

## Diagnostic Value of Pepsinogen I and II for Pre-cancerous Gastric Lesions in Dyspeptic Patients

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### ABSTRACT

**AIM:** Determining the diagnostic value of pepsinogen I and II as a noninvasive way for evaluation of precancerous gastric atrophy in comparison with endoscopic biopsy.

**METHODS:** Five specimens obtained by upper endoscopy of above 40-year-old dyspeptic patients were evaluated by updated Sydney classification. Intestinal metaplasia and any type of dysplasia were interpreted as a premalignant lesion. Serum pepsinogen I and II levels were measured and their diagnostic efficacy indices for precancerous lesions were determined.

**RESULTS:** Overall, 176 patients (92 men; mean age, 53.97±10.25) participated. Pepsinogen I and II levels were lowest in corpus involvement ( $P=0.0001$ ). With the progression of gastritis, the mean level of pepsinogen I decreased, but the decrease in pepsinogen II and pepsinogen I/II ratio were meaningful in dysplasia and in different pathologic situations ( $P=0.0001$ ). For the detection of premalignant lesions, the sensitivity, specificity, positive and negative predictive values of pepsinogen I<70 ng/mL were 58%, 82%, 78% and 64%, respectively while for pepsinogen II<7.5 ng/mL, they were 45%, 65%, 58% and 52%. These values for pepsinogen I/II<3 were 32%, 95%, 38% and 57%, respectively. In case of positive results of all the three mentioned items, the values were 15%, 97.6%, 87.5% and 52%, respectively.

**CONCLUSION:** The low sensitivity limits the ability of these biomarkers for screening of premalignant lesions, but they could

have a role as one of the first steps in the evaluation of high risk gastric cancer patients.

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**Key words:** Gastric cancer screening; Serum pepsinogen; Metaplasia; Dysplasia

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### INTRODUCTION

Gastric cancer is the fourth most common cancer and the second etiology of cancer mortality around the world<sup>[1]</sup>. In Iran, it is also the most common cancer of men and the third cancer in women<sup>[2]</sup>. Chronic active gastritis due to *H. pylori* infection can result in the loss of gastric glands and secretory properties of the stomach in some patients known as atrophic gastritis and this condition may lead to intestinal metaplasia and finally dysplasia<sup>[3,4]</sup>. The prevalence of these lesions depends on the prevalence of *H. pylori* infection in the society, genetic properties and the host's immunologic factors<sup>[5]</sup>. For example, in Japan with a high rate of gastric cancer, *H. pylori* prevalence in the general population is 60% and atrophic gastritis and intestinal metaplasia has been reported in 80% and 40% of infected individuals and only 10% and 5% of the non infected population, respectively. The annual rate of progression has been reported as 0 to 10% for intestinal metaplasia and 73% for gastric dysplasia<sup>[6]</sup>.

Today finding a noninvasive and economic screening tool in the high-risk population for gastric cancer is an important health strategy in most of the countries. Despite the gold standard of diagnosis of premalignant gastric lesions, which is direct endoscopic biopsy and histologic examination, acceptance of these endoscopic procedures by the general population is poor and due to this poor compliance, most of the gastric cancers are diagnosed in advanced stages.

Pepsinogen I and II are markers of gastric atrophy. The association between these markers and the histologic pattern of gastritis may be helpful in the primary selection of at risk patients for endoscopy

