Effects of vagus nerve preservation and vagotomy on peptide YY and body weight after subtotal gastrectomy

Hyung Hun Kim, Moo In Park, Sang Ho Lee, Hyun Yong Hwang, Sung Eun Kim, Seun Ja Park, Won Moon

Abstract

AIM: To investigate the relationship between the function of vagus nerve and peptide YY3-36 and ghrelin levels after subtotal gastrectomy.

METHODS: We enrolled a total of 16 patients who underwent subtotal gastrectomy due to gastric cancer. All surgeries were performed by a single skilled surgeon. We measured peptide YY3-36, ghrelin, leptin, insulin, growth hormone levels, and body weight immediately before and one month after surgery.

RESULTS: Vagus nerve preservation group showed less body weight loss and less increase of peptide YY3-36 compared with vagotomy group (-5.56 ± 2.24 kg vs -7.85 ± 1.57 kg, P = 0.037 and 0.06 ± 0.08 ng/mL vs 0.19 ± 0.12 ng/mL, P = 0.021, respectively). Moreover, patients with body weight loss of less than 10% exhibited reduced elevation of peptide YY3-36 level, typically less than 20% [6 (66.7%) vs 0 (0.0%), P = 0.011, odd ratio = 3.333, 95% confidence interval (1.293, 8.591)].

CONCLUSION: Vagus nerve preservation contributes to the maintenance of body weight after gastrectomy, and this phenomenon may be related to the suppressed activity of peptide YY3-36.

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Key words: Peptide YY; Ghrelin; Vagotomy; Gastrectomy; Body weight

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INTRODUCTION

Body weight loss is a common and serious outcome in patients with gastric cancer who are treated by gastrectomy[1]. Weight loss is correlated with declines in postoperative quality of life and is the most reliable indicator of malnutrition, which impairs immune function, infection susceptibility, and survival[2,3]. Postoperative body weight loss can be explained by mechanisms such as reduced food intake, appetite loss caused by the reduced reservoir or delayed gastric emptying[15], diarrhea[8] and malabsorp-
tion. Malabsorption, in turn, is linked to secretion of gastric acid and pancreatic insufficiency. In addition, it was recently suggested that alterations of endocrine status, such as reduced gastrin or ghrelin, and increased cholecystokinin levels might be involved in weight loss after gastrectomy. However, the mechanism of body weight loss after gastrectomy has not been fully clarified.

The 28-amino acid peptide ghrelin is the endogenous ligand for the growth hormone secretagogue receptor 1a, which stimulates the release of growth hormone from the pituitary gland. The majority of ghrelin is produced by X/A-like endocrine cells of the gastric oxyntic mucosa, and smaller amounts are secreted by other organs, such as the intestine, pancreas, kidney and hypothalamus. Ghrelin has a number of physiologic effects that result in positive energy balance, such as promoting the appetite signal in the hypothalamus as an antagonist to leptin, stimulating gastrointestinal activities such as peristalsis, gastric acid secretion, and pancreatic excretion through the vagal nerves, and regulation of fat metabolism. Peptide YY3-36, a 36 amino acid gut-derived hormone, reduces food intake over the short term in animals and in humans by stimulating hypothalamic neuropeptide Y receptors. Preprandial decreases and postprandial increases in plasma peptide YY3-36 concentrations suggest that peptide YY3-36 is one of satiety signals. Peptide YY3-36 is suggested to be involved in intermediate term inhibition of food intake, in contrast to the classical short term regulators such as cholecystokinin. Dose-dependent reductions in food intake following peripheral peptide YY3-36 administration are observed in both fasting and freely feeding rodents. In healthy human volunteers, intravenous infusion of peptide YY3-36 caused a sustained decrease in appetite and food intake for more than 24 h. Moreover, gastric bypass results in a more robust peptide YY3-36 response to caloric intake, which, in conjunction with decreased ghrelin levels, may contribute to the sustained efficacy of this procedure. One animal study suggested that peptide YY release is inhibited by a vagal cholinergic mechanism due to significant elevations of basal and food-induced release of peptide YY after truncal vagotomy.

