



Association Between Gut Regulatory Hormones and Post-operative Weight Loss Following Gastrectomy in Patients With Gastric Cancer

Hye-Kyung Jung,^{1*} Chung Hyun Tae,¹ Hye Ah Lee,² Ko Eun Lee,¹ Chang Mo Moon,¹ Seong Eun Kim,¹ Ju Young Seoh,³ and Joo-Ho Lee⁴

Departments of ¹Internal Medicine, ²Microbiology, and ⁴Surgery, College of Medicine, Ewha Womans University, Seoul, Korea; and ³Clinical Trial Center, Mokdong Hospital, Ewha Womans University, Seoul, Korea

Background/Aims

Post-operative weight loss in patients with gastric cancer lead to a poor quality of life and long-term survival. This study aims to evaluate the effects of gut regulatory hormones on post-operative weight loss in patients with subtotal gastrectomy for gastric cancer.

Methods

This prospective study was conducted for 12 months post-surgery in 14 controls and 13 gastrectomy patients who underwent subtotal gastrectomy for gastric cancer. Serum plasma ghrelin, glucagon-like peptide-1, gastric inhibitory peptide-1, peptide YY, insulin, and homeostatic model assessment for insulin resistance responses to a standardized test meal were recorded at multiple time points before and after gastrectomy at 4 and 12 months.

Results

The mean weight difference between the pre-operative state and the 4-month period was significantly reduced to 6.6 kg ($P = 0.032$), but significant weight reduction was not observed from 4 months to 12 months. The plasma levels of glucagon-like peptide-1, gastric inhibitory peptide-1, and peptide YY were significantly increased 4 months postoperatively compared to the pre-operative state (all $P = 0.035$); however, pre-operative levels and relative changes over a period of 0-4 months of hormones were not correlated with body weight changes. Only the pre-operative ghrelin at peak had a negative correlation with changes in weight reduction in the 4 months after surgery ($\rho = -0.8$, $P = 0.024$).

Conclusions

Significant weight reduction was common after subtotal gastrectomy for gastric cancer with a negative correlation pre-operative plasma ghrelin levels. Incretin hormones are modestly but significantly increased after subtotal gastrectomy; however, these changes did not affect the weight changes.

(J Neurogastroenterol Motil 2022;28:409-417)

Key Words

Gastrectomy; Ghrelin; Glucagon-like peptide-1; Stomach neoplasms; Weight loss

Received: July 26, 2021 Revised: October 31, 2021 Accepted: November 24, 2021

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*Correspondence: Hye-Kyung Jung, MD, PhD

Department of Internal Medicine, College of Medicine, Ewha Womans University 1071, Anyangcheon-ro, Yangcheon-gu, Seoul 07895, Korea
Tel: +82-2-2650-2874, Fax: +82-2-2650-2874, E-mail: junghk@ewha.ac.kr

Introduction

Gastric cancer is one of the most common malignancies and the fourth leading cause of cancer-related death.¹ In 2017, the standardized incidence of gastric cancer in Korea was 57.9 per 100 000, which was the second most common after thyroid cancer with high mortality.² In 2019, gastric surgery was the most frequently performed on cancer patients after colon and liver cancer.³ The prevalence of gastric cancer is high in Asia and is the most common cause of gastric resection, rather than bariatric surgery. Most patients who undergo gastrectomy for gastric cancer experience weight loss as an inevitable postoperative complication. Postoperative weight loss was related to poor long-term survival of gastric cancer patients after gastrectomy.⁴ However, overweight patients showed a higher survival rate in long-term follow-up observations for more than 9 years post-surgery than underweight patients or those with normal weight.⁵

Several studies have shown different gut hormonal changes due to various surgical modalities. Sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB) have become popular and effective surgeries for obesity.⁶ Though proven effective and safe, their underlying mechanism related to weight reduction remain unclear. Anatomical reduction in gastrointestinal (GI) tissue or volume may decrease the nutritional intake.⁷ In addition, weight loss can continue due to changes in gut hormones after surgery, which is emerging as a more important mechanism.⁶ Weight reduction and glycemic control after SG and RYGB was comparable in a recent randomized controlled trial,⁸ while a significant large weight reduction and better glycemic control were achieved in another study using RYGB at 5 years after surgery.⁹ In other studies, glucose and nutrient absorption in the GI tract as well as gut hormonal changes differed depending on the bariatric surgical method.¹⁰ Postprandial glucose and protein absorption after RYGB was accompanied by higher secretion of insulin, glucagon-like peptide 1 (GLP-1), peptide YY (PYY), and cholecystokinin and lower ghrelin levels compared to SG and controls. However, there are fewer studies on the physiological mechanisms behind weight loss after gastric cancer surgery than those after bariatric surgery.

