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The Relationship of MMP-3 Levels with the Degree of Helicobacter Pylori Gastritis

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ABSTRACT

Gastritis is an inflammation in the stomach tissue that can occur either acutely or gradually as a chronic condition. Incidence of gastritis in Indonesia is high, which is 274,396 cases out of 238,452,952 inhabitants. One of the most common causes of gastritis is Helicobacter pylori (H. pylori). Matrix metalloproteinase (MMP) is a dependent proteinase that is able to break down almost all extracellular matrix proteins. It is known from several studies that MMP is closely related to gastric ulcer disease and cancer. At present, in vivo and in vitro studies have established the activation of several MMPs associated with H. Pylori infection. There were 80 samples obtained through consecutive sampling in March-June 2019. Gastritis was ensured by endoscopy (Olympus, Tokyo, Japan). H.pylori is established through a change in color from yellow to red, magenta, pink, or orange in the examination of Campylobacter Like Organism test (CLO). MMP-3 level examination using a serum MMP3 was measured using RayBio Human MMP-3 and MICA ELISA kits (Norcross, GA). Data were collected and analyzed using SPSS version 22. There was a significant relationship between MMP-3 levels and the severity of H. pylori gastritis, namely between the degree of neutrophil infiltration (p = 0.016), atrophy (p = 0.001), and intestinal metaplasia (p <0.001).

Key Words: Gastritis, Helicobacter Pylori, MMP-3

INTRODUCTION

Gastritis is an inflammation in the stomach tissue that can occur either acutely or gradually as a chronic condition.[1] Incidence of gastritis in Indonesia is high, which is 274,396 cases out of 238,452,952 inhabitants. Previous studies have highlighted the importance of MMPs in diseases involving mucosal inflammation. MMP is a dependent proteinase that is able to break down almost all extracellular matrix proteins. MMP takes part in many biological processes such as tissue remodeling, wound healing, and embryonic development and also plays a role in tumor invasion and metastasis through degradation of connective tissue, basement membrane and matrix stroma. Overactivity of MMPs causes damage to the host by causing damage connective tissue.[2]

It is known from several studies that MMP, is closely related to gastric ulcer disease and cancer. At present, vivo and in-vitro studies have established the activation of several MMPs associated with H. Pylori infection. In accordance with its proteolytic nature, increased MMP production has been documented in several human diseases characterized by tissue degradation, including H. pylori infections associated with gastritis and gastrointestinal ulcers.[3]

METHOD

Patient Selected

There were 80 samples obtained through consecutive sampling in March-June 2019. Gastritis was ensured by endoscopy (Olympus, Tokyo, Japan). Mucosa undergoes edema, erythema (spotted, patchy, linear), exudate, bleeding, erosion and histopathology (marked by

inflammatory cells in the gastric mucosa) is diagnosed with gastritis. H.pylori is established through a change in color from yellow to red, magenta, pink, and orange in the examination of Campylobacter Like Organism (CLO)test. MMP-3 level examination using a serum MMP3 was measured using RayBio Human MMP-3 and MICA ELISA kits (Norcross, GA).

Data analysis

Data analysis of total antioxidant level on H.pylori gastritis patients were univariate and bivariate. Univariate analysis to determine the characteristics of H.pylori gastritis patients and the prevalence of H.pylori gastritis patients. Bivariate analysis to determine the ratio of total serum antioxidant levels between positive and negative H.pylori gastritis patients using independent T-test and ANOVA test. All data were analyzed by SPSS 22 version. A value of $p<0.05$ with a 95% confidence interval was considered statistically significant.

RESULT

Most subjects were male (61.25%) with a median age of 47 years. Most ethnic groups are Batak (57.5%), followed by Javanese (35%) and Acehnese (7.5%). Most jobs a

re private employees (43.8%). Generaly subjects with high school education (51.3%). The median value of BMI is 23.16 kg / m2. 35% of the subjects were infected with H. pylori. The mean MMP-3 in the study subjects was 1.98 ng/mL (Table 1). Most subjects have mild Chronic Inflammation (55%). And most of them have normal neutrophil infiltration (41,3), followed by mild neutrophil infiltration (37,5%), moderate (17,5%), and severe (3,8%). There isn't any atrophy or normal (83,8%), followed by mild atrophy (11,3%), and moderate atrophy (5%). The result of intestinal metaplasia is normal (95%), and followed by mild intestinal metaplasia (5%). (Table 2).

