Relationship of Age and Blood Type to Apo-E Gene Polymorphism in First Derivative Coronary Heart Patients in Bengkulu City

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ABSTRACT

Background: Atherosclerosis is the thickening of the walls of blood vessels by cholesterol, causing blockage of blood flow. The term coronary heart disease (CHD) or coronary artery disease is a cardiovascular disease associated with atherosclerosis. Coronary Heart Disease (CHD) has two risk factors, namely risk factors that cannot be modified including genetics, age, blood type and gender. Research on the APO E gene polymorphisms in the first generation of CHD and non-CHD patients in Bengkulu city showed that the APO E gene polymorphisms with the most potential for CHD were found in 9 of the 21 samples of CHD derivatives examined. This study aims to determine the relationship between age and blood group on the apo-e gene polymorphism in the first generation of CHD in Bengkulu city. By knowing the relationship of these factors so that preventive actions can be taken in dealing with CHD in Bengkulu City.
Method: Research method This research is a descriptive observational study using aresearch design in *cross sectional* which the measurement of the variables is carried out simultaneously. The study was conducted on 42 samples with a parental history of CHD and without CHD. Blood group data was obtained from blood examination using a blood group test kit, while age data was obtained from *informed* consent filled out by the patient. Data analysis used the chi square test to see the relationship between age and the apo E gene polymorphism and the ANOVA test to see the relationship between blood type and the apo E gene polymorphism.
Research: ResultsThe results of the SPSS analysis showed a significant relationship between age and blood type and the apo gene polymorphism. -e in the first generation of CHD sufferers in Bengkulu City. Age < 30 years has a risk factor (*Realtive Risk)* 0.47 times greater than age > 30. Blood type B has a risk factor (*Realtive Risk)* 8 times > than group A. Group A has a risk factor (*Realtive Risk)* 0. 25 times > blood type O. Blood type B has a risk factor (*Realtive Risk)* 0.5 times > blood type O.
Conclusion: This study shows a significant relationship between age and blood group factors on the apo E gene polymorphism so that action can be taken preventive.

Keywords: Age, blood type, polymorphism, Apo E gene, CHD

INTRODUCTION

Non-communicable diseases (NCDs) in Indonesia account for 73% of deaths and 35% of them are caused by cardiovascular disease. The results of the Basic Health Research (Riskesdas) in 2018 stated that the highest percentage of heart disease in Indonesia occurred in North Kalimantan at 2.2%, followed by DI Yogyakarta and Gorontalo with 2.0%, DKI Jakarta, East Kalimantan and Central Sulawesi. with 1.9%. In addition, the prevalence of heart disease in Bengkulu province is 1.3%. (Ministry of Health of the Republic of Indonesia, 2018)

Atherosclerosis is an event where the walls of the blood vessels are thickened by cholesterol, eventually reducing the elasticity

of the blood vessels, then blockage of blood flow occurs (Swierzewski 2000; Dalimartha 2001). Atherosclerotic plaques have a lipid-rich core and then overgrowth covers smooth muscle cells, eventually closing the collagen-rich connective tissue (Sherwood, 2013). If atherosclerosis is experienced in the blood vessels leading to the heart so that it can cause coronary heart disease, and if atherosclerosis occurs in the blood vessels to or in the brain, a person can have a stroke (Insull, 2009).

The term coronary heart disease (CHD) or coronary artery disease is a cardiovascular disease associated with atherosclerosis (Li *et al.*, 2016). In general, coronary heart disease (CHD) has two risk factors, namely risk factors that cannot be modified including genetics, age, blood type and gender. Meanwhile, modifiable risk factors include hypertension, alcohol consumption, smoking and diabetes. These two factors are interrelated (Rachel Hajar, 2017).

The completion of the human genome project is the basis for establishing the approximately 25,000 protein-coding genes that humans possess. This is the key to knowing diseases caused by heredity and diseases affecting humans, because the discovery states that all diseases have changes in genetic structure. Polymorphism is a phenomenon of changes or called gene mutations where these changes do not cause changes in protein structure but only cause variations in protein function. Polymorphism has no clinical effect, but can determine susceptibility to a disease. Polymorphism has an impact on changes in the susceptibility of a population to disease. The incidence of polymorphism will continue to be inherited so that the number of polymorphisms can vary in each ethnic group (Triwani and Irsan Saleh, 2015).

