A CORRELATION BETWEEN LP-PLA$_2$ AND MONOCYTE LEVELS IN ATHEROSCLEROSIS RISK SUBJECTS

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КОРРЕЛЯЦИЯ УРОВНЕЙ LP-PLA2 И МОНОЦИТОВ У ЛЮДЕЙ С РИСКОМ АТЕРОСКЛЕРОЗА

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Abstract

Background: Cardiovascular disease (CVD) is the most significant cause of death worldwide. More than 17.9 million people died from CVD, of which 85% deceased due to heart disease. On the other hand, atherosclerosis is one of the most dominant CVD in most developing countries and developed countries. Lp-PLA_2 is an enzyme produced by inflammatory cells and a pro-atherogenic protein in atherosclerosis. In the process, monocytes will produce Lp-PLA_2 so that it may hydrolyse oxLDL into lysophosphatidylcholine (lysoPC) and oxidized fatty acids (oxFA), atherogenic proteins involved in atherogenesis. A chronic inflammatory process that occurs in atherosclerosis requires early detection to avoid CVD severity. **Objective:** The research aims to determine the correlation between Lp-PLA_2 concentration and monocyte count as well as percentage in cohorts linked to risk of atherosclerosis. Methods: This study was a descriptive correlational analysis of the population with conditions at risk of atherosclerosis. The total number of respondents sampled in this research was 86. We used the ELISA method to measure Lp-PLA2 concentration and the Hematology Analyzer method to measure monocyte count and percentage. **Results:** The relationship between monocyte and LP-PLA2 level accounts for a probability value of 0.028. The correlation coefficient of 0.789 is categorized as very strong. **Conclusion:** increase in the concentration of Lp-PLA2 correlates with monocyte count and percentage in a population with conditions at risk of atherosclerosis.

Keywords: atherosclerosis, enzyme, Lp-PLA_2, inflammatory cells, monocytes population, pro-atherogenic marker

Резюме. Актуальность: Сердечно-сосудистые заболевания (ССЗ) являются наиболее серьезной причиной смерти во всем мире. От сердечно-сосудистых заболеваний умерло более 17,9 млн человек, из них 85% — от болезней сердца. С другой стороны, атеросклероз является одним из наиболее распространенных ССЗ в большинстве развивающихся и развитых стран. Lp-

PLA2 является ферментом, синтезируемым воспалительными клетками, и проатерогенным белком при атеросклерозе. При этом моноциты продуцируют Lp-PLA2 для гидролиза oxLDL в лизофосфатидилхолин (lysoPC) и окисленные жирные кислоты (oxFA), атерогенные белки, участвующие в атерогенезе. Хронический воспалительный процесс, возникающий при атеросклерозе, требует раннего выявления во избежание утяжеления ССЗ. Цель: исследование направлено на определение корреляции между концентрацией Lp-PLA2 и количеством моноцитов, а также процентом в группах лиц, связанных с риском атеросклероза. Методы: настоящее исследование представляло собой описательный корреляционный анализ населения с состояниями, подверженными риску атеросклероза. Общее количество лиц, отобранных в этом исследовании, составило 86. Мы использовали метод ELISA для измерения концентрации Lp-PLA2 и метод гематологического анализатора для измерения количества и процентного содержания моноцитов. Результаты. Взаимосвязь между уровнем моноцитов и LP-PLA2 составляет значение вероятности 0,028. Коэффициент корреляции 0,789 относится к категории очень сильных. Заключение: увеличение концентрации Lp-PLA2 коррелирует с количеством и процентом моноцитов в популяции с состояниями риска атеросклероза.

Ключевые слова: атеросклероз, фермент, Lp-PLA2, клетки воспаления, популяция моноцитов, проатерогенный маркер.

Introduction

Cardiovascular disease (CVD) is the most significant cause of death worldwide. More than 17.9 million people died from CVD, 31% of all deaths in the world, of which 85% globally were due to heart disease [1]. On the other hand, atherosclerosis is one of the most dominant CVD in most developing countries and developed countries. Therefore, a high mortality rate has been registered with this disease. Most Asian countries experience challenges from cardiovascular disease, with mortality rates varying from 103 to 366 per year in adults reported by newly published studies. Elevated cholesterol levels in the population have become a frequent cause. Older men and people with dyslipidemia, hypertension, and diabetes are at high risk of cardiovascular disease. Over the past decade, there has been a tendency to escalate atherosclerotic charges, especially in East Asia, with an increase of 117.2% and 115.3% of total deaths and disability-adjusted by 2015 [2].

