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# Serum gastrin levels in different stages of distal gastric carcinogenesis: Is there a role for serum gastrin in tumor growth?

**STOMACH**

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Original Article

## ABSTRACT

**Background/Aims:** Elevated levels of serum gastrin (SG) have been associated with tumorigenic effects in a number of gastrointestinal cancers. We decided to investigate the relationship between SG and gastric epithelial lesions.

**Materials and Methods:** A total of 90 patients with gastric epithelial lesions (hyperplastic polyp, 12; adenoma, 41; early gastric cancer, 29; advanced gastric cancer, 8) were enrolled as the case group and 79 patients without epithelial lesions were enrolled as the control group.

**Results:** Serum gastrin levels were significantly different between the case and control groups ($p<0.001$). A high SG level (>80 pg/mL), intestinal metaplasia, and a pepsinogen I/II ratio <3 were independently associated with an increased risk of epithelial lesions (odds ratio: 14.6, 9.4, and 4.1, respectively, $p<0.05$). SG levels in case subjects showed a unimodal distribution pattern as the disease progressed. The mean SG level was highest in those with hyperplastic polyps and then decreased significantly to the control level in the gastric cancer group. Higher SG levels in each disease category were not associated with increased tumor size, synchronicity, invasiveness, presence of lymph node metastasis, or a higher cellular proliferation index ($p>0.05$).

**Conclusion:** An increased SG level was an independent and potent risk factor for gastric epithelial lesions. However, it does not seem to relate with distal gastric tumor growth. Serial decreases in SG levels should be considered a warning sign in index hypergastrinemic patients with no prior *Helicobacter pylori* eradication.

**Keywords:** Gastrin, gastritis, atrophic, pepsinogen, stomach neoplasms

## INTRODUCTION

Chronic *Helicobacter pylori*-induced gastritis progresses through the sequential stages of atrophic gastritis, intestinal metaplasia, and dysplasia to gastric adenocarcinoma (1). The identification and surveillance of these premalignant lesions could potentially lead to early detection and treatment of advanced precursor and gastric carcinoma lesions (2,3). The risk for gastric carcinogenesis is positively correlated with the degree of baseline atrophy (4). Although endoscopy with gastric biopsies has been documented as the best option for gastric neoplasm screening, atrophic border assessment by endoscopy alone has also been associated with gastric cancer risk and is correlated with the histological findings of atrophy (5,6). In several Asian-Pacific countries, several non-invasive tests have been developed recently and have gained attention as candidates for new gastric cancer screening tests (7). These include tests for measuring serum pepsinogen I (PG-I), pepsinogen II (PG-II), and serum gastrin (SG), altered levels of which may reflect preneoplastic gastric mucosal conditions (8,9). Of these markers, SG not only reflects gastric mucosal atrophy but may also act as a potential cofactor during gastric adenocarcinoma development.

Accumulating evidence suggests that altered local and plasma concentrations of gastrin may affect the risk of developing an epithelial gastric tumor by altering key

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cellular processes including proliferation, apoptosis, migration, and angiogenesis (10). In animal models such as transgenic INS-GAS mice, hypergastrinemia acted as a cofactor with *Helicobacter* infection during gastric adenocarcinoma development (11). However, it is still unclear whether gastrin is a central player or a secondary phenomenon in the development of gastric adenocarcinoma (12). To date, only a few clinical studies have shown that hypergastrinemia is related to gastric hyperplastic polyp (HP), which often regresses after *Helicobacter* eradication therapy (13-15).

The primary aim of this study was to determine whether hypergastrinemia is associated with tumor growth or advanced tumor pathology. The secondary goal was to evaluate the effectiveness of SG in predicting precancerous or cancerous gastric lesions.

