Serum Pepsinogen and Gastrin Levels: Reliable Markers to Predict Small Intestinal Bacterial Overgrowth

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Cite this article as: Kim DB, Jo IH, Paik C, Kim Y, Lee JM. Serum pepsinogen and gastrin levels: Reliable markers to predict small intestinal bacterial overgrowth. *Turk J Gastroenterol.* 2022;33(3):213-220.

ABSTRACT

Background: *Serum pepsinogen, a useful indicator of gastric acidity, could reflect small intestinal bacterial overgrowth. The aim of this study is to evaluate the relationship between small intestinal bacterial overgrowth and profiles including pepsinogen or gastrin.*

Methods: *We conducted a prospective study with 62 patients with a functional gastrointestinal disorder. All patients underwent glucose breath test for small intestinal bacterial overgrowth, immediately followed by upper endoscopy to survey gastric injury and Campylobacter-like organism test for Helicobacter pylori and serum laboratory tests including gastrin, pepsinogen I and II.*

Results: *The positivity to small intestinal bacterial overgrowth was 17.7%. Significantly, low total hydrogen concentration during a glucose breath test, low prevalence for gastric injury, and high H. pylori positivity rate were shown in groups with pepsinogen I/II ratio ≤ 3.5 compared to those with pepsinogen I/II ratio > 3.5 or in groups with serum gastrin > 35.4 pg/mL comparing to those with serum ≤ 35.4 pg/mL, respectively. A high gastrin level was independently associated with H. pylori infection. A proportionally correlated tendency between pepsinogen I/II ratio and total hydrogen concentration was shown, whereas that of inverse proportion between H_2 and gastrin was observed. Old age was solely independent predicting factor for small intestinal bacterial overgrowth (P = .03) in the multivariate analysis.*

Conclusion: *Old age was significantly related to the presence of small intestinal bacterial overgrowth in functional gastrointestinal disorder patients. Although pepsinogen and small intestinal bacterial overgrowth seem irrelevant, elevated gastrin level may cautiously indicate a decreased breath hydrogen concentration. Further studies should consider the function of intestinal motility and gastric acidity in patients with hydrogen-producing small intestinal bacterial overgrowth.*

Keywords: *Gastrin, glucose breath test, Helicobacter pylori, pepsinogen, small intestinal bacterial overgrowth*

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) refers to a clinical status consisting of an increase in the number and/or type alteration of bacteria in the small intestine causing symptoms of bloating, diarrhea, and malabsorption. Several factors, such as anatomical abnormalities, decreased gastric acid or antibacterial secretion, and intestinal motility disorder, can predispose individuals to the development of SIBO.[1,2]

Decreased gastric acid conditions, such as gastrectomy or taking medications that suppress gastric acid secretion, may be associated with SIBO. In previous studies, 12%-78% of patients with gastrectomy presented with SIBO using a glucose breath test (GBT).[3,4] In addition, prolonged use of proton pump inhibitors (PPIs) may alter this environment by inducing chronic gastric acid suppression and resultant hypochlorhydria, which may promote bacterial growth in the small bowel.[5,6]

Previous studies on SIBO mostly focused on gastric acid-related clinical or medical status such as gastrectomy, or long-term use of acid inhibitor agents, while few have measured the function of gastric acid secretion itself. Recent studies reported that serum pepsinogen (PG) can be used as a marker of gastric atrophy.[7,8] PG I is produced in the corpus, while PG II is produced both in the antrum and corpus in the stomach. In conditions like atrophy of the corpus or antrum of the stomach, the respective PG I and II levels are decreased in the blood circulation. PG level and PG I/II ratio in the serum indicate gastric atrophy and can reflect the status of gastric acid secretion. Moreover, gastric acidity affects serum gastrin level and promotes intestinal motor function.[9-12] Accordingly, it is

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Received: ***March 2, 2021*** *Accepted:* ***October 4, 2021*** *Available Online Date:* ***December 28, 2021***

DOI: ***10.5152/tjg.2021.201145***

possible that serum levels of PG and gastrin could predict the presence or absence of SIBO.

