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THE DIFFERENCES LEVEL OF INTERLEUKIN-22 BETWEEN POSITIVE AND NEGATIVE HELICOBACTER PYLORI GASTRITIS

P Nancy*[1], AS Gontar[2] & L Dharma[1]

[*1]Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik Hospital, Medan, Indonesia.

[2]Gastroenterohepatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik Hospital, Medan, Indonesia

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Abstract

Introduction: Helicobacter pylori (*H. pylori*) is the most common cause of chronic gastritis worldwide. *H. pylori* infection will cause an increase in mononuclear (MN) and polymorphonuclear (PMN) cell infiltration and will increase the production of proinflammatory cytokines namely Interleukin-22. This study aimsto determine differences of serum Interleukin-22 level between positive and negative Helicobacter pylori (*H. pylori*) patient groups.

Methods: This study was a cross-sectional study. Inclusion criteria are stated as followings: male or female aged ≥ 18 years old at Adam Malik General Hospital & Permata Bunda Hospital Medan started from May to August 2019, patients diagnosed with gastritis by an endoscopic, signed the patient consent forms, none of the patients had received antibiotics, a bismuth compound, H2 antagonists, proton pump inhibitors within the last four weeks before endoscopy. Patients with evidence of malignancy, immunosuppression, metabolic disorders, gastrointestinal haemorrhage, had a history of gastric surgery were excluded.*H. pylori* was examined by Campylobacter Like Organism test (CLO).Univariate and bivariate analysis (mann-whitney test), were done using SPSS version-22.

Results: Of the 60 subjects, they are divided into 2 groups; 32 subjects in the negative *H. pylori* group and 28 subjects in the positive *H. pylori* group. The median serum IL-22 level in positive *H. pylori* was 55,5 (23 – 104) pg / ml and negative *H. pylori* was 19 (16-23) pg / ml.

Conclusion: There were statistically significant (p<0,001) differences in serum IL-22 levels between positive and negative *H. pylori* patient groups.

Introduction

Helicobacter pylori (H. pylori)is a Gram-negative flagellate bacterium that infects gastric mucosa of the human.[1]H. pylori infection is asymptomatic in many cases. H. pylori infection is the most common cause of chronic gastritis in the world [2,3],associatedwithchronic inflammation of the gastric mucosa (gastritis) and can cause peptic ulceration and gastric cancer.[4]Most of these infections occur in developing countries with a percentage between 70-90% while only 40-50% occur in industrialized countries.[2,3] The prevalence of H. pyloriinfectionin Asia including in Indonesia, is very high.[5,6]The research from Gontar et al report that the prevalence from eightygastritis patients that were admitted to Endoscopy Unit at Permata Bunda Hospital, Medan and Adam Malik General Hospital, Indonesia between May and December 2016, there were 45 (56.3%) H. pylori-infected patients and 33 (73.3%).[7]

Gastric inflammation, promoting neutrophils and lymphocytes recruitment, and increases the release of proinflammatorycytokines which causes gastric mucosa damage.[8,10]IL-22hasproinflammatoryeffectsduringH.pyloriinfection.[11,12]Shamsdin et al reported IL-22 levels significantly increased in the active chronic gastritis, compared to that uninfected groups (P=.005).

Based on information above, this study was prepared to determine the differences of Interleukin-22 levels in patients with H. pylori and non H. pylori gastritis, and perhaps from this research IL-22 can be used to diagnostic biomarkers for H. Pylori infection.

Material and methods

Patient Selection

This study was a cross-sectional study on fourty consecutive gastritis patients that were admitted to Endoscopy Unit at Adam Malik General Hospital and Permata Bunda Hospital, Medan, Indonesia. The independent variables were H. pyloripositive and negative and the dependent variable was serum IL-22.Research begins with library searches, title consultations, preparation of proposals, proposal seminars, research and data analysis and preparation of reports that require time from May 2019 to August 2019.

