

Changing Trends of Serum Pepsinogen I/II Ratio in Asymptomatic Subjects

Background/Aims: Gastric atrophy can be diagnosed by serum pepsinogen I/II ratio. The aim of this study was to investigate whether the changes of serum pepsinogen I/II ratio can be predicted by gastroscopy. **Materials and Methods:** Sixty healthy subjects who underwent screening for serum pepsinogen I/II levels, serum *Helicobacter pylori* (*H. pylori*) antibody, and gastroscopy for two sequential years were included. Endoscopic findings were classified into four different categories according to the degree of chronic atrophic gastritis; none, mild, moderate, and severe. Changes of the serum pepsinogen I/II ratio, body mass index, *H. pylori* antibody, and endoscopic findings were analyzed after a year. **Results:** The serum pepsinogen I/II ratio showed a tendency to decrease after a year in subjects with *H. pylori* infection ($P=0.013$) and those with moderate to severe atrophic gastritis ($P=0.004$), whereas it increased in subjects without *H. pylori* infection and those with none to mild atrophic gastritis. On multivariate analysis, the degree of atrophic gastritis was the only factor that was related to the changing trends of the serum pepsinogen I/II ratio (odds ratio=5.385, $P=0.023$). **Conclusions:** The degree of atrophic gastritis on endoscopic findings can predict the changes of the serum pepsinogen I/II ratio after a year. Regardless of the current status of *H. pylori* infection, the serum pepsinogen I/II ratio decreases after a year in subjects with moderate to severe atrophic gastritis. (*Korean J Helicobacter Up Gastrointest Res* 2012;12:96-102)

Key Words: Gastritis, atrophic; *Helicobacter pylori*; Gastroscopy; Pepsinogens

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is a vital first stage in gastric carcinogenesis of the atrophy-metaplasia-dysplasia-cancer process.¹ In addition, it is known that *H. pylori*-infected subjects with histological findings of severe gastric atrophy, corpus-predominant gastritis, or intestinal metaplasia have a higher risk of developing gastric cancer.² Therefore, the degree of atrophic gastritis seems to be important, as cancer development depends on the presence of extensive gastric atrophy. In daily clinical practice, atrophic gastritis is diagnosed by gastroscopic findings or by serum pepsinogen levels.

Serum pepsinogen has been used as a biomarker of gastric

inflammation and mucosal status including atrophic change, even before the discovery of *H. pylori*.^{3,4} Pepsinogen I is secreted only by the chief cells of the corpus and its serum values decline with increasing grades of atrophy of the gastric body due to a loss of oxyntic glands.³ Additionally, pepsinogen II is secreted by an antral gland, corpus chief cells, and the duodenal bulb in large quantities, therefore, pepsinogen II is not a direct measure of corpus atrophy.⁴ Although serum pepsinogen I and II levels do not discriminate nonatrophic gastritis against antrum-restricted or predominant atrophic gastritis, the utility of serum pepsinogen concentrations for the diagnosis of *H. pylori* infection and the evaluation of the grade of histological gastritis have been established.⁵ Moreover, a serum pepsinogen I concentration of less than 70 ng/mL and a pepsinogen I/II ratio

of less than 3.0 are now widely accepted as the cut-off point for gastric atrophy.⁶ *H. pylori* infection, gastritis, and glandular atrophy of the stomach can be evaluated via serum pepsinogen concentrations, allowing for the evaluation of gastric mucosal integrity.⁵

Several factors such as BMI, *H. pylori* infection, gastric ulcer, duodenal ulcer, reflux esophagitis, and other gastrointestinal diseases are suggested to be related to serum pepsinogen levels.⁷ In addition, a reduction in the area of fundic gland mucosa with the progression of atrophic gastritis is known to be well correlated with a stepwise reduction in the serum pepsinogen I level or the pepsinogen I/II ratio, thus serum pepsinogen levels are considered reliable markers for the progression of atrophic gastritis.⁸ However, the relationship between these factors and the changing trends of the serum pepsinogen I/II ratio continues to remain uncertain. In this study, we investigated serum pepsinogen levels for two sequential years in healthy subjects without any medical accommodations, and analyzed the factors related to the changes of the serum pepsinogen I/II ratio.