The aim of this study was prospective to investigate the relationship between SIBO using GBT and PG profiles including gastrin.

MATERIALS AND METHODS

This study was approved by the Institutional Research Ethics Board of the Catholic University of Korea (VC15OISI0027) and adhered to the Declaration of Helsinki. Written informed consent was acquired from all patients.

Study Populations

The study was prospectively performed at St. Vincent's Hospital, the school of medicine, the Catholic University of Korea from January 2016 to December 2017. We enrolled consecutive patients who visited the gastroenterology clinic in the institution and were older than 18 years of age, fulfilling the Rome III criteria[13] for a functional gastrointestinal disorder (FGID). Exclusion criteria were a history of thyroid disease, connective tissue disease, or gynecologic or gastrointestinal surgery. The patients who were treated with antisecretory agents such as histamine H_2 receptor antagonists or PPIs, prokinetics, antibiotics, probiotics, narcotics, bulking agents, laxatives, or antidiarrheal drugs within the previous 4 weeks, and those with prior *Helicobacter pylori* eradication, renal insufficiency, gastrointestinal disease, liver disease, a major psychiatric disease, or those who had underwent colonoscopy within the last 3 months that could hinder the breath test, were also excluded. Patients who took nonsteroidal anti-inflammatory drugs, aspirin, or thrombolytic agents within the previous 4 weeks were excluded to rule out drug-induced gastrointestinal injury.

Study Design

All patients were surveyed for demographics for age, sex, or body mass index and laboratory test for serum levels of PG I, PG II, and gastrin to evaluate the gastric acidity and gastrointestinal motility. They underwent the glucose hydrogen (H_2)–methane (CH_4) breath test to detect the status of intestinal bacterial overgrowth, immediately followed by upper endoscopy to investigate acute gastric injury including the *Campylobacter*-like organism (CLO) test for *H. pylori*.

Main Points

- *Old age was the independent factor to predict small intestinal bacterial overgrowth in patients with a functional gastrointestinal disorder.*
- *A high serum gastrin level > 35.4 pg/mL was independently associated with H. pylori infection.*
- *A tendency of inversely proportional correlation between total hydrogen concentration and serum gastrin level was shown.*

Glucose Breath Test

Glucose H_2–CH_4 breath test was used for the diagnosis of SIBO. The patients were presented to the gastrointestinal clinic after a minimum of 12 hours of fasting before the test. Smoking and physical exercise were not allowed for 30 minutes before and during the test. The end-expiratory breath samples were collected at baseline after ingestion of oral glucose solution in 75 g (DIASOL-S SOLN, Tae Joon Pharma, Seoul, Korea) and then for 120 minutes at every 10-minute interval. Breath tests of the samples were performed each time by gas chromatography equipment (Quintron BreathTracker SC; Quintron Instrument Company, Milwaukee, Wis, USA).

A positive GBT indicating SIBO was defined and classified as follows[14,15]: (1) an increase in H_2 concentration of more than 12 ppm above baseline within 90 minutes (glucose H_2 breath test-positive group) or (2) an increase in CH_4 concentration of more than 10 ppm above baseline within 90 minutes (glucose CH_4 breath test-positive group). The GBT (mixed)-positive group was defined when both conditions (1) and (2) were met.

Acute Hemorrhagic Gastric Injury and H. pylori Infection

H. pylori infection and acute hemorrhagic gastric injury were evaluated during an upper endoscopy. The clinical significance of acute gastric injury was defined as >10 bleeding spots with coalescent intramucosal blood or oozing determined by endoscopy.[16] The presence of *H. pylori* was identified by rapid urease test (CLO test; Halyard Health, Alpharetta, Ga, USA).