Recently, one study reported that reductions in visceral fat were significantly lower in patients in whom the vagus nerve was preserved than in patients who had undergone vagotomy, and concluded that the vagus nerve locally regulates amounts of intra-abdominal fat tissue. However, they did not mention the hormonal changes regarding the effect of vagotomy and vagus nerve preservation on body weight loss. Therefore, we aimed to reveal the correlation between the effect of vagus nerve preservation and vagotomy on peptide YY3-36 or ghrelin levels after subtotal gastrectomy in relation to body weight loss.

**MATERIALS AND METHODS**

**Patients**

Sixteen patients who underwent subtotal gastrectomy at Gospel Hospital, Kosin University College of Medicine, Busan, South Korea between January 2008 and January 2010 were enrolled in the study. The inclusion criteria were as follows: (1) adenocarcinoma of the stomach confirmed by histopathologic examination; (2) preoperative clinical staging of less than stage III A (International Union Against Cancer tumor, node, metastasis stage classification); (3) curative surgical treatment (R0) (i.e., subtotal gastrectomy with D1 or D2 lymph node dissection); and (4) age between 20 and 80 years. The exclusion criteria were the presence of any of the following: (1) cardiopulmonary, liver, or renal dysfunction; (2) active dual malignancy; (3) pregnancy; (4) past history of gastrointestinal surgery; and (5) postoperative complications after subtotal gastrectomy that could affect oral food intake, such as anastomotic leakage, pancreatitis, and mechanical ileus. Sixteen patients were randomized by sealed-envelope selection and divided into two study groups. The random allocation sequence was concealed until interventions were assigned. Nine patients were treated by subtotal gastrectomy with vagus nerve preservation (vagus nerve preservation group), and seven patients underwent both subtotal gastrectomy and vagotomy (vagotomy group). The study was approved by the Kosin University Ethics Committee, and all patients provided written informed consent before study entry in accordance with the Declaration of Helsinki.

**Operative procedures**

In seven cases, subtotal gastrectomy and bilateral truncal vagotomy were performed with D1 or D2 lymph node dissection followed by Billroth-I or Roux-en-Y reconstruction. The hepatic and celiac branches of the vagus nerve were preserved in nine patients who underwent Billroth-I or Roux-en-Y reconstruction after subtotal gastrectomy with D1 or D2 lymph node dissection. The greater omentum was largely preserved in all cases. All operations were performed by a surgeon with a history of over 1000 gastric cancer operations over the course of 20 years. An ultrasonic knife (Ultracision®, Ethicon Endo Surgery, Cincinnati, OH, United States) was used to prevent nerve damage in the vagus nerve preservation group. Electrical impulses were produced by a high-frequency ultrasound generator, transferred to a hand piece and converted into mechanical movement at a frequency of 55.5 kHz. This instrument was chosen because of the relatively low temperatures generated, ranging from 50 °C to 100 °C, which limit damage to adjacent tissue compared to conventional diathermy. Diathermy produces temperatures up to 400 °C, resulting in char formation and deleterious thermal effects to a distance of up to 1 cm from the blade, as well as the extensive formation of necrotic tissue.

**Body weight and blood sampling for hormone measurement in the fasted state**

Peptide YY3-36, ghrelin, leptin, insulin, and growth hormone levels as well as body weights were measured 1 d before surgery (day 1) and 1 mo after surgery (day 30). Venous fasting blood samples were taken early in the
morning on day 1 and day 30 for the measurement of plasma concentrations of the following hormones: peptide YY (s.c. enzyme-linked immunosorbent assay, Phoenix Pharmaceuticals Inc., Belmont, CA, United States), total ghrelin (radioimmunoassay, Linco Research Inc., St. Louis, MO, United States), leptin (radioimmunoassay, Linco Research Inc.), insulin (two-site sandwich immunnoassay, Siemens Medical Solutions Diagnostics, Los Angeles, CA, United States), and human growth hormone (radioimmunometric assay, Packard Instruments Inc., Chicago, IL, United States). Peptide YY (s.c.), insulin, and growth hormone levels were measured with the V-MAX 220 VAC enzyme-linked immunosorbent assay reader (Mo- lecular Devices, Sunnyvale, CA, United States), and peptide YY (s.c.) was measured with the COBRA II Gamma counter (Packard, Waltham, MA, United States), respectively. Ghrelin and leptin were analyzed with the COBRA II Gamma Counter (Packard, United States). Total protein, albumin, total cholesterol, and triglyceride levels were tested with the ADVIA 2400 (Siemens, Tarry-town, NY, United States).

