |

DS = dumping score; HR = hazard ratio; CI = confidence interval; DG = distal gastrectomy; TG = total gastrectomy; AJCC = American Joint Committee on Cancer; POD = postoperative day.

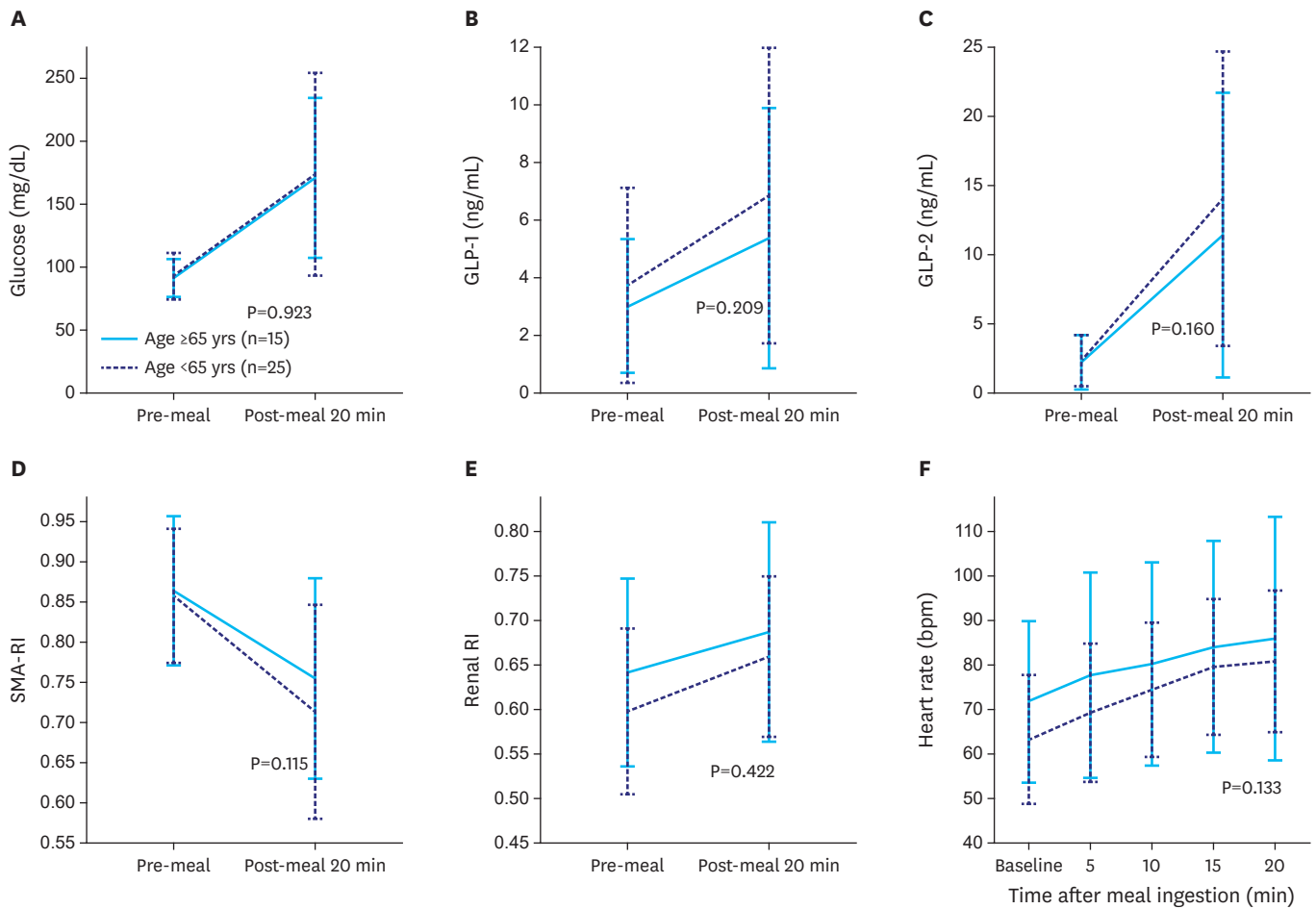
\*According to Sigstad's clinical diagnostic index, the subjects with dumping scores  $\leq$ 4 are considered “non-dumpers”; <sup>†</sup>In cases with Clavien-Dindo classification  $\geq$  II; <sup>‡</sup>(Preoperative body weight – postoperative body weight)/preoperative body weight  $\times$  100.

