ORIGINAL ARTICLE

Korean J Intern Med 2020;35:550-558
https://doi.org/10.3904/kjim.2018.282

Clinical correlation between serum pepsinogen level and gastric atrophy in gastric neoplasm

Jae Hwang Cha and Jin Seok Jang

Department of Internal Medicine, Dong-A University College of Medicine, Busan, Korea

Received: July 31, 2018
Revised : September 12, 2018
Accepted: October 1, 2018

Correspondence to
Jin Seok Jang, M.D.
Department of Internal Medicine, Dong-A University Medical Center, 26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea
Tel: +82-51-240-2609
Fax: +82-51-253-2087
E-mail: jsjang@dau.ac.kr

Background/Aims: The relationship between the serum pepsinogen (sPG) level and changes in gastric mucosa has been well studied. Here, we evaluated the usefulness of sPG (I, II, I/II ratio) and intragastric pH as a biomarker of severe gastric atrophy in gastric neoplastic lesions.

Methods: A total of 186 consecutive Korean patients with gastric neoplastic lesions underwent endoscopic submucosal dissection (ESD) in this study. The serologic atrophy group had sPG I level ≤ 70 ng/mL and an sPG I/II ratio ≤ 3.0. Before ESD, overnight fasting venous blood and gastric juice samples were collected to measure the sPG level and intragastric pH. The degree of gastric atrophy was estimated by endoscopy, and the rapid urease test was performed to investigate *Helicobacter pylori* infection.

Results: Patients who met the criteria of serologic atrophy showed more severe endoscopic atrophic changes (61% vs. 18%, $p = 0.000$). Older patients and those with more atrophic changes at the gastric upper body demonstrated both a lower sPG I level and a lower PG I/II ratio and more severe endoscopic atrophy. The sPG I/II ratio was the lowest in low grade dysplasia than in high grade dysplasia and early gastric cancer (EGC) ($p = 0.015$). In addition, patients who tested negative for serologic atrophy and *H. pylori* showed the lowest intragastric pH ($p = 0.000$).

Conclusions: A low sPG I level and a low I/II ratio were correlated with the severity of gastric atrophy in gastric neoplastic lesions, thus indicating it to be a sensitive biomarker of gastric precancerous lesions or EGC.

Keywords: Pepsinogens; Stomach neoplasms; Gastric mucosa; Atrophy

INTRODUCTION

Recently, serum pepsinogen I (sPG I) and PG II (sPG II), serum gastrin-17 (sG-17), and immunoglobulin G anti-*Helicobacter pylori* antibodies were proposed as non-invasive markers to assess the status of the gastric mucosa in patients with dyspeptic symptoms [1,2]. Both pepsinogen I (PG I) and PG II are precursors of pepsin. PG II is produced by all gastric glands (namely, oxyntic, cardiac, and pyloric) as well as duodenal (Brunner's) glands, but PG I is secreted exclusively by oxyntic glands, which reflects its corpus secretion capacity [3]. Previous studies have shown that the sPG I level and/or I/II ratio reflect the morphological [4,5] and functional status of the gastric mucosa [6-8]. Several studies have reported the relationship between the sPG level and gastric mucosal changes [9,10]. Measuring the sPG I and sPG II levels offered a non-invasive and straightforward means of mass screening for gastric cancer in Japan when compared with endoscopy [11,12]. Moreover, recent studies have reported that advanced gastric atrophy is associated with high-fasting intragastric pH [13,14].

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

As in Japan, the prevalence of *H. pylori* (59.6% among adults aged ≥ 16 years in 2005) is high in Korea [15], but the efficacy of the sPG level and intragastric pH as a non-invasive marker for gastric atrophy in neoplastic lesions remains to be evaluated in Korea.

This study determined whether the sPG level and intragastric pH are related with the existence of gastric atrophy in gastric neoplastic lesions before endoscopic submucosal dissection (ESD). In addition, the relationships among the clinicopathological characteristics of gastric neoplasm, age, and sPG level in patients with gastric atrophy were investigated.

