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by I S Warno

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Fibrinogen and low-density lipoprotein (LDL) cholesterol levels with the occurrence of acute myocardial infarction: Is it correlated?

I Sulestiyo[1], J N E Putranto[2] and B Novitalia[1]

[1] Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2] Department of Cardiology and Vascular Medicine, Dr. Soetomo General Hospital, Surabaya, Indonesia

*Corresponding author : bunganovitalia90@gmail.com

Abstract. Fibrinogen is considered as a risk factor associated with cardiovascular disease, especially acute myocardial infarction (AMI). The role of increasing levels of fibrinogen in the thrombosis shows that there is an effect that causes the pathway to form thrombosis. Increased plasma high-density lipoprotein (LDL) cholesterol can also induce the development of atherosclerosis and is associated with AMI events. This study was an observational analytic study using cross-sectional approach, carried out from August-November 2015 in Dr. Soetomo Hospital Surabaya. Samples were 67 subjects who fulfilled inclusion and exclusion criteria. A total of 67 subjects were assessed, 47 (70.15%) were males and 20 (29.85%) were females. The mean age was 55,07 ± 11,02 years old, ranging from 30 to 85 years. AMI was diagnosed in 49 patients (26,87%). Management of AMI patients consisted of conservative medical therapy (42.86%), thrombolytic therapy (18.37%) and PPCI (38.77%). The statistic analysis revealed significant differences in plasma fibrinogen and LDL cholesterol levels between the AMI patient group and the control group. There was a significant correlation between fibrinogen levels and LDL cholesterol levels. Fibrinogen and LDL cholesterol levels are correlated with AMI risk factors. In subjects with AMI, there was higher fibrinogen and LDL cholesterol levels compared to non-AMI subjects.

1. Introduction

Globally, Coronary heart disease (CHD) has become a major contributor to the burden of the disease that is assessed based on disability-adjusted life-years (DALYs) [1]. At the same time, acute myocardial infarction (AMI), has shifted to low and middle-income countries, where more than 80% of deaths from cardiovascular disease occur worldwide [1,2]. This disease causes more than 2.4 million deaths in America, more than 4 million deaths in Europe and northern Asia, and more than a third of deaths in developed countries each year [2]. Although the treatment has experienced great progress in the past few decades, in-hospital mortality has been found in the range of 5-8% [3]. The diagnosis of AMI should be used when there is a presence of myocardial necrosis in myocardial conditions experiencing ischemia [4].

Fibrinogen, the precursor of fibrin, is an acute-phase inflammatory protein involved in blood clotting and is also a potentially suitable target for CHD. Many studies had demonstrated that the plasma

fibrinogen level was associated with CHD indicating that fibrinogen might be a possible causal factor, a therapeutic target, and a risk predictor in not only healthy persons but also those with cardiovascular diseases. Observational studies that showed an increase in plasma fibrinogen (g / L) which is correlated with increasing CHD. Levels of fibrinogen can also predict the development, progression, and negative prognosis of coronary heart disease (CHD) [5]. Increased plasma fibrinogen concentration is associated with the development of CAD through changes in platelet aggregate function due to increased plasma fibrinogen, through the amount of fibrin formation and accumulation and associated with the evolution of by atherosclerotic plaques and increased blood viscosity associated with thrombosis [6].

Plasma lipoprotein levels are known as independent risk factors for CHD. High levels of low-density lipoprotein (LDL-C) cholesterol is associated with an increased risk of CHD [7]. The initial mechanism that occurs in AMI is the erosion of atherosclerotic coronary plaques that are fragile and laden with lipids, which are then exposed to blood in the circulation and become the core and thrombogenic matrix of the plaque [1]. Atherosclerosis is a chronic inflammatory disease caused by lipids, specifically low-density lipoproteins (LDL), and leukocytes. This is characterized by the activation of endothelial cells, adhesive molecules and expression of monocytes/macrophages, and transmigration of DCs, T cells and some B cells into the intima, and also the transfer of modulated types from LDL to matrix components [8]. LDL particles with oxidative modification, both its proteins and lipid groups, known to be in atherosclerotic lesions and ready to be internalized by macrophages [9]. This study aims to find out the correlation between fibrinogen and LDL cholesterol levels with AMI by analyzing the data from laboratory findings of blood samples, considering both are risk factors of AMI.