In the present study, we aim (1) to compare the gut hormonal and weight changes between the pre-operative and post-operative periods after subtotal gastrectomy (STG) in patients with gastric cancer, and (2) to evaluate the association between dumping syndrome and gut hormones after gastric resection.

Materials and Methods

Study Subjects

This study was prospectively conducted on patients diagnosed with gastric cancer and control groups at a tertiary referral hospital in South Korea. Study groups were composed of patients with gastric cancer who had undergone uncomplicated laparoscopic subtotal gastrectomy with Billroth II operation and controls. Inclusion criteria were as follows: (1) those aged 20-75 years, (2) those who could understand and respond to the questionnaire themselves, and (3) those who voluntarily agreed to participate in this study and signed an informed consent form. The exclusion criteria were: (1) diabetes mellitus before surgery; (2) history of abdominal surgery except appendectomy; (3) peri-operative bleeding requiring blood transfusion during surgery; (4) patients who needed conversion to open surgery from laparoscopy, and patients with injury to adjacent organs or intestines during surgery; (5) post-operative complications after gastrectomy that could affect oral food intake, such as anastomotic leakage, mechanical ileus, wound infection or passage disturbance after surgery; (6) medical history of inflammatory bowel disease, ischemic colitis, pancreatic insufficiency, intestinal obstruction, or stricture; (7) serious uncompensated cardiovascular, respiratory, renal, or liver disease; and (8) pregnancy or breast feeding. Controls who met the above criteria with no history of abdominal surgery were recruited through local advertisements.

The study protocol was approved by the ethics committee at Ewha Womans Mockdong Hospital, and all subjects provided written informed consent to participate (ECT 13-20B-02).

Experimental Protocol

Thirteen gastric cancer patients underwent standard laparoscopic subtotal gastrectomy with Billroth II surgery due to early gastric cancer by an experienced surgeon. Among them, 11 patients were finally diagnosed with stage I cancer, and 2 patients with stage IIa (T₂N₁). Anthropometric measurements and hormonal changes were followed up before surgery and at 4 months and 12 months after surgery.

Patients visited the hospital in the morning after an overnight fast 1 day before surgery and each planned visit at the 4th and 12th post-operative months. Anthropometric measurements, including weight and height, were performed using a body-composition analyzer. A flexible intravenous catheter was placed in the superficial forearm vein for venous blood sampling for gut hormones (plasma

GLP-1, gastric inhibitory peptide 1 [GIP-1], PYY, and ghrelin) and biochemical parameters (glucose and insulin) when the patients were fasting (0 minute, baseline) in a hospital bed in a reclining position.

Three blood samples were collected at baseline; at 30 minutes and 120 minutes after the standardized meal, for measurement of glucose, insulin, GLP-1, GIP-1, PYY, and ghrelin. A standardized liquid meal (Encover solution; EN Otsuka Pharmaceutical, Hanamaki City, Japan), which contained 200 mL (200 kcal) with approximately 62% of the energy from carbohydrate, 20% from fat, and 18% from protein, was provided. Samples for hormone measurements at 30 minutes and 120 minutes were collected in ice-chilled tubes containing EDTA-2Na and/or aprotinin, centrifuged in the cold, and stored at -70°C . In addition, radioimmunoassays for total GLP-1, GIP-1, and ghrelin (Linco Research Inc, St. Louis, MO, USA) in EDTA plasma were carried out as previously described.¹¹ PYY was measured with an enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals Inc, Belmont, CA, USA) and insulin was assayed using a 2-site sandwich immunoassay (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA).¹² Serum glucose concentrations were determined using an Immulite 2000 analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA).

All subjects completed Sigstad's scoring questionnaire for the diagnosis of dumping syndrome at each visit. Fourteen healthy con-

trol subjects underwent venous sampling in the same manner.