METHODS

Patients

A total of 186 consecutive patients who underwent ESD (120 men; mean age, 63.3 ± 9.0 years) for gastric neoplastic lesions (low grade dysplasia [LGD], high grade dysplasia [HGD], and early gastric cancer [EGC]) in our institution from April 2010 to September 2011 were enrolled in this study. Overnight fasting venous blood and gastric juice samples were collected from the subjects before ESD to measure the sPG level and intragastric pH. Immediately after the endoscope was inserted into the stomach, 5 to 10 mL of gastric juice was aspirated through the suction channel of the endoscope and collected in a trap placed in the suction line. The pH content of the gastric juice was measured immediately after collection. Gastric acid was measured using a set of pH test papers (Toyo Roshi Kaisha, Tokyo, Japan), which consisted of two-step indicators: one test paper indicated pH with a sensitivity of 1 (1 to 11) and the second with a sensitivity of 0.2 for the order of 0.1. The degree of gastric atrophy was estimated endoscopically, and the rapid urease test (Campylobacter-like organism [CLO]) was performed to investigate the status of *H. pylori* infection.

The exclusion criteria included (1) taking any drug inhibiting gastric acid secretion (within 4 weeks), (2) a history of gastrectomy, (3) major organ failure, and (4) a history of drug allergy.

Serum PG levels

The overnight fasting serum samples were centrifuged, and both sPG I and sPG II levels were determined. Serologic gastric atrophy was defined as sPG I ≤ 70 ng/mL and sPG I/II ratio ≤ 3.0, as described in a previous study [16]. In addition, based on their sPG I level and sPG I/II ratio, the patients were classified into three groups: (1) PG 3+: sPG I ≤ 30 ng/mL and sPG I/II ratio ≤ 2.0; (2) PG 2+: sPG I ≤ 50 ng/mL and sPG I/II ratio ≤ 3.0, but not meeting the criteria for PG index 3+; and (3) PG 1+: not meeting the criteria for PG index 2+ or 3+.

Endoscopic examination

ESD was performed on the same day of blood sampling by an experienced endoscopist at our center. A gastric neoplasm was defined as EGC or adenoma with either LGD or HGD, based on the World Health Organization classification. The extent of atrophic mucosa was expressed in accordance with the Kimura-Takemoto classification of the atrophic pattern. Then, according to the endoscopic findings and the matched Kimura-Takemoto classification of the atrophic pattern, all patients were classified into three groups: (1) normal group—without atrophic change in any area; (2) mild group—closed-type atrophic pattern; and (3) severe group—open-type atrophic pattern.

All patients underwent the CLO test with biopsy samples.

Ethics approval

All procedures in the study that involved human participants were performed in accordance with the ethical standards of the Institutional Review Board of the Dong-A University Hospital (DAUHIRB-10-129) and in agreement with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients before the study.

RESULTS

Characteristics of the patients

A total of 186 patients (120 men, 64.5%) of an average age of 63.3 ± 9.0 years were analyzed. The pathology of gastric neoplasm was found to be compatible with tubular adenoma with LGD in 82 (44.1%), HGD in 37 (19.9%), and EGC in 67 patients (36%). Using histology and the CLO test, *H. pylori* infection was detected in 58 of the 186

patients (31.2%). Based on the results of endoscopic examination and the Kimura-Takemoto classification of atrophic patterns, the patients were classified into three categories: 0 case of non-atrophic gastritis (0%), 49 cases of mild atrophy (26%), and 137 cases of severe atrophy (74%).

Table 1 summarizes the patient characteristics, including the pathology of their gastric neoplasm, *H. pylori* infection status, degree of gastric atrophy, and the mean value of sPG and intragastric pH. The sPG level and intragastric pH are also described.

