

Clinical Study

Extensive Atrophic Gastritis Increases Intraduodenal Hydrogen Gas

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Objective. Gastric acid plays an important part in the prevention of bacterial colonization of the gastrointestinal tract. If these bacteria have an ability of hydrogen (H₂) fermentation, intraluminal H₂ gas might be detected. We attempted to measure the intraluminal H₂ concentrations to determine the bacterial overgrowth in the gastrointestinal tract. **Patients and methods.** Studies were performed in 647 consecutive patients undergoing upper endoscopy. At the time of endoscopic examination, we intubated the stomach and the descending part of the duodenum without inflation by air, and 20 mL of intraluminal gas samples of both sites was collected through the biopsy channel. Intraluminal H₂ concentrations were measured by gas chromatography. **Results.** Intra-gastric and intraduodenal H₂ gas was detected in 566 (87.5%) and 524 (81.0%) patients, respectively. The mean values of intra-gastric and intraduodenal H₂ gas were 8.5 ± 15.9 and 13.2 ± 58.0 ppm, respectively. The intraduodenal H₂ level was increased with the progression of atrophic gastritis, whereas the intra-gastric H₂ level was the highest in patients without atrophic gastritis. **Conclusions.** The intraduodenal hydrogen levels were increased with the progression of atrophic gastritis. It is likely that the influence of hypochlorhydria on bacterial overgrowth in the proximal small intestine is more pronounced, compared to that in the stomach.

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1. INTRODUCTION

Breath hydrogen (H₂) measurements are widely used to detect carbohydrate malabsorption [1–7]. Because bacteria represent the sole source of gut H₂, fasting breath H₂ gas has been used as a marker of colonic fermentation [8, 9]. If the fermentation occurs in the stomach, H₂ gas should be produced and released into the gastric lumen. Gastric acid plays an important part in the prevention of bacterial colonization of the stomach and the small intestine [10, 11]. Reduction of gastric acid secretion predisposes to infection with a variety of organisms [12–14]. Intestinal bacterial overgrowth during treatment with PPI was previously reported because of an intra-gastric neutral pH [15–18]. Atrophic gastritis is the most common cause of reduced gastric acid secretion and

Helicobacter pylori (*H.pylori*) seems to be the commonest cause of atrophic gastritis [19–22]. Then we attempted to collect endoscopically intraluminal gas from the stomach and the duodenum and analyze the H₂ concentration in order to determine the bacterial overgrowth in the upper digestive tract.

2. PATIENTS AND METHODS

2.1. Patients

Studies were performed in 647 consecutive patients undergoing upper endoscopy, 211 men and 436 women, 19 to 85 years old (mean 60.8 ± 12.9 years). Of the patients recruited in this study, women are preponderant for one reason or

TABLE 1: Intra-gastric and intraduodenal hydrogen levels in relation to endoscopic findings.

	Gastric ulcer	Duodenal ulcer	Gastritis
Number of patients	51	24	569
Age	64.5 ± 13.5	44.8 ± 10.7	61.4 ± 12.5
Male/female	34/17	18/6	156/413
Stomach (ppm)	6.1 ± 8.9	6.5 ± 12.4	8.7 ± 16.5
<i>P</i> values v.s.*	.13	.26	*
Duodenum(ppm)	22.2 ± 70.5	5.6 ± 6.8	12.8 ± 58.1
<i>P</i> values v.s.**	.12	**	.27

another. None of the patients had a history of use of PPI, H₂-receptor antagonist, antibiotics, steroids, or nonsteroidal anti-inflammatory drugs for a period of at least six months before the investigation. Twenty patients had a previous Billroth-II partial gastrectomy and were also excluded from analysis.

Blood samples for measurements of IgG antibody to *H.pylori* were taken prior to endoscopy. Serum samples were also examined for *H.pylori* antibody by an enzyme-linked immunosorbent assay (ELISA) using the EPI HM-CAP IgG (Enteric Products, Inc., NY) assays. All assays were performed in accordance with manufacturer's instructions. The calculated ELISA is read as positive if above 2.2.

