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ASSOCIATION BETWEEN *HELICOBACTER PYLORI* INFECTIONS WITH SERUM GASTRIN-17 LEVELS IN DYSPEPSIA PATIENTS

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ABSTRACT

Background: *Helicobacter pylori infection is known to interfere with gastric acid secretion. One of the most potent gastrointestinal hormones in triggering gastric acid secretion is gastrin. However, the role of Helicobacter pylori in increasing serum gastrin levels remains controversial.*

Objective: *To determine the relationship between Helicobacter pylori infection with serum gastrin-17 levels in dyspepsia patients in the Endoscopic Unit Department of Internal Medicine, Dr. Soetomo General Hospital Surabaya.*

Methods: *This study used a cross-sectional method that enrolled thirty of dyspepsia patients underwent endoscopy and gastric biopsy in the endoscopic unit of the Department of Internal Medicine Dr. Soetomo General Hospital Surabaya. The patients were divided into two groups, i.e., fifteen patients infected with Helicobacter pylori and not. Determination of Helicobacter pylori infection was using histopathological examination. In the other hands, gastrin-17 fasting serum levels were measured by ELISA method.*

Results: *The results showed median of gastrin-17 serum levels in the H. pylori-infected group {3.97 (0.54-19.43)} were higher than the uninfected group {1.28 (0.62- 2.71)}. From the statistical test, there was a significant difference between the two groups ($p = 0.002$) with the medium-value relationship between Helicobacter pylori infection and gastrin-17 serum levels ($\eta = 0.478$).*

Conclusion: *There was a relationship between Helicobacter pylori infection with increased of gastrin-17 serum levels in dyspeptic patients.*

KEYWORDS: *dispepsia, Helicobacter pylori, gastrin-17*

INTRODUCTION

Dyspepsia is a discomfort from the upper abdominal area. It remains a health problem in the worldwide. The etiology of dyspepsia is varied and complexed, including *Helicobacter pylori* infection (*H. pylori*) [*Talley NJ, Vakil N, 2005, Ford A, Moayyedi P, 2013*]. *Helicobacter pylori* infection is found in nearly half of the world's population. This infection is quite high in Asia as well with prevalence ranging from 40.6% to 90%. In the other hands, the prevalence of *Helicobacter pylori* infection in Indonesia is about 22.1%, Meanwhile in Surabaya only about 11.5% [*Ohashi S et al., 2002, Chey WD, Wong BC, 2007, Takaishi S et al., 2009, Hunt RH et al., 2011, Miftahussurur M et al., 2015, Syam AF et al., 2015*].

H. pylori infection lead to various gastrointestinal diseases such as functional dyspepsia, peptic ulcer, mucosa-associated lymphoid tissue lymphoma, gastric atrophy, to gastric carcinoma. *H. pylori* infection causing a disturbance of gastric acid secretion that allegedly to play a role in the incidence of dyspepsia symptoms. Gastric acid secretion is regulated by several factors including the autonomic nervous system and the gastrointestinal hormone. One of the most potent gastrointes-

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tinal hormones in triggering gastric acid secretion is gastrin, that also has a trophic effect on the gastric mucosa as a carcinogenic cofactor that allegedly involved in the mechanism of disorder occurrence [*Huang X-Q, 2000, Kaneko H et al., 2002, Konturek SJ et al., 2006, Harmon RC, Peura DA, 2010, Garza-González E et al., 2014*]. Some studies have shown a significant increase in serum gastrin levels in patients infected with *H. pylori* [*Mossi S et al., 1993, Kim JH et al., 1999, Chuang CH, et al., 2004, Isomoto H et al., 2005, Elseweidy MM et al., 2010*], but several other studies have not shown significant increases in serum gastrin levels [*JJonsson B et al., 1998; Honarkar Z, 2006; Arinton I, 2010; Jung T et al., 2016*]. Thus the role of *H. pylori* in increasing serum gastrin levels still remains controversial.