Table 1. The clinical and pathological characteristics of the patients (n = 186)

Characteristic	Value
Age, yr	63.3 ± 9.0
Sex	
Male	120 (64.5)
Female	66 (35.5)
Pathology of gastric neoplasm	
LGD	82 (44.1)
HGD	37 (19.9)
EGC	67 (36)
Helicobacter pylori infection status	
Present	58 (31.2)
Absent	128 (68.6)
Degree of atrophy	
Normal	0
Mild	49 (26)
Severe	137 (74)
Serum level, ng/mL	
sPG I	55.1 ± 44.1
1+	58.6 ± 7.6
2+	30.1 ± 10.6
3+	15.9 ± 6.7
sPG II	18.1 ± 12.8
sPG I/II ratio	3.2 ± 1.8
1+	2.6 ± 0.5
2+	2.4 ± 0.4
3+	1.3 ± 0.4
Intragastric pH	6.2 ± 1.2

Values are presented as mean ± SD or number (%).
LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; sPG, serum pepsinogen.

Clinical characteristics according to endoscopic atrophy

Considering that there was no non-atrophic gastritis patient, the 186 patients were divided into two groups according to their degree of endoscopic atrophy (mild or severe). The characteristics of each group are described in Table 2.

The mean age in the severe atrophy patient group (64.1 ± 9.0 years) was higher than that in the mild atrophy patient group (61.1 ± 8.4 years) ($p = 0.04$). In addition, patients who matched the criteria of serologic atrophy were more common in the severe atrophy group (61%) than in the mild atrophy group (18%) ($p = 0.000$). Patients with severe atrophy had a lower sPG I level (46.7 ± 37.4 vs. 78.6 ± 52.6) and a lower sPG I/II ratio (2.9 ± 1.6 vs. 4.2 ± 1.8) than those with mild atrophy ($p = 0.000$), although their sPG II level was comparable ($p = 0.058$).

Clinical characteristics according to *H. pylori* and serologic atrophy

All enrolled patients were divided into the serologic atrophy group (n = 92) and serologic non-atrophy group (n = 94) by criteria; both groups were further divided into two subgroups based on the presence of *H. pylori* infection: serologic atrophy (+)/*H. pylori* (+); serologic atrophy (+)/*H. pylori* (–); serologic atrophy (–)/*H. pylori* (+); and serologic atrophy (–)/*H. pylori* (–).

Severe endoscopic atrophy type was more common in the serologic atrophy group than in the serologic non-atrophic group, irrespective of the *H. pylori* infection status, although the difference was not statistically significant.

The mean sPG I/II ratio was the highest in the serologic atrophy (–)/*H. pylori* (–) group (4.8 ± 1.8) and the lowest in the serologic atrophy (+)/*H. pylori* (–) group (2.0 ± 0.7).

Intragastric pH was the lowest in the serologic atrophy (–)/*H. pylori* (–) group (5.8 ± 1.4) and > 6 in the other groups.

Table 3 describes the clinical characteristics of the patients according to their serologic atrophy and *H. pylori* infection status.

Characteristics according to gastric neoplasm pathology

No significant difference was noted in the degree of endoscopic atrophy in the three groups: LGD, HGD, and

https://doi.org/10.3904/kjim.2018.282

Table 2. Clinical characteristics according to endoscopic atrophy

Characteristic	Mild atrophy (n = 49)	Severe atrophy (n = 137)	*p* value
Age, yr	61.1 ± 8.4	64.1 ± 9.0	0.040
Sex			0.226
Male	28 (57.1)	92 (67.1)	
Female	21 (42.9)	45 (32.6)	
Pathology of gastric neoplasm			0.885
LGD	21 (42.9)	61 (44.5)	
HGD	11 (22.4)	26 (19.0)	
EGC	17 (34.7)	50 (36.5)	
Helicobacter pylori infection status			0.370
Present	18 (36.7)	40 (29.2)	
Absent	31 (63.3)	97 (70.8)	
Location			0.925
Upper	9 (18.4)	26 (19.05)	
Lower	40 (81.6)	111 (81.0)	
Serological atrophy			0.000
Positive	9 (18)	83 (61)	
Negative	40 (82)	54 (39)	
Serum level, ng/mL			
sPG I	78.6 ± 52.6	46.7 ± 37.4	0.000
sPG II	21.1 ± 15.3	17.1 ± 11.6	0.058
sPG I/II ratio	4.2 ± 1.8	2.9 ± 1.6	0.000
Intragastric pH	6.1 ± 1.2	6.3 ± 1.2	0.332

Values are presented as mean ± SD or number (%).
LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; sPG, serum pepsinogen.

