Acute gastric injury after ingestion of substrate with hyperosmolar glucose and benzoate inversely related with small intestinal bacterial overgrowth

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ABSTRACT

Background/Aims: *The occurrence of gastrointestinal symptoms and the presence of small intestinal bacterial overgrowth (SIBO) could be determined after ingestion of substrate with highly concentrated glucose for glucose breath test (GBT), after which endoscopic images for acute gastric injury have not been clarified. The aims of this study were to investigate the prevalence and relationship of acute gastric injury with SIBO after GBT.*

Materials and Methods: *A cohort of 235 patients with functional gastrointestinal symptoms undergoing breath test with 50 g glucose solution, immediately followed by upper endoscopy were surveyed. The acute gastric injury in endoscopic images and the GBT for hydrogen (H_2) or methane (CH_4) were assessed.*

Results: *The prevalence of acute gastric injury was 28.1% (66/235) after GBT. There were significant differences in GBT positivity (+) with and without gastric injury (25.8% vs 40.8%, p=0.03). In subtypes, GBT (H_2) + was significantly lower in group with gastric injury than in the group without. No differences were seen in GBT (CH_4) + between two groups. On multivariate analysis, the subtype of GBT (H_2) + (Odds ratio (OR)=0.42; 95% Confidence interval (CI)=0.20-0.90; p=0.03) inversely and female (OR=2.11; 95% CI=1.11-4.00; p=0.02) were significantly related with gastric injury. Whereas gastric injury was the only independent related factor for GBT + inversely (OR=0.51; 95% CI=0.27-0.97; p=0.04).*

Conclusion: *Highly concentrated glucose might provoke acute gastric injury, which could predict the absence of SIBO.*

Keywords: *acute gastric injury, glucose breath test, sodium benzoate, small intestinal bacterial overgrowth*

INTRODUCTION

The nutritional composition of foods or drinks can have a great influence on gastrointestinal problems. Recently, studies have found that a high intake of concentrated carbohydrate solutions has been reported to induce gastrointestinal symptoms (1-4). Although the pathophysiology is unknown, a high rate of hyperosmolar glucose ingestion could produce gastric distension and delayed gastric emptying (2, 4, 5). Fundamentally, ingested food stimulates gastric acid secretion, gastric barrier formation, and function (6). Nowadays, people are forced to consume foods that contain preservatives, some of which, such as sodium benzoate, are known mucosal irritants (7). Therefore, it is worth examining the mucosal damage to the gastrointestinal tract after the ingestion of various components. Gastric acid plays a pivotal role in the pathogenesis of diseases by facilitating the mucosal inflammation in the stomach and upper intestinal tract (8). The integrity of the gastric mucosa is maintained through a balance between gastric acid secretion and the mucosa's defense mechanism against gastric acid. Parietal cells, mainly located in the body, secrete acid, which is modulated by cholinergic neurotransmission, endocrine secretion of the peptide hormone of gastrin, and paracrine secretion of prostaglandins and histamine.

Small intestinal bacterial overgrowth (SIBO) is a condition characterized by an abnormally high bacterial population level in the small intestine and is related to irritable bowel syndrome (IBS) and various abdominal symptoms. SIBO is commonly found in patients with a loss of defense mechanisms against enteric bacteria including decreased intestinal motility and reduced status of gastric acid (9, 10). Recently, use of a hydrogen (H_2)-methane (CH_4) breath test after ingestion of glucose load was proposed as an alternative method to assess SIBO. In clinical prac-

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tice, our institute uses the glucose breath test (GBT) with a commercial substrate containing glucose and preservative sodium benzoate, which is immediately followed by upper endoscopy for gastrointestinal symptoms, we encountered numerous cases for acute hemorrhagic gastric lesions. We hypothesized that the substrate for GBT might contribute to the formation of gastric lesion, because gastric acidity might affect contrastively both the harmful effect for gastric injury and protective effect for SIBO. The aims of this study were to investigate the prevalence of acute gastric injury and SIBO, and to analyze the relationship between SIBO and acute gastric injury in patients with functional gastrointestinal symptoms, who underwent GBT immediately followed by an upper endoscopy.

MATERIALS AND METHODS

This study was approved by the Institutional Research Ethics Board of our institute (VC15RISI0124) and adhered to the Declaration of Helsinki.