The examination, diagnosis, and management of diseases that related to *H. pylori* infection are considerate as an economic problem. The quality of life's impact of *H. pylori*-infected dyspeptic patients also has a lower score than uninfected [*Groeneveld PW et al., 2001, Buzas GM, 2006, Lansdorp-Vogelaar I, Sharp L, 2013*]. Various studies have been conducted to determine the effect of gastrin on *H. pylori* infection, that showed significantly increased of serum gastrin in *H. pylori*-infected patients compared to *H. pylori*-uninfected [*Mossi S et al., 1993, Elseweidy MM et al., 2010*]. However, a study conducted by Jonsson BH and Honarkar Z were obtained different results [*Jonsson BH et al., 1998, Honarkar Z, 2006*]. This related to the measurement method of determining the infection of *H. pylori* and gastrin type.

Based on the description, it is necessary to do research with a more of appropriate method. Gastrin-17 is 95% gastrin in the antrum, that could stimulate gastric acid secretion five times stronger than Gastrin-34. The determination of *H. pylori* infection was using histopathologic examination, in addition having a high degree of sensitivity and specificity also could be used to evaluate the tissue damage [*Taj Y et al., 2003, Schubert ML, Peura DA, 2008*]. Thus, this study using histopathologic methods to determine the presence of *H. pylori* infection and measured gastrin-17 serum levels as a measurement of gastrin levels.

Material and Methods

Research Design and Population

This research uses the cross-sectional method with an observational analytic. It used consecutive sampling of dyspepsia patients aged 18 to 60 years old, that come to an endoscopic unit of Department of Gastroenterol-Hepatology Internal Medicine Dr. Soetomo General Hospital Surabaya. The data obtained since November 2014 to June 2015 that also willing to participated by signing informed consent. Dyspeptic symptoms will lasted for at least 3 months. The patients were not allowed to take medications that used as eradicate *H. pylori* infection, PPI, H2 receptor antagonists, and NSAIDs or steroids in the last 2 weeks also smoke within 1 month before recruited in this study.

This study excluded the patients with categorized; upper and lower gastrointestinal bleeding, impaired renal function, infection, gallbladder disease or cirrhosis of hepatitis, upper gastrointestinal obstruction, gastric mucosal atrophy, history of alcohol drinking, history of gastric surgery, or contra-indicated examination endoscopy and the last gastric biopsy.

Symptom Parameters

Dyspepsia patients are patients who experience chronic or recurrent pain or discomfort in the upper abdomen. Discomfort is defined as painless of negative subjective, that include symptoms such as full satiety, bloating fullness of the upper abdomen, or nausea [*Abdullah M et al., 2009*].

Density of *Helicobacter pylori*

H. pylori infection is an infection of the gastric mucosa by *H. pylori*, it was based on histopathology examination results by 2 anatomical pathologists of Dr. Soetomo General Hospital Surabaya [*Matsuda NM et al., 2009*]. The density of *H. pylori* is the number of *H. pylori* colonization that categorized into nonexistent, mild, moderate, and severe according to the Sydney Update System. Mild *H. pylori* density is if the *H. pylori* colonization found only in one place or slightly across the entire field of vision. Moderate *H. pylori* density is if the *H. pylori* colonization found to be widely spread in separate areas. Lastly, severe *H. pylori* density is if the colonization of *H. pylori* almost covers the gastric surface [*Kusters JG et al., 2006*].

Gastrin-17 Serum Levels

Gastrin-17 serum levels were serum levels in a fasting state that examined by the ELISA method and defined by the unit of *pmol/L* [*Schubert ML, Peura DA, 2008, Sulaksana M et al., 2015*].

Gastritis

Gastritis is a gastric mucosal inflammation on histologic examination that discovered the presence of neutrophil and eosinophils in acute gastritis, also lymphocyte and plasma cell in chronic gastritis. Chronic gastritis is inactive when mononuclear infiltration is present and no polymorphonuclear was found or slightly. While, chronic gastritis is active when mononuclear infiltration and polymorphonuclears were found [*Rugge M et al., 2011*]. Gastritis distribution is divided into 3, i.e., antrum predominant gastritis, corpus predominant gastritis, and pangastritis. Antrum-predominant gastritis is if the degree of inflammation in antrum higher than in corpus. Corpus predominant gastritis is if the degree of inflammation in the corpus higher than in antrum. While pangastritis is if the degree of inflammation in antrum the same as in corpus [*Kayacetin S, Guresci S, 2014*].