EGC. However, the sPG I/II ratio was significantly lower in the LGD and HGD groups than in the EGC group; it showed the lowest value in the LGD group (Table 4) (p = 0.015).

Subgroup analysis of serological atrophy group

We sub-analyzed several characteristics, including the mean age, *H. pylori* infection status, location of atrophic lesions, and sPG level, for the serologic atrophy group, which was again divided into three groups according to the PG index (Table 5). As the PG index increased from 1+ to 3+, the mean age of the patients and the percentage of the upper (proximal) gastric atrophy lesion were significantly increased in a stepwise manner (p = 0.000, p = 0.020, each, respectively).

DISCUSSION

Gastric cancer is one of the major cancers in the world, especially in East Asian countries such as Korea and Japan. The incidence and mortality of gastric cancer have decreased in several regions, including Korea, owing to advancements in diagnosis and treatment. However, with the rapid aging of the population, the absolute numbers of new cases and deaths from gastric cancer are expected to increase [17].

Correa's hypothesis that "the intestinal type of gastric cancer develops from chronic inflammation leading to atrophic gastritis, intestinal metaplasia, dysplasia and cancer" has been widely accepted, and this pathogenesis may be caused by *H. pylori* infection [18]. A previous study revealed that chronic atrophic gastritis carries an 18-fold increased risk of gastric cancer in antral-predominant

Table 3. Clinical characteristics according to *Helicobacter pylori* and serologic atrophy status

Characteristic	Serologic atrophy group (n = 92)		Serologic non-atrophy group (n = 94)	
	H. pylori (+) (n = 27)	*H. pylori* (–) (n = 65)	*H. pylori* (+) (n = 31)	*H. pylori* (–) (n = 63)
Age, yr	59.7 ± 10.0	65.4 ± 8.3	59.0 ± 8.3	65.0 ± 8.4
Sex, male:female	15:12	46:19	15:16	44:19
Pathology				
LGD	13	31	17	21
HGD	8	12	6	11
EGC	6	22	8	31
Degree of atrophy				
Mild	9 (9.8)		40 (42.6)	
	4 (14.8)	5 (7.7)	14 (45.2)	26 (41.3)
Severe	83 (90.2)		54 (57.4)	
	23 (85.2)	60 (92.3)	17 (54.8)	37 (58.7)
Serum level, ng/mL				
sPG I	38.6 ± 18.7	30.0 ± 18.5	95.3 ± 49.4	68.6 ± 48.3
sPG II	18.1 ± 5.8	14.6 ± 8.0	28.9 ± 16.9	16.5 ± 13.9
sPG I/II ratio	2.1 ± 0.6	2.0 ± 0.7	3.6 ± 1.3	4.8 ± 1.8
Intragastric pH	6.4 ± 0.6	6.5 ± 0.9	6.3 ± 1.4	5.8 ± 1.4

Values are presented as mean ± SD or number (%).
LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; sPG, serum pepsinogen.

atrophic gastritis and a 4.6-fold risk in corpus atrophic gastritis [19]. Currently, gastric cancer and atrophic gastritis are screened and diagnosed mainly by endoscopy and biopsy. However, due to the associated discomfort and cost-effectiveness, several non-invasive tests have recently been proposed as alternatives. As the severity of atrophic gastritis increases, normal gland function is lost and enzyme production is affected. Therefore, sPG produced by the gastric mucosa has been found to act as a marker of gastric mucosal status [4-8], and a low sPG I level and a low PG I/II ratio have been associated with severe gastric atrophy [4,5,20].