Statistical Methods

The levels of plasma insulin, homeostatic model assessment for insulin resistance (HOMA-IR), GLP-1, GIP-1, PYY, and ghrelin are presented as mean \pm SD of area under curve (AUC) 0 minute to 120 minutes, for 30 minutes. Body mass index (BMI) was calculated as weight in kilograms divided by height per square meter. Insulin sensitivity was assessed based on the reciprocal of the HOMA-IR, which was calculated from 3 separate blood samples in the basal state.¹³

The sample size was calculated as $n = 8$ in each group to detect a significant difference in the primary endpoint, basal and peak levels of ghrelin between those of the pre-operative state and those of the postoperative state with 80% power and a-sided α -error of 0.05.¹⁴ The present study included 13 patients and 14 controls in consideration of follow-up loss because of long-term follow-up for up to a year.

Continuous variables that did not satisfy the Shapiro-Wilk test underwent logarithmic transformation. Group differences in the peak and AUC levels of hormones at pre-operative state were tested using the Mann-Whitney U test. In subtotal gastrectomy subjects, the Wilcoxon signed-rank test was performed to test for changes in hormones and weight by period (before surgery, 4 months, and 12

Table 1. Baseline Characteristics and Hormone Levels Between Subjects Scheduled for Subtotal Gastrectomy and 14 Controls

Parameter	Subtotal gastrectomy (n = 13)	Controls (n = 14)	P-value
Age (yr)	59.2 \pm 10.4 (45-75)	49.6 \pm 5.8 (36-56)	< 0.001
Sex (M:F)	8:5	7:7	0.411
BMI (kg/m ²)	24.6 \pm 2.8	22.5 \pm 2.3	< 0.001
< 25	8	13	
25-30	5	1	
Baseline hormone levels			
Insulin _{AUC} (IU/mL \times min)	5.8 (4.1-8.2)	6.6 (5.8-7.5)	0.165
Insulin _{peak} (μ IU/mL)	81.3 (58.4-113.2)	100.4 (88.0-114.7)	0.040
Ghrelin _{AUC} (ng/mL \times min)	631.0 (440.8-821.1)	555.8 (362.9-748.7)	0.488
Ghrelin _{peak} (ng/mL)	5.2 (3.6-6.7)	4.6 (3.0-6.1)	0.564
GLP-1 _{AUC} (μ g/mL \times min)	1.7 (1.1-2.5)	2.3 (1903.0-2798.8)	0.031
GLP-1 _{peak} (ng/mL)	23.4 (15.9-34.5)	35.1 (28.9-42.7)	0.024
GIP-1 _{AUC} (μ g/mL)	2.8 (1.2-6.6)	9.1 (7.3-11.3)	0.005
GIP-1 _{peak} (ng/mL)	32.1 (11.4-90.3)	138.1 (110.3-172.9)	0.010
PYY _{AUC} (ng/mL \times min)	5.0 (3.2-7.7)	1.6 (5.9-4.4)	0.013
PYY _{peak} (pg/mL)	45.4 (31.4-65.7)	37.6 (13.4-104.9)	0.621
HOMA-IR	2.2 (1.3-3.6)	2.0 (1.8-2.3)	0.381

M, male; F, female; BMI, body mass index; AUC, area under curve; GLP-1, glucagon like peptide-1; GIP-1, gastric inhibitory peptide; PYY, Peptide YY; HOMA-IR, homeostatic model assessment for insulin resistance.

Age, sex, and BMI are presented as mean \pm SD (range), n, or mean (95% CI).

months after surgery). The Bonferroni method was used to correct for multiple comparisons. The correlation between body weight changes over the 4 months postoperatively with the gut hormones at pre-operative state was assessed using the partial Spearman's correlation adjusted for age and sex. Additionally, by calculating the relative change in hormones for 4 months after surgery, the correlation with the relative change in body weight was analyzed. Differences in weight and gut hormones according to the presence of dumping syndrome at postoperative 12 months were evaluated using the Mann-Whitney *U* test. Statistical analysis was performed using SPSS (version 26.0; IBM Corp, Armonk, NY, USA). Statistical significance was set at $P < 0.05$.

Results

Baseline Anthropometric Characteristics and Hormonal Levels

A total of 13 candidates scheduled for STG were screened for eligibility and underwent a baseline hormone test 1 day before surgery (stage I, $n = 11$; stage IIa, $n = 2$). Eight subjects visited and underwent hormone tests both at 4th months and 12th months after STG as planned in the study. We also enrolled 14 controls who

did not have a history of GI surgery. As shown in Table 1, the age and BMI of STG group were significantly higher than those of the control group (59.2 ± 10.4 years vs 49.6 ± 5.8 years, $P < 0.001$; 24.6 ± 2.8 kg/m² vs 22.5 ± 2.3 kg/m², $P < 0.001$, respectively). The peak and AUC levels of GLP-1 ($P = 0.024$ and $P = 0.031$, respectively) and GIP-I ($P = 0.010$ and $P \leq 0.005$, respectively) were lower in the pre-operative STG group than in the normal controls, but HOMA-IR and ghrelin levels were not significantly different. The AUC level of PYY was significantly higher in the STG group than that in the controls ($P = 0.013$).