Inclusion criteria are stated as followings: male or female aged ≥ 18 years old, patients were diagnosed with gastritis on endoscopy and histopathologic examination, willing to be recruited in the study and signed the patient consent forms. None of the patients had received antibiotics, a bismuth compound, H2 antagonists, proton pump inhibitors or immune modulating drugs within the last four weeks before endoscopy.

Patients with evidence of malignancy, immunosuppression, metabolic disorders, or gastrointestinal haemorrhage, and patients who had a history of gastric surgery were excluded. This study was approved by the local ethics committee. During endoscopy examination, gaster biopsy specimens were taken for Campylobacter Like Organism Test (CLO) and from venous blood were examined Serum Levels of IL-22.

Helicobacter pylori Detection

The Rapid urease test (CLO test, Kimberly- Clark, Utah, USA) was used to establish diagnosis of H. pylori infection. The results were read within 24 hours. Yellow is considered a negative result. A positive result was reported if the color changed from yellow to red, magenta, pink or deep orange within 24 h of incubation at room temperature.[9]

Serum Levels of IL-22

Venous blood was drawn using a serum separator tube and allowed to clot for 30- 45 minutes at room temperature before centrifugation for 15 minutes at approximately 1,000 g. Serum was immediately stored frozen in aliquots at -20^{o}C until assays for IL-22 were performed. Circulating IL-22 levels were examined in serum using the Quantikine Human ELISA (Quantikine, R&D System, Inc., Minneapolis).

Statistical Methods

SPSS version 22 (SPSS Inc., Chicago) was used for the analysis. The data were analyzed using univariate and bivariate analysis with 95% confidence interval. Bivariate analysis was carried out using a Mann Whitney tests and Spearman correlation test was used to analyze the correlation between IL-22. With a significance levels set at $p<0.05$.

Results

From the 60 subjects patient of gastritisthere were 36 (60%) male patients and 24 (40%) female patients. Three major occupations of the patients were private employees (40%), entrepreneur (31.7%), and housewife (23.3%). There were 28 (46.7%) H. pylori-infected patients. (Table 1).

Table 1: Basic characteristics of the subjects

Basic characteristics	n = 60
Sex, n (%)	
Male	36 (60)
Female	24 (40)
Age, Mean (SD), years	48,75 (8,44)
BMI (SD), kg/m^2	23,18 (3,71)
Tribe, n (%)	
Bataknese	31 (51,7)
Javanese	25 (41,7)
Aceh	4 (6,7)

Occupation, n (%)	
House wife	14 (23,3)
Private employees	24 (40)
Enterpreneur	19 (31,7)
Civil servants	3 (5)
Educational Status, n (%)	
Primary school	3 (5)
Junior high school	15 (25)
Senior High School	32 (53,3)
College	10 (16,7)
H. Pylori	
Positive	28 (46,7)
Negative	32 (53,3)

Using Mann Whitney test, there was significant difference in the mean serum Interleukin-22 between patients with H. pylori positive and negative (p = 0.001) (Table 2)

Tabel 2. Serum Interleukin-22 Levels between Gastritis Helicobacter pylori Positive and Negative

	Helicobacter pylori		
	Positif	**Negatif**	**p**
	n=28	**n=32**	
Interleukin-22, Median (Min-Max), pg/ml	55,5 (23 – 104)	19 (16-23)	<0,001

Diagnostic Value of Interleukin-22 for Predicting H. pylori

From the analysis using the ROC curve it was found that the area under the ROC curve (AUC) was 99.8% (95% CI: 99.2%- 100%).In this study Interleukin-22 has a very good ability to predict the presence of H. pylori (p <0.001).