As the oxyntic gland's atrophy progresses, the sPG I level decreases. In addition, when pyloric gland metaplasia of the proximal stomach occurs, the sPG II level increases. However, in severe atrophic gastritis, the sPG II level generally decreases to normal. Thus, the levels of sPG I and sPG II and the sPG I/II ratio reflect the morphological and functional status of the gastric mucosa. Based on several previous studies, a low sPG I level and a low sPG I/II ratio are reliable biomarkers for atrophic gastritis of the gastric fundus and are related with the severity of atrophy [4,21].

Although various cut-off values have been suggested for atrophic gastritis and gastric cancer, a sPG I level ≤ 70 ng/mL and a sPG I/II ratio ≤ 3 have frequently been used with a sensitivity of 73.2% to 84.6% and a specificity of 70% to 73.5%, respectively [11,22-24]. In the present study, we also defined serologic gastric atrophy as a sPG I level ≤ 70 ng/mL and a sPG I/II ratio ≤ 3. Patients who matched this criteria of serologic atrophy were more common in the severe atrophy group (61%) than in the mild atrophy group (18%) (p = 0.000). In addition, patients with severe atrophy showed a lower serum level of sPG I and a lower sPG I/II ratio than those with mild atrophy (p = 0.000). The mean sPG II level decreased slightly in the severe atrophy group than in the mild atrophy group, although the levels were comparable (17.1 ± 11.6 vs. 21.1 ± 15.3, respectively; p = 0.058). These results revealed the same tendency as reported by previous studies.

In addition, older patients and those with more atrophic changes at the upper gastric body (atrophic lesions located in the upper region) demonstrated a lower sPG

https://doi.org/10.3904/kjim.2018.282

Table 4. Characteristics according to gastric neoplasm pathology

Characteristic	Total (n = 186)	LGD (n = 82)	HGD (n = 37)	EGC (n = 67)	*p* value
Endoscopic atrophy					0.885
Mild	49 (26.3)	21 (25.6)	11 (25.4)	17 (29.7)	
Severe	137 (73.7)	61 (74.4)	26 (74.6)	50 (70.3)	
Serological atrophy					0.311
Positive	92	44	20	28	
Negative	94	38	17	39	
PG index					0.087
PG 1+	24	7	5	12	
PG 2+	34	17	6	11	
PG 3+	34	20	9	5	
Serum level, ng/mL					
sPG I	55.1 ± 44.1	50.1 ± 43.4	50.4 ± 42.2	63.8 ± 45.3	0.132
sPG II	18.1 ± 12.8	17.9 ± 13.6	17.0 ± 12.5	19.1 ± 12.0	0.715
sPG I/II ratio	3.2 ± 1.8	2.9 ± 1.7	3.2 ± 1.6	3.7 ± 1.8	0.015
Intragastric pH	6.1 ± 1.2	6.3 ± 1.2	6.4 ± 1.0	6.1 ± 1.3	0.302

Values are presented as number (%) or mean ± SD.
LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; PG, pepsinogen; sPG, serum pepsinogen.

I level and a lower sPG I/II ratio, but more severe endoscopic atrophy. In these patients, serologic and endoscopic atrophy was more severe.

Using histology and the CLO test, *H. pylori* infection was detected in 58 of 186 patients (31.2%), with 18 patients (36.7%) showing mild atrophy and 40 (29.2%) showing severe atrophy. However, these results do not suggest a lesser association between *H. pylori* infection and gastric atrophy. Although the CLO test has a high sensitivity and specificity of 85% to 97% and 92%, respectively, it also has the possibility of a false negative result in atrophic gastritis or intestinal metaplasia due to uneven mucosal distribution of the bacteria [25,26]. Moreover, in the advanced stage of the disease, due to disease-related clearance of the infection, there is a possibility of underestimating *H. pylori* infection [27].