Weight Reduction Pattern

Weight reduction occurred in all 13 subjects in the postoperative state. As a result of analyzing the weight changes of STG since pre-operative state, the weight at each point tended to decrease over time; 65.0 kg (95% CI, 58.3-71.8 kg) at pre-operative state; 58.4 kg (95% CI, 51.4-65.5 kg) at 4 months; 58.0 kg (95% CI, 47.2-68.7 kg) at 12 months, respectively (Fig. 1). The average weight difference between the pre-operative state and the 4-month period after STG was significantly reduced to 6.6 kg ($P = 0.032$), but the average weight decreased by 0.5 kg from 4 months to 12 months and was not statistically significant ($P > 0.999$).

Changes of Body Weight and Gut Hormone After Subtotal Gastrectomy

The peak and AUC levels of the gut hormone profile by standardized meal stimulation were measured pre-operatively and at 4 months and 12 months post-operatively. The peak and AUC levels of GLP-I were significantly increased after post-operative 4 months compared to the pre-operative state (both $P = 0.03$); however, there was no significant interval change between post-operative 4 months and 12 months (Table 2). The plasma AUC level of GIP-1 was significantly increased 4 months postoperatively compared to the pre-operative state ($P = 0.035$); however, there was no significant changes in the peak level of GIP-1 at postoperative 4 months ($P = 0.083$) and at 12 months after surgery ($P = 0.518$). There were no significant differences of the peak and AUC levels of insulin in post-operative 4 months ($P = 0.052$ in peak level of insulin and $P = 0.075$ in AUC level of insulin). The peak levels of circulating PYY were significantly increased after 4 months postoperatively compared to the pre-operative state ($P = 0.035$). However, ghrelin showed no significant difference in the mean value for each period (Table 2).

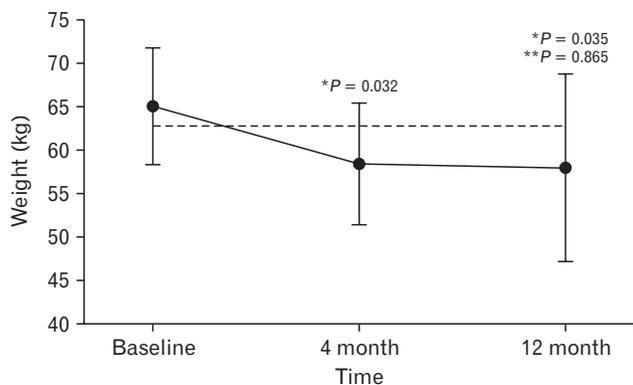


Figure 1. Weight change before and after surgery. The dashed line means the average value of the control group at baseline. Results are presented as means with 95% CI. *P*-values were tested by Wilcoxon signed-rank test with Bonferroni method. **P*-values presented the comparison between pre-operative state and post-operative 4 months and 12 months and ***P*-value presented the comparison between 4 months and 12 months.

Table 2. Changes in Gut Hormones After Subtotal Gastrectomy in Patients With Stomach Cancer