## MATERIALS AND METHODS

### Study population

A retrospective case-control study was undertaken on patients who underwent both upper endoscopy and a baseline blood test for fasting SG at Hallym University Kangnam Sacred Heart Hospital between June 2010 and May 2012. According to the institutional policy, baseline SG and/or PG-I and II levels were assessed if baseline endoscopy detected a gastric neoplasm or high-risk gastritis or subjects they had family history of gastric cancer. Cases included patients with histology-confirmed gastric epithelial neoplasm or HP. Patients with signet ring cell or poorly differentiated advanced gastric cancer (AGC), gastric cancer located within upper one-third, and synchronous extragastric cancer or metastases were excluded. Controls included dyspeptic or asymptomatic outpatients, in whom gastric epithelial neoplasm was not detected during baseline upper endoscopy. Other exclusion criteria included concomitant hepatic or renal impairment (stage 3-5 CKD and dialysis-treated end-stage renal disease), previous gastric surgery, active gastroduodenal ulcer, and treatment with antisecretory agents or antibiotics within 4 weeks prior to SG measurements. All patients provided written informed consent. The Institutional Review Board of the hospital approved the study protocol.

### Endoscopy and atrophy assessment

Upper gastrointestinal endoscopy was performed in all study subjects by a single experienced endoscopist (JBK). The presence of gastric atrophy was confirmed by visualization of the submucosal vessels caused by mucosal thinning in the antrum and body regions of the stomach. The grade of gastric atrophy was estimated according to the endoscopic atrophic border as reported by Kimura and Takemoto (16). This classification divides the extent of atrophy into a closed type (C-type) and an open type (O-type). In the C-type, the atrophic border appears on the lesser curvature of the stomach, while in the O-type, there is no atrophic border on the lesser curvature, but the border extends along the anterior and posterior walls of the stomach. The C and O-type are subdivided as follows: the atrophic border crosses the angulus on the lesser curvature in the C1 pattern, the lower and middle parts of the corpus in the C2 pattern, and the upper part of the corpus in the C3 pattern. The atrophic border, which is parallel to the vertical axis of the stomach, is on the lesser curvature in the O1 pattern, on the anterior and posterior wall in the O2 pattern, and on the greater curvature in the O3 pattern. The endoscopic atrophic grade was defined as follows: none (C0), mild (C1, C2), moderate (C3, O1), or severe (O2, O3). The C1 pattern represents highly localized antral gastritis, with subsequent lines representing increasing extension through the lesser and greater curvatures. The O3 pattern represents extensive atrophic gastritis, affecting almost the entire stomach.

### Histological examination and *Helicobacter pylori* tests

A gastritis assessment was performed on an as-needed basis. In patients with epithelial lesion, gastritis assessment was made on random biopsies or in adjacent non-tumorous tissues in resected specimens (n=40). In the control group, random or targeted mucosal biopsy specimens (i.e., erosions) were assessed. Histological interpretation was based on the updated Sydney System where inflammation, mucosal atrophy, and intestinal metaplasia were classified by degree into 4 categories (17): none, 0; mild, 1; moderate, 2; and severe, 3. The diagnosis of resected gastric epithelial neoplasia was confirmed by two different pathologists (JWK and MKS) according to the Vienna classification (18). When there was mixed histology in a single lesion or synchronous lesions with different histology, disease classification was made based on the most advanced histology. Except for AGC cases, all tumor sizes were measured microscopically. Expression of Ki-67 proliferation marker was evaluated in select cases (n=21). *Helicobacter pylori* infection status was assessed by a combination of rapid urease test during endoscopy, histology, and detection of serum anti-immunoglobulin G antibodies with commercial enzyme-linked immunosorbent assay kits (Green Cross Medical Science Corp, Seoul, South Korea). The patients were considered positive for *Helicobacter pylori* infection if ≥1 tests were positive.

### Serologic testing for PG-I, PG-II and gastrin

Fasting serum was collected from all subjects before or 2-3 days after initial diagnostic endoscopy. Samples were centrifuged immediately at 4 °C and stored at -70 °C until required. SG levels (normal values 0-110 pg/mL) were measured using a radioimmunoassay method (Green Cross Medical Science Corp, Seoul, South Korea). Serum concentrations of PG-I (normal value, 50-160 ng/mL) and PG-II (normal values 3-25 ng/mL) were measured using enzyme-linked immunosorbent assay (Green Cross Medical Science Corp, Seoul, South Korea), and the PG I/II ratio (normal value, 4-20) was calculated. Serologic atrophy was defined as PG-I ≤70 ng/mL and a PG I/II ratio ≤3.