Kikuchi et al. [28] observed a lower level of sPG I and a lower sPG I/II ratio in the *H. pylori*-positive group. Ito et al. [29] reported improvements in gastric atrophy and intestinal metaplasia and increases in the sPG I level and in the sPG I/II ratio after *H. pylori* eradication in patients with atrophic gastritis, as explained by the pathophysiology of *H. pylori* infection. In a past study, a polypeptide secreted by *H. pylori* stimulated the chief cells directly and promoted the synthesis and secretion of pepsinogens, mainly PG II [30]. However, long-term persistent infection may cause PG gene mutation and glandular cell damage, which may result in corpus atrophy, decrease in the capability of PG I secretion, and increased gastric pH. PG II is secreted extensively, including in the metaplastic pyloric gland. Therefore, the sPG II level is almost constant and the sPG I/II ratio is correspondingly decreased [3-7]. In the present study, the mean sPG I/II ratio was the highest in the serologic atrophy (–)/*H. pylori* (–) group (4.8 ± 1.8) and the lowest in the serologic atrophy (+)/*H. pylori* (–) group (2.0 ± 0.7). Furthermore, severe endoscopic atrophy type was more common in the serologic atrophy group than in the serologic non-atrophy group, irrespective of *H. pylori* infection, although the difference was not statistically significant.

In our study, gastric neoplastic lesions were classified into LGD, HGD, and EGC by our endoscopic pathology findings. The value of the sPG I/II ratio was the lowest in the LGD group than in the HGD and EGC groups (p = 0.015). Chang et al. [31] reported that the sPG I/II ratio was significantly lower in patients with LGD than in those with functional dyspepsia and that the ratio was not further decreased in patients with HGD, EGC, and

Table 5. Subgroup analysis of serological atrophy group

Characteristic	Serologic atrophy group (n = 92)			
	PG 1+ (n = 24)	PG 2+ (n = 34)	PG 3+ (n = 34)	*p* value
Age, yr	58.3 ± 8.5	63.2 ± 8.6	68.0 ± 8.2	0.000
Sex, male:female	15:9	26:8	20:14	0.303
Pathology of gastric neoplasm				0.059
LGD	7 (29.2)	17 (50)	20 (58.8)	
HGD	5 (20.8)	6 (17.6)	9 (26.5)	
EGC	17 (34.7)	50 (36.5)	5 (14.7)	
Helicobacter pylori infection				0.035
Present	11 (45.8)	5 (14.7)	11 (32.4)	
Absent	13 (54.2)	29 (85.3)	23 (67.6)	
Location				0.020
Upper	1 (4.2)	7 (20.6)	10 (29.4)	
Lower	23 (95.8)	27 (79.4)	24 (70.6)	
Endoscopic atrophy				0.088
Mild	5 (20.8)	1 (2.9)	3 (8.8)	
Severe	19 (79.2)	33 (97.1)	31 (91.2)	
Serum level, ng/mL				
sPG I	58.6 ± 7.6	30.1 ± 10.6	15.9 ± 6.7	0.000
sPG II	24.2 ± 7.7	13.0 ± 5.9	12.1 ± 4.1	0.000
sPG I/II ratio	2.6 ± 0.5	2.4 ± 0.4	1.3 ± 0.5	0.000
Intragastric pH	6.3 ± 0.1	6.7 ± 0.8	6.4 ± 1.0	0.137

Values are presented as mean ± SD or number (%).
PG, pepsinogen; LGD, low grade dysplasia; HGD, high grade dysplasia; EGC, early gastric cancer; sPG, serum pepsinogen

AGC. These results of severe serologic atrophy in LGD comprehensively imply that LGD can be considered as a serious precancerous lesion that rationalizes the endoscopic resection of the lesion.

There are several limitations in our study. First, it was conducted at a single center and included a small sample size. Second, as we conducted the survey of patients with precancerous lesions and EGC before ESD, no normal control group or advanced gastric cancer group existed in our study. Third, we defined "serologic atrophy" using cut-off values of sPG I level ≤ 70 ng/mL and the sPG I/II ratio ≤ 3.0 with high sensitivity and specificity, respectively, based on previous studies. However, these cut-off values may not be suitable in Korea, because they may vary with regard to ethnicity, diet, environment, and disease epidemiology, thus necessitating further studies on the appropriate sPG cut-off value for gastric atrophy among Korean patients. Forth, the serum *H. pylori* antibody status was not evaluated in this study.