Parameter	Pre-operative state		Post-operative 4 months		Post-operative 12 months		0-4 month change	4-12 month change	0-12 month change
	Means	95% CI	Means	95% CI	Means	95% CI	<i>P</i> for Wilcoxon signed-rank test ^a		
Insulin _{AUC} (IU/mL × min)	5.8	4.1-8.2	11.2	6.0-21.1	11.9	6.2-22.6	0.075	0.183	0.529
Insulin _{peak} (μIU/mL)	81.3	58.4-113.2	168.4	88.0-322.2	266.4	99.7-433.1	0.052	0.054	0.054
Ghrelin _{AUC} (ng/mL × min)	631.0	440.8-821.1	857.7	621.0-1094.3	907.0	727.2-1086.8	0.052	> 0.999	0.084
Ghrelin _{peak} (ng/mL)	5.2	3.6-6.7	7.1	5.2-8.9	7.4	5.8-8.9	0.101	> 0.999	0.084
GLP-1 _{AUC} (μg/mL × min)	1.7	1.1-2.5	2.6	1.5-4.4	2.6	1.3-5.5	0.035	> 0.999	> 0.999
GLP-1 _{peak} (ng/mL)	23.4	15.9-34.5	38.9	21.9-69.0	38.3	17.0-86.4	0.035	> 0.999	> 0.999
GIP-1 _{AUC} (μg/mL × min)	2.8	1.2-6.6	8.0	4.0-15.7	9.2	3.4-2.4	0.035	> 0.999	0.519
GIP-1 _{peak} (ng/mL)	32.1	11.4-90.3	115.5	58.1-229.6	113.9	35.3-367.6	0.084	> 0.999	0.519
PYY _{AUC} (ng/mL × min)	5.0	3.2-7.7	11.0	4.7-25.9	3.1	1.1-8.2	0.107	0.347	> 0.999
PYY _{peak} (pg/mL)	45.4	31.4-65.7	95.6	43.2-211.7	42.03	15.5-114.1	0.035	> 0.999	> 0.999
HOMA-IR	2.2	1.3-3.6	2.1	1.1-4.2	2.0	1.2-2.7	> 0.999	0.129	0.0831

^a*P* for Wilcoxon signed-rank test with multiple comparison.

AUC, area under curve; GLP-1, glucagon like peptide-1; GIP-1, gastric inhibitory peptide-1; PYY, Peptide YY; HOMA-IR, homeostatic model assessment for insulin resistance.

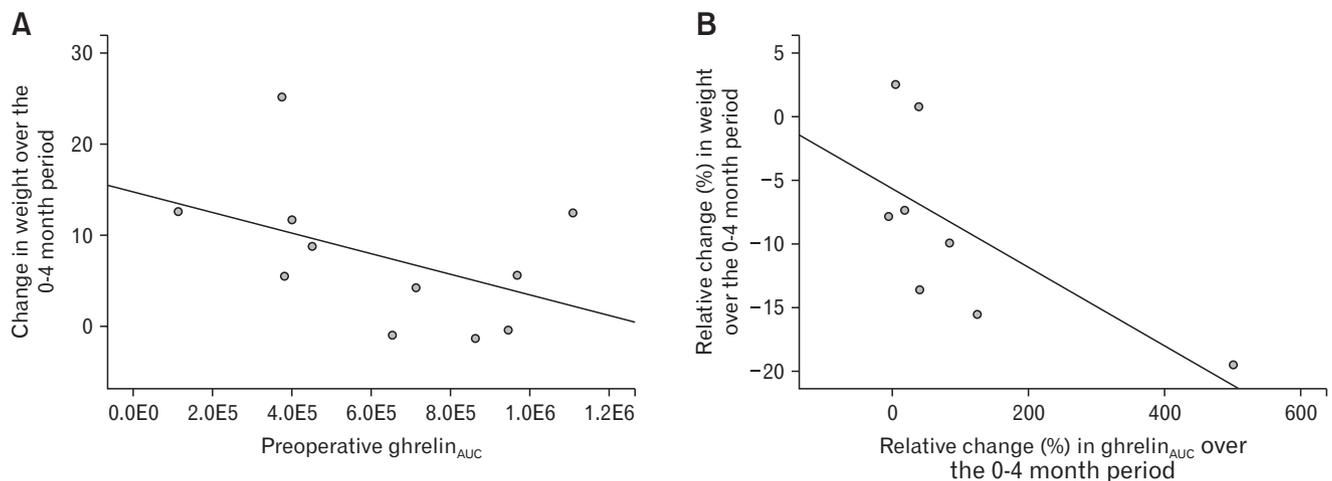


Figure 2. The correlation between gut hormones and body weight changes after subtotal gastrectomy. (A) The pre-operative AUC level of ghrelin negatively correlated with change of the weight loss (Δ = weight at 4 months after surgery – weight at pre-operative state) in the 4 months after surgery, showing significant negative correlation under adjusting for age and sex ($\rho = -0.8$, $P = 0.024$). (B) The relative change in weight loss over a period of 0-4 months negatively correlated with the relative change to the plasma AUC level of ghrelin and showed a borderline significance after adjusting for age and sex ($\rho = -0.8$, $P = 0.070$). Relative change was calculated as a percentage after calculating the difference between the values at the pre-operative state from the value at 4 months after surgery, then dividing it by the value at the pre-operative state.