2. Methods

This study was an observational analytic study with a cross-sectional design. This study was conducted in the intensive cardiac care unit and low care unit, Dr. Soetomo General Hospital, Surabaya, from August 2015 - November 2015. The research sample was taken by purposive sampling. We enrolled male or female patients above 30 years old who were willing to participate in the study and signed the informed consent. Subjects with a history or having a stroke, unregulated diabetes mellitus, liver disease, or coagulopathy were excluded from the study.

We obtained the subject's baseline demographics based on medical report. AMI was assessed based on the medical record, including the main complaints and medical history, electrocardiogram, cardiac marker, and echocardiography. The diagnosis of AMI was based on the Europian Society of Cardiology (ESC) guidelines [4,10]. Fibrinogen and LDL cholesterol levels were measured using venous blood. The therapy consisted of conservative, thrombolytic drugs, and primary percutaneous coronary intervention (PPCI), were also determined.

The categorical variables were presented as proportion, while continuous variables were presented as mean and standard deviation (mean±SD). The relationship between fibrinogen and LDL cholesterol levels in patients with AMI was analyzed using the Pearson correlation test if the data were normally distributed, and Spearman correlation as an alternative. Data from the study were analyzed by program R version 3.0.2. Statistical significance was considered when a p-value <0.05.

3. Results

3.1. Characteristics of subjects

We enrolled 67 subjects with baseline characteristics as described in Table 1. Based on sex, there were 47 males (70.15%) and 20 females (29.85%) subjects. The youngest was 30 years old, while the oldest was 85 years old, and the mean age was 55,07 ± 11,02. Subjects with AMI were 49 (73.13%) patients, while subjects without AMI were 18 (26.87%) patients. In the AMI group, the conservative therapy using medication was 21 (42.86%) patients, thrombolytic therapy using streptase was 9 (18.37%) patients and PPCI therapy for 19 (38.77%) patients.

Table 1. Baseline characteristic of subjects.

Variables	n (%) / mean ± SD
Gender	
Man	47 (70.15)
Women	20 (29.85)
Age (years)	55,07 ± 11,2
Diagnosis	
AMI	49 (73.13)
Non AMI	18 (26.87)
Therapy	
Conservative	21 (42.86)
Thrombolytic drug	9 (18.37)
PPCI	19 (38.77)

3.2. Correlation between fibrinogen level with AMI

An unpaired T-test was performed to see the mean differences in fibrinogen level between IMA and non-IMA groups. There was a significant mean difference in fibrinogen levels between the IMA and non-IMA group, (449,949 ± 125,231 mg / dL vs 290, 233 ± 93,594 mg / dL, respectively) (Table 2).

Table 2. Fibrinogen levels between AMI and non-AMI.

Variable	Diagnosis	Mean	Standard deviation
Fibrinogen Level (mg/dL)	AMI	449.949	125.231
	Non AMI	290.233	93,.94

3.3. Correlation between LDL cholesterol level with AMI

Unpaired T-test was performed to see the mean difference in LDL cholesterol levels between IMA and non-IMA group. There was a significant mean difference in fibrinogen levels between the IMA and non-IMA group, (122.04 ± 34.88 mg/dL vs 90.50 ± 24.36 mg/dL, respectively) (Table 3).

Table 3. LDL cholesterol levels between AMI and non-AMI.

Variable	Diagnosis	Mean	Standard deviation
LDL Cholesterol Level (mg/dL)	AMI	122.04	34.88
	Non AMI	90.5	24.36

3.4. Correlation between fibrinogen levels with LDL levels

A statistical correlation test was conducted to determine the significance of the relationship between fibrinogen level and LDL cholesterol level. Because the data are normally distributed, the Pearson correlation analysis is used to determine the significance of the relationship. There was a relationship between fibrinogen level and LDL cholesterol level ($p = 0.007$). The strength of the correlation was weak, with a correlation strength value of 0.326 (Table 4). There is a direct correlation between the two variables which means that the higher the level of fibrinogen, thus the higher the level of LDL cholesterol.

Table 4. Correlation between fibrinogen levels and LDL cholesterol levels.

Variable	Mean	Standard deviation
Fibrinogen level	407.40	136.93
LDL cholesterol level	113.57	35.16

4. Discussion

The sample of this study were 49 patients with AMI who met the diagnosis criteria based on the European Society of Cardiology (ESC) guidelines [4,10] and 18 patients as a control group, who underwent inpatient care at the Cardiac Inpatient Unit of the Dr. Soetomo Surabaya during August 2015 - November 2015.