MATERIALS AND METHODS

1. Study population

Asymptomatic subjects who agreed on gastroscopy, serum *H. pylori* antibody test, and serum pepsinogen I and II levels measurement on the same day at the Health Care Center of Konkuk University Medical Center for two sequential years (between January 2010 and August 2011) were included in the study. Subjects showing insufficient data or incomplete study on gastroscopy, serum *H. pylori* antibody test, or serum pepsinogen levels were excluded from the study. In addition, subjects (i) who have a significant disease that needs further evaluation and/or management, (ii) who underwent *H. pylori* eradication, (iii) with recent intake of proton pump inhibitor, (iv) with renal failure, or (v) with a past history of gastric surgery were excluded from the study.

All of the subjects provided written informed consent prior to the procedure, and this study was approved by the Institutional Review Board of Konkuk University School of Medicine which confirmed that the study was in accordance with the ethical guidelines of the Helsinki Declaration.

2. Serum pepsinogen test

Fasting serum samples were centrifuged immediately at 4°C and serum pepsinogen concentrations were determined by a Latex-enhanced Turbidimetric Immunoassay (HBi Co., Anyang, Korea) as described in previous study.⁹ Serum pepsinogen I and II levels were checked twice in a year interval in all subjects, respectively. Atrophic gastritis was diagnosed when the serum pepsinogen I/II ratio was less than 3.0 since I/II ratio is a serologic biomarker for the degree of atrophy, not a gold standard test for atrophic gastritis.^{6,8}

3. *H. pylori* serology

Anti-*H. pylori* IgG was measured using an ELISA that detects human serum antibodies to *H. pylori* (Platelia™ *H. pylori* ELISA; Bio-Rad, Marnes-la-Coquette, France). The Platelia™ *H. pylori* ELISA has a sensitivity of 100% and a specificity of 90% in adults. *H. pylori* infection was determined when anti-*H. pylori* IgG test revealed positive.

4. Gastroscopic examination

Gastroscopy was performed for each subjects without knowledge of the serological data on serum pepsinogen levels. All the electronic endoscopic images were converted into the tagged image format using an EVIS-260 system (Olympus Optical Co., Ltd., Tokyo, Japan) with a magnetic optical disk drive for each case. Electronic gastroscopic images were analyzed by one endoscopist (JH Yang) to exclude interobserver variability.

Endoscopic findings were classified into four different categories: (1) no atrophy when there was no evidence of atrophy on the endoscopic finding (grade 0), (2) mild atrophy when there was a 'salt and pepper' like atrophic mucosa without permeability of blood vessels (grade 1), (3) moderate atrophy (closed-type atrophic gastritis) when atrophic mucosal change was limited to the antrum showing permeability of blood vessels (grade 2), and (4) severe atrophy (open-type atrophic gastritis) when atrophic mucosal change was extended up to the gastric corpus showing permeability of blood vessels (grade 3) (Fig. 1). Our classification was based on the fact that gastritis can be classified into antral gastritis, corpus gastritis, and pan-gastritis based on the Updated Sydney system and Kimura-Takemoto classification.^{10,11} Moreover, in atrophic gastritis, mucosal and submucosal capillaries and vessels are visible without excessive distention by air because of marked atrophy and thin-