Research conducted by Yolanda, R (2020) regarding the polymorphism of the APO E gene in the first derivatives of CHD and non-CHD patients in Bengkulu city showed that the polymorphism of the APO E gene with the most potential for CHD was found in 9 of the 21 samples of CHD derivatives examined. The identification of the APO E gene polymorphism that has been carried out is to determine the genetic variation in the first generation of patients with CHD. So that it can identify patients who are at risk for CHD and preventive measures can be taken (Raharjo, Joesoef and Setianto, 2009). However, research on the relationship between age and blood group on APO E gene polymorphisms in Bengkulu City has never been studied. Therefore, this study was to analyze the relationship between age and blood group to the APO E gene polymorphism in the first generation of CHD patients in Bengkulu City. Based on the analysis of the background of the problem above, the formulation of the problem in this research is **Is there a relationship between age and class on the APO E Gene Polymorphism in First Derivatives of Patients with Coronary Heart Disease (CHD) in Bengkulu City?**

MATERIALS AND METHODS

This research is a descriptive observational study using aresearch design in *cross sectional* which the measurement of the variables is carried out simultaneously. The purpose of this study was to determine the relationship between age and blood group to the APO E gene polymorphism in the first generation of patients with coronary heart disease (CHD) as a risk factor for the incidence of CHD in Bengkulu city. Blood sampling and blood group checking will be carried out in Bengkulu city.

Research has a population that is a large number of subjects who have certain characteristics. The first generation of CHD sufferers in the city of Bengkulu is the population in this study. The sample is part of the population selected by a certain method so that it can be claimed to represent the population (Sastroasmoro and Ismael, 2014). The determination of the sample size in this study refers to previous research (Yolanda, R (2020)) which is as many as 21 samples, where the possibility of samples experiencing dropout is about 2 samples (10% of the total sample). This study has an independent variable, namely the first

derivative of patients with coronary heart disease (CHD) while the dependent variable is the polymorphism of the APO E gene.

The data collection will be divided into two data, namely primary data and secondary data. Note the primary data that will be obtained in the form of a blood sample to be examined and the blood group *quisoner* of the patient's agefirst derivative CHD patients while secondary data obtained in the form of medical records of patients with coronary heart disease (CHD)examined

This studyrequires tools such as; 1). Blood group card, 2). Pen Lancet, 3). Blood Lancet, 4). Toothpick, 5). Gloves, 6). Mask . The ingredients needed are: 1) Blood (1 cc), 2) Anti A Serum, Anti B Serum, Anti AB Serum, Anti O 3) Cotton, 4) Alcohol 70%, 5). tissue. The procedure for taking blood and checking blood groups from the first generation of CHD sufferers in the city of Bengkulu is as follows:

a. Filling out theSheet *Informed Consent* by a sample of the first generation of CHD patients
b. Swab fingers using cotton that has been given 70% alcohol
c. Use a *blood lancet* to prick fingers
d. Blood The first thing that comes out is cleaned with a *tissue.*
e. The finger is pressed slightly so that the blood comes out and then drops the blood on the blood type paper 4 times.
f. Each drop of blood on the blood group paper is given Anti-A, Anti-B, Anti-AB and anti-O reagents
g. .
h. After the results of the blood group examination have been known, the patient can save the blood group card.
i. Record the results of each patient's blood type

RESULT

A. Research Subject Characteristics

The frequency distribution of the sample characteristic data such as blood group, age, and history of the disease in the elderly can be seen in Table 4.1 below. The table shows that most of the research subjects have characteristics with an age range of <30 years (88.1%). Research subjects found more blood type O (57.1%) than blood group B (28.6%) and blood type A (14.3%). Subject's parents with a history of coronary heart disease (CHD) (50%) and without a history of CHD (50%).

Table 1 shows the frequency of the apolipoprotein E genotype. This gene has 3 genotypes, namely E2, E3 and E4. Among the three types of genotypes, polymorphism with type E4 is the most likely to develop CHD and atherosclerosis. Table 4.2 shows that there are 9 genotypes of type E4 (21.4%), E3 25 people (59.5%) and E2 as many as 8 people (19.1%). The apo E4 gene is a major contributor in increasing the risk of CHD events or atherosclerosis events (Fallah *et al*., 2011). The results of the distribution data above (table 1) were then analyzed against the apolipoprotein E genotype frequency data (table 2) using statistical analysis on age and blood group parameters.