2.2. Collection of intraluminal gas samples

Endoscopy was performed after a topical anesthesia gargle after a fasting period of more than 12 hours and without previous exercise. The patients were also requested to brush their teeth in the evening, but not in the morning of, the study. All patients ate meals of their own choice in the evening of the study. At the time of endoscopic examination, we intubated the stomach without inflation by air, and 20 mL of intra-gastric gas was collected through the biopsy channel using a 30 mL syringe. The first 5 mL was discarded for reduction of dead-space error. Once the pylorus is located, the tip of the endoscope is advanced into the descending portion of the duodenum. After that, 20 mL of intraduodenal gas was collected again by the same way. Intra-gastric and intraduodenal hydrogen concentrations were immediately measured by gas chromatography using Breath Analyzer TGA-2000 (TERAMECS Co., Ltd., Kyoto) and expressed in parts per million (ppm). Linear accuracy response range was 2 to 150 ppm. After collecting an intraduodenal gas sample, the endoscopist inflated the stomach by air and observed the gastric mucosa. Operators involved in the measurement of breath samples were blinded for age, sex, and endoscopic diagnosis.

2.3. Grading of atrophic gastritis

In this study, atrophic gastritis was classified into four stages by observing the location of the atrophic border in the stomach [23]; closed type and open type (O-1, O-2, and O-3). For closed type, the atrophic borderline is located at the

lesser curvature. In the stage O-1, the atrophic borderline lies between the lesser curvature and the anterior wall of the body. In the stage O-3, the atrophic region spreads throughout the entire stomach. Stage O-2 is in-between O-1 and O-3. Stages O-1 to O-3 constitute the advanced stages of atrophic gastritis.

2.4. Statistical analysis

Data of intra-gastric and intraduodenal hydrogen were presented as mean ± SD (standard deviation). Comparisons of groups were made using the unpaired *t*-test. A *P* value of <.05 was accepted as indicating statistical significance.

3. RESULTS

Endoscopic findings included gastric ulcer (51 patients), duodenal ulcer (24), gastric cancer (3), and gastritis (569). All of patients with gastric ulcer, duodenal ulcer, and gastric cancer had a positive result of *H.pylori* serology. Among 569 patients with gastritis, 389 were seropositive.

Over all, intra-gastric and intraduodenal hydrogen gases were detected in 566 (87.5%) and 524 (81.0%), respectively. The mean values of intra-gastric and intraduodenal hydrogen gas were 8.5 ± 15.9 (0–219) and 13.2 ± 58.0 (0–828) ppm, respectively.

Intra-gastric and intraduodenal H₂ values and characteristics of patients in relation to endoscopic diagnosis are summarized in Table 1. The duodenal ulcer group showed a significantly younger mean age than the other groups. The intra-gastric H₂ level was the highest in gastritis group followed by the duodenal ulcer group, and the gastric ulcer group. The intraduodenal H₂ level was the highest in the gastric ulcer group among three groups.

Mean intra-gastric and intraduodenal H₂ concentrations at different stages of atrophic gastritis are summarized in Table 2. The mean levels of intra-gastric H₂ gas in patients with closed type, stages O-1, O-2, and O-3, were 10.5 ± 17.3 ppm, 7.4 ± 10.2 ppm, 8.0 ± 12.0 ppm, and 7.5 ± 17.0 ppm, respectively. The intra-gastric H₂ level was the highest in patients with gastric mucosa of closed type and was significantly higher than in those with O-3 stage atrophic gastritis (*P* = .031). In contrast, the intraduodenal H₂ level was the highest in patients with O-3 stage atrophic gastritis among four groups. There was a progressive increase with

TABLE 2: Intra-gastric and intraduodenal hydrogen levels in relation to the grade of atrophic gastritis.

	Closed type	O-1	O-2	O-3
Number of patients	200	66	101	280
Age (mean \pm SD)	55.3 \pm 13.9	58.1 \pm 13.6	59.1 \pm 12.5	66.1 \pm 9.8
Male/female	60/140	22/44	39/62	90/190
Stomach (ppm)	10.5 \pm 17.3*	7.4 \pm 10.2	8.0 \pm 12.0	7.5 \pm 17.0
<i>P</i> values v.s.*	*	.085	.105	.031
Duodenum (ppm)	7.1 \pm 12.7	4.4 \pm 8.2	8.1 \pm 18.5	21.5 \pm 86.1
<i>P</i> values v.s.**	.009	.055	.061	**

the progression of atrophic gastritis. The mean levels of intraduodenal H₂ in patients with closed type, stages O-1, O-2, and O-3, were 7.1 \pm 12.7 ppm, 4.4 \pm 8.2 ppm, 8.1 \pm 18.5 ppm, and 21.5 \pm 86.1 ppm, respectively. The maximum of intraduodenal H₂ was 828 ppm and found in 74-year-old female with O-3 stage atrophic gastritis.