In conclusion, a low sPG I level and a low sPG I/II ratio are closely related to the severity of gastric atrophy and dysplasia, but intragastric pH was not relevant. The age and location of atrophic lesions are related to the severity of gastric atrophy. We concluded that the sPG test is useful as a marker of gastric precancerous lesions and EGC; therefore, it is helpful not only in diagnosing a benign disease status with a high malignancy risk or early stage of gastric malignancy but also in improving the patient's compliance and cost-effectiveness of screening. This test may also help in the primary selection of high-risk patients with premalignant gastric lesions who need endoscopic examination and biopsy.

https://doi.org/10.3904/kjim.2018.282

KEY MESSAGE

1. A low serum pepsinogen I level and a low I/II ratio were correlated with the severity of gastric atrophy in gastric neoplastic lesions.
2. This study showed that serum pepsinogen test is useful as a marker of gastric precancerous lesion and early gastric cancer.
3. It is helpful to not only diagnose at benign disease status with high malignancy risk or early stage of gastric malignancy, but also improve patient's compliance.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This study was supported by Dong- A university fund 2018.

REFERENCES

1. Oksanen A, Sipponen P, Miettinen A, Sarna S, Rautelin H. Evaluation of blood tests to predict normal gastric mucosa. Scand J Gastroenterol 2000;35:791-795.
2. Korstanje A, den Hartog G, Biemond I, Lamers CB. The serological gastric biopsy: a non-endoscopical diagnostic approach in management of the dyspeptic patient: significance for primary care based on a survey of the literature. Scand J Gastroenterol Suppl 2002;236:22-26.
3. Foltmann B. Gastric proteinases: structure, function, evolution and mechanism of action. Essays Biochem 1981;17:52-84.
4. Samloff IM, Varis K, Ihamaki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology: a study in relatives of patients with pernicious anemia. Gastroenterology 1982;83(1 Pt 2):204-209.
5. Borch K, Axelsson CK, Halgreen H, Damkjaer Nielsen MD, Ledin T, Szesci PB. The ratio of pepsinogen A to pepsinogen C: a sensitive test for atrophic gastritis. Scand J Gastroenterol 1989;24:870-876.
6. Vaananen H, Vauhkonen M, Helske T, et al. Non-endoscopic diagnosis of atrophic gastritis with a blood test: correlation between gastric histology and serum levels of gastrin-17 and pepsinogen I: a multicentre study. Eur J Gastroenterol Hepatol 2003;15:885-891.
7. Samloff IM, Secrist DM, Passaro E Jr. A study of the relationship between serum group I pepsinogen levels and gastric acid secretion. Gastroenterology 1975;69:1196-1200.
8. Feldman M, Richardson CT, Lam SK, Samloff IM. Comparison of gastric acid secretion rates and serum pepsinogen I and II concentrations in occidental and oriental duodenal ulcer patients. Gastroenterology 1988;95:630-635.
9. Miki K, Ichinose M, Shimizu A, et al. Serum pepsinogens as a screening test of extensive chronic gastritis. Gastroenterol Jpn 1987;22:133-141.
10. Iijima K, Abe Y, Kikuchi R, et al. Serum biomarker tests are useful in delineating between patients with gastric atrophy and normal, healthy stomach. World J Gastroenterol 2009;15:853-859.
11. Miki K. Gastric cancer screening using the serum pepsinogen test method. Gastric Cancer 2006;9:245-253.
12. Kitahara F, Kobayashi K, Sato T, Kojima Y, Araki T, Fujino MA. Accuracy of screening for gastric cancer using serum pepsinogen concentrations. Gut 1999;44:693-697.
13. Ruiz B, Correa P, Fontham ET, Ramakrishnan T. Antral atrophy, Helicobacter pylori colonization, and gastric pH. Am J Clin Pathol 1996;105:96-101.
14. Jaskiewicz K, Van Helden PD, Wiid IJ, Steenkamp HJ, Van Wyk MJ. Chronic atrophic gastritis, gastric pH, nitrites and micronutrient levels in a population at risk for gastric carcinoma. Anticancer Res 1990;10:833-836.
15. Yim JY, Kim N, Choi SH, et al. Seroprevalence of Helicobacter pylori in South Korea. Helicobacter 2007;12:333-340.
16. Kang JM, Kim N, Yoo JY, et al. The role of serum pepsinogen and gastrin test for the detection of gastric cancer in Korea. Helicobacter 2008;13:146-156.
17. Jung KW, Park S, Won YJ, et al. Prediction of cancer incidence and mortality in Korea, 2011. Cancer Res Treat 2011;43:12-18.
18. Namekata T, Miki K, Kimmey M, et al. Chronic atrophic gastritis and Helicobacter pylori infection among Japanese Americans in Seattle. Am J Epidemiol 2000;151:820-830.
19. Sipponen P, Kekki M, Haapakoski J, Ihamaki T, Siurala M. Gastric cancer risk in chronic atrophic gastritis: statistical calculations of cross-sectional data. Int J Cancer