Study Populations

The study was conducted at St. Vincent's Hospital, a teaching and referral hospital of the Catholic University of Korea. The medical records, charts, and digitalized archived images of consecutive patients with gastrointestinal symptoms including abdominal pain/discomfort, bloating, nausea, heartburn, abdominal distention, or change in bowel movement, who underwent GBT, immediately followed by an upper endoscopy between March 2010 and April 2015, were surveyed. If the subjects clinically needed to get a medical examination for an upper endoscopy and breath test, our institute performed the upper endoscopy just after breath test, if available. All patients included in this study were older than 18 years of age. Initially, patients were excluded if they had a history of diabetes mellitus, connective tissue disease, thyroid disease, or gastrointestinal surgery. We recommended that before the breath test, antisecretory agents such as proton pump inhibitors (PPI)s or histamine $(H)_2$ receptor antagonists, antibiotics, probiotics, prokinetics, laxatives, bulking agents, antidiarrheal drugs, or narcotic use should be stopped. Exclusion criteria included the following: having a gastrointestinal disease, renal insufficiency, liver disease, a major psychiatric disease, hearing impairment, or masticatory dysfunction; having undergone colonoscopy within the previous 3 months, all of which would be a hindrance to the breath test (11, 12). Patients with obstetric and gynecologic surgeries such as hysterectomy and cesarean operation, and patients with incomplete data were also excluded. In addition, patients taking nonsteroidal anti-inflammatory drugs, aspirin or thrombolytic agents, within the previous 4 weeks were excluded to rule out drug-induced gastric injury.

MAIN POINTS

- *The revalence of acute hemorrhagic gastric injury after high osmolar glucose load in our cohort study was 28.1%.*
- *Female and the GBT (H2) negativity (-) to be the significant independent factors for the presence of acute hemorrhagic gastric injury.*
- *The presence of acute gastric injury to be the significant independent predicting factors for the GBT negativity (-).*

Demographics

Demographic data, comorbidities, concurrent use of drugs, and a bowel symptom questionnaire for IBS using Rome III criteria were routinely surveyed during the GBT. These data were used for evaluation and diagnosis of patients with clinically suspected gastrointestinal disorders.

Glucose Breath Test

The GBT was performed after an overnight fast of at least 12 h. The breath test started 30 min after mouth wash with 20 mL of 0.05% chlorhexidine and water. Smoking and physical exercise were not allowed for 30 min before and during the test. Patients were instructed to take 50 g of glucose (DIASOL-S SOLN 100 mL, 2.78 Osm Tae Joon Pharma, Seoul, Korea), which contains 60 mg of sodium benzoate as a preserving agent. End expiratory breath samples were collected and breath H_2 and CH_4 values were estimated at baseline, and then at every 10-min intervals for 120 min. Duplicate samples were taken at each time with the equipment of the breath test (the Quintron SC breathtracker; Quintron Instrument Company, Milwaukee, WI, USA). GBT positivity (+) for H_2 (GBT [H_2] +) or CH_4 (GBT [CH_4] +) indicating a diagnosis of SIBO was defined as (1) a baseline H_2 or CH_4 concentration of more than 15 ppm, or (2) an increase in the breath H_2 or CH_4 concentration of more than 12 ppm above the baseline value within 60 min after ingestion of the glucose solution (9, 13, 14). Positivity including both GBT (H_2) + and GBT (CH_4) + was classified as GBT (both) + status.

Acute Hemorrhagic Gastric Injury

An acute hemorrhagic gastric injury of clinical significance was defined as >10 bleeding spots with coalescent intramucosal blood or oozing (Figure 1) as determined on endoscopy (15). The initial endoscopic images of the gastric mucosa, before full inflation of the stomach during the endoscopic procedure, were surveyed to differenti-