Characteristis	**n**	**%**
Age		
<30	37	88.1
>30	5	11.9
Blood Type		
A	6	14.3
B	12	28.6
O	24	57.1
History of Disease in Parents		
CHD	21	50
Non-CHD	21	50

Table 1 Frequency Distribution Characteristics of Research Subjects (n = 42)

Genotype Apolipoprotein E		
E2 N (%)	E3 n (%)	E4 n (%)

First Derivative CHD	2 (4.8)	10 (23.8)	9 (21.4)*
First Derivative Non-CHD	6 (14.3)	15 (35.7)	0 (0)
Total	8 (19.1)	25 (59.5)	9 (21.4)

Table 2. Apolipoprotein E Genotype Frequency (n= 42) (Yolanda R, 2020)

B. **Chi-Squared Test for the age variable The**

test and analysis of the age variable on the apo E gene polymorphism was carried out using the *T-test* in the SPSS program. Based on these tests, obtained a significant value with a p value < (0.05). This shows that there is an average difference between the age variable and the apo E gene polymorphism variable. Table 4.3 shows the characteristics of the sample based on age.

		History of		
		CHD	NON CHD	Total
Age	<30 Years	21	16	37
	>30 Years	0	5	5
Total		21	21	42

Table 3. Characteristics of Sample by Age

Calculation of ODDS RATIO for Age factor
With the following formula:

$$\boldsymbol{Odds\ Ratio} = \frac{(n_{11})(n_{22})}{(n_{12})(n_{21})}$$

$$Odds\ Ratio = \frac{(16.5)(0.5)}{(21.5)(5.5)} = 2.11$$

The Odds results above indicate that patients aged less than 30 years have a tendency to have APOE4 gene polymorphisms 2.11 times greater than in patients aged 30 years and over.

Calculation of the *Relative Risk* of Age Factor
With the following formula:

$$\boldsymbol{RR} = \frac{Cumulative\ Incidence\ Exposed\ group\ \left(\frac{a}{N1}\right)}{Cumulative\ Incidence\ Unexposed\ group\ \left(\frac{b}{N0}\right)}$$

$$RR = \frac{(16.5)/(38)}{(5.5)/(6)} = 0.47$$

This indicates that age Patients less than 30 years of age were 0.47 times more likely to have APOE4 gene polymorphisms than patients aged 30 years and over.

C. **ANOVA Test for Variable Blood Type ABO**

The test results with *One Way ANOVA* obtained a significance value of 0.034 or less than 0.05. This shows that H0 is rejected. Thus, the blood type variable affects the incidence of apo E gene polymorphisms. After that, Duncan's further test was carried out to see the difference in the effect of the three groups of ABO blood group variables.

		History ofDisease		Total
		NON CHD	CHD	
Goldar	A	5	1	6
	B	8	4	12
	O	8	16	24
Total		21	21	42

Table 4.4. Distribution of Research Samples on Blood Type

Test ODDS RATIO B vs A
With the formula:

$$\boldsymbol{Odds\ Ratio} = \frac{(n_{11})(n_{22})}{(n_{12})(n_{21})}$$

$$Odds\ Ratio = \frac{(4)(5)}{(8)(1)} = 2.5$$

This means that patients with blood type B have a tendency to have the APO E4 gene polymorphism 2.5 times greater than patients with blood group A.

Relative Risk (RR) B vs A test
Using the formula :

$$\boldsymbol{RR} = \frac{Cumulative\ Incidence\ Exposed\ group\ \left(\frac{a}{N1}\right)}{Cumulative\ Incidence\ Unexposed\ group\ \left(\frac{b}{N0}\right)}$$

$$RR = \frac{(4)/(12)}{(1)/(6)} = 8$$

This means that patients with blood type B are 8 times more at risk of having APOE4 gene polymorphisms than patients with blood group A

