Original Article

Predictive role of serum pepsinogen level as a serological marker of gastritis

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ABSTRACT

Background: *Gastritis is a prevalent and insidious disorder that usually causes an inflammation of the gastric mucosa, which may be related to dietary habits, socioeconomic status and* Helicobacter pylori *infections. Serum pepsinogen I and II have been proposed as non-invasive biomarkers for gastric mucosal changes, including gastritis, particularly in association with* H. pylori *infection. This study aimed to evaluate the predictive role of serum pepsinogen levels as serological markers for gastritis.*

Methods: *This cross-sectional study was performed in the Department of Gastrointestinal Hepatobiliary & Pancreatic Disorders (GHPD) and test performed in the Immunology Department of BIRDEM General Hospital, Dhaka from January to December of 2023. A total of 65 patients were selected by a random sampling technique and sent for endoscopy. Serum samples were collected to measure pepsinogen in those patients by using a Chemiluminescence Immunoassay (CLIA) and anti-*H. pylori *IgG by using Enzyme-Linked Immunosorbent Assay (ELISA).*

Results: *Among 65 patients, 45 were diagnosed as gastritis and 20 were as non-gastritis following endoscopy. Thirty nine (39/65, 70.9%) were* H. pylori *IgG positive in the gastritis group and in the non-gastritis group 16 (29.1%) were* H. pylori *IgG positive. Both serum pepsinogen levels I (279.65±159.82) µg/L and pepsinogen II (22.61 ± 17.64) µg/L were significantly higher in the gastritis group than the non-gastritis group ($p<0.05$). The present study did not demonstrate a statistically significant association between* H. pylori *IgG seropositivity and serum pepsinogen I ($p=0.269$) and II ($p=0.958$) levels.*

Conclusion: *Serum pepsinogens were increased among the gastritis group than the non-gastritis group though most of the patients were found positive of anti-*H.pylori *IgG. Therefore, compared to the* H. pylori *antibody test, serum pepsinogen is recommended as a superior non-invasive marker.*

Key words: *Serum pepsinogen, H.pylori, gastritis.*

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INTRODUCTION

Gastritis remains a global public health issue, linked to socioeconomic status, lifestyle and living conditions. It affects 50.8% of people in developing countries and 34.7% in developed nations, with prevalence higher in men.[1] Rates have declined more in developed than in developing regions and men were generally more likely than women to get gastritis.[1]

Helicobacter pylori is the leading cause of gastritis worldwide, though gastritis also occurs in *H. pylori*-negative patients with functional dyspepsia or non-erosive reflux. *H. pylori* infection affects about 10% of children in developed and up to 50% in developing countries, with higher prevalence in South America and Asia.[2] While *H*. pylori-related gastritis is declining in Western countries, autoimmune gastritis is rising, affecting 2–5% of the population.[3] In contrast, *H. pylori*–induced gastritis remains common, seen in 40.7%

of Nigerian children and with infection rates of 66% in rural and 47% in urban Chinese populations.[4] The prevalence of *H. pylori* in Bangladesh is considered high, with studies showing a wide range of results, from 59.1% to over 90% in some cases.[5] About half of those with chronic gastritis and *H. pylori* develop atrophic gastritis and 5% reach severe stages.[6] A large retrospective study found that about 6% of patients with severe gastric dysplasia developed cancer within 5 years.[7]

Serum pepsinogens, secreted mainly into the gastric lumen with only about 1% entering the blood, are classified as pepsinogen I and II. Pepsinogen I is produced by mucosal cells in stomach fundus, while pepsinogen II originates from chief cells, pyloric glands and the proximal duodenal mucosa.[8] Human pepsinogens have a diagnostic value for various gastro-duodenal disorders, especially for peptic ulcers, atrophic gastritis and gastric cancer. The pepsinogen I/II ratio can provide even better information on the extent of chronic gastritis. In the stomach, it combines with hydrochloric acid to form pepsin, which is most active at *pH* 1.5–2.5 and becomes inactive at neutral *pH*. Pepsin partially digests proteins into peptides, later broken down or absorbed in the intestine, with small amounts entering the bloodstream.[10]