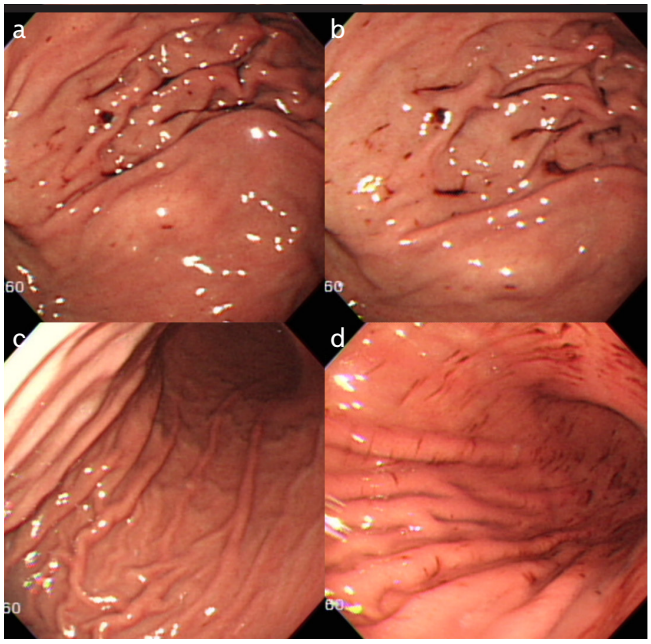

Figure 1. a-d. The endoscopic images of acute gastric injury immediately after GBT. An upper endoscopy showed multiple acute gastric mucosal lesions with fresh blood clots at high body before inflation (a) and on inflation (b), without any evidence of mucosal lesions in the low body and antrum (c). The image of endoscopy demonstrated acute gastric mucosal lesions in both antrum and body with fresh blood clots scattering at whole gastric mucosa (d).

ate iatrogenic gastric injury because of air inflation or the scope itself. The status of Helicobacter pylori (*H. pylori*) was evaluated in patients with acute gastric lesions, who underwent antral or body biopsy for histopathology with Giemsa stain.

Analysis

Clinical evaluations included age, sex, body mass index (BMI), history of smoking or hypertension, the presence of IBS according to the acute gastric injury, or the result of the GBT. The endoscopic data including location of gastric lesions and the presence of *H. pylori* were determined. The H_2 profiles of the GBT in patients with acute gastric injury were compared with those without gastric injury. Associations between gastric injury and GBT + including subtypes were evaluated. Continuous data were expressed as means ± standard error and were analyzed using independent samples *t* tests. Categorical variables were expressed as quantities and were analyzed using Chi-square tests or the Fisher's exact test. Multiple stepwise logistic regression analysis was used to identify independent factors associated with the status of GBT or the presence of acute gastric injury. All the analyses were performed with a statistical software package (version 20.0; SPSS Inc). A p- value of <0.05 was considered significant for all tests.

RESULTS

Study Populations

During the study period, a total of 1,074 consecutive patients who were suspected to have functional gastrointestinal diseases underwent GBT. Among them, 296 patients underwent a GBT, immediately followed by an upper endoscopy. Subjects were excluded owing to a history of hysterectomy, cesarean operation, having incomplete data, or a history of drugs with the potential for gastric injury. After GBT, patients who were diagnosed with gastric cancer, inflammatory bowel diseases, and thyroid diseases were also excluded. In addition, patients taking the nonsteroidal anti-inflammatory drugs, aspirin or thrombolytic agents, within the previous 4 weeks were excluded to rule out drug-induced gastric injury (Figure 2). Ultimately, a total of 235 patients were included in the analysis. The mean age of the patients was 50.0 ± 1.0 years (range=19-85 years) and 94 patients (40.0%) were men.

Characteristics and GBT According to the Presence of Acute Gastric Injury

In total, 66 patients (28.1%) were found to have an acute gastric injury in endoscopic images taken after glucose load. All the lesions included the gastric body: 51 patients (77.3%) a lesion in the gastric body only and 15 (22.7%) showed injury at both the antrum and body. There were no differences between patients with and those without acute gastric injury regarding age, BMI, history of smoking or hypertension, and IBS, except for sex, which showed a predominance in women (p=0.02) (Table 1). In all, 53 patients with acute gastric injury underwent a biopsy to determine the status of *H. pylori* during the endoscopic procedure. Among them, only three patients (5.7%) were revealed to have *H. pylori*. The breath H_2 concentrations in the patients with gastric injury were significantly lower at the time points of 10, 20, 40, 50, 60, 70, 80, 90, 100, 110, and 120 min compared with those without acute gastric injury (Figure 3). The GBT + was 25.8% (17/66) in patients with gastric injury and 40.8% (69/169) in those without gastric injury (p=0.03). In the subtypes, the GBT (H_2) + and breath H_2 concentrations were significantly lower in the group with acute gastric injury than in those without gastric injury. However, there was no difference in the GBT (CH_4) + and breath CH_4 concentrations between the two groups (Table 1). Multivariable logistic re-