PG I, PG II, and Gastrin

GBT was conducted immediately after collecting fasting serum samples for PG I, PG II, and gastrin. The levels for PG I and II were surveyed by turbidimetric immunoassay using a Beckman Coulter AU5800 chemistry analyzer (Beckman Coulter Inc., Brea, Calif, USA). The measurement of gastrin levels was investigated by radioimmunoassay using an Immulite 2000 immunoassay system (Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The cut-off value for PG I/II ratio 3.5 was used to predict atrophic gastritis, which

was expected to be related to gastric acidity.[17] PG I/gastrin (PGI/G) ratio, known as a potentially discriminatory marker of gastric secreting capacity,[18] was also evaluated. To determine the cut-off level of serum gastrin, the receiver operating characteristic (ROC) curves of total breath H_2 concentrations and serum gastrin were evaluated.

Analysis

The clinical evaluations included demographics, acute gastric injury, rapid urease test, GBT profiles, and serum PG with gastrin levels according to the presence of SIBO and cut-off values of PG ratio or gastrin. Continuous data are expressed as mean ± standard deviation and were analyzed using independent sample *t*-tests, whereas the categorical variables are expressed as quantities and were analyzed using chi-square tests or Fisher's exact test. The Pearson coefficient (γ) was used to evaluate the correlation between total breath H_2 or CH_4 concentration and PG ratio or gastrin level, respectively. Multiple stepwise logistic regression analysis was used to identify the independent factors associated with SIBO, PG ratio, or gastrin level. *P* values <.05 were considered significant for all tests. Statistical Package for the Social Sciences (SPSS) software version 18.0 (SPSS Inc., Chicago, Ill, USA) was used in all analyses.

RESULTS

Study Populations

Initially, 64 consecutive patients were enrolled. Two subjects were excluded from the analysis due to poor GBT preparation (n = 2). The baseline characteristics of the finally enrolled 62 patients are shown in Table 1.

Table 1. Baseline Characteristics of Patients (N = 62)

Demographics	
Age (years)	49.84 ± 13.73
Gender	
Male	19 (30.6)
Female	43 (69.4)
BMI (kg/m^2)	23.69 ± 3.73
Endoscopic finding	
Positive CLO	22 (35.5)
Acute gastric injury with hematin	20 (32.3)
Positive GBT	11 (17.7)
H_2	6 (9.7)
CH_4	2 (3.2)
Mixed	3 (4.8)
PG profiles	
PG I (ng/mL)	51.88 ± 23.98
PG II (ng/mL)	13.23 ± 9.04
Gastrin (pg/mL)	34.13 ± 42.55
PG I/PG II ratio	4.48 ± 1.45
PG I/PG II ratio	
>3.5	49 (79.0)
≤3.5	13 (21.0)

Data are expressed as mean ± SD or number (%). BMI, body mass index; CLO, rapid urease test; GBT, glucose breath test; H_2, hydrogen; CH_4, methane; PG, pepsinogen.

Comparison of Variables by GBT Positivity Status or CLO Test Result

No differences were significantly found in demographic characteristics, endoscopic findings, or PG profiles, except in age and the CLO test positivity according to GBT results (Table 2). Patient with CLO test positivity demonstrated significantly lower PG I/II ratio and prevalence of acute gastric injury, but higher profiles of PG I, II, gastrin, and PG I/G ratio than those with CLO test negativity (Table 3). Multivariate logistic regression analysis indicated the preference of old age being only independently associated with the positivity to GBT (Table 4).

Comparison of Variables by Serum PG I/II Ratio of 3.5 and Serum Gastrin of 35.4 pg/mL

There were no significant differences in demographic characteristic or GBT positivity except a significantly higher positivity rate on the CLO test, whereas a significantly lower prevalence of acute gastric injury, lower total breath H_2 concentrations and lower PGI/G ratio, or a lower tendency toward GBT (H_2)-positive and GBT (mixed)-positive in the patients with a PG I/II ratio ≤ 3.5 than in those with a PG I/II ratio > 3.5, or in the patients with a serum gastrin level > 35.4 pg/mL than in those with gastrin ≤ 35.4 pg/mL, respectively (Table 5). Using ROC curves, the optimal cut-off value of serum gastrin was 35.4 pg/mL. Significant differences were shown in the breath H_2 of all the measured time points (Figure 1A), but no differences were seen in the breath CH_4 level according to the PG I/II ratio 3.5 (Figure 1B). Depending on whether the value of serum gastrin was higher or lower than 35.4 pg/mL, the breath H_2 of all the measured time points was significantly different (Figure 2), while no differences were seen in the breath CH_4 level. In multivariate logistic regression analysis, no independent factors were associated with the PG I/II ratio ≤ 3.5, whereas *H. pylori* infection was independently related to a serum gastrin level > 35.4 pg/mL (Table 6).

