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Association between VEGF -2578 C> A Polymorphism with VEGF Serum Levels in Gastritis with Helicobacter Pylori

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ABSTRACT

Mucosal damage in people with gastritis causes the production of VEGF. VEGF is a neoangiogenesis function to repair damaged tissue. Excess production can cause cancer risk. VEGF genotype polymorphisms are thought to affect the production of serum VEGF levels. The aim of this study was to determine the relationship between VEGF - 2578 C> A polymorphism and serum VEGF levels in H. pylori gastritis.

Method: *cross-sectional* study was conducted at H. Adam Malik General Hospital and Network Hospital with 100 samples. Endoscopic examination was performed to assess the gastric mucosa and a tissue biopsy was performed. The urea breath test (UBT) test and the Campylobacter like organism (CLO) test to determine H. pylori infection. VEGF - 2578 C> A was checked by Polymerase Chain Reaction (PCR). The data will be analyzed by univariate and bivariate.

Result: One hundred people with gastritis, of which 59 people were infected with H. pylori. In this study, H. pylori infection did not have a significant relationship with VEGF levels. VEGF - 2578 C> A polymorphisms also had no relationship to serum VEGF levels.

Conclusion: There is no correlation between VEGF - 2578 C> A polymorphism with VEGF serum levels (p> 0.05).

Keywords: *VEGF polymorphisms, VEGF - 2578 CA, H. pylori, Gastritis*

INTRODUCTION

Gastritis is one of the most common health problems. WHO estimates the incidence of gastritis around 1.8 to 2.1 million people in the world each year. Meanwhile, in Southeast Asia, there are 583,635 cases of gastritis every year. The incidence of gastritis in Indonesia itself is very high, namely 247,396 cases out of 238,452,952 people.[1] Infection with Helicobacter pylori (H. pylori) is the most common cause of chronic gastritis worldwide. In industrialized countries as much as 50% of adults are infected, while in developing countries, the prevalence is higher, at around 90%.[2]

H. pylori play a role in the activation of angiogenesis where there is a significant increase in the infected mucosa of H. pylori. Angiogenesis occurs as a result of an increase in pro-angiogenic factors. Vascular Endothelial Growth Factor (VEGF) is the most potent pro angiogenic factor.[3]

Polymorphism does not cause changes in protein structure but only results in variations in protein function. VEGF gene polymorphisms can be found at many different locations and have an influence on

the risk of developing cancer.[4] Several SNPs are involved as the etiology of malignancy, one of which is the VEGF-2578C> A polymorphism which is located in the promoter part of the VEGF gene. This polymorphism is closely related to the increased expression of VEGF which can affect the production of VEGF protein.[5] The number of VEGF levels will indirectly affect the tendency of the character of a tumor, both in size and spread. So that the VEGF serum contributes to the individual's susceptibility to developing cancer which can affect the prognosis of the disease.[6]

In previous studies, there was an increase in serum VEGF levels in patients with H. pylori gastritis with the polymorphism VEGF-634 G> C in the GG and GC genotypes. Meanwhile, H. Pylori gastritis patients with VEGF + 936C> T polymorphism did not find any association with serum VEGF levels.[7] As far as the investigators are concerned, no study has linked the VEGF -2578C> A polymorphism to serum VEGF levels in patients with H. pylori gastritis. This study was conducted to analyze differences in VEGF serum levels against VEGF -2578 C>A polymorphism in gastritis patients with *H. pylori*

MATERIAL AND METHODS

This study was a cross-sectional study on 100 consecutive gastritis patients that were admitted to the Endoscopy Unit at H. Adam Malik and Network Hospital in Medan, North Sumatra, Indonesia. The data was collected in 2020. All patients with diagnosis of gastritis based on their histopathological examination, at least 18 years old and willing to take part were included. The exclusion criteria were have history of H. pylori eradication treatment in the last 6 month or currently get antibiotic that was one of regimen for eradication, history of using proton pump inhibitor, H2 receptor antagonist within last one month, patients with systemic disease, pregnancy or malignancy.

This study was approved by the Institutional Review Board of North Sumatra University. Endoscopy was performed to assess the gastric mucosae (presence of edema, erythema, bleeding, erosion). The tissue biopsy was performed on the greater and lesser curvature of the distal antrum, the lesser curvature at incisura angular, the anterior and posterior wall of the proximal corpus. The specimens were then sent to laboratory for microscopic evaluation. Genomic DNA then extracted and purified using the High Pure PCR Template Preparation Kit. Analysis of the VEGF - 2578 C> A was performed using real-time polymerase chain reaction (RT-PCR).

Statistical Methods

Data analysis was performed in the univariate and bivariate (Mann-Whitney & Chi-Square test) analyzes using the SPSS 22nd version (SPSS Inc., Chicago). A value of $P < 0.05$ with a 95% confidence interval was considered statistically significant

RESULT

Respondent Characteristics

The number of respondents in this study was about 100 patients who met the inclusion criteria. Based on the largest age range in this study was > 49 years, around 52 people (52%). The mean age in this study was around 47.02 with the largest number of participants being male as many as 54 people (54%). Based on occupation, the majority of patients who became respondents in this study were self-employed around 56 people (56%).

In this study, most participants with high education were 82 people (82%) followed by 82 people (82%) who did not use alcohol, the most participants with light smokers were 56 people (56%), who did not have a high-salt diet of 84 people (84%), 56 not overweight (56%) and more participants without a family history of gastric cancer (96%).