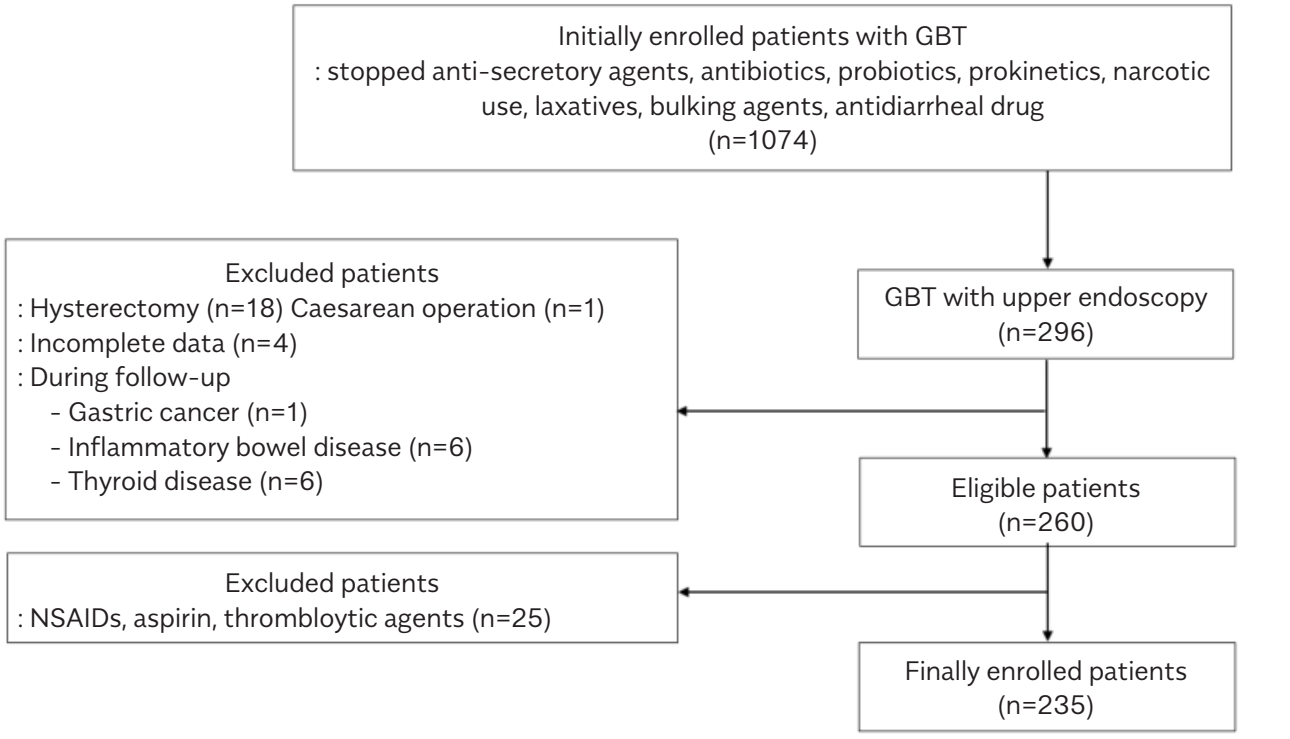

Figure 2. Study flow diagram.

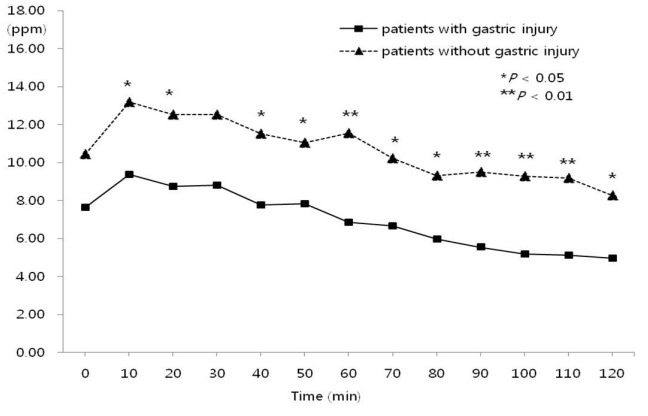

Figure 3. The profiles of glucose hydrogen (H_2) breath test between patients with and without acute gastric injury.

gression analysis showed female sex and the GBT (H_2) negativity (–) to be the significant independent factors for the presence of acute gastric injury (Table 2).