Table 2. The Profiles of Demographic, Endoscopic, and Pepsinogen According to the Positivity to GBT

	GBT		
	Negativity (n = 51)	Positivity (n = 11)	*P*
Demographics			
Age (years)	47.84 ± 13.11	59.09 ± 13.27	.01
Gender			
Male	14 (27.5)	5 (45.5)	.24
Female	37 (72.5)	6 (54.5)	
BMI (kg/m^2)	23.71 ± 4.00	23.57 ± 2.22	.91
Endoscopic			
Positive CLO	21 (41.2)	1 (9.1)	.04
Acute gastric injury	16 (31.4)	4 (36.4)	.75
PG profiles			
PG I (ng/mL)	50.86 ± 23.10	56.61 ± 28.48	.48
PG II (ng/mL)	13.47 ± 9.81	12.10 ± 3.85	.65
Gastrin (pg/mL)	32.45 ± 35.34	41.91 ± 68.69	.51
PG I/gastrin ratio	2.29 ± 1.19	2.66 ± 1.31	.36
PG I/PG II ratio	4.42 ± 1.43	4.77 ± 1.54	.47
PG I/PG II ratio			
>3.5	39 (76.5)	10 (90.9)	.29
≤3.5	12 (23.5)	1 (9.1)	

Data are expressed as mean ± SD or number (%). GBT, glucose breath test; BMI, body mass index; CLO, rapid urease test; PG, pepsinogen.

Correlations Between Total Breath H_2 or CH_4 Concentration and Serum PG I/II Ratio or Gastrin Level

A proportional correlated tendency between breath H_2 concentration and serum PG I/II ratio (r = 0.21, P = .1) but an inversely proportional tendency between breath H_2 and serum gastrin level (r = -0.21, P = .1) was shown (Figure 3). There were no significant correlations or tendencies between total breath CH_4 concentration and serum gastrin or PG I/II ratio, respectively.

DISCUSSION

This study showed that although PG and gastrin profiles were not independently associated with the presence of SIBO, possible relationships could be inferred between serum gastrin known to stimulate intestinal motility and a decreased H_2 status during GBT.

Although the etiology of SIBO is very complex and remains to be elucidated, our findings revealed that old age was the independent predicting factor of the presence of SIBO. Previous studies already demonstrated that SIBO is more common in old age.[19,20] The suggested pathophysiological mechanisms could be the decreased intestinal transit in advanced age. On univariate analysis, GBT-positive was

Table 3. The Profiles of Demographic, Endoscopic, and Pepsinogen According to the HP Infection

	Positive CLO		
	Negativity (n = 40)	Positivity (n = 22)	*P*
Demographics			
Age (years)	50.30 ± 15.69	49.00 ± 9.46	.73
Gender			
Male	12 (30.0)	7 (31.8)	.88
Female	28 (70.0)	15 (68.2)	
BMI (kg/m^2)	23.32 ± 3.47	24.34 ± 4.16	.31
Endoscopic			
Acute gastric injury	19 (47.5)	1 (4.5)	<.01
GBT			
Total H_2	189.10 ± 192.71	142.32 ± 160.04	.34
Total CH_4	162.08 ± 104.31	134.82 ± 76.85	.29
Subtypes	10 (25.0)	1 (4.5)	.04
H_2	6 (15.0)	0 (0)	.16
CH_4	2 (5.0)	0 (0)	
Mixed	2 (5.0)	1 (4.5)	
Mixed + H_2	8 (20.0)	1 (4.5)	.1
Mixed + CH_4	4 (10.0)	1 (4.5)	.45
PG profiles			
PG I (ng/mL)	46.35 ± 18.87	61.94 ± 29.07	.01
PG II (ng/mL)	9.41 ± 3.39	20.18 ± 11.72	<.01
Gastrin (pg/mL)	25.00 ± 36.82	50.73 ± 47.90	.02
PG I/gastrin ratio	2.59 ± 1.17	1.94 ± 1.18	.04
PG I/PG II ratio	5.08 ± 1.24	3.40 ± 1.37	<.01