Table 1. Baseline and clinical characteristic of subjects

Characteristic	n = 80
Gender [a]	
Male	49 (61.25)
Female	31 (38.75)
Age (years) [b]	47 (24 – 66)
Ethnic [a]	
Batak	46 (57.5%)
Java	28 (35%)
Acehnese	6 (7.5%)
Occupation [a]	
Private employee	35 (43.8%)
Housewive	18 (22.5%)
Entrepreneur	22 (27.5%)
Civil servants	5 (6.3%)
Education [a]	
Elementary school	3 (3.8%)
Junior High School	20 (25%)
High School	41 (51.3%)
University	16 (20%)
BMI (kg/m^2) [b]	23.36 ± 3.75
H. pylori [a]	
Positive	28 (35%)
Negative	52 (65%)
MMP-3 (ng/mL) [c]	1.98 ± 1.16

[a] Categoric data: n(%)
[b] Numeric data, not normal distribution: median (min-max)
[c] Numeric data, normal distribution: mean ± SD

Table 2. Degree of gastritis

Degree of gastritis	n (%)
Chronic inflammation	
Normal	0 (0%)
Mild	44 (55%)
Moderate	26 (32.5%)
Severe	10 (12.5%)
Neutrophil infiltration	
Normal	33 (41.3%)
Mild	30 (37.5%)
Moderate	14 (17.5%)
Severe	3 (3.8%)
Atrophy	
Normal	67 (83.8%)
Mild	9 (11.3%)
Moderate	4 (5%)
Severe	0 (0%)
Intestinal metaplasia	
Normal	76 (95%)
Mild	4 (5%)
Moderate	0 (0%)
Severe	0 (0%)

There were significant differences in MMP-3 levels between the degrees of neutrophil infiltration ($p = 0.016$), atrophy ($p = 0.001$), and intestinal metaplasia ($p <0.001$). MMP-3 levels were significantly higher in severe degree neutrophil infiltration (3.61 + 1.54 ng / mL) than normal (1.64 + 1.09 ng / mL). MMP-3 levels were significantly higher in moderate (3.38 + 0.86 ng / mL) and mild (2.88 + 1.55 ng / mL) atrophy than normal (1.64 + 1.09 ng / mL). MMP-3 levels were significantly higher in mild intestinal metaplasia (4.06 + 0.98 ng / mL) than normal (1.87 + 1.07 ng / mL). There were no differences in MMP-3

levels among the degree of chronic inflammation (p> 0.05). (Table 3)

Table 3. The difference of MMP-3 levels between degrees of gastritis

Degree of gastritis	MMP-3 levels (ng/mL)	p
Chronic inflammation		0.077
Mild	1.83 ± 1.09	
Moderate	1.95 ± 1.15	
Severe	2.74 ± 1.34	
Neutrophil infiltration		0.016*
Normal	1.64 ± 1.09	
Mild	2.03 ± 1	
Moderate	2.32 ± 1.3	
Severe	3.61 ± 1.54 #	
Atrophy		0.001*
Normal	1.77 ± 1.01	
Mild	2.88 ± 1.55 #	
Moderate	3.38 ± 0.86 #	
Intestinal metaplasia		<0.001*
Normal	1.87 ± 1.07	
Mild	4.06 ± 0.98	

**p<0.05, # significant compared to normal degree*

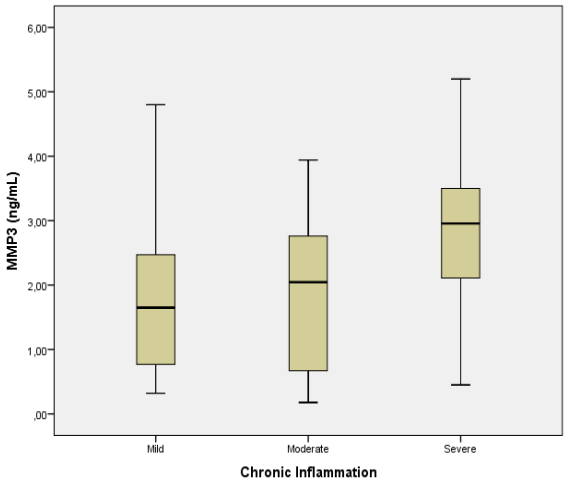

Figure 1. Boxplot diagram of MMP-3 levels based on the degree of chronic inflammation

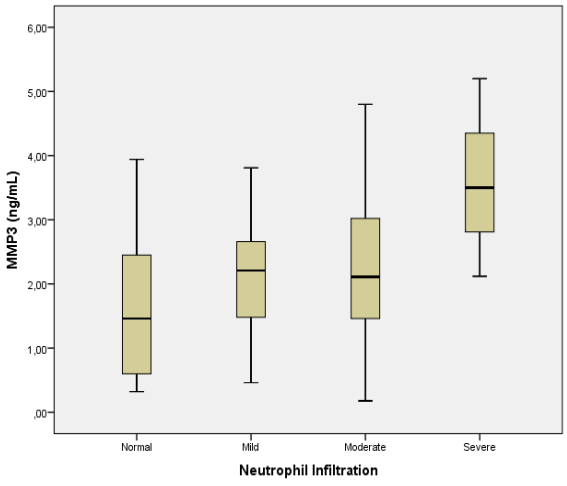

Figure 2. Boxplot diagram of MMP-3 levels based on the degree of neutrophil infiltration