In terms of the incidence of H. Pylori infection in the participants, about 56 (56%) were positive for H. Pylori. In this study, Vascular Endothelial Growth Factor

(VEGF) levels were examined with minimum value of 65.3 pg / ml and a maximum value of 2526.90 pg / ml with a median of 390 pg / ml. Based on the median value, divided by low VEGF levels <390 pg / ml and high VEGF levels ≥ 390 pg / ml with 50 participants each (50%).

Table 1. Characteristics of Research Subjects

Characteristics	n = 100 (%)
Age, average, years	47.02
19-29 years	13 (13)
30 - 39 years	18 (18)
40 - 49 years	17 (17)
> 49 years	52 (52)
Gender, n (%)	
Male	54 (54)
Women	46 (46)
Employment, n (%)	
College student	3 (3)
IRT	35 (35)
entrepreneur	56 (56)
Farmer	1 (1)
Labor	2 (2)
BUMN	2 (2)
Civil servants	1 (1)
Education, n (%)	
Low education	18 (18)
Higher education	82 (82)
Alcohol Use, n (%)	
Yes	15 (15)
Not	85 (85)
Smoking, n (%)	
Moderate - Heavy	44 (44)
Light	56 (56)
Diet high in salt, n (%)	
Yes	16 (16%)
Not	84 (84%)
Overweight, n (%)	
Yes	44 (44)
Not	56 (56)
Family history of Ca. Gaster, n (%)	
Yes	4 (4)
Not	96 (96)
H. pylori infection, n (%)	
Positive	59 (59)
Negative	41 (41)
VEGF level, median (min - max) (pg / ml)	390 (65.3 - 2526.90)
Low	50 (50)
High	50 (50)

Relationship between H. pylori infection and VEGF levels

Based on the Mann - Whitney test, there was no significant relationship between H. pylori infection and VEGF levels (p = 0.069)

Table. 2 Relationship between H. Pylori Infection and VEGF Levels

Serum level (pg / ml)	H. Pylori infection		P
VEGF	Positive n (%)	Negative n (%)	0.069
	59 (59)	41 (41)	

Differences in Serum VEGF Levels between Genotypes of VEGF - 2578C> A Polymorphism in H. Pylori Gastritis

From the PCR examination, there were 45 respondents (45%) with the CC genotype followed by 41 respondents (41%) with the CA genotype and 14 respondents with the AA genotype (14%).

Table 3.Polymorphism of VEGF 2578C> A

VEGF 2578C> A	n (%)
Genotype	
CC	45 (45)
CA	41 (41)
A A	14 (14)

Relationship between VEGF Serum Levels and VEGF-2578 C> A Polymorphisms in H. Pylori Gastritis

Based on the *Chi square* test, there was no significant relationship between VEGF serum levels and VEGF - 2578 C> A polymorphism in gastritis patients with H. Pylori infection (p = 0.151).

Table 4. Relationship between VEGF Serum levels and VEGF-2578 C> A Polymorphisms

VEGF 2578 C> A polymorphism	VEGF levels (Pg / ml)		Total n (%)	P
	Low n (%)	High n (%)		
CC	18 (40)	27 (60)	45 (100)	0.151
CA	25 (61)	16 (39)	41 (100)	
A A	7 (50)	7 (50)	14 (100)	

DISCUSSION

The genetic polymorphisms of VEGF - 2578 C> A are located in the promoter region which can affect the production of VEGF protein and have higher serum VEGF levels than other VEGF sites.[8] VEGF-2578 C> A can appear in recurrent miscarriage, pre-eclampsia, Alzheimer's disease, breast cancer, colon cancer.[9]

In China, a study conducted by Liu, W et al on the relationship of VEGF genetic polymorphisms to the development, risk, prognostic and survival of cancer where in their study found no relationship between VEGF-2578 C> A polymorphisms with the risk of Gastric cancer.[10]

Research conducted by Tzanakis et al in Greece on 100 patients with gastric

cancer where the polymorphism VEGF - 2578 C> A affected the development and growth of gastric tumors (p = 0.025). This is possible because the basic nature of angiogenesis is to help tumor development by increasing blood flow to tumor cells so that it can affect tumor growth.[11]

Changes in variations in DNA allele sequences can change the production or activation of VEGF which can cause different tumor growth between individuals. The contribution of VEGF polymorphisms to serum VEGF levels depends on the variant of the location of the particular VEGF gene. VEGF which is located in the 3'unstranslated region of the gene, namely the VEGF 935 C> T polymorphism can affect plasma VEGF levels.[7]

Research by Al Habboubi, H in 2011 examining 519 healthy populations found that the polymorphism of VEGF - 2578 C> A had no effect on serum levels of VEGF - 2578 C> A (p = 0.688).[8] This study is different from previous studies in kidney transplant recipients where the VEGF-2578 polymorphism can affect serum VEGF levels.[12]

There are many studies on the relationship of VEGF - 2578 C> A polymorphisms to the risk of gastric cancer. However, there are still no studies on the VEGF 2578 C> A polymorphism on serum VEGF levels in gastritis patients with H. pylori infection. In this study, based on the *chi square* test, there was no correlation between VEGF - 2578 C> A polymorphism on serum VEGF levels in gastritis patients with H. pylori infection (p = 0.151).

CONCLUSION

Based on this study, there was no significant correlation between VEGF - 2578 C> A polymorphism on serum VEGF levels (p = 0.151) in gastritis patients with H. pylori infection.

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Ethical Approval: Approved

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