Correlation Between Gut Hormones and Body Weight Changes After Subtotal Gastrectomy

When calculating the relative change in body weight between the pre-operative and postoperative 4 months in the STG group, the median weight was reduced by 8.9% compared to the pre-operative state. There was no significant change in ghrelin levels at

4 months and 12 months from pre-operative state. However, the AUC level of pre-operative ghrelin negatively correlated with the change in weight loss in the 4 months after surgery, showing a significant negative correlation ($\rho = -0.8$, $P = 0.024$) after adjusting for age and sex (Fig. 2A). After adjusting for age and sex, the relative change in weight loss over a period of 0-4 months was not correlated with the relative change in the plasma AUC level of ghrelin

Table 3. Changes in Gut Hormones According to the Presence of Dumping Syndrome at Post-operative 12 Months

Parameter	No dumping syndrome (n = 11)			Dumping syndrome (n = 3)			P-value ^a
	25th percentile	50th percentile	75th percentile	25th percentile	50th percentile	75th percentile	
Pre-operative weight (kg)	49.3	57.3	63.9	77.8	80.0	84.4	0.050
Post-operative weight (kg)	47.3	57.3	60.2	59.1	70.0	77.7	0.275
Pre-operative gut hormones							
Insulin _{AUC} (IU/mL × min)	3.8	4.4	5.2	5.3	5.6	5.9	0.564
Insulin _{peak} (μIU/mL)	54.8	65.6	70.5	74.8	77.4	79.9	0.258
Ghrelin _{AUC} (ng/mL × min)	544.5	710.5	838.1	372.4	409.6	446.8	0.248
Ghrelin _{peak} (ng/mL)	4.7	6.2	6.9	3.0	3.1	3.3	0.248
GLP-1 _{AUC} (μg/mL × min)	1.0	1.2	1.3	1.3	1.6	1.9	0.258
GLP-1 _{peak} (ng/mL)	13.3	15.5	15.8	15.7	21.4	27.1	0.248
GIP-1 _{AUC} (μg/mL × min)	0.5	0.5	2.3	2.3	3.4	4.5	0.248
GIP-1 _{peak} (ng/mL)	2.1	10.0	18.0	19.6	36.4	53.3	0.121
PYY _{AUC} (ng/mL × min)	6.1	6.4	9.5	2.5	2.9	3.3	0.083
PYY _{peak} (pg/mL)	62.2	75.4	93.8	25.5	31.2	36.9	0.083
Post-operative gut hormones							
Insulin _{AUC} (IU/mL × min)	7.7	10.6	17.5	7.7	10.9	20.1	0.827
Insulin _{peak} (μIU/mL)	119.5	169.2	281.0	115.7	161.8	322.5	0.827
Ghrelin _{AUC} (ng/mL × min)	588.9	595.7	978.8	843.9	907.5	928.3	0.513
Ghrelin _{peak} (ng/mL)	4.9	5.2	8.2	6.8	7.0	7.4	0.513
GLP-1 _{AUC} (μg/mL × min)	1.4	2.1	4.1	1.4	2.1	4.3	0.827
GLP-1 _{peak} (ng/mL)	21.9	33.9	66.3	20.6	30.8	69.9	0.827
GIP-1 _{AUC} (μg/mL × min)	6.7	11.9	18.1	3.7	5.9	14.9	0.513
GIP-1 _{peak} (ng/mL)	105.6	191.4	293.1	52.0	85.0	241.8	0.827
PYY _{AUC} (ng/mL × min)	6.1	6.4	9.5	2.5	2.9	3.3	0.083
PYY _{peak} (pg/mL)	62.2	75.4	93.8	25.5	31.2	36.9	0.083

^aP-value for Mann-Whitney *U* test.

The hormone levels are presented by quartiles of log-transformed values: Q2, 25th percentiles; Q3, median; Q4, 75th percentiles; AUC, area under curve; GLP-1, glucagon like peptide-1; GIP-1, gastric inhibitory peptide; PYY, Peptide YY.

($\rho = -0.8, P = 0.070$) (Fig. 2B). In comparison for pre-operative state and 12 months after surgery, pre-operative ghrelin levels were associated with postoperative weight reduction ($\rho = -0.8, P = 0.024$), but the level of change in ghrelin was not significantly related ($\rho = -0.8, P = 0.070$).