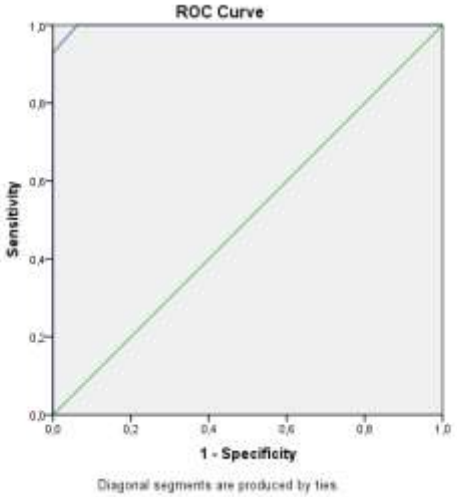

Figure 1. Diagnostic Value of Interleukin-22 for predicting H. pylori

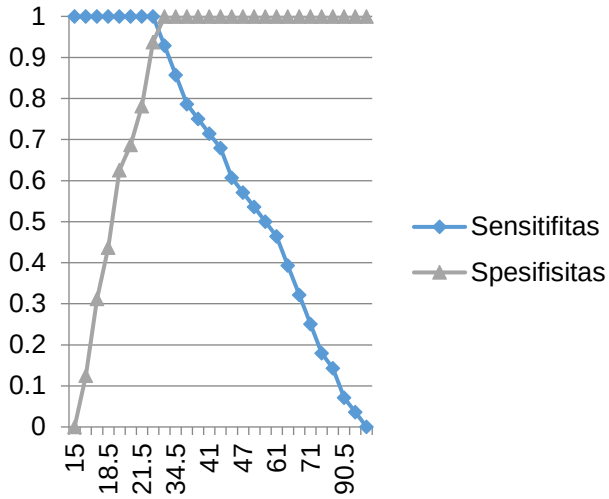

Figure 2. Interleukin-22 sensitivity and specificity curves for the presence of H. pylori

Based on the sensitivity and specificity curve in Figure 2, the Cut Off value for Interleukin 22 is 22.5. By using a cut-off point of 22.5, the sensitivity value of Interleukin-22 is 100% and specificity is 93.8%. The accuracy of Interleukin-22 in predicting H. pylori is 96.7%.

Discussion

Gastritis is a health problem most often found in clinical practice.[13] Gastritis is an inflammatory process in the gastric mucosa and submucosa in response to injury (injury) which can be acute or chronic.[4,10]IL-22hasproinflammatoryeffectsduringH.pyloriinfection.[9]

H. pylori has a major virulence protein, the cagA gene (cytotoxin-related gene A). Cag A positive strains can cause gastric ulcers. Cag A positive H. pylori stimulates Dendritic Cells (DC) to secrete interleukin-23 (IL-23) and Cag A positive H. pylori induces gastric epithelial cells for IL-22R1. The release of IL-23 induces T cells that have the potential to differentiate into T Helper (Th22). Polarization of Th22 cells develops in the gastric mucosa where IL-22 cytokines are released and resulted in increased inflammation within the gastric mucosa thus contributing to the development of H. pylori related gastritis. [9,11] In this study, we determined the frequency of IL-22 in H. pylori infected and H. pylori uninfected patients. The results showed an increase in frequency of IL-22 in gastritis H. pylori infected groups compared with the uninfected group.

In a similar experiment, Zhuang et al. reported a higher frequency of T-Helper 22 (Th22) cells and IL-22 in the gastric mucosa of H. pylori infected patients which suggested a cellular network that included Th22 cells inducing a pro-inflammatory state both in humans and mice. Zhuang et al also found a relationship between IL-22 level and the severity of gastritis in patients infected with H. pylori.[9]

Chen reported that IL-22, a cytokine IL-22 mainly produced by Th22, protected the host against certain gram-negative bacteria.[1] Shamsdin et al reported IL-22 and TNF-α levels significantly increased in the active chronic gastritis, compared to that uninfected groups (P=.005).[12]

Conclusion

Serum IL-22 levels were significantly increased in the infected H. pylori group compared to non H. pylori. Therefore, we propose that IL-22 may act as a diagnostic biomarkers for H. pylori infection.

Disclosure

All authors have contributed to the manuscript equally. None of the authors have direct or financial conflicts of interest with this paper and material contained herein.

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