ODDS test RATIO A vs O

With the formula:

$$\boldsymbol{Odds\ Ratio} = \frac{(n_{11})(n_{22})}{(n_{12})(n_{21})}$$

$$Odds\ Ratio = \frac{(1)(8)}{(16)(5)} = 0.1$$

means that patients with blood type A have a tendency to have the APOE4 gene polymorphism 0.1 times greater than in patients with blood group O

Test Relative Risk (RR) A vs O

With formula:

$$\boldsymbol{RR} = \frac{Cumulative\ Incidence\ Exposed\ group\ \left(\frac{a}{N1}\right)}{Cumulative\ incidence\ Unexposed\ group\ \left(\frac{b}{N0}\right)}$$

$$RR = \frac{(1)/(6)}{(16)/(24)} = 0.25$$

This means that patients with blood type A are 0.25 times more likely to have APOE4 gene polymorphisms than in patients with blood type O

Test ODDS RATIO B vs O

With the formula:

$$\boldsymbol{Odds\ Ratio} = \frac{(n_{11})(n_{22})}{(n_{12})(n_{21})}$$

$$Odds\ Ratio = \frac{(4)(8)}{(16)(8)} = 0.25$$

This means that patients with blood type B have an APOE4 gene polymorphism 0.25 times greater than patients with blood type O

Test RELATIVE RISK (RR) B vs O

With the formula :

$$\boldsymbol{RR} = \frac{Cumulative\ Incidence\ Exposed\ group\ \left(\frac{a}{N1}\right)}{Cumulative\ Incidence\ Unexposed\ group\ \left(\frac{b}{N0}\right)}$$

$$RR = \frac{(4)/(12)}{(16)/(24)} = 0.5$$

This means that patients with blood type B are 0.5 times more likely to have APOE4 gene polymorphisms than patients with blood type O.

DISCUSSION

This study was conducted on 42 samples that met the criteria. The sample was divided into 2 groups based on the history of parental disease, namely the CHD derivative group and the non-CHD derivative group. From the results of the frequency distribution of research subjects, most of the samples have characteristics with an age range of <30 years (88.1%) and >30 years (11.9%). The size of the sample with an age range of <30 years was due to the selection of samples from the first generation of patients with CHD and non-CHD patients who were still at a relatively young age. This is also in line with research conducted on South Asian populations who tend to be at high risk of developing CHD even at a young age. (Jafar, Qadri, and Chaturvedi, 2008).

The age frequency distribution data were then analyzed by SPSS using the chi-square test. The relationship between the age variable and the apo E gene polymorphism can be used by using the T test (non-parametric), the t-test value is significant because the value is 0.000 < alpha (0.05). This means that there is an average difference between the age variable and the apo E gene polymorphism. The relationship between age and the Apo E gene polymorphism has also been analyzed previously. the incidence of CHD will be smaller (Kulminski et al, 2013). Genetic factors inherited from both parents with CHD were found in 9 of 21 samples aged <30 years and detected having the apo E4 gene (Yolanda, R. 2021).

The Apo E4 gene is a gene that determines a person's risk of developing

CHD. Molecular studies have shown the relationship between APO E4 gene polymorphisms and the risk of CHD is still being studied in populations in various parts of the world. In research conducted by Yusuf. FA and Iqbal.MP in 2018 regarding the relationship of Apo E gene polymorphisms to Asian populations showed that the prevalence of the presence of the Apo E4 gene in Asians was associated with the risk of CHD. A recent study conducted on the Hakka population of Southern China showed that the presence of the Apo E4 gene could increase the risk of CHD (Qinghua L, et al. 2021). The Apo E4 gene is thought to increase the absorption of residual lipoproteins in the liver. In vivo studies found that the E4 isoform is catabolized at twice the rate of the E3 isoform, indicating that apo E4 is more effective than apo E3 in modulating the direct uptake of residual VLDL chylomicrons in the liver.