4. DISCUSSION

Before the discovery of *H. pylori* infection in 1983 [24], many investigators reported that an increased number of bacteria had been found in the stomach in patients with achlorhydria or hypochlorhydria [25]. The type and numbers of microbial flora present in the stomach are affected by gastric pH [26–28], and a rise in intra-gastric pH has often been associated with an increased number of bacteria in gastric juice [29–31]. Atrophic gastritis is the most common cause of reduced gastric acid secretion. Therefore, if atrophic gastritis is closely related to the gastric and intestinal bacterial overgrowth, it is possible, we suggest, that intra-gastric and intraduodenal hydrogen, reflecting the fermentation by bacteria in the stomach and the duodenum, should be detected in subjects with atrophic gastritis.

The gold standard for bacterial overgrowth, against which intraluminal gas analysis must be compared, is gastric and duodenal fluid culture. Actually, the microbial flora, which is dominated by *Viridans streptococci*, *coagulase negative Staphylococci*, *Haemophilus sp.*, *Neisseria spp.*, *Lactobacillus spp.*, *Candida spp.*, and *Aspergillus spp.* [32, 33], has been demonstrated. However, the study of gastrointestinal flora by direct methods is cumbersome, primary due to its inaccessible location. In addition, the results of identification and quantification of microbes in samples from the gastrointestinal tract are significantly influenced by difficulties in accurate tube placement, contamination during insertion, delay between sampling and inoculation of culture media, and inadequate anaerobic isolation techniques.

In the present study, of all 647 subjects, intra-gastric H₂ was detected in 566 (87.5%) and ranged from 1 to 219 ppm, whereas intraduodenal H₂ was done in 524 (81.0%), ranging from 1 to 828 ppm. This suggested that more than 80% of endoscoped patients had H₂-producing bacteria in the stomach or the jejunum. Moreover, intraduodenal H₂ levels were higher in patients with stage O-3 atrophic gastritis than in other groups, and there was a progressive increase with the

progression of atrophic gastritis. In contrast, the intra-gastric H₂ level was the highest in patients with gastric mucosa of closed type and was significantly higher than in those with O-3 stage atrophic gastritis. These results suggest that extensive atrophic gastritis may be more closely related to bacterial overgrowth in the jejunum, compared to that in the stomach.

Fried et al. [18] reported that most of the bacteria identified from the duodenal aspirates belonged to species colonizing the oral cavity and pharynx, suggesting a descending route of colonization. Husebye et al. [33] also reported that fasting hypochlorhydria associated with gastric colonization of microbes belonging to the oro- and nasopharyngeal flora is highly prevalent in healthy old people. At the normal acidic gastric pH, it has been thought that the stomach is sterile or contains swallowed organisms [34]. Although the pathogenesis of swallowed organisms is unknown, it is reasonable to suppose from the results of our study that these oral bacteria should continuously enter the stomach and produce H₂ gas. Furthermore, it is likely that the influence of hypochlorhydria on bacterial overgrowth in the proximal small intestine is more pronounced, compared to that in the stomach.

Few studies on intra-gastric and intraduodenal H₂ concentrations have been reported, and the clinical features and pathogenesis of intraluminal H₂ gas are not clear. Bacteria represent the sole source of gut hydrogen, and H₂ gas is produced at a rate of 4 L for every 12.5 g of undigested carbohydrate [35]. H₂ gas is either absorbed by diffusion or consumed by bacteria to reduce carbon dioxide to methane or acetate. The intra-gastric H₂ concentration was considered to reflect directly the intra-gastric fermentation and the presence of H₂-producing bacteria in the stomach. Since the intra-gastric H₂ level is not affected by absorption or metabolism of H₂ unlike a breath H₂ level, a trace of H₂ should be detected in patients with intra-gastric fermentation.

In summary, unexpectedly, intra-gastric and intraduodenal H₂ was detected in more than 80% of all subjects in this study, and the intraduodenal H₂ level was increased with the progression of atrophic gastritis. Although it is unknown whether intraluminal fermentation is related to digestive diseases, a large amount of intra-gastric and intraduodenal H₂ may cause abdominal symptoms. We have to make a further study to evaluate whether bacterial overgrowth in the stomach or the proximal small intestine is associated with some clinical symptoms or gastrointestinal diseases.

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