**Table 1** The situation of *H. pylori* and CagA according to sex, age, endoscopic findings and pathology.

			CagApos	CagANeg	P value	<i>H. pylori</i> pos	<i>H. pylori</i> neg	P value
Age	<50 (n=70)	y	25(14%)	45(26%)	0.3	39(22%)	31(17.5%)	0.61
	(53.97±10.25)	≥50 (n=106)	46(26%)	60(34%)		55(31%)	51(29.5%)	
Sex	Male (n=92)		32(18%)	60(34%)	0.11	49(28%)	43(24%)	0.96
	Female (n=84)		39(22%)	45(26%)		45 (26%)	39(22%)	
Endoscopic findings:	Normal		19(11%)	25(14%)	0.8	22(12.5%)	22(12.5%)	0.88
	Antrum		37(21%)	52(30%)		47(27%)	42(23%)	
	Corpus		9(5%)	19(11%)		16(9.5%)	12(7.5%)	
	Erosive		6(3%)	9(5%)		9(5%)	6(3%)	
Pathologic findings:	Normal		8(4.5%)	26(15%)	0.054	16(9.5%)	18(10%)	0.66
	ACG		10(6%)	24(13.5%)		20(11.5%)	14(8%)	
	QCG		8(4.5%)	9(5%)		10(6%)	7(4%)	
	Metaplasia		34(19%)	33(18.5%)		33(18.5%)	34(19%)	
	Dysplasia		11(6.5%)	13(7.5%)		15(8.5%)	9(5%)	
Total			71(40%)	105(60%)		94(53%)	82(47%)	

**Table 2** The mean level of pepsinogen I, II and I/II ratio according to sex and age.

	Age		P value	Sex		P value	Total
	<50 y	≥50 y		Male	Female		
PG I*	86.39±51.70	97.61±66.39	0.33	100.11±63.11	85.53±58.17	0.11	93.15±61.06
PG II	12.13±8.63	15.99±14.45	0.04	16.39±14.13	12.34±10.30	0.03	14.46±12.58
PG I/II	10.50±7.94	10.06±11.04	0.77	10.18±9.67	10.31±10.21	0.93	10.24±9.90

\*PG = Pepsinogen.

**Table 3** The mean level of pepsinogen I, II and I/II ratio according to *H. pylori* and CagA.

	CagA		P value	<i>H. pylori</i>		P value	Total
	Pos	Neg		Pos	Neg		
PG I*	90.14±55.94	95.18±64.48	0.59	91.82±61.77	94.68±60.59	0.75	93.15±61.06
PG II	16.64±14.22	12.98±11.17	0.058	14.47±13.45	14.44±11.59	0.98	14.46±12.58
PG I/II	10.04±9.89	10.37±9.95	0.82	11.12±11.93	9.23±6.81	0.2	10.24±9.90

\*PG=Pepsinogen.

and biopsy of premalignant gastric lesions. But the diagnostic value of serologic parameters has not been obvious in clinical trials. The aim of this study was to determine the diagnostic value of serology as a noninvasive way in detecting premalignant gastric lesions in comparison with histology by endoscopic biopsy.

## OBJECTS AND METHODS

All dyspeptic patients over 40-years of age in the gastroenterology clinic of Imam Hospital, Ahwaz from September 2010 to January 2011 were enrolled into the study. After obtaining a thorough history about the past medical profile including cardiovascular disorders, chronic liver or kidney diseases, drug consumption, especially antibiotics, PPI and H2 blockers and a history of familial gastric cancer, the patients underwent an upper endoscopy.

Exclusion criteria included a history of gastric cancer, previous gastrectomy, duodenal ulcer, *H. pylori* eradication or antibiotic consumption in the last month. Five endoscopic biopsy samples were obtained including two samples from the corpus (one from the lesser curvature and one from the greater curvature), two samples from the antrum (2 cm proximal to the pylorus) and one sample from the incisura angularis; consequently, the samples were sent to the pathology laboratory in formalin preservative. The samples were stained by hematoxylin-eosin and investigated according to Update Sydney classification by two pathologists who had no information about the endoscopy results and the patients' clinical profiles.

The blood sample was obtained from all the patients and was sent to the laboratory in a few hours. Then the samples were centrifuged and the serum was frizzed in -70°C and after collecting the samples, serum pepsinogen I and II were measured by ELISA (Biohit kit, Finland) and the samples were also checked for CagA by ELISA (Diapro kit, Italy). The cutoff points of these markers for the evaluation of gastritis according to present references were defined as pepsinogen I, 70 ng/mL; pepsinogen II, 7.5 ng/mL; and pepsinogen I/II ratio, 3. The pathologic results were also reported as chronic active

gastritis, chronic quiescent gastritis, intestinal metaplasia, dysplasia and normal mucosa.