### Statistical analysis

The Student's *t*-test (parametric test) or the Mann-Whitney U test (nonparametric test) was used to compare pairs of inde-

pendent continuous variables. The Fisher's exact test or chi-squared test was used to compare categorical variables. For comparison of more than 2 groups, the Kruskal-Wallis test was used. The relationship between atrophic biomarkers was evaluated by Pearson's or Spearman's rank correlation analysis. A multivariate analysis was performed with the control versus case group as a dependent variable. Independent variables were SG level, PG I/II ratio, the degree of endoscopic atrophy, histologic atrophy, gastritis activity, and the presence of intestinal metaplasia. Additional independent variables with a known or probable association with gastric epithelial lesion, such as age, family history of gastric cancer, and *Helicobacter* infection status were also included. Variables showing at least a moderate association (p<0.1) in univariate analysis were added to the multiple logistic regression model to identify independent predictors for the presence of gastric epithelial lesion. Results are presented as odds ratios with 95% confidence intervals (CI), and a p-value of <0.05 indicated statistically significant differences. All analyses were performed using commercially available software (SPSS-Software 12.01, SPSS Inc, Chicago, IL, USA).

## RESULTS

### Patient characteristics

A total of 212 patients who met the inclusion criteria were initially enrolled in this study. Forty-three patients were excluded according to the exclusion criteria. A total of 169 patients (93 men and 76 women) were included in the final analysis (Figure 1). The mean patient was 58.1±11.4 years (range, 27-83). Ninety patients had gastric epithelial lesions (12 with HP, 41 with gastric adenoma, 29 with early gastric cancer [EGC], and 8 with AGC). The 79 patients without gastric epithelial lesions constituted the control group. The characteristics of the patients in both groups are shown in Table 1. There were no significant differences between the groups in the distribution of sex, body mass index, and *Helicobacter pylori* infection. The mean age in the case group was significantly higher than that in the control group (p<0.001). The incidence of a family history of gastric cancer was significantly higher in the control group than in the case group (p<0.001).

### Endoscopic, histological, and serologic gastric atrophy

Patient age was significantly correlated with both the severity of endoscopic atrophy on a 0-6 scale (r=0.41, p<0.001) and the serum PG I/II ratio (r=-0.26, p=0.001). Moreover, the presence of glandular atrophy or intestinal metaplasia in histological sections was significantly associated with older age (55.1±11.2 vs. 60.9±10.3, p<0.01, and 52.6±11.5 vs. 61.2±9.9, p<0.001, respectively). SG levels were not correlated with age (r=0.15, p=0.054).

**Table 1.** Clinical characteristics of subjects

| | Epithelial lesion (+) (n=90) | Epithelial lesion (-) (n=79) | p |
|---|---|---|---|
| Sex, male, n (%) | 53 (58.9) | 40 (50.6) | 0.353 |
| Age (y), mean (SD) | 61.8 (9.9) | 53.9 (11.6) | <0.001 |
| Height (cm), mean (SD) | 160.3 (8.6) | 162.6 (8.4) | 0.121 |
| Weight (kg), mean (SD) | 62.6 (9.9) | 62.1 (12.0) | 0.820 |
| Alcohol, n (%) | 19 (24.7) | 15 (28.3) | 0.687 |
| Current smoker, n (%) | 23 (29.5) | 15 (28.3) | 1.000 |
| Family history of gastric cancer, n (%) | 10 (13.0) | 33 (55.9) | <0.001 |
| *Helicobacter* infection, n (%) | 75 (83.3) | 58 (73.4) | 0.134 |