Data are expressed as mean ± SD or number (%). CLO, rapid urease test; GBT, glucose breath test; BMI, body mass index; PG, pepsinogen.

Table 4. Multivariate Analysis for the Risk Factors of Indicating Positive GBT

	OR	95% CI	*P*
Old age	1.07	1.01-1.14	.03
The positive CLO	16.02	0.85-303.12	.06

OR, odds ratio; CLO, rapid urease test.

Table 5. The Profiles of Demographic, Endoscopic, GBT, and Abdominal Symptoms According to the Cut-Off Value of PG I/II Ratio 3.5 or Serum Gastrin 35.4 pg/mL

	PG Ratio			Gastrin (pg/ml)		
	>3.5 (N = 49)	≤3.5 (N =13)	*P**	>35.4 (N = 13)	≤35.4 (N = 49)	*P*
Demographics						
Age (years)	49.02 ± 14.98	52.92 ± 6.91	.18	51.08 ± 6.54	49.51 ± 15.11	.58
Gender						
Male	15 (30.6)	4 (30.8)	.99	4 (30.8)	15 (30.6)	.92
Female	34 (69.4)	9 (69.2)		9 (69.2)	34 (69.4)	
BMI (kg/m^2)	23.57 ± 3.95	24.12 ± 2.83	.63	23.36 ± 4.04	23.77 ± 3.68	.73
Endoscopic						
Positive CLO	13 (26.5)	9 (69.2)	<.01	11 (84.6)	11 (17.4)	<.01
Gastric injury	19 (38.8)	1 (7.7)	.03	0 (0)	20 (40.8)	<.01
GBT profiles						
Total H_2 (ppm)	195.69 ± 196.65	85.08 ± 54.34	<.01	92.31 ± 55.94	193.78 ± 197.59	<.01
Total CH_4 (ppm)	157.04 ± 98.15	134.92 ± 87.31	.46	138.38 ± 85.81	156.12 ± 98.67	.56
Positive GBT	10 (20.4)	1 (7.7)	.29	1 (7.7)	10 (20.4)	.29
Subtypes						
H_2	6 (12.2)	0 (0)	.30	0 (0)	6 (12.2)	.31
CH_4	1 (2.0)	1 (7.7)		1 (7.7)	1 (2.0)	
Mixed	3 (6.2)	0 (0)		0 (0)	3 (6.1)	
H_2 + mixed	9 (18.4)	0 (0)	.09	0 (0)	9 (18.4)	.1
CH_4 + mixed	4 (8.2)	1 (7.7)	.96	1 (7.7)	4 (8.2)	.96
PG profiles						
PG I (ng/mL)	50.61 ± 19.09	56.67 ± 37.88	.42	61.17 ± 36.66	49.41 ± 19.12	.12
PG II (ng/mL)	10.30 ± 3.97	24.28 ± 13.59	<.01	24.21 ± 13.50	10.32 ± 4.11	<.01
Gastrin (pg/mL)	21.12 ± 10.11	83.15 ± 74.17	.01	89.46 ± 69.72	19.45 ± 6.06	<.01
PGI/G ratio	2.68 ± 1.11	1.12 ± 0.70	<.01	1.03 ± 0.66	2.71 ± 1.07	<.01
PG I/II ratio	5.04 ± 1.01	2.38 ± 0.69	<.01	2.69 ± 1.08	4.96 ± 1.12	<.01

Data are expressed as mean ± standard deviation or number (%). BMI, body mass index; CLO, rapid urease test; GBT, glucose breath test; H_2, hydrogen; CH_4, methane; PG, pepsinogen.

inversely related to CLO positivity despite no significance on multivariate analysis shown in Table 4. However, the results of a recent study were inconsistent with those of our study, which indicated that *H. pylori* infection was significantly related to the presence of SIBO.[9] A plausible explanation for this is that the increase in the ammonia concentration increases the pH of the gastric mucus, which may promote bacterial growth in the stomach and small intestine, and subsequently, *H. pylori*-induced gastric mucosal cell injury leads to atrophy of the gastric mucosa.