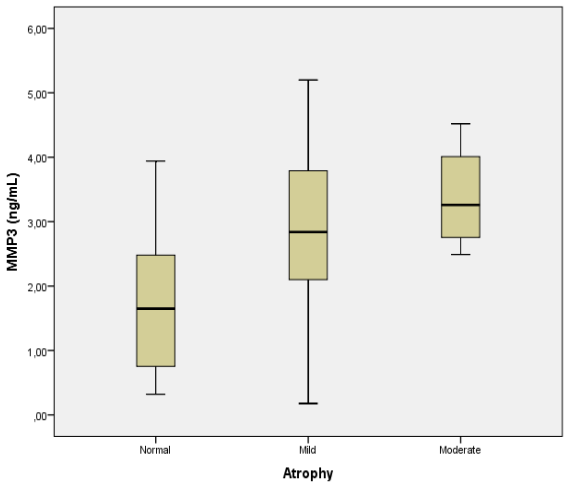

Figure 3. Boxplot diagram of MMP-3 levels based on degree of atrophy

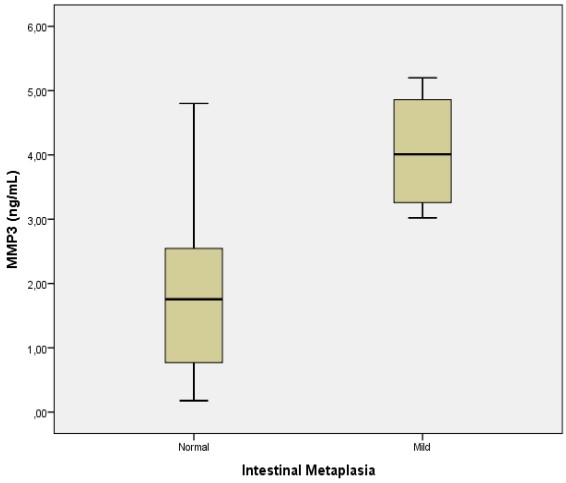

Figure 4. Boxplot diagram of MMP-3 levels based on the degree of intestinal metaplasia

DISCUSSION

In this study, it was showed that majority of gastritis patients were male (62.5%). This result is similar to the research conducted by Chen, et al in China with 2,051 people (51.7%) of whom were men.[4] Other study by Dairi, et al in Indonesia also showed similar results that 24 people (60%) patients with gastritis are men.[5] However, study by Akeel et al in Egypt did not show the same result that 207 people (51.2%) gastritis sufferers are women.[6] This difference may be due to the influencing by various other factors, such as racial, demographic, and other comorbid factors such as Gastroesophageal Reflux Disease disorders.[7] Some factors in the work are known to affect the virulence of H. pylori and also the immune response to

infection. In this study, housewives were obtained the highest percentage. A study by Tajalli et al found things be related to the findings of this study, where gastritis is more common among women who live in a crowded environment. This is because these women are more likely to have close contact with children, which is said to often transmit H. pylori infection. Most gastritis sufferers were found in the Batak tribe (57.5%), followed by Javanese (35%) and Acehnese (7%). Our previous study also showed similar results where gastritis sufferers were most often found in the Batak tribe (57.5%) then Javanese (30%) and Acehnese (12.5%). There was a significant relationship between MMP-3 levels and the severity of H. pylori gastritis, namely between the degree of neutrophil infiltration ($p = 0.016$), atrophy ($p = 0.001$), and intestinal metaplasia ($p < 0.001$). How MMP-3 contributes to tissue damage in gaster is not fully understood. But this result is supported by a study by A number of past *in vitro* and *in vivo* studies have suggested that none of the major families of proteolytic enzymes are required for neutrophil transmigration across the vessel wall. Huber and Weiss (1989) showed that neutrophil migration across an *in vitro* vessel wall construct could not be blocked with either serine proteinase or metalloproteinase inhibitors.[8] Although this "negative" finding could be explained by a failure of the high molecular weight natural inhibitors to access the protected site, a subsequent study by Mackarel et al. (2000) came to a similar conclusion based on the use of synthetic low molecular weight proteinase inhibitors.[9] Other study provides evidence that host promoter polymorphisms of MMP-3 contribute to increased individual susceptibility to duodenal ulcers in females after H. pylori infection in Taiwan. The MMP-3 promoter genotypes may serve to screen out patients at risk and target for H. pylori eradication in order to stop the ulceration process among H. pylori-infected patients without ulcers yet.[10]

CONCLUSION

There is an association between serum level MMP-3 and gastritis due to H.pylori infection. There were significant differences in MMP-3 levels between the degrees of neutrophil infiltration and intestinal metaplasia. MMP-3 levels were significantly higher in severe degree neutrophil infiltration than normal. MMP-3 levels were significantly higher in moderate and mild atrophy than normal. MMP-3 levels were significantly higher in mild intestinal metaplasia than normal. There were no differences in MMP-3 levels among the degree of chronic inflammation.

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