The patients with gastric or duodenal ulcers on endoscopy, those without enough biopsy samples and those unjustified to perform blood chemistry check were excluded from the study.

After collecting the laboratory and pathology reports, cases reported as intestinal metaplasia or any kind of dysplasia were assumed as premalignant lesions. The data were analyzed by SPSS 19 for Windows (SPSS Inc., Chicago, Ill, USA). The mean levels of pepsinogen were compared according to sex, age, endoscopic findings, different pathologies in biopsy samples, *H. pylori* test results and serum CagA. A P value less than 0.05 was interpreted as significant. The patients epidemiologic specifications were compared by  $\chi^2$  test.

Sensitivity, specificity, positive and negative predictive values were determined and ROC curve was plotted to differentiate metaplasia and dysplasia from other pathologies.

This study was approved by the research and technology department and ethical committee of Ahwaz Jundishapour Medical University and a consent form was obtained from all patients (establishing no.: U-179).

## RESULTS

Overall, 180 patients with GI complaints were enrolled into the study and four patients were excluded after performing upper endoscopy with the diagnosis of duodenal ulcer. The remaining 176 patients with a mean age of 53.97±10.25 (40-85) years including 92 men (mean age, 53.7±9.7 years) and 84 women (mean age, 54.26±10.8 years) (P=0.71) were evaluated. Dyspepsia was the most common symptom in the first visit (84.1%) and antral involvement was the most common endoscopic finding (48.3%). CagA was positive in 40% of the patients and in 53% of the pathologies *H. pylori* was reported present and these values had no significant differences according to sex, age, endoscopic findings and pathologic reports (P>0.05) (Table 1).

The mean level of pepsinogen I was 93.15±61.06 and this value

**Table 4** The mean level of pepsinogen I, II and I/II ratio according to endoscopic findings.

	Endoscopic findings					P value	Total
	Normal	Antrum	Corpus	Erosive			
PG I*	129.66±70.33	84.06 ± 55.77	73.09 ± 45.06	77.40 ± 49.55		0.0001	93.15 ± 61.06
PG II	21.61±12.91	12.36 ± 12.32	10.38 ± 9.03	13.52 ± 11.51		0.0001	14.46 ± 12.58
PG I/II	7.05±3.46	11.52 ± 11.15	10.50 ± 9.76	11.55 ± 13.37		0.09	10.24 ± 9.90

\*PG=Pepsinogen.

**Table 5** Mean pepsinogen I,II and I/II according to pathologic findings.

	Endoscopic findings					P value
	Normal	ACG**	QCG**	Metaplasia	Dysplasia	
PG I*	147.61 ± 63.75	106.62 ± 45.97	109.83 ± 48.35	67.80 ± 50.83	55.86 ± 47.90	0.0001
PG II	23.52 ± 14.06	11.06 ± 9.67	10.36 ± 7.88	14.62 ± 13.30	8.90 ± 7.27	0.0001
PG I/II	7.24 ± 3.45	14.58 ± 9.12	16.69 ± 18.49	8.71 ± 8.63	8.05 ± 8.63	0.0001

\*PG=Pepsinogen, \*ACG=Active Chronic Gastritis, \* QCG=Quiescent Chronic Gastritis.

**Table 6** Sensitivity, specificity, positive and negative predictive values for serum biomarkers of the stomach.

	Sensitivity	Specificity	PPV	NPV
PG I	58%	82%	78%	64%
PG II	45%	65%	58%	52%
PG I/II	32%	95%	38%	57%
Gastric Panel	15%	97.6%	87.5%	52%

\*PPV=Positive predictive value, \*NPV=Negative predictive value.

was not statistically significant according to sex, age, positive CagA and *H. pylori* ( $P>0.05$ ) (Tables 2, 3). The mean level of pepsinogen II was  $14.46\pm 12.58$ , which was significantly higher in men and over 50 years than other groups ( $P=0.03$  and  $P=0.04$ , respectively). This value was higher in patients with positive CagA than the negative group ( $P=0.058$ ), but it showed no difference between *H. pylori* groups ( $P= 0.98$ ). The levels of pepsinogen I and II were significantly lower in corpus involvement ( $P=0.0001$ ) (Table 4).