H. pylori infection causes gastric mucosal inflammation and affects pepsinogen levels. Serum pepsinogen I and II increase in non-atrophic gastritis, though pepsinogen II shows wide variation, leading to little correlation with gastric acid output in *H. pylori*-positive individuals and report elevated pepsinogen levels in such infections.[10] In addition to this direct impact of *H. pylori*, the stomach inflammatory condition caused by *H. pylori* also raises pepsinogen levels.[11]

Recently, serum pepsinogen I and II, serum gastrin-17 (G-17) and immunoglobulin G anti-*H. pylori* antibodies were proposed as non-invasive markers to assess the status of the gastric mucosa in patients with dyspeptic symptoms. Several studies have reported the relationship between the serum pepsinogen level and gastric mucosal changes. Measuring the serum pepsinogen I and II levels offered a non-invasive and straight forward means of mass screening for gastric cancer in Japan when compared with endoscopy.[12] The study aimed to evaluate serum pepsinogen levels in patients with gastritis and compare them with conventional diagnostic markers.

METHODS

This cross-sectional study was carried out among patients attending in the GHPD outdoor at BIRDEM General Hospital, Dhaka between January and December of 2023. The Institutional Review Board, BIRDEM General Hospital approved the research protocol prior to the commencement of the study no. BIRDEM/IRB/2022/336. A total of 65 patients were selected by random sampling technique and sent for endoscopy on the basis of inclusion and exclusion criteria. Among them, 45 patients were found to have gastritis and 20 were found to be endoscopically normal. All subjects were tested for anti-*H.pylori* IgG and estimation of serum pepsinogen levels to the evaluate status of gastric secretion. Under quality control and safety procedures for sample collection, 3 ml of venous blood was collected from each patient in a plain red vacutainer tube. Serum was separated from whole blood for all specimens immediately by using fine centrifugation. Serum pepsinogen I and II analyzed by using a Chemiluminescence Immunoassay (CLIA) and anti-*H.pylori* IgG by using Enzyme-Linked Immunosorbent Assay (ELISA). Data was analyzed using Statistical Package for Social Sciences (SPSS) version 26.

RESULTS

Socio-demographic status of the recruited study groups

Total patients were 65; 45 were diagnosed with gastritis and other 20 were found normal on endoscopy. The mean age difference between the gastritis and the non-gastritis group was not statistically significant (p=0.92) (Table I).

The gender distribution showed that in the endoscopically gastritis group, 16 (35.6%) were male and 29 (64.4%) were female. In the endoscopically non-gastritis group, 12 (60%) were male and 8 (40%) were female. Male to female ratio among the gastritis and non-gastritis groups were 0.55:1 and 1.5:1, respectively. The difference in gender distribution within the groups was not significant (p=0.066).

Among the study, subjects the frequency and distribution of socioeconomic status, dietary habits, non-steroidal anti-inflammatory drugs (NSAIDs) use, smoking status, alcohol consumption and betel nut

chewing were observed. The differences in these variables were compared in two groups of study subjects and were not found statistically significant except for dietary habits (p=0.026) (Table II).

Association of *H. pylori* status with study subject

Among study subjects in the gastritis group, thirty nine (70.9%) were *H. pylori* IgG positive and six (60.0%) were *H. pylori* IgG negative. In the non-gastritis group, sixteen (29.1%) were *H. pylori* IgG positive and four (40.0%) subjects *H.pylori* IgG were negative. The difference of *H. pylori* IgG status compared in the two groups and statistically was not found significant (p<0.05). (Table III).

In the gastritis group, elevated pepsinogen I and II levels were observed in 88.5% and 88.2% of subjects, respectively, compared to 11.5% and 11.8% in the non-gastritis group. Both differences were statistically significant (p<0.05 for PG I, p=0.001 for PG II) (Table IV).