The occurrence of SIBO is expected to result in a prominent loss of gastric acid secretion, a protective mechanism against enteric bacteria, after gastrectomy or achlorhydria.[4,21] Our study investigated the functional condition of the gastric mucosa and acidity through serum levels of PG I, PG II, and gastrin, which reflect the functional status of the gastric mucosa and level of gastric acidity,[17,18,22] or acute gastric injury with hematin on endoscopic imaging.[20] A low levels of PG I and PG I/II ratio are useful indicators of the status of atrophic gastritis. Our study utilized PG I/II ratio of 3.5 as a cut-off value, recently reported as a useful predictive marker to differentiate atrophic gastritis of the corpus of the stomach. Besides, PGI/G ratio was determined to represent an effective acid peptic secretory capacity.[18]

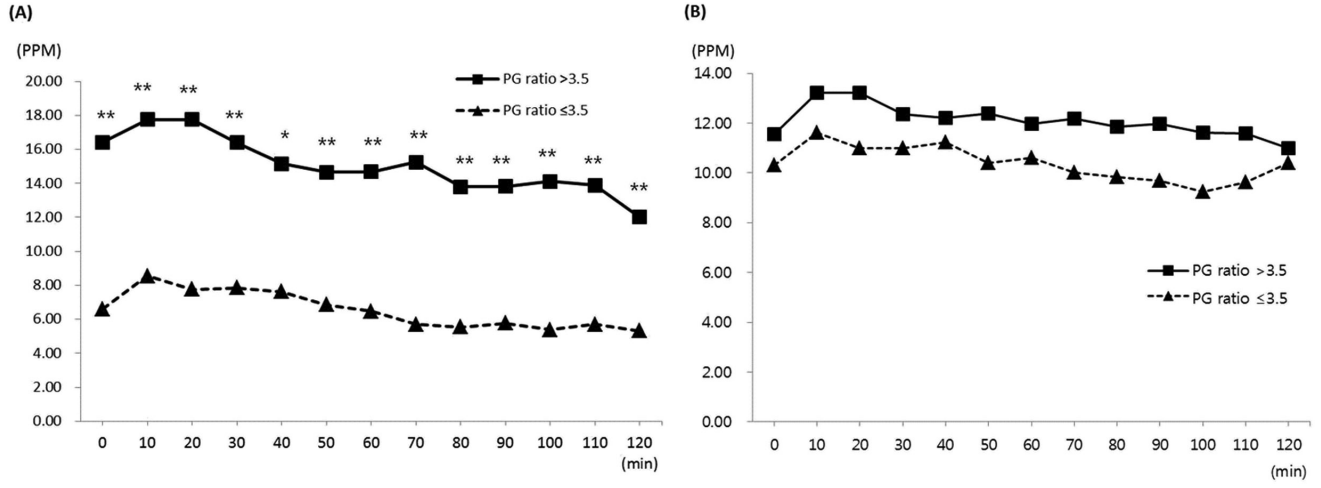

Figure 1. The profiles of breath hydrogen (H_2) (A) and methane (CH_4) (B) during the glucose breath test according to the cut-off value of a PG I/II ratio of 3.5 (*$P < .05$; **$P < .01$).