Many CVD risk factors (smoking, dyslipidemia, hypertension) are known to lead to atherosclerosis. It begins with dysfunction of endothelial function. Endothelial function plays a central role in vasomotor abnormalities and inflammatory responses [3]. Dysfunction of these tissues happens due to inflammatory response followed by plaque formation. Plaque consists of cholesterol, fatty acid, calcium, and fibrin, leading to blockage at the artery wall. Blockage of the artery wall by the plaque will reduce the flow of blood and oxygen supply [4]. The abrupt change mechanism is associated with acute thrombosis in atherosclerotic plaque that is eroded, cracked or ruptured. The rupture of atherosclerotic plaque is associated with unstable atherosclerotic plaque changes that are volatile and easily torn. Therefore, laboratory tests are also intended to detect early plaque phase changes before arterial plaque rupture [5, 6].

Arterial plaque rupture will cause a lesion that will attract circulating monocytes to the lesion area [7]. The interaction between leukocytes, platelets, and blood vessel

cells leads to monocyte production in the bone marrow, releasing it into an artery and attaching it to the endothelial cell. Continuous recruitment of monocytes to the lesion will cause the accumulation of macrophages. Macrophages will ingest oxidised lipoprotein into developing plaques through scavenger receptors [8]. In this process, macrophages cause the expansion of the necrotic nucleus of atherosclerotic plaque, fibrous capsule depletion, and destabilisation of plaque resulting in rupture of arterial plaque, which will initiate atherosclerosis [9].

Many endogenous factors affect the occurrence of atherosclerosis, both protective factors and aggravating factors. Monocytes are a type of protective cell, but they also play a role in induction of atherosclerosis. Monocytes are white blood cells related to granulocytes, which are white blood cells designed to kill bacteria. Monocytes are produced in the bone marrow and then released into the bloodstream. Young monocyte cells start as monoblasts in the bone marrow. Once released, they leave the bone marrow and circulate through the bloodstream for a few hours before getting to other tissues, such as the spleen and lungs. Once monocytes are embedded in tissues, they become macrophages. Macrophages support healthy immune function by destroying and ingesting pathogens. They also help lymphocyte cells recognise pathogens and create antibodies against them [10, 11]. Rupture at the blood vessel will cause a lesion, attracting the circulating monocytes to the lesion area. The interaction between leukocytes, platelets, and blood vessel cells leads to monocyte production in the bone marrow and release to circulating blood. Continuous recruitment of monocyte to the lesion will cause the accumulation of macrophages. Macrophages ingest oxidised lipoproteins through scavenger receptors and lipid-rich cells, contributing to the physical aspect of plaque development [12].

In this process, macrophages, lymphocytes and mast cells produce an enzyme known as Lipoprotein-associated phospholipase A2 (LP-PLA2) [13]. LP-PLA2 hydrolyses

oxidised LDL (oxLDL) to produce lysophosphatidylcholine (lysoPC) and oxidised fatty acids (oxFA). LysoPC and oxFA will cause endothelial dysfunction, inducing apoptosis of smooth muscle cells and macrophages that cause the expansion of the necrotic nucleus of atherosclerotic plaque, fibrous capsule depletion, and destabilisation of plaque resulting in rupture of arterial plaque. Therefore, the localisation of LP-PLA2 in atherosclerotic lesions and their association with plaque instability supports a potential causal role for LP-PLA2 in cardiovascular disease (CVD) [14].

A chronicle inflammatory process occurs at different stages of atherosclerosis [15], and the stages of atherosclerosis development are essential stages that require early detection to avoid CVD severity. Research shows that increased levels of LP-PLA2 are linearly correlated with increased risk of CVD. However, it is known that LP-PLA2 can be pro-inflammatory and anti-inflammatory at certain stages in the mechanism of CVD pathology. This research seeks to prove the anti-inflammatory role of LP-PLA2. Therefore, the researchers sought to analyse the correlation between the monocyte population and LP-PLA2 levels as two variables that can be used as markers for the early stages of atherogenesis, hopefully in time to prevent severe disease.