1985;35:173-177.
20. Yamada S, Matsuhisa T, Makonkawkeyoon L, Chaidatch S, Kato S, Matsukura N. Helicobacter pylori infection in combination with the serum pepsinogen I/II ratio and interleukin-1beta-511 polymorphisms are independent risk factors for gastric cancer in Thais. J Gastroenterol 2006;41:1169-1177.
21. Sitas F, Smallwood R, Jewell D, et al. Serum anti-Helicobacter pylori IgG antibodies and pepsinogens A and C as serological markers of chronic atrophic gastritis. Cancer Epidemiol Biomarkers Prev 1993;2:119-123.
22. Yoshihara M, Sumii K, Haruma K, et al. Correlation of ratio of serum pepsinogen I and II with prevalence of gastric cancer and adenoma in Japanese subjects. Am J Gastroenterol 1998;93:1090-1096.
23. Hattori Y, Tashiro H, Kawamoto T, Kodama Y. Sensitivity and specificity of mass screening for gastric cancer using the measurement of serum pepsinogens. Jpn J Cancer Res 1995;86:1210-1215.
24. Dinis-Ribeiro M, Yamaki G, Miki K, Costa-Pereira A, Matsukawa M, Kurihara M. Meta-analysis on the validity of pepsinogen test for gastric carcinoma, dysplasia or chronic atrophic gastritis screening. J Med Screen 2004;11:141-147.
25. Yoo JY, Kim N, Park YS, et al. Detection rate of Helicobacter pylori against a background of atrophic gastritis and/or intestinal metaplasia. J Clin Gastroenterol 2007;41:751-755.
26. Shin CM, Kim N, Lee HS, et al. Validation of diagnostic tests for Helicobacter pylori with regard to grade of atrophic gastritis and/or intestinal metaplasia. Helicobacter 2009;14:512-519.
27. Weck MN, Gao L, Brenner H. Helicobacter pylori infection and chronic atrophic gastritis: associations according to severity of disease. Epidemiology 2009;20:569-574.
28. Kikuchi S, Kurosawa M, Sakiyama T, et al. Long-term effect of Helicobacter pylori infection on serum pepsinogens. Jpn J Cancer Res 2000;91:471-476.
29. Ito M, Haruma K, Kamada T, et al. Helicobacter pylori eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. Aliment Pharmacol Ther 2002;16:1449-1456.
30. Lorente S, Doiz O, Trinidad Serrano M, Castillo J, Lanas A. Helicobacter pylori stimulates pepsinogen secretion from isolated human peptic cells. Gut 2002;50:13-18.
31. Chang YW, Hwangbo Y, Lee JW, et al. Clinical parameters including serum pepsinogen level and management strategy in patients with premalignant gastric dysplasia. Eur J Gastroenterol Hepatol 2011;23:405-410.

https://doi.org/10.3904/kjim.2018.282