ORIGINAL ARTICLE

Serum Gastrin Level and Pepsinogen I/II Ratio as Biomarker of Helicobacter pylori Chronic Gastritis

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ABSTRACT

Aim: to find out biomarker as diagnostic tool of H. pylori chronic gastritis.

Methods: the design of present study was a diagnostic test and there were 104 subjects with H. pylori chronic gastritis who fulfilled the inclusion and exclusion criteria. The diagnosis of H. pylori chronic gastritis was based on histopathological examination and PCR with ureC primer of the gastric biopsy specimen. In addition, we also performed the examination of serum gastrin, pepsinogen (PG) I and PG (pepsinogen) II level. By using analysis of receiver operating characteristic (ROC), an optimal cut off point of serum gastrin, PGI and PGII level as well as PGI/PGII ratio was determined.

Analysis of bivariate logistic regression was used to determine the involved independent variables and possibilities as biomarkers. Significance level was determined by p value < 0.05.

Results: we found optimal cut off points on serum gastrin, PGI and PGII level as well as the PGI/PGII ratio at 5.89 pmol/L; 82.5 µg/L; 6.48 µg/L and 13.6 respectively. By using the analysis of bivariate logistic regression, we found gastrin level with p = 0.078 (OR 2.75; 95%CI 0.89-8.45) and PGI/PGII ratio with p = 0.000 (OR 14.63; 95%CI 3.55-60.63). The opportunity of gastrin level and PGI/PGII ratio as biomarkers was 0.8 with 47% sensitivity, 83% specificity, 74% PPV, 61% NPV, 65% accuracy, LR+ = 2.76 and LR- = 0.64.

Conclusion: gastrin level of >5.89 pmol/L and PGI/PGII ratio ≤ 13.6 can be utilized as biomarkers of H. pylori chronic gastritis.

Key words: dyspepsia, chronic gastritis, Helicobacter pylori, gastric cancer, polymerase chain reaction, PCR with ureC primer.

INTRODUCTION

H. pylori has been identified as an etiologic factor of gastric cancer,1-3 which by various studies has been proven as the beginning of Correa multi-step model of gastric carcinogenesis.4 It is initiated by chronic gastritis, gastric atrophy, intestinal metaplasia, dysplasia which leads to gastric cancer. Prevention on developing gastric cancer should be performed as early as possible, i.e. on the risk factors and precursor lesions including chronic gastritis, gastric atrophy, and intestinal metaplasia. To identify the occurrence of precursor lesions of gastric cancer, biomarker tests are necessary. Several studies have reported their study result on biomarkers for gastric atrophy and intestinal metaplasia. Selection for early findings of H. pylori chronic gastritis become important since the treatment results of gastric atrophy and intestinal metaplasia are still controversial.5-11

H. pylori infection and gastric mucosal histological features may be revealed by endoscopic biopsy;12 however, such method is invasive, costly and frequently intolerable. Therefore, it is necessary to perform a non-invasive approach through blood serological assay13 based on gastric mucosal gland secretory function, i.e. pepsinogen I (PGI), pepsinogen II (PGII) and gastrin level as well as the PGI/PGII ratio.14,15 PGI/PGII ratio is utilized because PGII is secreted both by the gastric glands and the non-gastric glands.16,17 PGII cut-off point alone may not differ the chronic atrophic and non-atrophic gastritis.18

Based on the abovementioned consideration, we need to conduct a study to find out a non-invasive diagnostic method for H. pylori chronic gastritis.
METHODS

The present study was conducted in the ward at the Department of Internal Medicine, Margono Regional Public Hospital, Soekarjo, Purwokerto by using one-year diagnostic test design. There were 104 patients with dyspepsia who were included as the eligible study subjects. Afterward, gastric endoscopy and biopsy were carried out to obtain the gastric specimens. Histopathological examination and PCR were performed on the specimens. Moreover, a blood test for examining the gastrin, PGI and PGII level was also done in accordance with examination protocol of Biohit manufacturer instruction.19-21

Subjects participating in the present study were patients aged ≥45 years with dyspepsia symptoms, histopathological diagnosis of chronic gastritis and H. pylori positive results based on the PCR ureC examination. Subjects excluded from the study were patients who already had antibiotics treatment and anti-secretion agents (such as proton pump inhibitor, H2 inhibitor and antacids) within 1 week prior to the examination. In addition, patients with history of gastric surgery, alcoholics, smoker and concomitant severe disease (cardiovascular, chronic renal failure and bleeding disorder) were also excluded.

Sample size was determined based on the Pepe formula.22 There were 36 subjects for positive- H. pylori chronic gastritis group and 36 subjects for negative- H. pylori chronic gastritis group. By considering 10% drop-out, a sample size of 80 subjects was necessary. The drop-out included exceedingly small biopsy size, error in preservation, preparation of pathological specimens, blood hemolysis, error in blood storing and instrument error for interpreting the serum.

The test for data normality was performed prior to hypothesis testing by using the Kolmogrov-Smirnov test. Hypothesis testing with unpaired variables was carried out to compare the gastrin, PGI, and PGII level as well as the PGI/PGII ratio between the positive - H. pylori chronic gastritis group and negative - H. pylori chronic gastritis group by using t-test.

Determination of optimal cut-off points for gastrin, PGI, and PGII level as well as the PGI/PGII ratio was done by using ROC analysis. Bivariate logistic regression analysis was used to determine the involvement of independent variables and the biomarker opportunity.

Statistical significance level was determined as p value <0.05. The statistical analysis was done by using SPSS program for Windows version 11.5 and MedCalc ver. 8.01.