Pre-operative levels and relative changes over a period of 0-4 months of insulin, GLP-1, GIP-1, PYY, and HOMA-IR were not significantly correlated with body weight changes.

Evaluation of Body Weight and Gut Hormone Difference by Dumping Syndrome in 12 Months After Subtotal Gastrectomy

According to the Sigtard criteria, 1 patient experienced dumping syndrome 4 months after surgery, and 3 patients experienced dumping syndrome in 12 months. We compared the difference between body weight changes and gut hormones between 3 patients with dumping syndrome at 12 months and those without dumping

syndrome. The results were presented in the median and quartile ranges because the sample size in each group was small. The pre-operative body weight of the group with dumping syndrome tended to be higher than that of the group without dumping syndrome (80.0 kg [interquartile range, 77.8-84.4 kg] vs 57.3 kg [interquartile range, 49.3-63.9 kg], $P = 0.050$); however, there was no significant difference in the change in body weight at 12 months after surgery according to the presence of dumping syndrome. The pre-operative hormone levels and hormonal changes after surgery were not significantly different according to the presence of dumping syndrome in the 12 months after surgery (Table 3).

Discussion

Patients who undergo gastrectomy for gastric cancer often experience postsurgical weight loss, perioperative weight changes, and their nutritional status is associated with short- and long-term

outcomes after surgery in gastric cancer patients.¹⁵ However, this mechanism is not fully understood. Our study revealed that pre-operative ghrelin level, which is an appetite regulating gut hormone, is an important predictor of postoperative weight loss in patients who underwent STG due to gastric cancer. The AUC level of pre-operative ghrelin negatively correlated with the change in weight loss in the 4 months after surgery, showing a significant negative correlation ($\rho = -0.8, P = 0.020$) after adjusting for age and sex. In the postoperative state, postprandial gut hormones, including GLP-1, GIP-1, and PYY, were exaggerated compared to those in the pre-operative state, as well as controls; however, it did not affect the postoperative weight loss or glucose metabolism in gastric cancer patients.

The mechanism of weight loss in patients undergoing gastrectomy for gastric cancer may be complicated. Subtotal or total gastric resection can negatively affect the digestion and absorption of food due to a decrease in gastric capacity, including gastric motor and secretory function.¹⁶ Several studies have shown that patients who underwent distal gastrectomy for gastric cancer had better nutritional outcomes, including food intake and weight loss compared with total gastrectomy.¹⁷ Furthermore, in patients with pouch reconstruction after total gastrectomy, had improved food intake compared to those without a gastric reservoir.^{17,18} However, other studies revealed that gastric reservoir did not improve the nutritional benefit.^{18,19}

In the present study, pre-operative ghrelin level was an important predictor of postoperative weight loss. Although ghrelin was initially discovered as an endogenous ligand for the growth hormone secretagogue receptor,²⁰ subsequent studies reported that ghrelin increases food intake and body weight, plays a powerful role in energy homeostasis.²¹ The stomach is the principal site of ghrelin synthesis and the gastric fundus, the most abundant source, produces 10 times more of the hormone than the duodenum, which is the next richest site.^{22,23} Endogenous ghrelin is a physiological meal initiator whose circulating levels should rise before and fall after every meal, while peripheral ghrelin administration stimulates appetite and food intake.²⁴ Therefore, it is predictable that postoperative weight loss may be reduced in patients with high pre-operative ghrelin secretion.

Surprisingly, postprandial ghrelin suppression does not require luminal nutrient exposure in the stomach or duodenum, but in the small bowel with post-absorptive events. It is related to plasma insulin, intestinal osmolality, and enteric neural signaling, not gastric distension.²⁵ Appetite regulating gut hormone secretion is altered after RYGB and SG towards a more anorectic profile, which is likely to facilitate diet compliance and weight loss. In bariatric surgery, exten-

sive rearrangement of the upper GI tract results in the accelerated entry of nutrients into the small intestine. It is accompanied by exaggerated meal-related release of several gut hormones involved in appetite regulation and glucose homeostasis, including GLP-1 and PYY.^{26,27} Ghrelin concentrations are reduced early after RYGB, but have been restored to the pre-operative state with time.²⁷ In patients with STG due to stomach cancer, plasma ghrelin levels did not decrease after 4 months and 12 months of gastrectomy. This is suggestive of a balanced increase in ghrelin secretion due to weight loss, despite the increase in GLP-1 and PYY in the postoperative state. A functioning vagus nerve is required for the appetite-stimulating effect of ghrelin.²⁸ Because of the operative technique of preserving the vagus nerve and remnant source of ghrelin, some degree of ghrelin on STG may be increased by negative feedback of postoperative weight reduction. Previous studies conducted in patients with STG reported a 50-70% decline in plasma ghrelin levels 7 days after surgery, but long-term data have shown that ghrelin levels recover to pre-operative conditions.² However, this study measured plasma ghrelin levels in different groups of patients pre-operatively and postoperatively, rather than cohort studies conducted in the same group. In addition, this study had a limitation in measuring gut hormones once during fasting, which varies greatly depending on the meal.