SD: standard deviation

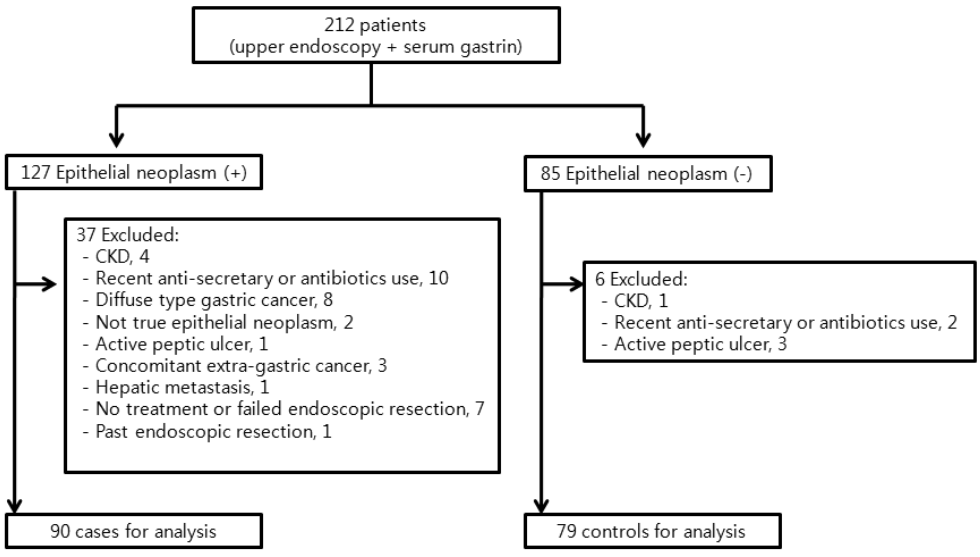


**Figure 1.** Flow diagram of patients.

The severity of endoscopic atrophy was significantly correlated with both PG I/II ratio (r=-0.57, p<0.001) and SG levels (r=0.33, p<0.001), whereas the presence of histological atrophy or intestinal metaplasia was associated with a lower PG I/II ratio alone (4.1±2.0 vs. 2.9±1.7, p=0.001, 4.1±2.2 vs. 3.1±1.7, p=0.01, respectively).

Differences in markers for gastric atrophy between groups are shown in Table 2. Although there were no significant differences in the severity of histological atrophy between the groups, advanced-stage gastric atrophy was more prevalent in the case group than in the control group (p<0.001). The prevalence of intestinal metaplasia was more common in cases than in controls (p<0.001). There was a significant difference in the SG level between case and control groups (p<0.001). In multivariate analysis, a high SG level (>80 pg/mL), the presence of intestinal metaplasia, and a PG I/II ratio <3 were independently associated with increased odds of having epithelial neoplasm or HP (Table 3).

### SG levels according to the *Helicobacter* infection status

In subgroup analysis, according to *Helicobacter pylori* infection status, there were no differences in SG levels between infected and non-infected patients, both in case and control subjects (Supplementary Table 1). SG levels in patients with a higher gastritis index (i.e., inflammatory degree, atrophy, or intestinal metaplasia) in adjacent tumor-free tissue did not differ from those in counterparts (Supplementary Table 2).

### SG levels according to the severity of gastric precancerous or cancerous lesions

The mean SG level was significantly higher in patients with HP, gastric adenoma with low-grade dysplasia (LGD), and gastric adenoma with high-grade dysplasia (HGD) (114.2±71.1, 100.8±79.0, 97.7±65.5 pg/mL, respectively) than in controls (54.6±46.2 pg/mL), patients with EGC (59.5±34.8 pg/mL), and those with AGC (67.9±21.4 pg/mL, p<0.001). The mean SG level of patients with EGC or AGC was not significantly different from that of controls (p>0.5). There was a trend toward a decrease in SG levels as the lesions progressed in patients with precancerous lesions, but this did not reach statistical significance. A similar but inverse pattern was observed for the PG I/II ratio (Figure 2).

While the PG I/II ratio was significantly correlated with the severity of endoscopic atrophy in the control (r=-0.55, p<0.001), gastric adenoma (r=-0.61, p<0.001) and EGC (r=-0.50, p<0.01) groups, SG correlated with the severity of endoscopic gastric atrophy in the control group alone (r=-0.42, p<0.001). Similarly, a significant correlation between SG and PG I/II ratio was observed in the control group alone (r=-0.40, p<0.001).