CLO positivity was well correlated with low values of PG I and II, PG I/II, and PGI/G ratios, and a low prevalence of acute gastric injury indicative of low gastric acidity. In contrast, GBT positivity was not associated with PG profiles. In the past, anti-acid secretory agents such as PPIs might have caused bacterial overgrowth. However, recently conflicting results exist in the literature regarding the effect of PPIs on breath test results, and the current guideline does not routinely recommend stopping PPIs before performing a GBT.[5,23] The various etiologies of SIBO have been suggested as impaired intestinal motility or alteration in anatomical structure, or defective antibacterial mechanisms with a low gastric acid secretory capacity. There is a possibility that the condition of a partially affected gastric acid status with normal gastrointestinal anatomy may have little impact on SIBO.

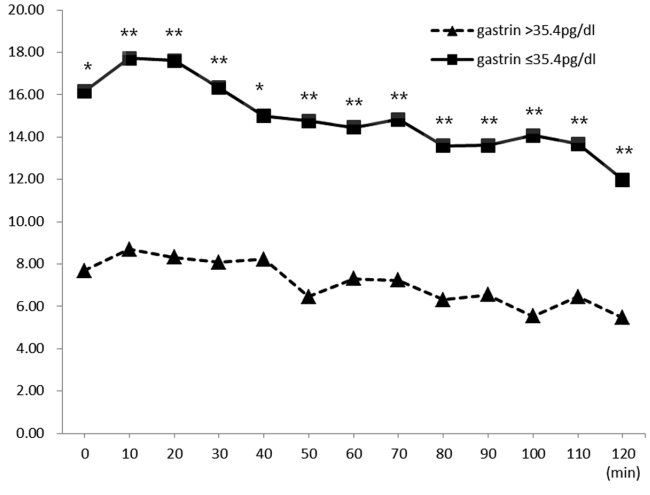

Figure 2. The profiles of breath hydrogen (H_2) according to the cut-off value of serum gastrin level of 35.4 pg/mL (*$P < .05$; **$P < .01$).

Gastrin, a peptide hormone, has a pivotal role in secreting hydrochloric acid into the stomach and enhancing gastric motility. It is primarily released in response to vagal and gastrin-releasing peptide (GRP) stimulation secondary to the ingestion of peptides and amino acids, gastric distension, and an elevated stomach pH.[10,24] Accordingly, in the condition of a low gastric acidic status indicative of low profiles of PG, serum gastrin or GRP increases, promoting gastrointestinal motile function and regulating intestinal peristaltic reflex.[11,12] Our study showed significant low breath H_2 levels at most time points and total H_2 during GBT in the patients with low profiles of PG, unlike those with high gastrin levels. We enrolled the patients without any history of abdominal operation in whom acid peptic secretory capacity is seldom

Table 6. Multivariate Analysis for the Risk Factors of Indicating the Value of PG I/II Ratio ≤3.5 or Gastrin > 35.4 pg/mL

	OR	95% CI	*P*
PG I/II ratio ≤ 3.5			
Positive CLO	4.31	0.81-22.73	.09
Presence of acute gastric injury	0.17	0.01-2.16	.17
Total H_2 concentration	1.01	0.99-1.02	.18
Gastrin > 35.4 pg/mL			
Positive CLO	15.12	1.10-208.26	.04
Total H_2 concentration	1.00	0.99-1.01	.54

OR, odds ratio; PG, pepsinogen; CLO, rapid urease test; H_2, hydrogen.

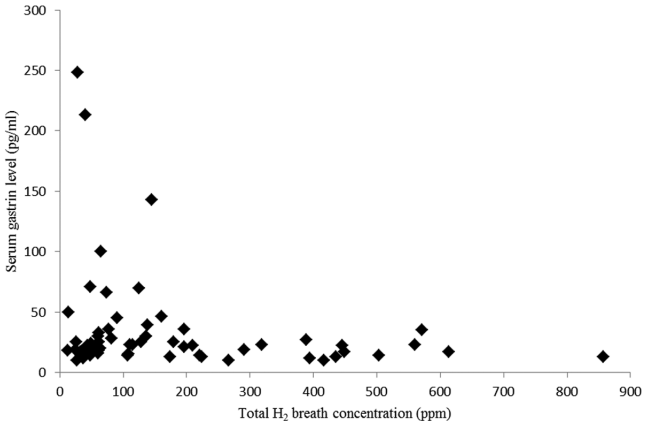

Figure 3. A tendency toward a correlation between total breath hydrogen (H_2) concentration and serum gastrin level.