Along with GLP-1, GLP-2 is also a GI hormone secreted from the GI tract upon meal ingestion and stimulates nutrient absorption and intestinal blood flow [10,22,23]. Regarding the relationship between GLP-2 and splanchnic blood flow, Hansen et al. [22] suggested that a meal-induced increase in SMA blood flow is metabolically mediated by GLP-2. In our study, the postprandial increases in blood GLP-2 levels and SMA blood flow were significantly greater in patients who underwent gastrectomy than those in the controls. These results are consistent with those of previous studies based on bariatric surgery [9,10,23].

As inferred from the coordinated nature of regional and systemic hemodynamics, some investigators considered meal-induced increases in splanchnic blood flow to be an initial event for systemic postprandial hemodynamic changes [24-26]. The researchers suggested that meal-induced splanchnic blood pooling influences systemic hypotensive stress ensued by tachycardia, hypotension, drowsiness, and restlessness, which are the main vasomotor symptoms of early dumping syndrome. Furthermore, meal-induced splanchnic vasodilatation was accompanied by renal vasoconstriction as a homeostatic response of the kidney to prevent systemic hypotension [27,28]. In our study, meal-induced SMA vasodilatation (RI decrease) was more exaggerated in patients who underwent gastrectomy, in whom the heart rate increase was also greater than those in the controls. Furthermore, the renal vasoconstriction (RI increase) occurred significantly more often only in patients who underwent gastrectomy.

Among the biochemical and hemodynamic parameters assessed in our study, blood glucose level showed the most notable relationship with the Sigstad's clinical diagnostic index in patients who underwent gastrectomy, although the relationship was not statistically significant. (area under the curve=0.658; P=0.088) (**Supplementary Fig. 3**). Instead, among

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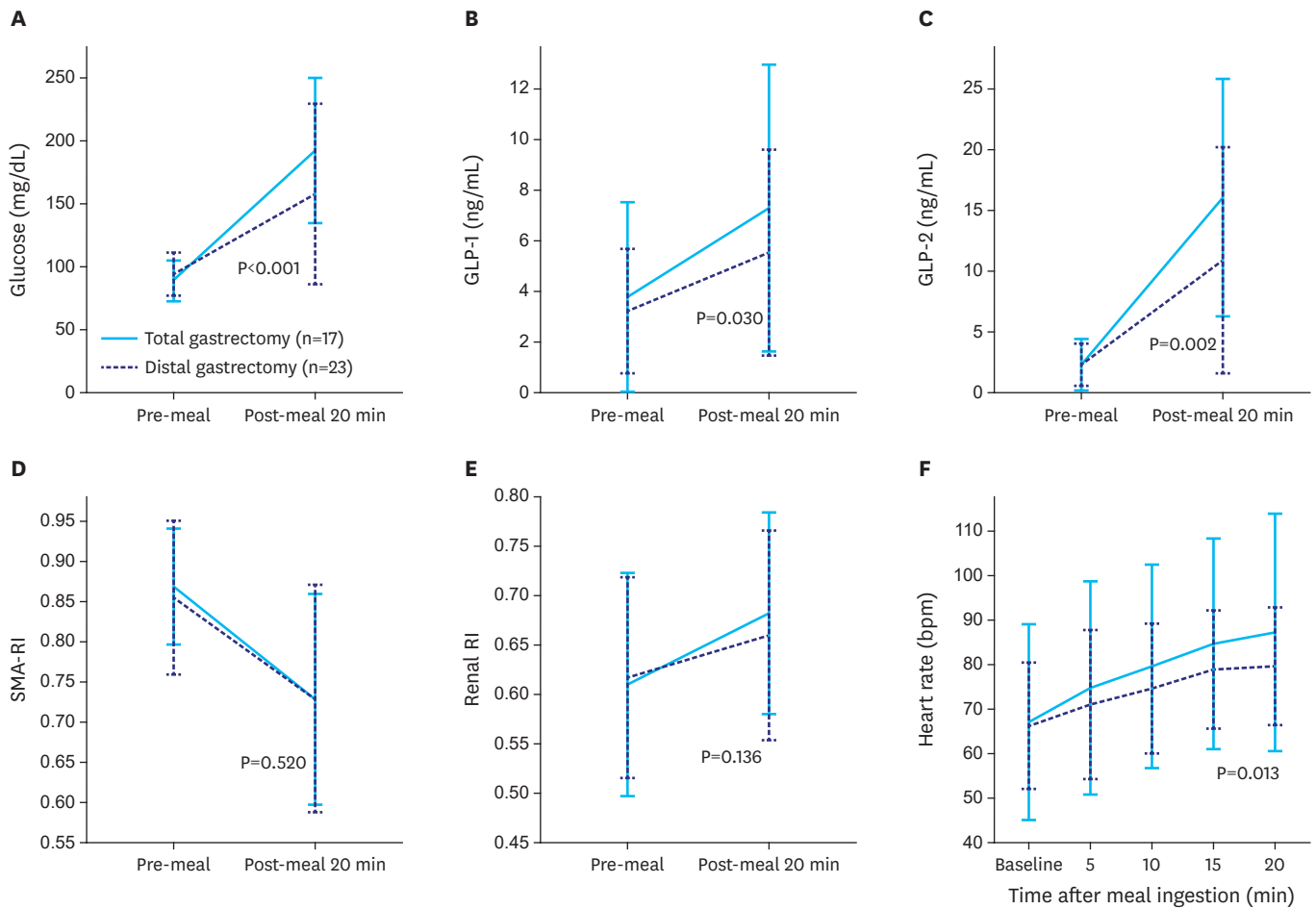