A randomized clinical trial revealed that intravenous infusion of recombinant ghrelin significantly increased food intake and attenuated weight reduction after total gastrectomy.²⁹ However, its long-term effects remains unclear, and further studies are necessary with subcutaneous or oral administration.

A previous study showed that abnormalities in circulating hormones in patients with dumping syndrome after gastrectomy.³⁰ Rapid gastric transit results in the expansion of the hyperosmolar chyme into the lumen of the small intestine. Exaggerated gut hormones such as GLP-1 have been postulated to partially contribute to early and late dumping syndrome after gastrectomy.³⁰ In our study, GLP-1 levels were increased after gastrectomy; however, there was no correlation according to the presence of dumping syndrome. The small load of fast-absorbing nutrients preferentially activates the upper-increasing hormone (ie, GIP), while the intake of larger meals containing more complex nutrients that require broader digestion also activates the distal incretin (ie, GLP-1 or PYY).²⁶ The most dramatic gut hormonal changes were reported in patients who underwent bariatric surgery. After bariatric surgery, the postprandial plasma GLP-1 levels were increased up to 5-10 times within several days after surgery.^{27,31} GLP-1 is responsible for increased insulin secretion and improved post-prandial glucose

tolerance after RYGB and sleeve gastrectomy. Since a significant number of patients who have undergone bariatric surgery have glucose intolerance and insulin resistance, these GI hormonal changes after surgery normalize glucose metabolism and maintain continuous weight reduction. However, in patients with gastric cancer surgery, it is suggested that the increase in incretin after STG is statistically significant, but the effect on weight loss was minimal due to a modest increase in incretin compared to bariatric surgery and glucose metabolism.

The present study had several strengths. First, while existing studies have mostly been short-term follow-ups within hours or weeks after surgery, the present study has been followed up to 12 months after gastric cancer surgery to measure weight changes and gut hormones. Therefore, we can represent the causal relationship between gut hormones and weight loss after STG. Second, we measured gut hormones before and after meals for 2 hours with a standardized diet. Because gut hormones are activated or suppressed more than 10 times with meals, measuring hormones using a standardized method is one of the most important factors influencing the results. This study has some limitations. We used a liquid formula as a standardized meal, which is likely to produce results that are different from solid diets, although the calories and nutrients are the same. Second, the age and BMI of the control group were different from those of the patients. It was difficult to recruit a control group matching the gastric cancer group. In particular, BMI of the pre-operative gastric cancer group was higher than that of the control group but lower than 25 kg/m², which is the cutoff value of obesity, and GLP-1 and GIP-1 were lower than those in the control group, however, it is difficult to know whether this modest difference affects weight change after surgery. Data analysis was conducted by adjusting for these variables to minimize this effect. Another limitation is that we could not directly investigate the dietary amount and postprandial nutritional absorption after surgery to assess the effect of ghrelin.

In conclusion, significant weight reduction was common after STG for gastric cancer, and these changes negatively correlated with pre-operative plasma ghrelin levels. Incretin hormones such as GLP-1, GIP-1, and PYY are modestly, but significantly increased after STG for gastric cancer; however, these changes did not affect the post-operative weight reduction or metabolic changes.

Financial support: This research was supported by a grant of The Korean Society of Neurogastroenterology and Motility (2014).

Conflicts of interest: None.

Author contributions: Ko Eun Lee, Ju Young Seoh, and Joo-Ho Lee acquired data; Hye Ah Lee and Hye-Kyung Jung analyzed and interpreted data; Hye-Kyung Jung, Chung Hyun Tae, Chang Mo Moon, Seong Eun Kim, and Hye Ah Lee prepared figure, drafted, and revised the manuscript; Hye-Kyung Jung designed and supervised the study; and all authors read and approved the final manuscript.

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