The proportions between male and female samples in this study were 70.15% and 29, 85%, respectively. The results of the other study found that the proportion of AMI was higher in men. This could be caused by premenopausal conditions, that women are protected from the progression of coronary disease [11]. Based on age, the incidence of AMI occurred at an average age of 55 years with a range of 30 to 73 years, with the age of older women undergoing hospitalization. Symptoms of AMI in the elderly are different compare to the young age. Symptoms are usually not typical and the location is more above that of the substernal. The pain threshold in older people is higher than the young age [12]. These results are in line with the other studies, which stated that the incidence of AMI increases with age, and the age of women undergoing inpatient care is relatively older than men [13]. Another study also showed that AMI events peak at ages 50-75 years [11].

Old age is a high-risk condition for the occurrence of AMI, so it requires the right choice of therapy. Revascularization therapy has a better advantage than conservative therapy, either with the percutaneous coronary intervention (PCI) or thrombolytic using streptease. In our study, 57.14% of all AMI patients were treated with revascularization and more than 75% of them underwent PCI. This is because the thrombolytic therapy in the elderly can cause bleeding complications, especially strokes, compared to PCI therapy, which provides better benefits [14]. Many patients underwent conservative therapy (42.86%) due to cost consideration and a patient's fear of complications from the act of revascularization. Reperfusion action in AMI patients has a lower risk of death compared to those who have not. The choice of reperfusion therapy was carried out if there were no contraindications. Factors that are contraindicated will increase along with aging, and the selection of AMI therapy in the elderly is more conservative due to the late onset of chest pain [12].

Epidemiological studies show an association between increased fibrinogen levels and increased risk of cardiovascular disease including coronary heart disease. In this study, there was a significant difference in fibrinogen levels between AMI patients and non-AMI patients. The average fibrinogen level of AMI patients was 449.949 mg/dL compared to non-IMA patients of 290.233 mg/dL. This is consistent with the other study which concluded that AMI patients had higher fibrinogen levels than normal patients, and fibrinogen levels were independently associated with AMI incidence in multivariate analysis [15]. Fibrinogen plays an important role in the body's pathological processes such as inflammation, atherogenesis, and thrombogenesis. The inflammatory process is mediated by the results of interactions through leukocytes. The deposition of fibrin causes the initial formation of atherogenesis and stimulates cell proliferation and collagen synthesis in the intima layer of blood vessels [16]. Thrombogenesis is regulated by the balance of coagulation and fibrinolysis pathways. The damage to the blood vessel walls will cause thromboplastin tissue to trigger the coagulation pathway. Fibrinogen is also involved in the process of platelet aggregation. It is an important component of the coagulation pathway. Increased plasma fibrinogen levels trigger a prothrombotic state or a hypercoagulability state [15].

LDL cholesterol is an important cause of CHD. Observational studies show an association between LDL cholesterol concentration and the risk of CHD. In this study, there was a significant mean difference in the LDL cholesterol level between AMI patients and non-AMI patients. The mean LDL

cholesterol level in AMI patients was 122.04 mg/dL, compared to non-AMI patients of 90.50 mg/dL. High LDL cholesterol levels were also found in the other study in hospitalized AMI patient population [17].

The initial stage of the atherosclerosis process involves the infiltration of LDL cholesterol, which is trapped in the sub intima tunica of blood vessels. LDL cholesterol then undergoes modification or oxidation into oxidized LDL cholesterol which will be swallowed by macrophages and forms foam cells. Endothelial dysfunction results from oxidized LDL causes an increase in free radicals. The endothelium will also express adhesion molecules and attract leukocytes into the subendothelial region. Leukocytes will attract monocytes and become macrophages that migrate into the intima tunica. Furthermore, fat streaks will be formed, which will then form an atherosclerotic plaque [1,2].

Fibrinogen and LDL cholesterol are risk factors for CHD. Both have the same characteristics as the cause of atherosclerotic plaques. These two variables share the same inflammatory process in atherosclerotic plaques development, which is the initial basis for the occurrence of acute myocardial infarction. In this study, there was a significant relationship between fibrinogen and LDL cholesterol levels. We can conclude that if there is an increase in fibrinogen level, then the LDL cholesterol level will also increase. This is consistent with the previous study which stated that fibrinogen level, triglycerides level, systolic blood pressure, and LDL cholesterol level were higher in AMI patients compared to healthy subjects [18].

5. Conclusion

There is a significant and positive correlation between the increased fibrinogen and LDL cholesterol level with the incidence of AMI. Examination of fibrinogen can be considered as an addition to determine the prognostic and selection of therapeutic strategies in the management of AMI.

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