Material & Methods

Research Design

This research was a cross-sectional study. The sample population of this research was chosen by total sampling among 86 people who attended health examination with risk factors of atherosclerosis based on American College of Cardiology (ACC) and American Heart Association (AHA) guidelines in Malang, East Java, Indonesia. We used human venous blood sampling to determine the concentration of LP-PLA2 and circulating monocytes. Examination of blood profiles was conducted at the Saiful Anwar Central Hospital Laboratory, Malang. Measurement of LP-PLA2 and

monocyte concentrations was conducted in the Bioscience Laboratory, University Brawijaya, Malang.

Measurement of LP-PLA2

Blood obtained from respondents was placed in an EDTA vacutainer containing anticoagulant and incubated for 10-20 minutes. Blood in the EDTA vacutainer was then centrifuged for 20 minutes at 2000-3000 rpm. Blood was then diluted with standard buffer solution. On the tube samples, 40 μL sample buffer solution was entered into the plate with 10 μL sample buffer solution consistent with dilution factor; they were then well shaken. The sample was then incubated for 30 minutes at 37°C. The concentrated buffer was diluted with water, and then 50 μL HRP-conjugated reagent was added to each tube, except for the control tube. The solution was incubated for 10 minutes and washed back. Fifty microliters of chromogen A and B solution were added into both tubes, shaken well, and incubated at 37°C for 15 minutes. Fifty microliters stop anti-dilution provisions were added into each tube to stop the reaction. The colour of the sample in the tube changed from blue to yellow. The optical absorption of the samples was read at 450 nm using a microtiter plate reader.

Measurement of Monocytes

Monocytes were measured using the Hematology Analyzer method. The capillary tube is filled with blood. The specimen flows down the tube until it is near the dry end. The dry end was inserted vertically into the sealant and pushed to the tray's bottom. The tube is twisted to remove it from the sealant and to prevent the sealing plug from being extracted. The sealed end of the tube was tapped on a flat surface to help ensure proper sealant contact in the tube. The prepared capillary tube was then wiped off. The capillary tube was put carefully in the centrifuge tube holder with the sealant end down. All tube positions were numbered on the rotor and can be used to record the position of each patient specimen. With the tube holders and

hematocrit tubes in place, the lid was locked by firmly pressing down. Measurement of monocyte cells was based on the optical double-angle light scattering method (2°-5°).

Ethics Clearance

The Medical Research Ethics Committee, Medical Faculty of the University of Brawijaya approved the research (Letter Number 277/EC/KEPK-S1-PD/11/2018).

Data analysis

Data analysis used the SPSS v.17 application with a confidence level of 95% (p<0.05). Normality was tested with the Kolmogorov-Smirnov method, followed by one-way ANOVA, with post-hoc Tukey HSD. Correlations between variables were analysed using Pearson's correlation test.

Results

Baseline Characteristics of Participants

The data below shows the characteristics of the 86 people based on age category, gender, body mass index (BMI), blood pressure, fasting blood sugar level, and lipid profile.

Table 1. Baseline variables of the participants

Table 2. Statistical characteristics of the variables

Based on Table 1, the data homogeneity is known to be different. To ensure that in this study, LP-PLA and Monocyte levels were not affected by other factors (age, sex, body mass index (BMI), blood pressure and fasting blood sugar), we analyzed using the Kruskal Wallis test. The data is homogeneous. Based on these tests, gender, age, body mass index (BMI), blood pressure, fasting blood sugar, and lipid

profiles showed significance for monocytes. In Lp-PLA2, significant differences come from gender, age, body mass index (BMI), blood pressure and fasting blood sugar ($p<0.05$).

The normality test for monocyte levels and LP-PLA2 produced by Kolmogorov Smirnov analysis resulted in $p=0.072$ and $p=0.115$, respectively, with a probability of $p=0.200$ and $p=0.007$. Therefore, it can be known that the monocyte data is declared normally distributed (probability>0.05); meanwhile, LP-PLA2 is not.

Based on Spearman correlation analysis, the relationship between monocytes and LP-PLA2 produced a probability value of 0.028. These results indicate that the probability is less than the level of significance (probability<0.05). Thus, it can be stated that there is a significant relationship between monocytes and LP-PLA2. The positive correlation coefficient indicates that the relationship between monocyte and LP-PLA2 concentration is directly proportional, meaning: higher monocyte levels matched higher LP-PLA2 concentrations. The correlation coefficient of 0.789 is categorised as very strong. This result means that the relationship between monocyte levels and LP-PLA2 concentration is significant and strong.