### Statistical analysis

Statistical analysis was performed using the SPSS software (version 16.0, SPSS, Chicago, IL, United States). Differences between the vagus nerve preservation group and the vagotomy group, including sex, age, stages of gastric cancer, body weight, body mass index (BMI), and laboratory values were assessed by Fisher’s exact tests and Mann-Whitney U test. Wilcoxon signed rank test was used to calculate the changes between pre and post-operative values in body weight, BMI, peptide YY (s.c.), ghrelin, leptin, insulin, growth hormone, and other laboratory profiles of all patients. The differences in body weight, BMI, hormones, and other laboratory values between two groups one month after operation were calculated by Mann-Whitney U test. Fisher’s exact tests were used to validate the correlation among vagus nerve preservation, body weight loss of less than 10%, and peptide YY (s.c.) level increases of less than 20%. Statistical significance was set at a P value of < 0.05.

### RESULTS

#### Patient characteristics

The study flow diagram is summarized in Figure 1. There was no significant difference in age, sex, body weight, BMI, clinical stage of gastric cancer, pathologic types, and laboratory profiles including hormone values between the two groups. Table 1 summarizes the clinical and laboratory background of the 16 patients who completed the study.

#### Changes of body weight and hormones

All patients demonstrated body weight loss (preoperative body weight: 62.51 ± 9.02 kg vs postoperative body weight: 56.02 ± 8.32 kg, P < 0.001) with decreased BMI (23.71 ± 2.94 kg/m² vs 21.33 ± 2.62 kg/m², P < 0.001). All patients have increased peptide YY (s.c.) (0.41 ± 0.09 ng/mL vs 0.52 ± 0.15 ng/mL, P = 0.020), and decreased ghrelin (787.34 ± 421.33 pg/mL vs 506.21 ± 201.10 pg/mL, P = 0.007) postoperatively. Insulin levels were significantly increased in most patients (4.59 ± 6.12 mIU/L vs 1.86 ± 1.49 mIU/L, P = 0.001). There was no correlation between the basal values of peptide YY (s.c.) and the extent of body weight loss. There were no significant changes in leptin and growth hormone levels after surgery. No significant differences were found in albumin, protein, triglyceride, and total cholesterol levels either. Vagus nerve preservation group showed less decrease in...
body weight (-5.56 ± 2.24 kg vs -7.85 ± 1.57 kg, P = 0.037) and BMI (-1.91 ± 1.04 kg/m² vs -2.91 ± 0.39 kg/m², P = 0.031) than vagotomy group. Moreover, less elevation of peptide YY was observed in vagus nerve preservation group (0.06 ± 0.08 ng/mL vs 0.19 ± 0.12 ng/mL, P = 0.021) than vagotomy group. Total protein, albumin, total cholesterol, and triglyceride levels did not show significant changes between two groups after surgery. These results were presented in Table 2. Vagus nerve preservation group showed significantly lower post-operative peptide YY value than vagus nerve preserved group (0.44 ± 0.07 ng/mL vs 0.62 ± 0.17 ng/mL, P = 0.020). However, there were no differences in other post-operative values between two groups. These post-operative findings were described in Table 2.

### DISCUSSION

Weight loss is a common complication after gastrectomy. However, the effects of different surgical procedures associated with gastrectomy on postoperative body weight loss and hormonal changes are not well understood. In the present study, we examined changes in body weight, peptide YY, ghrelin, leptin, growth hormone, and insulin levels in vagus nerve preservation and vagotomy groups.

Although all 16 patients who underwent subtotal gastrectomy exhibited body weight loss, the vagus nerve preservation group demonstrated significantly less decreases in body weight and BMI than the vagotomy group. This study reproduces the findings of Melissas et al[7] who postulated that this phenomenon might be explained by the energy saving function of the vagus nerve as a major parasympathetic nerve innervating visceral organs. The sympathetic nervous system predominates during energy-spending catabolic states, whereas in energy-saving anabolic states the parasympathetic nervous system prevails[24,25]. Anatomical and physiological studies have demonstrated the innervation of adipose tissue by sympathetic nerves, which in turn accelerate lypolysis of adipocytes[26,27]. The vagotomy group showed significantly greater visceral fat mass reduction than the vagus nerve preservation group[7]. In our study, vagus nerve preservation presented 3.333 fold more chance than vagotomy group for body weight loss less than 10% (95% CI from 1.293 to 8.591).