Statistical Analysis

This study, an analysis performed to assess the association between *Helicobacter pylori* infection and gastrin-17 serum levels in dyspepsia patients was by using t-test analysis and Mann-Whitney test, also Eta test to analysis the strength of relationships.

Results

Basic Characteristics of Research Subject

Thirty dyspepsia patients were enrolled and performed in Endoscopic Unit of Department Gastroentero-Hepatology of Internal Medicine Dr. Soetomo General hospital Surabaya. Thirty (30) patients were divided into 2 groups, i.e., 15 patients in the *H. pylori*-infected group and 15 patients in the *H. pylori*-uninfected group. General characteristics of research subjects are shown in Table 1.

Nineteen of (63.3%) female sex patients were enrolled in this study with the mean age was 46.47 ± 10.31 years old. The education level of the subjects in this study showed a varied outcome from non-school to university, with the highest number 33.3% was senior high school. This study obtained that the most complaints were; nausea (90.0%) and epigastric pain (90.0%). In the *H. pylori*-infected group, all patients had epigastric pain (100.0%) while, the H. the pylori-uninfected group, was nausea (100.0%).

The most endoscopic result was superficial gastritis about 53.3%. In the *H. pylori*-infected group, endoscopic features with superficial gastritis, erosive gastritis, and gastroduodenitis were 53.3%, 33.3%, 13.3% respectively. While in the *H. pylori*-uninfected group were superficialis gastritis, erosive gastritis, and gastroduodenitis, peptic ulcer respectively were 53.3%, 33.3%, 6.7%. From the results of the study, endoscopic representation with gastroduodenitis was commonly in the *H. pylori*-infected group.

Description of Histopathology in Research Subject

In the results of the histopathologic examination, infected and uninfected subjects of *H. pylori* showed a description of gastritis distribu-

Table 1.

General characteristics of research subjects

Variable	Total (n=30)	H. pylori Un-infected (n=15)	H. pylori infected (n=15)
Sex, n(%)			
Male	11 (36.7)	5 (33.3)	6 (40.0)
Female	19 (63.3)	10 (66.7)	9 (60.0)
Ages (y/o)	46.47±10.31	44.60±12.49	48.33±7.54
Education, n(%)			
un-educated	1 (3.3)	1 (6.7)	0
Elementary School	8 (26.7)	3 (20.0)	5 (33.3)
Vocational High School	3 (10.0)	2 (13.3)	1 (6.7)
Senior High School	10 (33.3)	4 (26.7)	6 (40.0)
College	8 (26.7)	5 (33.3)	3 (20.0)
Symptoms, n(%)			
Nausea	27 (90.0)	15 (100.0)	12 (80.0)
Vomit	14 (46.7)	6 (40.0)	8 (53.3)
Epigastrium Pain	27 (90.0)	12 (80.0)	15 (100.0)
Bloated	13 (43.3)	7 (46.7)	6 (40.0)
Easily Satiated	13 (43.3)	7 (46.7)	6 (40.0)
Endoscopic Results, n(%)			
Gastritis superficialis	16 (53.3)	8 (53.3)	8 (53.3)
Gastritis erosiva	10 (33.3)	5 (33.3)	5 (33.3)
Gastroduodenitis	3 (10.0)	1 (6.7)	2 (13.3)
Ulkus peptikum	1 (3.3)	1 (6.7)	0

Table 2.