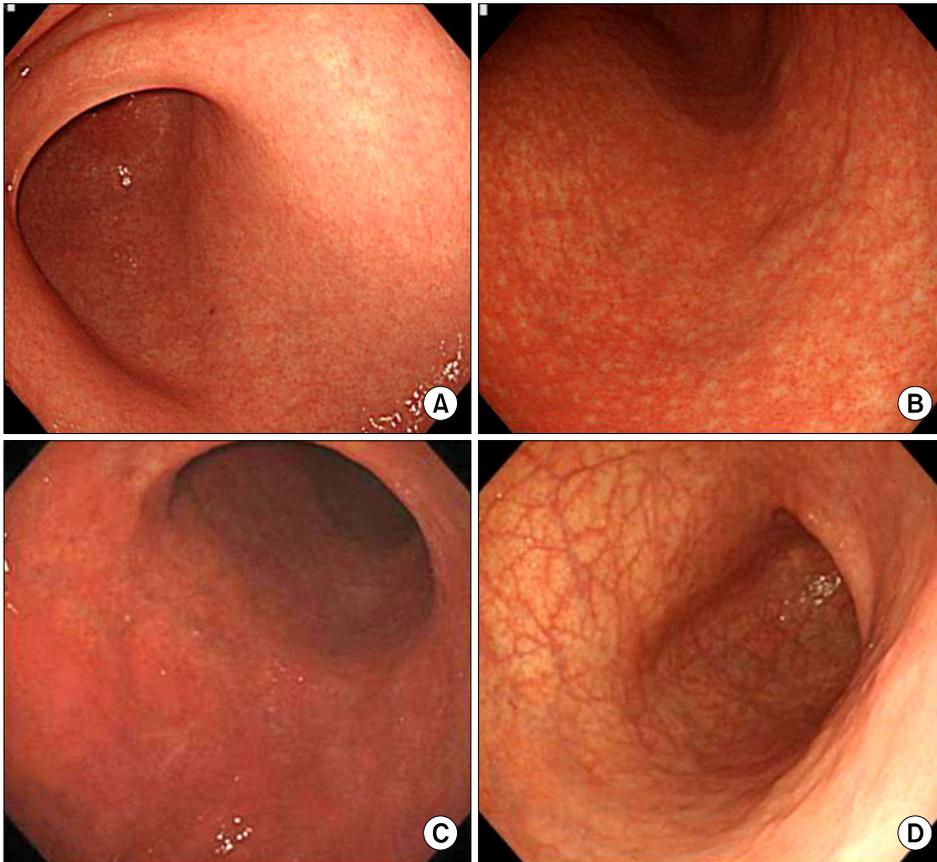


Fig. 1. The degree of atrophic changes on endoscopic findings. (A) No atrophy (grade 0). There is no atrophic change on the endoscopic finding. (B) Mild atrophy (grade 1). Patchy atrophic changes are noticed without transparent vessels. (C) Moderate atrophy (grade 2). Transparent vessels are noticed on the antrum. (D) Severe atrophy (grade 3). Transparent vessels are noticed throughout the antrum and corpus.

ning of mucosa.

5. Statistical analysis

Statistical analyses were done using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). A *P* value less than 0.05 was considered significant. The data were reported as mean±SD for continuous variables and percentage with 95% CI for categorical variables. A multivariate analysis was performed with 5 confounding factors (age, gender, BMI, *H. pylori* antibody and endoscopic findings) to identify clinical correlation with the changes of serum pepsinogen I/II ratio.

RESULTS

1. Demographic data

A total of 63 subjects underwent serum pepsinogen measurement, anti-*H. pylori* IgG test, and gastroscopic examination for two sequential years. Of 63 subjects, three subjects were excluded from the study since two did not visited after a year and one underwent subtotal gastrectomy. In summary, 60 healthy subjects (39 male and 21 female) were eligible for

analysis. The mean age of the total subjects was 54.4±9.1 years, and mean BMI was 24.3±2.6 kg/m². Thirty-nine subjects showed positive anti-*H. pylori* IgG test (39 out of 60, 65%), and the status of *H. pylori* infection did not change after a year in all subjects.

The subjects were divided into two groups based on the changes of the serum pepsinogen I/II ratio after a year; (i) subjects who showed an increased pepsinogen I/II ratio group after a year (n=26) and (ii) subjects who showed a decreased pepsinogen I/II ratio group after a year (n=34). Basal characteristics including age, gender, BMI, *H. pylori* infection, and degree of atrophic gastritis are summarized in Table 1.

2. Differences between the subjects

Decreased pepsinogen I/II ratio group showed higher prevalence of *H. pylori* infection (*P*=0.013) than the increased group. The serum pepsinogen I/II ratio was decreased in 29 subjects (85.3%) who had a moderate to severe degree of chronic atrophic gastritis, while subjects without *H. pylori* infection and those with none to a mild chronic atrophic gastritis showed a tendency to have an increased pepsinogen I/II ratio after a year

Table 1. Basal Characteristics of the Subjects with Increased Serum Pepsinogen I/II Ratio and Decreased Serum Pepsinogen I/II Ratio

	Subjects with increased serum pepsinogen I/II ratio after a year (n=26)	Subjects with decreased serum pepsinogen I/II ratio after a year (n=34)	P value
Age (yr)	53.4±10.0	55.2±8.5	0.446
Gender (male : female)	16 : 10	23 : 11	0.785
Body mass index (kg/m ²)	24.27±2.46	24.31±2.81	0.963
<i>H. pylori</i> infection	12 (46.2)	27 (79.4)	0.013 ^a
Degree of atrophic gastritis			0.004 ^a
No atrophy	3 (11.5)	2 (5.9)	
Mild atrophy	12 (46.2)	3 (8.8)	
Moderate atrophy	5 (19.2)	18 (52.9)	
Severe atrophy	6 (23.1)	11 (32.4)	

Values are presented as mean±SD or n (%).

H. pylori, *Helicobacter pylori*.

^aStatistically significant.