### Differences in tumor characteristics according to SG levels

The tumor characteristics of each case group were compared according to high or low SG levels. In this analysis, the 50th percentile value was used as a cut-off point to define high or low SG status. In the early epithelial neoplasm group, SG levels were not associated with tumor size, synchronicity, invasiveness, lymph node metastasis, or the degree of cell prolif-

**Table 2.** Comparison between two groups according to the degree of gastritis, atrophy, and serum gastrin

| | Case (n=90) | Control (n=79) | p |
|---|---|---|---|
| Endoscopic atrophy, n (%) | | | <0.001 |
| None | 13 (14.6) | 35 (44.3) | |
| Mild | 24 (27.0)) | 14 (17.7) | |
| Moderate | 31 (34.8) | 23 (29.1) | |
| Severe | 21 (23.6) | 7 (8.9) | |
| Histologic atrophy†, n (%) | | | 0.781 |
| None | 21 (23.9) | 13 (27.1) | |
| Mild | 36 (40.9) | 18 (37.5) | |
| Moderate | 26 (29.5) | 16 (33.3) | |
| Marked | 5 (5.7) | 1 (2.1) | |
| Intestinal metaplasia†, n (%) | | | <0.001 |
| None | 9 (10.2) | 19 (39.6) | |
| Mild | 22 (25.0) | 9 (18.8) | |
| Moderate | 29 (33.0) | 15 (31.3) | |
| Marked | 28 (31.8) | 5 (10.4) | |
| Inflammatory activity†, n (%) | | | |
| ≤ Mild | 30 (34.1) | 14 (29.2) | 0.434 |
| Moderate | 38 (43.2) | 28 (37.5) | |
| Marked | 20 (22.7) | 16 (33.3) | |
| Serologic atrophy‡, n (%) | 46 (51.1) | 15 (19.0) | < 0.001 |
| Serum pepsinogen§, mean (SD) | | | |
| Pepsinogen I | 58.5 (44.3) | 55.9 (25.1) | 0.630 |
| Pepsinogen II | 23.3 (15.6) | 15.7 (10.5) | <0.001 |
| Pepsinogen I/II ratio | 2.7 (1.5) | 4.3 (2.0) | <0.001 |
| Serum gastrin | | | |
| Mean (SD) | 86.0 (62.8) | 54.6 (46.2) | <0.001 |
| High gastrin (>110 pg/mL), n (%) | 18 (20.0) | 4 (5.1) | 0.005 |
| Quartile | | | <0.001 |
| Quartile I (<38.0) | 12 (13.3) | 33 (41.8) | |
| Quartile II (38.1-54.0) | 23 (25.6) | 18 (21.8) | |
| Quartile III (54.1-79.9) | 22 (24.4) | 20 (25.3) | |
| Quartile IV (80<) | 33 (36.7) | 8 (10.1) | |

†A total of 136 samples (case, 88; control, 48) were histologically evaluated.
‡Defined as pepsinogen I ≤70 ng/mL and a pepsinogen I/II ratio ≤3.
§A total of 162 samples (case, 88; control, 74) were analyzed for serum pepsinogen profiling.
SD: standard deviation

eration (p>0.05). Similar results were observed in the HP group (Table 4). Furthermore, SG levels did not correlate with tumor size in the gastric adenoma (r=-0.05, p=0.78) or EGC (r=-0.03, p=0.86; Pearson correlation) groups, suggesting that SG is not related to tumor progression.

In the EGC group, intestinal-type carcinoma was more prevalent among patients with a high SG status than among those with a low SG status (100% vs. 69.2%, p=0.04). The mean SG levels in patients with antral lesions (n=70, 86.5±63.8 pg/mL) or body lesions (n=15, 78.7±60.0 pg/mL) were not significantly different (p=0.470).

## DISCUSSION

Gastrin is normally produced at high levels by endocrine (G) cells located in the gastric antrum and is often upregulated in the setting of acid suppression and *Helicobacter pylori* infection (19). In some cases, the increase in SG may relate to increased cytokine release in the vicinity of antral G cells. Alternatively, the increase in SG may be secondary to *Helicobacter pylori* colonization of the gastric body and fundus, resulting in decreased acid secretion and reduced inhibitory feedback on gastrin release (19). The interpretation of hypergastrinemia in a chronic gastritis setting, however, is difficult owing to the complex interplay between gastritis severity, the extent or severity of corpus atrophy, and concomitant use of proton pump inhibitors.