All patients in this study showed increased peptide YY levels after subtotal gastrectomy. A previous study demonstrated that stomach gastrin inhibited peptide YY secretion in rats[28]. All study patients lost the antrum after subtotal gastrectomy, therefore reducing the effect of stomach gastrin on peptide YY. This is a possible explanation for the elevation of peptide YY levels in these patients. An alternative explanation for this phenomenon is that there is a negative correlation between fasting peptide YY levels and markers of adiposity[28,29,30]. In addition, fasting peptide YY levels are significantly higher in anorexia nervosa sufferers than normal weight controls. In rodent studies, mice exposed to a high-fat diet develop anorexia nervosa sufferers than normal weight controls. However, the effects of different surgical procedures associated with gastrectomy on postoperative body weight elevation of peptide YY levels in these patients. This is a possible explanation for the elevation of peptide YY levels in these patients. An alternative explanation for this phenomenon is that there is a negative correlation between fasting peptide YY levels and markers of adiposity[28,29,30]. In addition, fasting peptide YY levels are significantly higher in anorexia nervosa sufferers than normal weight controls. In rodent studies, mice exposed to a high-fat diet develop anorexia nervosa sufferers than normal weight controls.
obesity and a concomitant reduction in circulating peptide YY.\(^{[32,33]}\)

Vagus nerve preservation group demonstrated significantly less increase in peptide YY\(^{3-36}\) than vagotomy group in the present study. Moreover, the vagus nerve preservation group demonstrated a tight correlation with increases in peptide YY\(^{3-36}\) levels of less than 20%. According to a previous animal study, truncal vagotomy resulted in significant elevations of basal and food-induced release of peptide YY\(^{3-36}\). This suggests that peptide YY release is inhibited tonically, probably through a vagal cholinergic mechanism. Adrenergic pathways did not participate in food-stimulated peptide YY release. However, electrical stimulation of the splanchnic nerves increased basal levels of peptide YY, suggesting that the sympathetic nervous system affects the release of peptide YY\(^{3-36}\). This agrees with our finding that the vagus nerve preservation group showed reduced elevation of peptide YY\(^{3-36}\) levels in comparison to the vagotomy group, although increased peptide YY\(^{3-36}\) levels were observed in both groups. An alternative explanation for more elevation of peptide YY\(^{3-36}\) in the vagotomy group could be a compensatory increase in peptide YY\(^{3-36}\) secretion in response to reduced peptide YY\(^{3-36}\) signaling to the hindbrain via the vagus. Thus peptide YY\(^{3-36}\) may exert its effects on body weight by acting centrally, via vagal stimulation, or both. Many lines of evidence suggest that peptide YY\(^{3-36}\) exerts its effects on feeding via the hypothalamus; intra-arcuate injection of peptide YY\(^{3-36}\) reduces feeding, whereas Y2-antagonist injection has the opposite effect\(^{[34]}\). Thus, vagotomy, transection of hindbrain-hypothalamic pathways, can cause compensatory increase of peripheral peptide YY\(^{3-36}\).

When correlations between body weight loss and increase of peptide YY\(^{3-36}\) levels were performed, patients who demonstrated body weight loss of less than 10% exhibited lower increases in peptide YY\(^{3-36}\) levels, less than 20%. Because vagus nerve preservation is associated with lower increases in peptide YY\(^{3-36}\) levels and reductions in body weight loss, it is not clear whether the lower increase in peptide YY\(^{3-36}\) levels actually caused less body weight loss. However, we cannot exclude the possibility that peptide YY\(^{3-36}\) levels influence body weight, as peptide YY\(^{3-36}\) knockout mice in comparison to wild-type mice showed the partial gastrectomy and intestinal resection by 30% after intravenous infusion of peptide YY\(^{3-36}\). Chronic administration of peptide YY\(^{3-36}\) inhibits food intake and reduced body weight gain in mice, rabbits, and rhesus macaques\(^{[32,33,36]}\). In addition, daily food intake, body weight, and body fat are increased in peptide YY knockout mice in comparison to wild-type mice\(^{[32]}\). Although the number of patients enrolled in the present study was limited, these findings suggest that elevated basal peptide YY\(^{3-36}\) levels may contribute to body weight loss after subtotal gastrectomy.