Characteristics According to the Positivity to GBT

There were no differences between the GBT-positive and GBT-negative patients regarding demographic factors such as age, sex, BMI, history of smoking or hypertension, and IBS (Table 3). As shown in Table 3, GBT + was significantly but inversely related to acute gastric injury. Specifically, there was a significant difference in the location of the injury, indicating that the extent of injury was inversely associated with GBT +. GBT + was found in 2.3% (2/86) of the patients with gastric injury in both the antrum and body, 17.4% (15/86) of those in the body only, and 80.2% (69/86) in those without injury. Negative GBT results were found in 8.7% of the patients with gastric lesions in both at antrum and body, 24.2% of those in the body only, and 67.1% of those without injury (p=0.05). Multivariable logistic regression analysis showed the presence of acute gastric injury to be a significant independent predicting factor for GBT – (OR=0.51; 95% CI=0.27-0.97; p=0.04).

DISCUSSION

This study showed that acute hemorrhagic gastric lesions after substrate for GBT including high osmolar glucose with sodium benzoate as a preserving agent were not uncommon. They appear to be associated with gastric acidity or intestinal motility, and could predict the presence of result of GBT.

Table 1. Characteristics of the patients with or without acute gastric injury after GBT.

	Acute gastric injury		
Demographics	No (n=169)	Yes (n= 66)	p
Age (year), mean±SE	50.53±1.12	48.71±1.86	0.39
Sex, n (%)			0.02
Male	76 (45.0)	18 (27.3)	
Female	93 (55.0)	48 (72.7)	
BMI, mean±SE	23.90±0.22	24.33±0.36	0.30
Smoke, n (%)			0.29
Yes	61 (36.1)	19 (28.8)	
No	108 (63.9)	47 (71.2)	
Hypertension, n (%)			0.61
yes	19 (11.2)	9 (13.6)	
no	150 (88.8)	57 (86.4)	
IBS, n (%)			0.29
yes	29 (17.2)	9 (13.6)	
no	140 (82.8)	57 (86.4)	
GBT, n (%)			0.03
GBT +*	69 (40.8)	17 (25.8)	
GBT −**	100 (59.2)	49 (74.2)	
Subtypes, n (%)	0.04		
GBT (H2) +	53 (31.4)	11 (16.7)	
GBT (CH4) +	7 (4.1)	5 (7.6)	
GBT (both) +	9 (5.4)	1 (1.5)	
GBT −	100 (59.2)	45 (74.2)	
Breath H_2-CH_4 excretion†, mean ± SE			
H_2 concentration, ppm	134.78±12.83	90.41±13.49	0.02
CH_4 concentration, ppm	78.09±9.6	67.96±12.45	0.56

BMI: Body mass index; IBS: Irritable bowel syndrome; GBT: glucose breath test; H_2: hydrogen; CH_4: Methane; SE: standard error.
*GBT positivity.
**GBT negativity.
†Calculated between 0 to 120 min during GBT; expressed as mean±SE.

During our clinical investigation, GBT immediately followed by upper endoscopy revealed a fair proportion of patients with acute hemorrhagic gastric injury (Figure 1). In this study, we defined acute hemorrhagic gastric lesion as at least 10 lesions with fresh blood, which were relevant on a clinically significant mucosal scoring scale (15). The prevalence of acute gastric injury after glucose load was 28.1%. Literature (1, 4, 5) showed that the ingestion of fiber, fat, protein, and concentrated carbohydrate solutions were associated with the risk of gastrointestinal symptoms. The osmolality of 50 g glucose solution is as high as 2.78 Osm and the rate of ingestion is within 1 min. The literature indicate that ingestion of carbohydrate solution with high osmolality (500 mOsm/L) and at a high rate (>1.0 to 1.5 g/min) can increase and worsen the gastrointestinal symptoms (4, 5). The preservative as sodium benzoate also has mucosal irritation effect, which significantly releases histamine and prostaglandin from the mucosa (7).