Association of *H. pylori* IgG with serum pepsinogen I and pepsinogen II

Among the studied subjects, 34 (81.0%) subjects with normal pepsinogen I level were *H. pylori* IgG positive and 21 (91.3%) with increased pepsinogen I level were *H. pylori* IgG positive. Twenty (62.5%) subjects with normal pepsinogen II level and 22 (67.7%) with increased pepsinogen II level were *H. pylori* IgG positive. The difference in serum pepsinogen I and serum pepsinogen II level compared in *H. pylori* IgG status was not found to be significant (p=0.269) and (p=0.958) (Table V).

Table I. Age distribution among the study subjects (N=65)

Age (years)	Gastritis (N=45) n(%)	Mean ± SD	Non-gastritis (N=20) n (%)	Mean ± SD	P value
18-35	14 (31.1)	42.58±10.51	7 (35.0)	42.25±13.98	0.92
36-50	18 (40.0)		7 (35.0)		
>50	13 (28.9)		6 (30.0)		

Data are expressed as frequency and percentage and tests are done by the Chi-square test. P< 0.05 (Significant)

Table II. Socio-demographic status of the study subjects (N=65)

Variables		Endoscopically Gastritis N=45, n (%)	Endoscopically normal N=20, n (%)	P value
Socioeconomic status	Lower	9 (20)	2 (10)	0.211
	Middle	17 (80)	17 (85)	
	Higher	0 (0)	1 (5)	
Dietary habit	Healthy	18 (40)	14 (70)	0.026*
	Poor	27 (60)	6 (30)	
History of taking NSAIDs	Never used	21 (46.7)	14 (70)	0.082
	Sometimes used	24 (53.3)	6 (30)	
Smoker	Yes	11 (24.4)	4 (20)	0.695
	No	34 (75.6)	16 (80)	
Alcohol	Yes	2 (4.4)	0 (0)	0.338
	No	43 (95.6)	20 (100)	
Tobacco user	Yes	10 (22.2)	3 (15)	0.502
	No	35 (77.8)	17 (85)	

Data are expressed as frequency and percentage and test are done by the chi-square P<0.05 (Significant)

Table III. Relation of *H.pylori* status with gastritis group

	H. *pylori*-positive n (%)	H. *pylori*-negative n (%)	P-value
Gastritis (N=45)	39(70.9)	6(60.0)	0.492
Non-gastritis (N=20)	16(29.1)	4(40.0)	

P-value obtained by the Fisher's exact test. P< 0.05 (Significant).

Table IV. Pepsinogen I and II value among study subjects (N=65)

Group	Pepsinogen I		P value	Pepsinogen II		P value
	Gastritis n (%)	Non-gastritis n (%)		Gastritis n (%)	Non-gastritis n (%)	
Normal	22 (56.4)	17 (43.6)	0.007	15 (48.4)	16 (51.6)	0.001
Increased	23 (88.5)	3 (11.5)		30 (88.2)	4 (11.8)	

P-value obtained by the Fisher's exact test. P< 0.05 (Significant).

Table V. Relation of H. *pylori* IgG with serum pepsinogen I and pepsinogen II

	H. *pylori* IgG				*H.pylori* IgG		
Pepsinogen I	Negative n (%)	Positive n (%)	P value	Pepsinogen II	Negative n (%)	Positive n (%)	P value
Normal	8(19.0)	34(81.0)	0.269	Normal	5(15.6)	26(84.4)	0.958
Increased	2(8.7)	21(91.3)		Increased	5(15.2)	29(84.8)	
Total	10(15.4)	55(84.6)		Total	10(15.4)	55(84.6)	

P-value obtained by the Chi-square test. P< 0.05 (Significant)

DISCUSSION

Chronic gastritis is a common global condition, primarily caused by *H. pylori*, leading to lifelong gastric mucosal inflammation and in some cases, atrophy with intestinal metaplasia.[6,13] Masjedizadeh et al. found no significant variation in pepsinogen with age or sex, though pepsinogen II was higher in men over 50.[14] Hokkanen et al. reported higher pepsinogen I in men regardless of *H. pylori* status, while Kim et al. observed gender-related differences influenced by age, smoking, alcohol and body weight.[15,16] Overall, pepsinogen levels vary with demographic and lifestyle factors but results remain inconsistent.