Distribution of histopathologic features in the study subjects

Histopathology	Total (n=30)	Uninfected-*H. pylori* (n=15)	Infected-*H. pylori* (n=15)
Gastritis Distribution, n (%)			
- *Antrum-predominant gastritis*	6 (20.0)	2 (13.3)	4 (26.6)
- *Corpus-predominant gastritis*	2 (6.7)	1 (6.7)	1 (6.7)
- *Pangastritis*	22 (73.3)	12 (80.0)	10 (66.7)
Inflammation Activity, n (%)			
- Inactived Gastritis Cronic	25 (83.3)	13 (86.7)	12 (80.0)
- Active Gastritis Cronic	5 (16.7)	2 (13.3)	3 (20.0)
Density of *H. pylori*, n (%)			
- None	15 (50.0)	15 (100.0)	0
- Mild	7 (23.3)	0	7 (46.7)
- Moderate	5 (16.7)	0	5 (33.3)
- Severe	3 (10.0)	0	3 (20.0)

tion, inflammatory activity, and *H. pylori* density. The distribution of each histopathologic picture are shown in table 2.

Histopathologic description in *H. pylori*-infected patients showed that most patients had pangastritis features, both in *H. pylori*-infected and uninfected patients. Based on inflammatory activity, chronic inactive gastritis was 83.3% and chronic gastritis active was 16.7%. Inactive gastritis chronic is the most common histopathologic outcome in the both groups. An active gastritis chronic feature was found in the *H. pylori*-infected group more than the *H. pylori*-uninfected group. In *H. pylori*-infected patients it was found that *H. pylori* density was mild then followed by moderate and severe.

Comparison of Gastrin-17 Serum Levels by Histopathology Overview

The mean of gastrin-17 serum levels in the *H. pylori*-infected group was 5.62 ± 5.47 *pmol/L* while uninfected group was 1.51 ± 0.77 *pmol/L*. The median gastrin-17 serum level in the *H. pylori*-infected group was 3.97 *pmol/L* with range 0.54-19.43 *pmol/L* while uninfected group was 1.28 *pmol/L* with range 0.62-2.71*pmol/L*. Mean and median gastrin-17 serum levels in the *H. pylori*-infected group were higher than in the uninfected group.

The results of histopathological examination were *H. pylori*-infected and uninfected might show inflammatory activity and *H. pylori* infection density. The results comparison of ratio gastrin-17 serum based on inflammatory activity in *H. pylori*-infected and uninfected patients are shown in table 3.

The mean and median gastrin-17 serum levels in active gastritis chronic were higher than inactive gastritis chronic in both *H. pylori*-infected and uninfected group. As well as In an inactive gastritis chronic, the *H. pylori*-infected patient group also obtained a higher mean and median of gastrin-17 serum levels than the *H. pylori*-uninfected group as well as active gastritis chronic.

The density of *H. pylori* divided into 4-groups; none, mild, moderate, and severe. The results comparison of ratio gastrin-17 serum was based on *H. pylori* density in *H. pylori*-infected and uninfected patients

Table 3.

Comparison of gastrin-17 serum levels based on inflammatory activity and on H. pylori density levels in H. pylori-infected and un-infected patients

Groups		n	Gastrin-17 Serum Levels (*pmol/L*) Mean ± SD	Median (min-max)
Inflammation Activity				
Uninfected-*H. pylori*	Inactive Chronic Gastritis	13	1.48±0.72	1.28 (0.62-2.71)
	Active Chronic Gastritis	2	1.69±1.41	1.69 (0.69-2.69)
Infected-*H. pylori*	Inactive Chronic Gastritis	12	4.26±4.97	3.65 (0.54-19.43)
	Active Chronic Gastritis	3	11.06±4.24	12.98 (6.20-14.0)
Density of *H. pylori*				
Uninfected-*H. pylori*	None	15	1.51 ± 0.77	1.28 (0.62-2.71)
Infected- *H. pylori*	Mild	7	4.35 ±6.73	1.64 (0.54-19.43)
	Moderate	5	5.79 ± 4.04	4.32 (3.57-12.98)
	Severe	3	8.32 ± 4.98	6.2 (4.75-14.00)

that are shown in table 3. The mean and median of gastrin-17 serum levels were highest in the severe *H. pylori* density (8.32 ± 4.98 *pmol/L* and 6.2 (4.75-14.00) *pmol/L*) groups. The higher *H. pylori* density, the higher the gastrin-17 serum levels as well.

Relationship between *H. pylori* Infection with Gastrin-17 Serum Level

The relation analysis of *H. pylori* infection and gastrin-17 serum levels was using the Mann-Whitney test, because the data obtained was not normally distributed while the relation strength analysis was using Eta test. The results of Mann-Whitney test analysis and Eta test are shown in table 4.