Gastrin is a diverse transcriptional activator that is associated with cell division, invasion, angiogenesis, and anti-apoptotic activity, which are all pivotal in the gain of malignant potential (12). These pro-carcinogenic roles of gastrin are well documented in preclinical studies (12). However, clinical studies addressing this issue are scarce. A few recent clinical studies support the pro-carcinogenic role of tissue gastrin and SG in the development of gastric and extragastric tumors, respectively (20-24). The origin of gastrin for these effects might be either serum-associated endocrine gastrin or autocrine gastrin produced by tumor cells. Unlike in normal mucosa, in which the expression is restricted to G cells, the gastrin gene is expressed *de novo* in non-endocrine epithelial cells within gastric adenocarcinoma (25). Nonetheless, it is uncertain whether hypergastrinemia, apart from its role in predicting the extent of gastric atrophy, is involved in the initiation and progression of gastric tumor.

**Supplementary Table 1.** Serum gastrin levels according to the Helicobacter infection status

| | Helicobacter- | Helicobacter+ | p |
|---|---|---|---|
| Cases (n=88) | 74.2±40.0 | 88.4±66.5 | 0.317 |
| HP (n=12) | 151.0±6.4 | 106.8±76.3 | 0.364 |
| Adenoma (n=40) | 61.7±25.1 | 103.9±76.3 | 0.324 |
| EGC (n=28) | 54.2±32.7 | 60.4±35.7 | 0.590 |
| AGC (n=8) | 69.5±26.7 | 65.3±12.9 | 0.816 |
| Control (n=77) | 67.2±81.8 | 49.9±20.6 | 0.262 |
| Total (n=165) | 70.1±66.9 | 71.7±65.1 | 0.881 |

Serum gastrin values (pg/mL) are expressed as means±standard.
HP: hyperplastic polyp; EGC: early gastric carcinoma; AGC: advanced gastric carcinoma

**Table 3.** Risks posed by atrophic markers for epithelial neoplasm or hyperplastic polyp

| | Univariate analysis | | Multivariate analysis‡ | |
|---|---|---|---|---|
| | OR (95% CI) | p | OR (95% CI) | p |
| Serum gastrin | | | | |
| (≥80 pg/mL) | 5.1 (2.2-12.0) | <0.001 | 14.6 (2.6-82.0) | 0.002 |
| Intestinal metaplasia | 5.8 (2.3-14.1) | <0.001 | 9.4 (2.1-41.6) | 0.003 |
| Serologic atrophy† | 4.5 (2.2-9.0) | <0.001 | 4.1 (1.1-16.7) | 0.046 |
| Endoscopic atrophy | | | | |
| (≥ moderate) | 2.3 (1.2-4.3) | 0.009 | 0.6 (0.2-2.0) | 0.371 |

†Defined as pepsinogen I ≤70 ng/mL and a pepsinogen I/II ratio ≤3.
‡Adjusted for age and a family history of gastric cancer.
OR: odds ratio; CI: confidence interval

**Supplementary Table 2.** Serum gastrin levels according to the severity of gastritis index analyzed in 40 adjacent tissues of resected specimens

| Degree | Inflammatory degree | | | Atrophy | | | Intestinal metaplasia | | |
|---|---|---|---|---|---|---|---|---|---|
| | ≤ Mild (n=14) | Mod (n=26) | p | ≤ Mild (n=27) | Mod (n=13) | p | ≤ Mild (n=15) | Mod (n=25) | p |
| SG | 89.7±42.8 | 102.8±71.6 | 0.990 | 92.5±57.9 | 110.1±72.7 | 0.549 | 99.3±53.3 | 97.5±68.8 | 0.507 |

SG: serum gastrin (pg/mL); Mod: moderate
Values are expressed as mean±standard deviation
Histologic analyses were performed on adjacent tissues from hyperplastic polyps (n=6), adenomas (n=19), and early gastric cancers (n=15).