▲ Subject who showed increased PG I/II ratio after a year
 ▽ Subject who showed decreased PG I/II ratio after a year

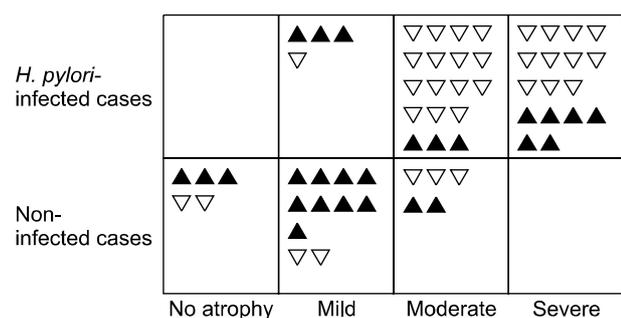


Fig. 2. The distribution of subjects according to the status of *Helicobacter pylori* (*H. pylori*) infection, endoscopic findings and serum pepsinogen (PG) I/II ratio. Black arrows indicate subjects who showed increased serum pepsinogen I/II ratio after a year, whereas white arrows indicate subjects who showed decreased serum pepsinogen I/II ratio. Once the endoscopic finding reveals a moderate to severe degree of atrophic gastritis, the serum pepsinogen I/II ratio had a tendency to decrease regardless of the status of *H. pylori* infection.

(*P*=0.004). Fig. 2 shows the distribution of altered pepsinogen I/II ratio according to the status of the *H. pylori* infection and the degree of atrophic gastritis. Most subjects who showed decreased pepsinogen I/II ratio were either those who had *H. pylori* infection or those who showed a moderate to severe atrophic gastritis on initial endoscopic finding.

3. Relationship between age, gender, BMI and serum pepsinogen levels

A multivariate analysis showed that the degree of chronic

Table 2. Multivariate Analysis on Factors That Are Related to Decreased Serum Pepsinogen I/II Ratio after a Year

	Multivariate OR (95% CI)	P value
Sex (male)	1.295 (0.310 ~ 5.418)	0.722
<i>Helicobacter pylori</i> infection (positive)	1.723 (0.411 ~ 7.225)	0.464
BMI (≥24 kg/m ²)	0.960 (0.258 ~ 3.578)	0.952
Atrophic gastritis (≥moderate degree)	5.385 (1.217 ~ 23.829) ^a	0.023 ^a
Age (≥55 yr)	1.318 (0.384 ~ 4.525)	0.662

^aStatistically significant.

atrophic gastritis was the only factor that was related to the changes of the serum pepsinogen I/II ratio (OR=5.385, *P*=0.023) (Table 2). Age, gender, and BMI were not correlated with decreased or increased serum pepsinogen I/II ratios after a year. The serum pepsinogen I/II ratio was decreased in subjects with a moderate to severe degree of atrophic gastritis after a year regardless of the status of *H. pylori* infection.

DISCUSSION

To the best of our knowledge, this is the first study to show the significance of endoscopically diagnosed atrophic gastritis on changing trends of the serum pepsinogen I/II ratio. Interestingly, our results show the changes were significantly related to the grade of atrophic gastritis on endoscopic findings regardless of the status of current *H. pylori* infection. The serum pepsinogen I/II ratio had a tendency to decrease in subjects

with moderate to severe atrophic gastritis, but not in those with none to mild atrophic gastritis. Our findings suggest that the most significant factor for predicting the risk of gastric carcinogenesis is the degree of atrophic gastritis diagnosed by endoscopic examination rather than the current status of *H. pylori* infection.

As the atrophic changes are induced by *H. pylori*-associated inflammation, one can assume that the serum pepsinogen I/II ratio will show a tendency to decrease. Notably, if the changes are prior to the “point of no return”, the serum pepsinogen I/II ratio may increase since there is still a chance of reversibility. Conversely, when the changes are ahead of the “point of no return”, the serum pepsinogen I/II ratio will continue to decrease due to its irreversibility. Although several studies have shown the significance of the serum pepsinogen I/II ratio,^{6,8,12-24} none of these showed the changing trends of its ratio in asymptomatic subjects according to the degree of endoscopic atrophic gastritis without any medical alterations. Interestingly, our study showed that the serum pepsinogen I/II ratio of the subjects with moderate to severe atrophic gastritis will continue to decline regardless of other confounding factors such as age, gender, BMI, and the *H. pylori* infection. Taken as a whole, gastric atrophy was not merely aggravated by the *H. pylori* infection itself, but continued to progress according to the degree of atrophic gastritis regardless of the current status of the *H. pylori* infection. Our results strongly suggest that moderate to severe atrophic gastritis are beyond the “point of no return”, since these subjects showed a decrease in the serum pepsinogen I/II ratio after a year.