From table 4, the Mann-Whitney test statistically showed that p = 0.002 significantly difference from gastrin-17 serum level in the *H. pylori*-infected group and the uninfected group. Whereas, the Eta test analysis was obtained a coefficient Eta (0.478) which show the strength of mild relation.

Discussion

In this study, there was a significant difference between gastrin-17 serum levels in the *H. pylori*-infected group and the *H. pylori*-uninfected group (p = 0.002). Wherein *H. pylori* infection with gastrin-17 serum levels had moderate (Eta coefficient 0.478). Gastrin-17 serum levels were higher in *H. pylori*-infected dyspepsia patients compared to the *H. pylori*-uninfected patients with median gastrin-17 serum levels in the *H. pylori*-infected group was 3.97 (0.54-19, 43) *pmol/L*.

Similar studies showed significant differences between total serum gastrin levels and *H. pylori* infection that were conducted by Kim J in Korea (p <0.05), Isomoto H in Japan in Japan (p = 0.005), and Efendi D in Indonesia (p = 0.017) [*Kim JH et al., 1999, Isomoto H et al., 2005, Arismendi-Morillo G et al., 2013*]. However, studies that showed significant differences between gastrin-17 serum levels and *H. pylori* infection were by Sokic-Milutinovic A in Serbia (p <0.01), Elseweidy M in Egypt (p <0.001), Zheng K in Japn (p <0.05), and Gong Y in China (p <0.001, both on examination with IgG and 14C-UBT) [*Sokic-Milutinovic A et al., 2005; Efendi D et al., 2009; Elseweidy M et al., 2010; Zheng K et al., 2012*].

Table 4.
Result of Mann-Whitney test analysis and Eta test of gastrin-17 serum level

Groups	n	Median (min-maks) (*pmol/L*)	p Value	Eta coefficient
Uninfected-H. pylori	15	1.28 (0.62 – 2.71)	0.002*	0.478
Infected-H. pylori	15	3.97 (0.54 – 19.43)		

Note: ** - Whitney's Test*

The results of this study showed a moderate relationship between *H. pylori* infection and gastrin-17 serum levels (η = 0.478). The relationship direction was unknown because it was only a non-linear relationship. A correlation study was conducted by Gong Y and co-autors (2014) in China that showed a moderate correlation between *H. pylori* infection with gastric function disorder indicate gastrin-17 serum levels> 3 *pmol/L* (r = 0.469, p = 0.000 for examination with serology IgG and r = 0.394, p = 0,000 for checks with 14C-UBT) [*Zheng KC et al., 2012*].

The increase serum gastrin levels caused by antigens from *H. pylori* such as urease, LPS, and porins could stimulate macrophages to produce cytokines. IL-8, IL-1β, TNF-α, and INFγ could directly trigger gastrin release from the G cells. *H. pylori* strain that carrying cagA could induce a stronger IL-8 response, and depends on NF-κB activation. Other than cytokines, Nα-Methyl histamine that produced by *H. pylori* as H3 receptor agonists also able to inhibit the secretion of somatostatin from the D cells, so gastrin secretion by G cells increases. Gastrin secreted by G cells will lead to circulation and affect the ECL cells to produce histamine. Histamine directly stimulates parietal cells that resulting acid secretion. The increased of gastric acid might cause dyspepsia [*Beales I et al., 1997; Huang X, 2000; Suerbaum S, Michetti P, 2002; Konturek S et al., 2006; Schubert M, Peura D, 2008; Gong Y et al., 2014;*]. But cytokine and cagA examinations were not performed in this study.

Gupta A and co-autors (1997) attempted to evaluate the density of G antrum cells through gastrin mRNA expression that showing the results of G cell density in patients with *H. pylori* infection was significantly greater than control. After eradication of *H. pylori*, G cell density was significantly lower than before the eradication. It was alleged that an increase in gastrin mRNA was directly associated

with *H. pylori* infection [*Gupta A et al., 1997*].