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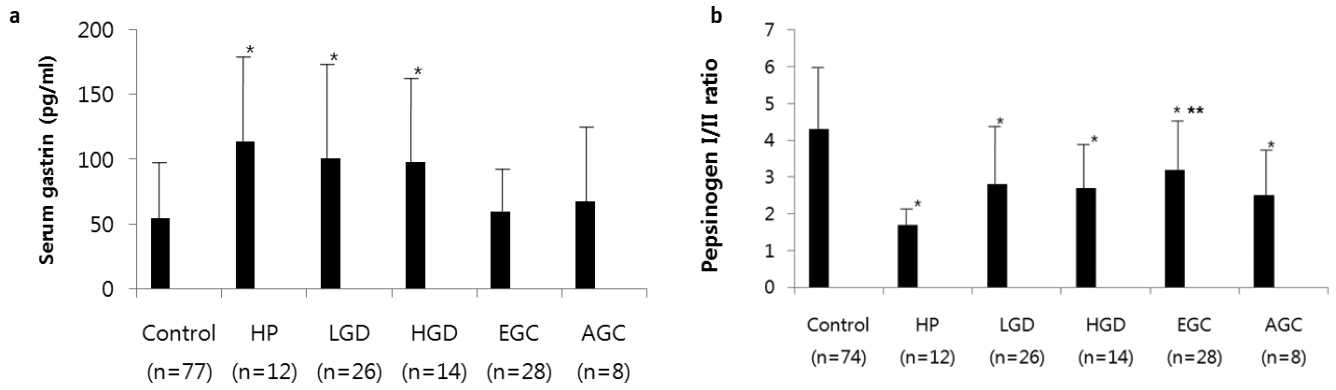


**Figure 2. a, b.** Serum gastrin levels and pepsinogen ratios according to the disease category. There was a significant difference in the SG levels and pepsinogen ratios between the groups (Kruskal-Wallis test p<0.001). Post-hoc analysis showed that the SG level was higher in the HP, LGD, or HGD groups than in the control or EGC groups. *denotes p<0.05 vs. control or EGC **(a).** Post-hoc analysis showed that the pepsinogen ratio was lower in the HP, LGD, EGC, or AGC groups than in the control group **(b).**

*denotes p<0.05 vs. control and **denotes p<0.05 vs. HP. On the graph, bars indicate the mean value and error bars indicate the standard deviation

**Table 4.** Differences in tumor characteristics according to serum gastrin levels

| | Gastrin-low† | Gastrin-high† | p |
|---|---|---|---|
| HP (n=12) | | | |
| Polyp size, cm (mean±SD) | 0.80±0.39 | 1.16±0.61 | 0.432 |
| Synchronous lesion, n (%) | 0/5 (0) | 2/7 (28.6) | 0.470 |
| Gastrin adenoma (n=41) | | | |
| Tumor size, cm (mean±SD) | 1.00±0.68 | 0.97±0.63 | 0.866 |
| Synchronous lesion, n (%) | 3/20 (15) | 1/18 (5.6) | 0.606 |
| EGC (n=29) | | | |
| Tumor size, cm (mean±SD) | 1.83±2.14 | 2.00±1.99 | 0.830 |
| Synchronous lesion, n (%) | 1/13 (7.7) | 2/14 (14.3) | 1.000 |
| SM invasion, n (%) | 4/10 (40.0) | 2/10 (20.0) | 0.628 |
| LN invasion, n (%) | 1/8 (12.5) | 1/10 (10.0) | 1.000 |
| Intestinal type‡, n (%) | 9/13 (69.2) | 14/14 (100.0) | 0.041 |
| Ki-67 (≥60%), n (%) | 9/12 (75.0) | 6/9 (66.7) | 0.781 |
| Early epithelial tumor (n=70) | | | |
| Tumor size, cm (mean±SD) | 1.43±1.60 | 1.31±1.33 | 0.740 |
| Synchronous lesion, n (%) | 4/32 (12.5) | 3/33 (9.1) | 0.708 |

†Low or high state of serum gastrin was determined by each cut-off level in each diagnosis group. The 50th percentile value was used as the cut-off. Cut-off levels in the gastric adenoma and EGC groups were 75 ng/mL and 50 ng/mL, respectively.