All patients in this present study demonstrated increased plasma insulin after operation. A previous study showed the partial gastrectomy and intestinal resection induced impaired oral glucose tolerance despite normal insulin concentrations\(^{[37]}\). Increased basal level insulin might reflect the impaired insulin tolerance in the present study although it was not proved by oral glucose tolerance test.

There are five limitations in our study. First, patient appetite was not assessed. Assessing subjects’ appetite on a visual analogue scale before and after surgery would have allowed us to evaluate the relationship between changes in peptide YY\(^{3-36}\) levels and changes in appetite. Second, unfortunately, this present study did not include...
data from meal-stimulated secretions of peptide YY or other hormones such as glucagon like peptide-1, which could have shed more light on the true interaction effects between vagus nerve preservation/vagotomy and gastrointestinal hormonal functions and body weight. Third, we did not evaluate body composition. Evaluating changes in body composition may have helped to elucidate the correlations between vagus nerve preservation, changes in peptide YY levels, and changes in specific body composition, especially visceral fat levels. Fourth, only total ghrelin was measured, since active octanoylated ghrelin is unstable. Although both total and active ghrelin appear to be regulated in a similar and parallel manner, future studies will need to focus on measurement of the biologically active form. Finally, small number of patients was enrolled in the present study.

In summary, body weight loss, increased peptide YY levels, and decreased ghrelin levels were observed in all patients after subtotal gastrectomy. Vagus nerve preservation group showed less decrease in body weight and BMI than vagotomy group. Less increase of peptide YY levels was observed in vagus nerve preservation group. Moreover, patients with body weight loss of less than 10% exhibited reduced elevation of peptide YY level, typically less than 20%. Based on these results and those of previous studies, we concluded that vagus nerve preservation resulted in reduced body weight loss after subtotal gastrectomy, in direct relation with peptide YY activities and suggest that vagus nerve should be preserved for preventing excessive body weight loss after subtotal gastrectomy due to gastric cancer.

**COMMENTS**

**Background**

Body weight loss is a common and serious outcome in patients with gastric cancer who are treated by gastrectomy. Weight loss is correlated with declines in postoperative quality of life and is the most reliable indicator of malnutrition, which impairs immune function, infection susceptibility, and survival. Patients who underwent vagus nerve-preserving procedures lose less body weight than patients treated with vagotomy after gastrectomy.

**Research frontiers**

Ghrelin has a number of physiologic effects that result in positive energy balance, such as promoting the appetite signal in the hypothalamus as an antagonist to leptin. Peptide YY is suggested to be involved in intermediate term inhibition of food intake, in contrast to the classical short term regulators such as cholecystokinin. Recently, one study reported that reductions in visceral fat were significantly lower in patients in whom the vagus nerve was preserved than in patients who had undergone vagotomy, and concluded that the vagus nerve locally regulates amounts of intra-abdominal fat tissue.

**Innovations and breakthroughs**

This study is the first to evaluate relationship between the differences in weight loss between patients treated with vagus nerve-preserving procedures and vagotomy and the changes of peptide YY and ghrelin levels after subtotal gastrectomy. Vagus nerve preservation group showed less decrease in body weight and BMI than vagotomy group. Less increase of peptide YY was observed in vagus nerve preservation group. Moreover, patients with body weight loss of less than 10% exhibited reduced elevation of peptide YY level, typically less than 20%. Based on these results, the authors concluded that vagus nerve preservation resulted in reduced body weight loss after subtotal gastrectomy, in direct relation with peptide YY activities

**Applications**

Present study showed that vagus nerve preservation resulted in less decrease in body weight and BMI than vagotomy group. Furthermore, this study suggested plausible peptide YY activities in this phenomenon. Considering these findings, the authors cautiously suggest to preserve vagus nerve during subtotal gastrectomy for less body weight loss.

**Peer review**

This is a good experiment study in which authors analyze the cause of the differences in weight loss between patients treated with vagus nerve-preserving procedures and vagotomy in the view of the changes of peptide YY and ghrelin levels after subtotal gastrectomy. The findings that vagus nerve preservation resulted in reduced body weight loss after subtotal gastrectomy, in direct relation with peptide YY activities suggesting the possible role of peptide YY in this phenomenon.

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