Table 2. Independent factors for acute gastric injury after GBT (multivariate analysis).

Variables	OR	95% CI	p
Sex (female)	2.11	1.11-4.00	0.02
GBT (All) +	0.51	0.26-0.97	0.04
GBT (H2) +	0.42	0.20-0.90	0.03
GBT (CH4) +	1.70	0.28-6.06	0.42
GBT (both) +	0.20	0.02-11.69	0.14

GBT: glucose breath test; OR: Odds ratio; CI: Confidence interval.

The suggested pathophysiologic mechanisms of gastric lesion after GBT could be related to basal status of gastric acidity. A study indicated that intragastric glucose inhibits gastric acid secretion and protects gastric mucosa from injury. However, the osmolality of glucose in this study was two times higher than that in the previous study, which could affect the direct mucosal damage (16). In addition, the component sodium benzoate has mucosal irritation effect, which is related with prostacyclin or histamine reaction (7). The direct mucosal stimulation of glucose and additives may contribute to the inflammation and irritation of gastric mucosa. Old age is one of the risk factors associated with mucosal friability and atrophy. However, there was no significant age difference according to the presence or absence of gastric injury in this study. Therefore, there is uncertainty about the estimation of the contribution of direct mucosal damage caused by glucose and sodium benzoate. The endoscopic images showed that all the lesions observed had fresh blood at the gastric body, which is known to contain the acid-secreting parietal cells, which is suggestive of an acute response to gastric acid. A higher propor-

Table 3. Characteristics of the patients according to the positivity to GBT.

	GBT		
Demographics	Negative (n=149)	Positive (n=86)	Negative (n=149)
Age (year), mean±SE	50.00±1.19	50.10±1.64	0.95
Sex, n (%)			0.89
Male	59 (39.6)	35 (40.7)	
Female	90 (60.4)	51 (59.3)	
BMI, mean±SE	24.01±0.23	24.04±0.32	0.93
Smoke, n (%)			0.94
Yes	51 (34.2)	29 (33.7)	
No	98 (65.8)	57 (66.3)	
Hypertension, n (%)			0.60
Yes	19 (12.8)	9 (10.5)	
No	130 (87.2)	77 (89.5)	
IBS, n (%)			0.44
Yes	22 (14.8)	16 (18.6)	
No	127 (85.2)	70 (81.4)	
Acute gastric injury, n (%)			0.03
Yes	49 (32.9)	17 (19.8)	
No	100 (67.1)	69 (80.2)	
Location of injury, n (%)			0.05
body and antrum	13 (8.7)	2 (2.3)	
body only	36 (24.2)	15 (17.4)	
none	100 (67.1)	69 (80.2)	

GBT: glucose breath test; BMI: Body mass index; IBS: Irritable bowel syndrome; SE: standard error.

tion of high glucose intake would occupy a greater gastric volume and induce gastric distension with delayed gastric emptying (2, 4, 5). In addition, on the contrary, dehydration from fasting might induce a gastric lesion vulnerable to mucosal ischemia (4).

This study excluded patients with a recent history of drugs that could induce gastric injury (15). *H. pylori* infection is known as the main cause of gastritis or peptic ulcers (8, 17). In our country, the survey of *H. pylori* was legally covered by public insurance only in the presence of a gastric lesion. Therefore, we could not perform the *H. pylori* for all the patients, but our study indicated low prevalence of *H. pylori* (5.7%). There was a low possibility that *H. pylori* was a risk factor for gastric injury in this study. Owing to the fact that this is a retrospective study, there was no baseline endoscopic examination before the performance of GBT to compare with the endoscopic findings after the substrate ingestion. However, baseline endoscopy can induce iatrogenic gastric mucosal injury, which may affect the interpretation of gastric mucosal damage in subsequent endoscopy after substrate ingestion. In this study, initial endoscopic images before full inflation were selected and analyzed to exclude the iatrogenic injury from air inflation or endoscopy equipment itself. We also performed lactulose breath test followed by upper endoscopy, and did an upper endoscopy with colonoscopy simultaneously after ingestion of polyethylene glycol-electrolyte powder with 4 L of water. However, we seldom found any acute hemorrhagic gastric lesions. Accordingly, the main cause of gastric lesions may be substrate solution for GBT itself in this study.