The results of the *Relative*Risk (RR) age variable showed that patients aged less than 30 years were 6.79 times more at risk of developing coronary heart disease than patients aged 30 years and over. Apart from the genetic factors above, this can be caused by several factors, first: The sample size <30 years of the first generation selected in this study was 88.1%. Second, the weight factor also affects the risk of CHD. In a study conducted on the Tunisian population, the apo E gene polymorphism played a role in determining plasma lipid levels. Significant interactions occur between apolipoprotein E polymorphisms, obesity, and changes in triglyceride levels thus corroborating epidemiological studies that the apo E4 gene increases the risk of hypertriglyceridemia among obese individuals (Jemaa, R et al, 2008). Lipid levels will change in the elderly along with their lifestyle in maintaining survival. Other factors are *lifestyle* such as smoking habits and psychological changes in the elderly. In elderly individuals, the vascular impact of apo E4 may be attenuated over time. Thus, in the elderly, the deleterious effects of apo E4 may not be exclusively mediated by apo E4 but also by other mechanisms (Mari H et al. 2010).

Data on the distribution of blood group samples showed that most of the samples were type O blood (57.1%), then blood type B (28.6%) and the smallest blood type A (14.3%). Blood type is a special code for a person that reflects the differences in the structure of carbohydrates and proteins on the surface of the erythrocyte membrane.

The results of the ANOVA test for ABO blood group variables on polymorphisms showed significant results (0.034 <0.05), meaning that blood type variables had an effect on the risk of coronary heart disease. Studies on the effect of ABO blood type have also been carried out. Research conducted on the Nigerian population, the results show that there is a very strong correlation between blood type and lipoproteins in female patients so that the incidence of CHD also increases (Bartimaeus and Waribo, 2017). This study suggests that the analysis and treatment management of CHD in Nigeria should also consider aspects of blood type. The effect of blood type on various diseases has also been widely studied. The effect of blood type on the incidence of cancer in Iraq, which was followed by patients aged 40-80 years, showed a positive correlation (Abas.S, Hamza. ZM, Khalaf. F. 2020). Even the latest research on the relationship of blood type to the disease Covid-19 also provides significant results. Studies of the population in Afghanistan show that a person with blood type A is more susceptible to COVID-19 disease (Sayfi. K, Alborz.MS, Saadat.M, 2021).

The results of the RR (test*Relative Risk*)show that patients with blood type B are 8 times more at risk than individuals with blood type A. Patients with blood type A are 0.25 times more at risk than patients with blood type O and patients with blood type B are 0.5 times more at risk. times than patients with blood type O. This means that individuals with non-O blood type have a greater risk of developing CHD. The results of metabolic studies show that a person with

blood type A has a gene that codes for a transferase that functions as a catalyst for the placement of terminal Naacetylgalactoxamine on the H antigen. People with blood type B will have a gene that codes for a transferase and locates terminal galactose. Individuals with blood type O do not have these two transferases, but still have the H antigen. This is because, in people with blood type O there is a single-base deletion in their gene, so people with blood type O have a protein. which do not have transferase activity (Franchini & Lippi, 2015).

The results of metabolic research conducted by Klop et al (2013) showed that non-O blood group had lower ery-ApoB than individuals with O blood type. Ery-ApoB was predicted to affect blood lipid cholesterol levels. Blood types that have lower ery-ApoB levels can have high blood lipid cholesterol levels. According to Ikayati's research (2016), hypertension patients showed that non-O blood group had higher blood cholesterol levels than blood group O. Total non-O cholesterol was 211.3 % and total blood type O cholesterol was 191.4 %.

The study of the relationship between age and blood type in the first generation of patients with APO E gene polymorphisms proved a significant relationship. Knowledge of this relationship can help in analyzing so that preventive action can be taken as early as possible.

CONCLUSION

Based on the statistical analysis carried out in this study, it can be concluded that:

1. There is a significant relationship between the age of the first-born patient with CHD and the APO E gene polymorphism in Bengkulu City. The T-test value showed significant results because the value was 0.000 < alpha (0.05).
2. RR (*Relative Risk)* shows that patients aged less than 30 years are 6.79 times more at risk of developing coronary heart disease (CHD) than patients aged 30 years and over.
3. There is a significant relationship between the blood group of patients with CHD and the APO E gene polymorphism in Bengkulu City. The results of the Annova test showed a significant value, namely (0.034 <0.05).
4. RR (*Relative Risk)* shows that patients with blood type B are 8 times more at risk than individuals with blood type A. Patients with blood type A are 0.25 times more at risk than patients with blood type O and patients with blood type B are 0.5 times more at risk than patients with blood type O. This means that non-O blood types are more at risk of developing CHD than individuals with blood type O.

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