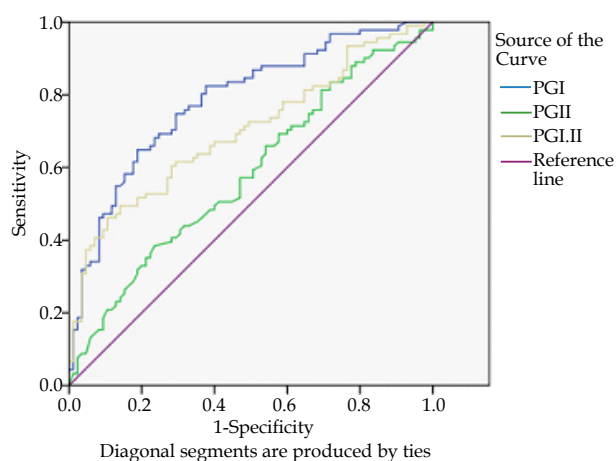
In patients with dysplasia or metaplasia, the mean level of pepsinogen I was very low and there was a significant difference between different types of gastritis and normal mucosa ( $P=0.0001$ ). The mean level of pepsinogen II was also significantly low in dysplasia ( $P=0.0001$ ), but in metaplasia, a similar result was not detected (Table 5). The mean pepsinogen I/II ratio was  $10.24\pm 9.9$  and this ratio did not show any significant differences according to sex, age, the condition of CagA and *H. pylori* and different endoscopic findings ( $P>0.05$ ) (Tables 2, 3 and 4), but in different pathologies this difference was significant ( $P=0.0001$ ) (Table 5).

With a cutoff point of 70 for pepsinogen I, the sensitivity and specificity for diagnosis of premalignant lesions was 58% and 82%, respectively and the positive and negative predictive values were 78% and 64%, respectively. For a pepsinogen II level of less than 7.5, the sensitivity, specificity, positive and negative predictive values for diagnosis of metaplasia and dysplasia were 45%, 65%, 58% and 52%, respectively. These values for pepsinogen I/II<3 were 32%, 95%, 38% and 57%, respectively. In case of positive results for all the three mentioned variables, the sensitivity, specificity, PPV and NPV were %15%, 97.6%, 87.5% and 52%, respectively (Table 6).

ROC curve for diagnosis of metaplasia and dysplasia from other pathologies is shown in figure 1. Accuracy of the test (area under curve) for pepsinogen I, II and I/II was 78%, 58% and 70%, respectively.

## DISCUSSION

In our study, the diagnostic value of serum profiles for screening of premalignant gastric lesions were investigated and it was elucidated that the sensitivity of these tests in differentiating premalignant lesions from normal mucosa is low and only pepsinogen I and I/II have a high specificity for the exclusion of premalignant lesions. Screening has an important role in diagnosis of early stages of



**Figure 1** ROC curve for PG I, PG II and PG I/II.

gastric cancer<sup>[7]</sup>. Direct endoscopic detection and histology is the gold standard for diagnosis of premalignant lesions including intestinal metaplasia and dysplasia. But this strategy is expensive and aggressive. In the recent years, many studies have been designed and performed for seeking a noninvasive, economic and reliable method for screening of these patients. One of these methods is to measure serum biomarkers of gastric mucosa including pepsinogen I, pepsinogen II and gastrin 17 for evaluation of the functional and histological condition of gastric mucosa<sup>[8]</sup>. Pepsinogen I is produced in the gastric fundus and corpus and pepsinogen II is secreted by all the gastric mucosa. In atrophic gastritis, the production of both of these pepsinogens is decreased, but production of type I is more affected than type II<sup>[9,10]</sup>. *H. pylori* is a primary etiology of gastric cancer and in 60% of the cases the microorganism has CagA genome. This genus code is one of the major proteins of *H. pylori* pathogenicity and in the presence of this protein the probability of ulcerogenicity is much more. Based on different studies, antibody against CagA is a sensitive method for diagnosis of this infection<sup>[11]</sup> Trefoil factor family (TFF) proteins (TFF1, TFF2, and TFF3) are soluble peptides secreted by gastrointestinal tract. TFF1, TFF2 were expressed in the foveolar epithelium, and TFF2 was expressed in the pyloric glands. TFF3s were scarcely expressed in the gastric mucosa detectable in goblet cells of intestinal metaplasia, TFF1, TFF2 and TFF3 are important in mucosal healing barrier and promotion of restitution after injury. TFF1, TFF2, and TFF3 can be check by enzyme-linked immunosorbent assay. The level of TFF1, TFF2 decreased but TFF3 don't change by eradication *h.pylori*. Therefore, the level of TFF3 can be use for detection precancerous lesion such as intestinal metaplasia and atrophic gastritis and even gastric cancer<sup>[12]</sup>. Serum levels of TFF3 as biomarker gastric cancer with a cutoff of 3.6 ng/mL had sensitivity and specificity 80.9% and