The suggested pathogenesis between gastric injury and GBT– could be related to the status gastric acidity and intestinal motility. In this study, female and GBT– were the independent factors related to acute gastric injury. Atrophic gastritis or intestinal metaplasia are associated with decreased acid secretion in the stomach (18, 19). In male, gastritis has a tendency toward more rapid progression to glandular atrophy, and intestinal metaplasia is more common (18). A study showed that the prevalence of atrophic gastritis is higher in men than in women (20). Accordingly, a predominance in women was associated with low gastric acid status in this study. The other factor of GBT + is inversely related to acute gastric injury. We hypothesize that the gastric lesions may have been induced from gastric acid, stimulated by the substrate with highly concentrated glucose with sodium benzoate. Gastric injury after GBT indirectly reflects the acidity in the stomach, which is an important defense mechanism against intestinal bacteria (9, 10, 21). The reason our study demonstrated an association between acute gastric injury and the subtypes of GBT (H_2) + but not GBT (CH_4) + is unclear. The SIBO has previously been affected by two representative intestinal barriers: intestinal motility and gastric acid secretion. Decreased gastric acid secretion, owing to acid suppressive agents such as PPIs or H_2 receptor antagonists, atrophic gastritis, or gastrectomy, results in GBT (H_2) + (9, 21-27). Whereas the literature reported that GBT (CH_4) + is more related to delayed intestinal transit

in the left colon, where methanogenic bacteria are predominantly found (11, 28-31). Therefore, the volume and extent of the upward distribution of colonic methanogenic bacteria from the distal colon are associated with the degree of colon transit. As such, there might be a possibility that H_2-producing bacteria are more affected by gastric acid. Further study is needed to validate the diagnosis of different subtypes of bacterial overgrowth by different defense mechanisms.

There are other possibilities to justify the finding that the rates of gastric injury were inversely related with GBT +. Such a severe mucosal injury possibly seems to affect gastric emptying. If the gastric emptying of glucose solution is delayed owing to acute gastric mucosal injury, the entrance of glucose into small intestine will be also delayed, and eventually may decrease bacterial fermentation. Accordingly, the correlation between gastric mucosal injury and false GBT– also can be suggested. On the contrary, the patients with rapid emptying have less stomach irritation from benzoate but show false GBT +. We need to study further with gastrointestinal transit and breath test. Nevertheless, the presence of acute gastric injury is inversely associated with the result of GBT itself.

Acute gastric injury is the only independent factor for predicting the GBT –. In this study, sex was significantly related to acute gastric injury (Table 2) but not with the status of GBT (Table 3). Sex has not been known to have any relation to intestinal bacterial overgrowth. Sex did not directly affect the GBT but it did affect indirectly it through the gastric acid secretion. All acute hemorrhagic gastric lesions were observed in the gastric body, in which the acid-secreting parietal cells of the oxyntic gland area are mainly located. The acute response of the acid producing cells to a glucose load might induce acute gastric lesions in the body. Interestingly, the GBT status is attributed to the extent of gastric injury. Among patients with extensive injury in both the antrum and body (n=5), the prevalence of GBT + was 13.3% (n=2), whereas among those with injury to the body (n=51), the prevalence was 29.4% (n=15) (Table 3). The suggested hypothesis is that the extent of the lesion reflects the status of high gastric acidity against enteric bacteria.

The limitation of the study was that data were reviewed retrospectively. To analyze the role of gastric acid and direct mucosal stimulation of substrate, more accurate data are needed, including diagnosis of gastric atrophy and gastric acidity before and after breath test. It was difficult to obtain these data as a limitation of retrospective research. However, the data were collected consecutively and prospectively in that the same standard approach was used for all patients. In clinical status, strict precautions were required to perform the breath test for evaluation regardless of academic studies (11, 12). Although the study did not measure the status of gastric acidity, the study showed that gastric acid might appear to be important determinant affecting gastric injury and GBT result. In addition, gastric injury itself could affect the gastric motility, influencing the result of GBT. Further study is needed to validate the status of gastric acidity or motility after substrate for GBT is ingested.

In conclusion, the ingestion of substrate containing a highly concentrated oral glucose solution can induce acute hemorrhagic gastric injury, and the gastric lesion could be inversely associated with the positivity to GBT.

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Informed Consent: N/A.

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