H. pylori infection causing hyperfunction of G antrum cells, thus secretion and gastrin synthesis will increase. Several studies have shown that serum gastrin levels were significantly higher in patients with *H. pylori* infection than controls. After complete eradication therapy, serum gastrin levels might significant drop as statistically [*Efendi D et al., 2009*].

H. pylori infection causing chronic gastritis, peptic ulcer, atrophic gastritis, intestinal metaplasia, and gastric cancer. Approximately 10% to 15% of chronically *H. pylori*-patients were inflamed primarily in the antrum, which tends duodenal ulcers to happen. Stomach acid production increased as a result of reduced anterior somatostatin and increased gastrin secretion [*Kaneko H et al., 2002, Schubert ML, Peura DA, 2008, Matsuda NM et al., 2009*]. In this study no peptic ulcers were obtained in the *H. pylori*-infected group. This because upper or lower gastrointestinal bleeding might one of the symptoms of a peptic ulcer that included in the exclusion criteria of the study. As well as atrophic gastritis and stomach cancer (especially those causing pyloric obstruction) that not found in the study subjects. In addition, the frequency rarely found in Surabaya in accordance with the research done by Hapsari (2013), that also included in exclusion criteria because it affects the gastrin-17 serum levels [*Copps J et al., 2009*].

Chronic *H. pylori* infection could disrupt gastric acid secretion either decrease or increase, depending on the severity and distribution of gastritis. Most patients infected with chronic *H. pylori* have manifestations of pangastritis and produce less than the normal amount of stomach acid. Decreased gastric acid secretion was attributed to the functional inhibition of parietal cells by either the product of *H. pylori* itself or the product of the inflammatory process. In conditions of oxyntic gland atrophy with loss of parietal cells, irreversible achlorhydria might occur [*Konturek SJ et al., 2006*]. To assess gastric acidity it requires gastric pH examination, but in this study was not performed.

The decreased mechanism of somatostatin secretion in *H. pylori* infection was not a fully known but it might involved cytokines that caused by inflammation and/or production of Nα-methylhistamine, a selective H3 receptor agonist. H3 receptor agonists spread in the antrum mucosa and interact with H3 receptors in antrum somatostatin cells that leading to inhibition of somatostatin secretion and then stimulating the gastrin secretion [*Schubert ML, Peura DA, 2008*]. Somatostatin examination was also not performed in this study.

The complex mechanism control of gastrin and histamine release that involving somatostatin in controlling gastric acid secretion might hampered in the presence of *H. pylori* infection. The suppression of D-cell activity causes hypergastrinemia and an increases of gastric acid secretion. It was present in *H. pylori*-infected patients with antrum-predominant gastritis description. *H. pylori* also directly stimulate ECL cells to release histamine in order to increase parietal cell secretion activity. *H. pylori* infection that involving the oxyntic gland area will develop into corpus-predominant gastritis. It also directly affect oxyntic cells to down-regulate subunit expression of proton pump (H +/ Na + -ATPase) which causes hypochlorhydria. This occurs in acute *H. pylori* infection and corpus-predominant gastritis. But most of the *H. pylori*-infected patients showed mixed gastritis/pangastritis and normal gastric acid secretion without a significant gastric disease [*Suerbaum S, Michetti P, 2002; Konturek S et al., 2006*]. In this study, the majority of patients had pangastritis features.

Some research limitations that affect the results of this study were; 1) the research design used was cross-sectional thus gastrin-17 serum levels were performed only once; 2) some confounding variables that known from the results subjective anamnesis, e.g., comorbidities, smoking history, history of drugs taken, and different of stress levels; 3) This study has not been able to assess the correlation of *H. pylori* infection with gastrin-17serum levels due to the limited number of study samples.

Conclusion

This study showed that there was a relationship between *H. pylori* infection with increase of gastrin-17serum levels ($\eta = 0.478$; $p = 0.002$). Median gastrin-17 serum levels in the chronic histopathology of active chronic gastritis were higher than inactive chronic gastritis in both *H. pylori*-infected and uninfected patients. The higher the density level of *H. pylori* associated with the higher gastrin-17 serum levels.

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