Discussion

LP-PLA2 is secreted by inflammatory cells; one of them is monocytes. LP-PLA2 binds with oxidised low-density lipoprotein (oxLDL) and breaks it into lysoPC and OxNEFA [14]. LP-PLA2 inducing formation lipid mediator through hydrolysis of fatty acids. It has been shown that increase in the concentration of LP-PLA2 in the blood indicates signs of plaque formation. It has also been shown that inhibiting the activity of LP-PLA2 reduced the lesion of intimal and progressive atherosclerosis [16]. Research also mentions that an increase in inflammatory cells

induces the concentration of LP-PLA2 to increase on the atherosclerotic plaque[7,17].

LP-PLA2 is related to atherosclerosis risk factors such as gender, age, BMI, blood pressure, blood glucose level and lipid profile. Gender independently influences the exitance of LP-PLA2: males have a high tendency towards high LP-PLA2 concentrations compared to females [18,19,20]. This research also proves a significant relationship between gender and Lp-PLA2. A high concentration of LP-PLA2 participants aged 62 years old and below indicates an increase in the risk factors of coronary heart disease; meanwhile, this is not applicable for those above 62 years old [21]. Research has also shown a significant relationship between age and Lp-PLA2. High BMI causes the concentration of LP-PLA2 to increase [22]. This research also proves a significant relationship between BMI and Lp-PLA2. In the case of hypertension, blood pressure is directly proportional to the concentration of LP-PLA2, where both increase together [23]. The research also proves a significant relationship between blood pressure and Lp-PLA2. Research has shown that diabetic retinopathy patients have a high concentration of LP-PLA2. This finding indicates that high sugar content in the blood will induce an increase in LP-PLA2 concentration [24]. The research also proves a significant relationship between fasting blood sugar and Lp-PLA2. Furthermore, patients with dyslipidemia undergo hypolipidemic medication for LDL level and LP-PLA2 concentration in the blood [25]. But the research shows there is no significant relationship between lipid profile and Lp-PLA2.

This research shows that the concentration of LP-PLA2 is high in the population with risk factors such as male, increase in age, non-smokers, underweight, normal blood pressure, low fasting blood sugar, and non-dyslipidemia. Meanwhile, the concentration of LP-PLA2 is low in the population with risk factors such as female, young age group, smokers, increase in BMI, increase in blood pressure,

increase in blood glucose level, and the condition of dyslipidemia. In addition, there was a significant relationship between Lp-PLA2 with gender, age, BMI, blood pressure and fasting blood sugar.

Based on the results received, the mean number and percentage of monocytes were high in: males; the age group of 30-49; smokers; obese class III; high blood pressure; high blood sugar level; and the population with dyslipidemia condition. Meanwhile, the mean number and percentage of monocyte were low in: the female age group of 50-69; non-smokers; normal BMI; normal blood pressure; the population with low blood sugar level; and the sample population with non-dyslipidemia condition. Based on previous research on monocytes, it is proven that risk factors can increase monocyte number and percentage . Although the difference in the result of monocyte received compared with previous research related to gender and number and percentage, females have a high number and percentage compared to males. Still, there was a significant relationship between gender and monocyte levels. There is a difference in the result received compared to previous research, which shows an increase in the age group lead to an increase in number and percentage, which proves the significant relationship between age and Lp-PLA2. Research shows BMI is directly proportional to the number and percentage cause both increases together, proving a significant relationship between BMI and monocytes. The increase in blood pressure and dyslipidemia will increase in number and percentages of monocytes. Both prove that it has a significant relationship with Lp-PLA2.

Monocytes in atherosclerotic lesions produce foam cells by breaking down oxLDL that contain lipid droplets. The accumulation of foam cells contributes to lipid storage and atherosclerotic plaque growth. The atherosclerotic plaque has a decreased ability to migrate the foam cells, leading to the resolution of inflammation and the development of other lesions into complex atherosclerotic

plaques [26]. Some of the risk factors of atherosclerosis, such as gender, age, body mass index (BMI), blood pressure, blood glucose level, and lipid profile, seem related to the number and percentage of monocytes in the body.

Previous research shows a relationship between gender and monocyte number and percentage. Females have a higher number and percentage of monocyte than males, due to the estrogen hormone [27]. Research shows that a body mass index (BMI) in the obese category will increase monocyte number and percentage [28]. Also, high blood pressure causes the number and percentage of monocytes to increase [29]. Research shows that the number and percentage increase in patients with dyslipidemia is due to the LDL elevation [30, 31].