RESULTS

The ROC analysis found optimal cut off points of gastrin, PGI, PGII level as well as PGI/PGII ratio at 5.89 pmol/L (Figure 3); 82.5 µg/L (Figure 4); 6.48 µg/L (Figure 5) and 13.6 (Figure 6), respectively.

Combined multivariable analysis for gastrin, PGI and PGII level as well as the PGI/PGII ratio was performed by using bivariate logistic regression with backward stepwise method. By logistic regression analysis (Table 1), we found that only variable of gastrin level (p = 0.22) and PGI/PGII ratio (p = 0.002)
were significant \((p < 0.25)\) or could be included in the logistic regression model. The opportunity of gastrin level \(>5.89\) pmol/L and PGI/PGII ratio \(\leq 13.6\) as the biomarkers of \textit{H. pylori} chronic gastritis was 0.8. Therefore, the gastrin level \(>5.89\) pmol/L and PGI/PGII ratio \(\leq 13.6\) can be used as the biomarkers of \textit{H. pylori} chronic gastritis.

Based on such results, the hypothesis of combined gastrin level and PGI/PGII ratio used as biomarkers of \textit{H. Pylori} chronic gastritis was acceptable.

Gastrin levels and PGI/PGII ratio can be used as biomarkers of \textit{H. pylori} chronic gastritis based on the following supporting evidences:

1. They fulfilled the criteria for diagnostic test
2. The sample size was in accordance with the Pepe formula
3. The gold standard of \textit{H. pylori} was using the PCR technique with ureC primer which is the most sensitive and specific primer of the available primers for detecting \textit{H. pylori}, which could avoid the imperfect gold standard bias.

Table 1. The opportunity of gastrin level and PGI/PGII ratio as the biomarkers of \textit{H.pylori} chronic gastritis

<table>
<thead>
<tr>
<th>Gastrin level</th>
<th>PGI/PGII Ratio</th>
<th>Opportunity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&gt; 5.89)</td>
<td>(\leq 13.6)</td>
<td>77</td>
</tr>
<tr>
<td>(\leq 5.89)</td>
<td>(\leq 13.6)</td>
<td>56</td>
</tr>
<tr>
<td>(&gt; 5.89)</td>
<td>(&gt; 13.6)</td>
<td>19</td>
</tr>
<tr>
<td>(\leq 5.89)</td>
<td>(&gt; 13.6)</td>
<td>8</td>
</tr>
</tbody>
</table>
4. The accuracy of gastrin level and PGI/PGII ratio was quite high with the opportunity of 0.8 and 43% sensitivity as well as 83% specificity.

**DISCUSSION**

Based on the present study, we found that the mean value of serum gastrin level in positive-\(H.\) pylori chronic gastritis (7.76 pmol/L) was greater than the negative-\(H.\) pylori chronic gastritis (6.08 pmol/L). However, it was statistically not significant (\(p = 0.418\)). Similar result was reported by some investigators.\(^{23-26}\) Kim et al\(^{23}\) in their report provides evidences of significant difference in serum gastrin level between the positive – cagA \(H.\) pylori and the negative – cagA \(H.\) pylori chronic gastritis. It may occur since the cagA is correlated to D cell densities and it is not correlated to the G-cell densities. Only the positive-cagA strain that can induce IL-8 and not all \(H.\) pylori strains can express the cagA. Examination of cagA gene was not performed in the present study.

The mean serum PGI level in positive-\(H.\) pylori chronic gastritis (114.8 pg/L) was greater compared to the negative-\(H.\) pylori chronic gastritis (104.42 pg/L). Moreover, the mean serum PGII level in positive-\(H.\) pylori chronic gastritis (10.5 µg/L) was greater than the negative-\(H.\) pylori chronic gastritis (7.81 µg/L). The PGI/PGII ratio in positive-\(H.\) pylori chronic gastritis (11.2) was lower than the negative-\(H.\) pylori chronic gastritis (13.8). Statistically, there was significant difference between the positive and negative-\(H.\) pylori chronic gastritis regarding the PGII level (\(p = 0.024\)) and PGI/PGII ratio (\(p = 0.001\)); while the PGI level indicated no significant difference (\(p = 0.363\)). Similar result was reported by Ito et al,\(^{25}\) Lopes et al,\(^{26}\) who suggest significant difference in serum PGI and PGII level and no significant difference in PGI/PGII ratio. Such results may be found since the subjects were children and the location of \(H.\) pylori chronic gastritis was mainly on the antrum part.

The present study concludes that the gastrin level >5.89 pmol/L and PGI/PGII ratio ≤13.6 can be used as the biomarkers of \(H.\) pylori chronic gastritis.

Several previous studies conclude that PGI/PGII ratio can be used as a biomarker for gastric atrophy.\(^ {29-35}\) Intestinal metaplasia\(^ {36}\) and gastric cancer.\(^ {37}\) Sipponen et al\(^ {16}\) utilize the serum gastrin and PGI level as a biomarker of gastric atrophy.

**Limitations of The Study**

There are some limitations regarding the present study, i.e. difficulties in controlling the true facts about the consumed medication and eating habit. Moreover, the present study did not examine virulence factors (vacA, cagA, napA, urease, Hsp60 and LPS), cytokines (IL-8, TNF-\(\alpha\) and INF-\(\gamma\)), the gastric Ca and NO level.

**CONCLUSION**

The present study concludes that the serum gastrin level and PGI/PGII ratio can be used as biomarkers for diagnosing chronic gastritis caused by \(H.\) pylori.

Results of the present study are suggested to be utilized as biomarkers for establishing diagnosis of chronic gastritis caused by \(H.\) pylori and as the basic data to initiate the eradication of \(H.\) pylori infection in order to prevent the peptic ulcer and gastric cancer.

**REFERENCES**