81.0% respectively. some study showed that combination TFF3 and pepsinogen level had better valid than alone pepsinogen for detection gastric precancerous lesions<sup>[13]</sup>.

Some of our findings differ from the results of Sheykholeslami *et al*'s study on first degree relatives of gastric cancer patients. In that study, the levels of pepsinogen I and II increased simultaneously with the severity of gastric atrophy, presence of metaplasia and also in patients with *H. pylori* infection<sup>[7]</sup>. On the contrary, our results showed that these values decrease in metaplasia and dysplasia in comparison with the normal mucosa. Although in our study it is elucidated that the sensitivity of these tests is low in differentiating metaplasia and dysplasia except for pepsinogen I and I/II which have a high specificity for exclusion of premalignant lesions. In Sheykholeslami *et al*'s<sup>[7]</sup> study, the sensitivity and specificity of pepsinogen II test in differentiating different types of gastritis is 80% and the sensitivity and specificity of pepsinogen I/II in the diagnosis of corpus gastritis is 13% and 97%, respectively and it is offered that pepsinogen II could be a reliable marker for screening of any kind of gastritis, but pepsinogen I and I/II or the combination of these markers do not have the ability to detect premalignant conditions in the high-risk population.

In Eurohepygast study on dyspeptic patients, the level of pepsinogen II was also higher in different types of gastritis in comparison with the normal mucosa and the sensitivity and specificity of this test was reported low<sup>[12]</sup>. On the other hand, in Shiotani *et al*'s<sup>[13]</sup> study it has been shown that the levels of pepsinogen I and I/II in patients with a history of gastric cancer were significantly less than the control group and the sensitivity and specificity of these tests were low. In a Korean study by Kim Jang-Rak *et al*'s<sup>[8]</sup>, similar results were also reported.

The sensitivity of these tests were low in two studies performed in Italy on dyspeptic patients, which were similar to our study, but the specificity was high (90-100%) and the mean levels of pepsinogen I and II in patients with *H. pylori* infection were significantly higher than the patients without infection<sup>[14,15]</sup>; whereas, in our study there was no difference between the two groups.

In the current study, the sensitivity of the gastric panel was low, but the specificity of pepsinogen I and I/II was high. While in another European multicenteric study on dyspeptic patients, the level of these values decreased simultaneously with the increase in the severity of atrophy, but the reported sensitivity (83%), specificity (95%) and positive (75%) and negative (97%) predictive values were high so they introduced these markers as a reliable index for the detection of atrophic gastritis<sup>[16]</sup>.

The results of Indonesian studies were also similar to our study and they recommended the use of these tests just for the high-risk population such as first degree relatives of gastric cancer patients as epidemiologic studies recommend<sup>[17]</sup>.

In many of these studies, elevation of gastrin-17 has also been used as a marker of gastric secretion and function and an index of atrophy, but because of unavailability of proper equipments in Khuzestan province, it was impossible to perform this test.

Finally, it seems that the low sensitivity of these tests in our study limits the ability of serum biomarkers for screening of premalignant lesions and may be these tests are just useful as the first step in the evaluation of patients at risk of gastric cancer and this study could be used as a base for other prospective studies.

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