Monocytes also produce LP-PLA2 [32]. Based on the research done, high activity of LP-PLA2 is one of the independent factors of inflammation and risk factors of cardiovascular disease. Research proves that a high concentration of LP-PLA2 causes an increase in the risk of stroke and coronary heart disease [33]. Meanwhile, monocytes produce oxidised LDL and HIF-1A, which will induce intercellular adhesion molecule (ICAM-1), vascular cell-1 adhesion molecule (VCAM-1), and enhance the endothelial adhesive properties in a proinflammatory-like effect [34]. Monocytes also produce LP-PLA2 to break down oxLDL into lysoPC and OxNEFA. These particles will cause fibrous cap formation on the blood vessel [35]. Based on the results obtained from this research, there is a significant relationship between monocyte levels and LP-PLA2. Furthermore, LP-PLA2 is directly proportional to monocytes. Therefore, it can be seen that both can be used to detect risk in the early stages of atherogenesis, hopefully with appropriate therapy to prevent severe disease.

Conclusion

There is a significant relationship between monocytes and LP-PLA2, and LP-PLA2 is directly proportional to monocyte levels. This research proves that LP-PLA2 tends to act as proinflammatory factor. Further research needs to be done to investigate LP-PLA2 activity because it seems like the concentration and activity of LP-PLA2 plays a role in formation of LP-PLA2 products, such as LysoPC and oxNEFA, which play different roles in atherosclerogenesis.

Conflict of Interest

The authors declare that there is no conflict of interest

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TABLES

Table 1. Baseline characteristics of the participants
Таблица 1. Исходные характеристики обследованных лиц

Variable переменная	Percen -tage %	Lp-PLA$_2$ (ng/mL) (нг/мл)		Monocyte моноциты		
		Mean Среднее	p-value	Number of cells per $10^3/\mu L$ Кол-во клеток на 10^3/мкл	Percentage (%)	p-value
Gender Пол						
Male Мужчины	56	0.105	0.032	0.287	7.26	0.042
Female Женщины	44	0.105		0.253	6.69	
Age возраст						
30 – 49	28	0.103	0.025	0.281	7.18	0.034
50 – 69	59	0.107		0.265	6.89	
70 – 89	13	0.103		0.283	7.14	
Body Mass Index (kg/m^2) Индекс массы тела						
Underweight пониженная вес	7	0.107	0.024	0.287	7.00	0.036
Normal Weight Нормальный вес	40	0.105		0.269	6.78	
Overweight избыточный вес	23	0.103		0.274	7.24	
Obese Class I Ожирение I класса	17	0.107		0.250	7.16	
Obese Class II Ожирение II класса	12	0.104		0.295	7.45	
Obese Class III Ожирение III класса	1	0.104		0.420	8.90	
Blood Pressure (mmHg) АД (мм.рт.ст.)						
90/60-130/80	31	0.108	0.028	0.252	6.57	0.031
>130/80	69	0.104		0.283	7.25	
Fasting Blood Sugar (mg/dL) уровень сахара крови натощак						
<70	52	0.106	0.039	0.268	6.75	0.045

70 – 99	20	0.105		0.264	7.46	
>99	28	0.104		0.282	7.89	
Lipid Profile (mg/dL) Липидный профиль						
Dyslipidemia дислипидемия	87	0.105		0.271	7.01	
Non-dyslipidemia нет дислипидемии	13	0.107	0.072	0.274	6.97	0.041

Table 2. Statistical characteristics of the variables
Таблица 2. Статистические характеристики переменных показателей

Variable Переменная		Min Мин	Max Макс	Mean Среднее	Standard Deviation Стандартное отклонение
Monocyte Моноциты	**Percentage (%)**	4.2	11	6.99	1.49
	Number (10^3/μL) Кол-во (10^3/мкл)	0.17	0.42	0.27	0.06
Concentration of LP-PLA$_2$ концентрация LP-PLA$_2$		0.08	0.13	0.11	0.01

TITLE PAGE

CORRELATION BETWEEN LP-PLA$_2$ AND MONOCYTE LEVELS IN ATHEROSCLEROSIS RISK SUBJECTS

Корреляция уровней LP-PLA2 и моноцитов у людей с риском атеросклероза

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