affected. We hypothesized that breath H_2 might be slightly influenced by gastric acidity rather than by motility function in patients with normal gastrointestinal anatomy. A previous study showed that gastrectomy reduces gastric acid secretion, while normal anatomical status with FGID is associated with altered intestinal transit, a condition in which gastric acid function remains intact.[21] In other words, the low PG profiles expected in cases of partially affected acidity could be compensated for elevated gastrin being a principal factor for enhancing intestinal motility to decrease the breath H_2 levels. This suggestion is not surprising since there is a tendency toward an inverse link between breath H_2 and gastrin levels in Figure 3. Therefore, the GBT results might be chiefly influenced by serum gastrin-related gastrointestinal motor function. Interestingly, no differences were seen in breath CH_4 levels by PG I/II ratio or gastrin cut off levels.

Methanogenic bacteria are reported to be related to constipation with delayed intestinal transit.[25] Accordingly, lactulose, a non-absorbable substrate that passes the small intestine into the colon, might have an advantage for detecting SIBO in subjects with methanogenic bacteria who are expected to have delayed intestinal transit because a substrate with glucose is easily absorbed in small intestine and rarely reaches the colon.[26-28] GBT may be unable to detect CH_4-producing bacteria. The other reason is that methanogenic bacteria are predominantly found in the left colon and relatively less affected by upper gastrointestinal polypeptide including gastrin or PG compared to H_2 -producing intestinal bacteria.[29,30]

Although the association between breath H_2 level during GBT and gastrin level did show any significance in the multivariate analysis, the small number of subjects may have limited the power of our statistical analysis. Thus, further research with large numbers of patients is needed to verify our results.

We surveyed the factors associated with gastrin or PG I/II ratio. A positive CLO was independently related to an increased serum gastrin level. *H. pylori* infection in the stomach is related to gastrin levels. The suggested physiologic mechanism is secondary to the reduction in somatostatin-secreting D-cells and subsequent dysregulation of gastrin secretion by G-cells.[31] This imbalance leads to a decreased pH, which consequently overwhelms the gastric mucosal defenses, often resulting in gastric mucosal damage. The main limitation of the study was that we did not directly measure gastric acidity status. Future studies are needed to estimate the intragastric pH and to measure intragastric PG profiles. Thus, an elevated gastrin level may suggest the presence of *H. pylori* or cautiously indicate a lack of breath H_2-producing intestinal bacteria.

In conclusion, although old age was the only independent significant risk factor for SIBO in FGID patients and PG profiles appear to be not independently associated with SIBO, elevated gastrin level may suggest the *H. pylori* infection in the stomach and cautiously indicate a lack of breath H_2-producing intestinal bacteria.

Ethics Committee Approval: This study was approved by the Institutional Research Ethics Board of the Catholic University of Korea (VC15OISI0027) in December 2015, and it was adhered to the Declaration of Helsinki.

Informed Consent: Written informed consent was acquired from all patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept – Kim D.B. and Paik C.N.; Design – Kim D.B., Jo I.H., and Paik C.N.; Supervision – Kim D.B., and Paik C.N.; Resources – Kim D.B., and Paik C.N.; Materials – Kim D.B., Kim Y.J., and Paik C.N.; Data Collection and/or Processing – Kim D.B., Jo I.H., and Paik C.N.; Analysis and/or Interpretation – Kim D.B., Jo I.H., and Paik C.N.; Literature Search – Kim D.B., Kim Y.J., and Paik C.N.; Writing Manuscript – Kim D.B., Jo I.H., and Paik C.N.; Critical Review – Lee J.M., Jo I.H., and Paik C.N.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study was sponsored by ILDONG Pharma Co., Ltd., Seoul, Korea. The authors are solely responsible for the contents, which do not necessarily represent the official views of ILDONG Pharma Co., Ltd.

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