‡Defined by Lauren's classification.

HP: hyperplastic polyps; EGC: early gastric carcinoma; SD: standard deviation; SM: submucosa; LN: lymph node

This study did not find any direct evidence that hypergastrinemia is related to distal gastric tumor growth. Although hypergastrinemia was the strongest independent risk factor associated with epithelial neoplasms or HP, increased SG levels were not associated with increased tumor size in any case subgroup. In addition, higher SG levels in the EGC group were not related to deeper invasion, the presence of lymph node metastasis, or a higher degree of cellular proliferation. Furthermore, SG levels did not differ according to the presence or absence of synchronous lesions. These results suggest that SG, besides its predictive value for gastric atrophy, neither exerts tumor-promoting activities nor has a tumor-initiating effect in each stage of distal gastric carcinogenesis. Another important finding of this study was an unexpected fall in SG levels in cancer subgroups. Unlike the PG I/II ratio that was not different between adenoma and cancer groups, SG levels were significantly lower in cancer groups than in the adenoma group and did not differ from those of controls. Interestingly, this observation is concordant with a previous study where SG levels were compared among 3906 serum samples from different gastric disease groups (9). In that study, SG levels progressively increased in groups with normal gastric mucosae to atrophic gastritis, then to those with gastric dysplasia, and then decreased significantly to the control level in the gastric cancer group. The authors of that study speculated that hypergastrinemia may be a good biomarker for differentiation of benign from malignant gastric disease. Another study, in which SG levels were compared in patients with HP or polypoid-type EGC also demonstrated that the combination of hypochlorhydria and hypergastrinemia was common in patients with gastric HPs, whereas hypochlorhydria without hypergastrinemia was common in those with EGC (26). However, the authors in both of these studies did not explain why SG levels were low in cancer. The reason for this change is unclear, but normal gastrin feedback regulation may be deranged in patients with distal gastric cancer. An immunohistochemical study based on a tissue array of 304 gastric cancer resection specimens from Korea demonstrated that 47.7% expressed gastrin within the tumor mass and that gastrin receptors were detectable within the malignant tissue in 56.5% (21). Considering that acquired growth signal autonomy is one of the main features of cancer (27), tumor-associated gastrin peptides, if any, could affect normal gastrin secretion in antral G cells via autocrine-paracrine pathways. This notion is partly

supported by our observation of poor correlations between SG and other traditional atrophic markers in the gastric adenoma and EGC groups, whereas such correlations were apparent in the control group. Another but more plausible explanation for the decrease in SG in the cancer group is that the background gastric mucosa condition in cancer is likely to be severe enough to further decrease the population of G cells. However, this was not further supported by our subgroup analyses of SG according to the *Helicobacter* infection status and severity of gastritis index in tumor-free mucosa. This study could have been strengthened if tissue analysis for gastrin and its receptor had been performed.

Our study has several limitations. First, the relatively small number of cases and its retrospective design might limit the results. Second, use of a non-uniform method of histologic assessment for gastritis may limit the validity of comparative results of baseline gastric mucosal status between the case and control groups. However, we attempted to minimize this drawback using the endoscopic atrophic scale and PG I/II ratio as baseline atrophic markers. Finally, bias might have occurred during the control selection process because fasting SG was selectively checked if subjects revealed a family history of gastric cancer or a medical history of high-risk gastritis. This could explain the different baseline characteristics between the two groups (i.e., family history of gastric cancer, age). Nevertheless, we believe that these results provide evidence that SG is not associated with tumor growth potential.

In summary, hypergastrinemia is a useful predictive marker for precancerous lesions (i.e., HP, gastric adenoma), but not for distal gastric cancer. In addition, SG does not seem to play a role in distal gastric tumor development and growth. Serial decreases in SG levels should rather be considered as a warning sign for index hypergastrinemic patients who do not have a history of *Helicobacter pylori* eradication. Further validation through larger, prospective studies is required to confirm these findings and to determine whether a decrease in SG could identify patients at high-risk for the development of cancer.

**Ethics Committee Approval:** Ethics committee approval was received for this study.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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