**Fig. 2.** Meal-induced changes in (A) glucose, (B) GLP-1, (C) GLP-2, (D) superior mesenteric artery RI, (E) renal RI, and (F) heart rate in patients aged ≥65 years (solid line) and <65 years (dotted line) who underwent gastrectomy. Values are means±2 standard deviation. GLP = glucagon-like peptide; RI = resistive index; SMA = superior mesenteric artery.

the clinical patient factors, distal gastrectomy was an independent factor associated with “non-dumper” (dumping score of 4 or below) and the degrees of postprandial increases in blood glucose, GLP-1, and GLP-2 levels and heart rate were significantly more prominent in patients with total gastrectomy than those in patients with distal gastrectomy. Previous studies reported higher incidences of early dumping syndrome in patients who underwent total gastrectomy than those in patients who underwent distal gastrectomy due to more accelerated nutrient delivery into the small intestine [1,29]. To our knowledge, this is the first study to identify a significant difference in the degree of postprandial changes in GI hormones and hemodynamics between patients who underwent distal or total gastrectomy. As early dumping syndrome is clinically characterized by GI and vasomotor symptoms related to 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. We performed a post-meal exam for blood samples and Doppler measurements 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

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**Fig. 3.** Meal-induced changes in (A) glucose, (B) GLP-1, (C) GLP-2, (D) superior mesenteric artery RI, (E) renal RI, and (F) heart rate in patients who underwent total gastrectomy (solid line) and those who underwent distal gastrectomy (dotted line). Values are means ± 2 standard deviation. GLP = glucagon-like peptide; RI = resistive index; SMA = superior mesenteric artery.

prominent within this period [7,9,11,12,17]. However, additional postprandial exams until 2–3 hours after meal ingestion in future studies would be more informative, especially concerning late dumping syndrome. Second, among the various Doppler parameters to quantify blood flow, we measured only RI, which does not require estimations of the Doppler angle or the vessel cross-sectional area, resulting in a reliable interobserver agreement compared to that for volume flow measurements [27,28,30,31]. Recent studies have directly measured the volume blood flow of intra-abdominal deep-seated vessels such as the SMA by magnetic resonance imaging or positron emission tomography [9,32]. However, practically, these methods are more burdensome for study participants than Doppler examinations.

In conclusion, the early postprandial changes in GI hormones and hemodynamics were greater in patients who underwent gastrectomy compared to those in controls. Among patients who underwent gastrectomy, these changes were more prominent after total gastrectomy than after distal gastrectomy, which was associated with a lower risk of early dumping syndrome. Our results suggest that early postprandial changes in GI hormones and hemodynamics play a crucial role in the pathophysiology of early dumping syndrome.



## ACKNOWLEDGMENTS

The statistical analysis in this study was supported by the Medical Research Collaborating Center, Seoul National University Hospital.

## SUPPLEMENTARY MATERIALS

### Supplementary Table 1

Sigstad's clinical diagnostic index for dumping syndrome

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### Supplementary Fig. 1

SMA Doppler ultrasound image of a 44-year-old man who underwent total gastrectomy 49 days prior. (A) Before and (B) 20 minutes after meal ingestion. The slope of the waveform dampened and the  $RI=(A-B)/A$  value decreased postprandially from 0.84 to 0.68, indicating increased SMA blood flow.

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### Supplementary Fig. 2

Renal Doppler ultrasound image in the same patient as in **Supplementary Fig. 1**; (A) before and (B) 20 minutes after meal ingestion. The slope of the waveform became steeper and the  $RI=(A-B)/A$  value increased postprandially from 0.65 to 0.70, indicating decreased renal blood flow.

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### Supplementary Fig. 3

ROC curve analysis of dumping syndrome in patients who underwent gastrectomy. The AUC was calculated for the meal-induced changes in blood glucose level ( $AUC=0.658$ ;  $P=0.088$ ). A meal-induced change (ratio=post/pre-meal blood glucose level) cut-off value of 1.76 had a sensitivity of 78.9% and a specificity of 61.9% in determining dumping syndrome.

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