The serum pepsinogen I/II ratio is closely correlated with the presence of histological atrophy and intestinal metaplasia,^{5,8,12,14} and there is great interest in determining at which point the disease will progress to the “point of no return” becoming irreversible in a stepwise model of change in the gastric mucosa once the *H. pylori* infection has led to intestinal-type gastric cancer. In our previous study,²⁵ we suggested that the risk of developing intestinal-type gastric cancer would continue to remain high during the process of gastric carcinogenesis in open-type chronic atrophic gastritis and metaplastic gastritis, but not in closed-type chronic atrophic gastritis and nonatrophic/nonmetaplastic cases. The significance of the location of the atrophic gastric border was also emphasized by a study of open-type chronic atrophic gastritis diagnosed by autofluorescence imaging.²⁶ In their study, extensive atrophic fundic gastritis was the only sig-

nificant predictor for the development of metachronous early gastric cancers. These findings that showed the significance of extensive chronic atrophic gastritis on cancer development are consistent with our current study that show a decreased serum pepsinogen I/II ratio in moderately to severe atrophic gastritis.^{25,26} When taking into account that serum pepsinogen I/II continued to decrease in moderate to severe atrophic gastritis, but not in none to mild atrophic gastritis, the identification of the so-called “point of no return” might be somewhere between mild and moderate to severe atrophic gastritis.

In this study, we have investigated two consecutive years of data of endoscopic findings in order to detect the changing trends of serum pepsinogen I/II ratio according to the degree of atrophic gastritis. Since the subjects did not receive any medical treatment, most of the subjects showed similar degrees of atrophic gastritis after a year. The degree of atrophic gastritis worsened only in a small proportion of the subjects (6 out of 60, 10.0%). The advantages of this study are that: (i) serum pepsinogen I/II ratios were checked in symptomatic adults for two sequential years using the same method, (ii) none of the subjects had a remarkable disease that required notable medical treatment during the follow-up period, thus, the natural course of serum pepsinogen levels were measured without bias, (iii) the status of *H. pylori* infection was exactly identical in every subject for two years, (iv) BMI was similar in all subjects showing changes of less than 10% during a one-year interval, and (v) endoscopic findings with regard to atrophic gastritis were analyzed with the serum pepsinogen I/II ratio on the same day, and were compared by the same person, at the same center, using the same method.

We also analyzed possible confounding factors that might be related to serum pepsinogen levels as suggested by previous studies.^{18,19} Notably, most of the previous studies are focused on the *H. pylori* infection with regard to the changes in the serum pepsinogen I/II ratio.^{7,27-30} A study even showed that a repeated examination of the serum pepsinogen level is not required in *H. pylori*-negative subjects.³¹ In their study, the serum pepsinogen status altered naturally in 16% of individuals during a nine-year follow-up which had a similar finding with our study. However, in their study, seroconversion to a serum pepsinogen positive state (serum pepsinogen I \leq 50 ng/mL and serum pepsinogen I/II ratio \leq 3) from a negative state was induced by active gastritis after the *H. pylori* infection, and the serum pepsinogen state did not alter in subjects without *H. pylori* be-

yond the initial nine years. Another study reported that the *H. pylori* infection, age and sex were associated with serum pepsinogen I, but not with serum pepsinogen II or pepsinogen I/II ratio.²⁰ Similarly, age, sex, and BMI were not significant factors in our study. The sole independent and significant factor for predicting the changing trends of serum pepsinogen I/II ratio was atrophic gastritis regardless of the current status of the *H. pylori* infection.

The limitation of our study is that we did not perform gastric biopsy during serial endoscopic examinations to confirm the degree of chronic atrophic gastritis. Despite the limitation, we could find that there is a decreasing tendency of serum pepsinogen I/II ratio among the moderate to severe atrophic gastritis after a year.

In conclusion, the degree of chronic atrophic gastritis on gastroscopy can predict the changing trends of the serum pepsinogen I/II ratio. The serum pepsinogen I/II ratio decreases in asymptomatic subjects with a moderate to severe degree of chronic atrophic gastritis, whereas it might increase in those with none to a mild degree of chronic atrophic gastritis. This indicates that care should be taken in subjects with a moderate to severe degree of atrophic gastritis since they suggest a higher risk of gastric carcinogenesis regardless of the current status of the *H. pylori* infection.

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