Gastritis can be diagnosed by invasive (endoscopy, histopathology) and non-invasive methods (anti-*H. pylori* IgG, urea breath test, fecal antigen test, serum pepsinogen levels and ratios). Endoscopy confirms specific types of gastritis but may be contraindicated in certain cardiac, respiratory or critical conditions. In such cases, serum pepsinogen offers a useful non-invasive alternative and reliable than anti-*H. pylori* IgG. Here serum pepsinogen could be a good serological marker than anti *H. pylori* IgG for the diagnosis of gastritis without an invasive procedure.

This study found no significant differences in serum pepsinogen I or II levels between different age groups (p = 0.92) or genders (p = 0.06). However, 60% of gastritis patients reported unhealthy eating habits, whereas 70% of non-gastritis participants maintained healthy diets, indicating a statistically significant difference between the groups (p = 0.026). Previous studies also report a strong link between poor diet and higher gastritis incidence.[17] The difference in *H. pylori* IgG antibody status between the gastritis and non-gastritis groups was not statistically significant (p > 0.05). In another study endoscopically diagnosed gastritis patients anti-

H. pylori IgG seropositivity was found in 127 patients (80.9%), whereas seronegativity was seen in the remaining 30 patients (19.1%).[18] In another study *H. pylori* IgG antibody was found positive in 487 (69.0%) of the blood serums of 705 patients taken into the study, whereas found negative in 218 (31.0%) in symptomatic patients of gastritis.[19]

In our study, serum pepsinogen I levels were found to be significantly higher among patients with gastritis compared to those without gastritis with the difference between the two groups reaching statistical significance ($p = 0.006$). Agkoc et al. showed serum pepsinogen I level was statistically higher in the patient group with chronic nonspecific gastritis compared to the patient groups with chronic atrophic gastritis and stomach cancer ($p< 0.05$).[20] Both patients with non-atrophic gastritis and healthy individuals in India had consistently high levels of serum pepsinogen I. On the other hand, atrophic gastritis patients have persistently low serum pepsinogen I levels.[21] The study demonstrated a statistically significant difference in serum pepsinogen II levels between the two groups ($p = 0.001$). The mean serum pepsinogen II concentration was 22.61 ± 17.64 ng/mL in the gastritis group and 10.64 ± 4.26 ng/mL in the non-gastritis group. *H. pylori*-positive patients had significantly higher serum pepsinogen II levels than *H. pylori*-negative individuals.[22] The difference in serum pepsinogen I and II level compared in *H. pylori* IgG status was not found to be significant ($p=0.269$) and ($p=0.958$), respectively. Both biomarkers are valuable non-invasive tools for diagnosing gastritis, offering an alternative to invasive procedures like endoscopy. However, serum pepsinogen has shown greater diagnostic accuracy and clinical relevance. It not only reflects gastric mucosal changes more reliably, particularly in detecting atrophic gastritis but also provides useful information on disease severity and progression. Compared to other serological tests like *H. pylori* antibody detection, serum pepsinogen levels are less influenced by previous infections and more closely reflect current gastric conditions, making them a useful non-invasive alternative for diagnosing gastritis.

Conclusion

Both serum pepsinogen I and II were increased among the gastritis group than the non-gastritis group though most of the patients were found to be positive of anti *H. pylori* IgG. So, serum pepsinogen is suggested as a better alternative non-invasive marker than *H. pylori* antibody test. Large-scale studies with histo-pathological information on the gastric mucosa should be evaluated in the future.

Authors' contribution: MK, MA and MM planned the study. ZFR, ALMS and JN collected and analyzed data. TMB, MM did literature search. NS, MA drafted manuscript with contribution of MK, MM. All authors read and approved the final manuscript for submission.

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