

Correlation Between Polimorphisme

By Taufik Indrajaya

Original article

The Correlation between Polymorphism of β Fibrinogen Gene -455 G/A and Serum Fibrinogen Level with The Severity of Coronary Artery Stenosis In Coronary Artery Disease Patient

Taufik Indrajaya¹, Yudhi Fadilah², Mediarty Yuwono³, Ali Ghanie⁴

Abstract

Background: Now a days coronary artery disease (CAD) becomes major cause of death. One among 7 deaths in America caused by CAD. CAD is an atherosclerosis process, which progressively develops into plaque that will lead to stenosis of coronary artery lumen. Several studies found that high serum fibrinogen level is an independent and significant to the severity of artery coronary stenosis. Serum fibrinogen level determined by genetic factor. Polymorphism of fibrinogen gene β -455 G/A seem plays an important role in plasma fibrinogen level. Although some studies showed a significant correlation between polymorphism and cardiovascular diseases, but some other studies report inversely. **Aim.** To evaluate the correlation between the polymorphism of fibrinogen gene β -455 G/A and serum fibrinogen level with the severity of artery coronary stenosis. **Method:** This is an analytic correlative study with prospective approach without comparison. Coronary angiography was performed in catheterization labor in the department of internal medicine, while DNA analysis and PCR done in the department of microbiology in General Hospital dr Muhammad Husin Palembang- Indonesia, since July 2015 until Agustus 2016. Samples are CAD patient who undergo for coronary angiography and fulfilled the criterias. The severity of stenosis in coronary artery determined by Gensini score. This study included 31 patient. **Results.** Among 31 CAD patients, this study found severe stenosis of coronary artery in 17 patients (53,1%), moderate in 5 patients (15,6%) and mild in 10 patients (31,2%). Genetic analysis showed that serum fibrinogen level was controlled by polymorphism of fibrinogen gene β -455 G/A, consecutively by genotype AA in 15 patients (48,4%), genotype GA in 12 patient (38,7%) and by genotype GG in 4 patients (12,9%). *Chi Square* test showed a significant correlation between polymorphism gene fibrinogen β -455 G/A and serum fibrinogen level ($p=0,039$). *Spearman's rho* test and no significant correlation between serum fibrinogen level and severity of coronary artery stenosis based on Gensini score ($r=0,142$; $p=0,447$). And also this study found no significant correlation between polymorphism gene fibrinogen β -455 G/A with the severity of stenosis in coronary artery ($p=0,512$). **Conclusion.** Although this study succeeded to prove that serum fibrinogen level was determined by polymorphism fibrinogen gene β -455 G/A, but there are no significant correlations between polymorphism fibrinogen gene β -455 G/A and serum fibrinogen level with severity of coronary artery stenosis in CAD patients. This study suggest to study other candidate gene to look for other cardiac risk beside this fibrinogen.

Keywords: Atherosclerosis; CAD; Gensini score; Polymorphism Fibrinogen Gen β -455 G/A

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Introduction

Coronary artery disease (CAD) is still being serious health problem caused by high morbidity and mortality rate. In 2008 there were 17,3 million death caused by cardiovascular diseases. More than 3 million of them died before the age of 60, therefore it can be prevented. Prevalence of CAD in Indonesia at 2013 was 0,5% or estimated 883.447 patients.^{1,2}

CAD is a heart disease caused by the narrowing of the coronary arteries due to the process of atherosclerosis or spasm or a combination of both. Atherosclerosis is a chronic inflammatory progression disease. These interactions include pathological processes such as endothelial dysfunction, monocyte recruitment, inflammation, smooth muscle proliferation, accumulation and lipid oxidation, necrosis,

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calcification and thrombosis.³⁻⁶

Fibrinogen is a glycoprotein synthesized in the liver, present in platelets alpha granules and soluble in plasma. In addition to being a very important component of the clotting process, fibrinogen is an acute phase of proteins in which levels will increase in response to infection, inflammation, stress, surgery, trauma, necrotic tissue, as a result of elevated levels of fibrinogen will cause plasma viscosity and intense platelet aggregation, and also erythrocyte aggregation.⁷⁻⁹

Studies by Gothenburg, N^{or}s, Framingham, PROCAM, GRIPS reported that fibrinogen is a risk factor for CAD occurrence and they proved that elevated fibrinogen levels are associated with CAD. The PROCAM (Prospective Cardiovascular ¹⁸ nster) study showed that with an increase in fibrinogen levels associated with LDL cholesterol, the risk of CAD became 6-fold.¹⁰ Ahmed et al reported high fibrinogen levels as an independent and significant factor with the severity of coronary artery stenosis.¹¹ De Luca et al and Zhang et al report the same with Ahmed et al.^{12,13}

Atherosclerosis in CAD is evaluated using an invasive examination known as coronary angiography or cardiac catheterization. Cardiac catheterization is a technique used as the best and most accurate technique to detect coronary blockage.¹⁴ Coronary artery stenosis may occur in part or total of one or more coronary arteries and their branches. Stenosis is significant if the stenosis is more than 50% stenosis, and will decrease blood flow if stenosis is more than 70%. Cardiac catheterization (coronary angiography) can see and measure the degree of coronary artery stenosis visually how much percent the decrease diameter compare to adjacent of normal segment. There are several methods might measure coronary artery stenosis, among others GRACE score and TIMI score, but in this study using Gensini score.¹⁵ Gensini score measurement has many benefits because it is easy and practical in examining the degree of coronary artery by examining the degree of coronary artery stenosis and the location of the anatomy of the artery.

Synthesis β chain is involved in the fibrinogen maturation process due to limiting of mature fibrinogen. Increased fibrinogen level will induce hypercoagulability that will promote the progression of atherosclerosis. The polymorphism of the β

fibrinogen gene contributes to fibrinogen serum level. Substitution of G by A at -455 gene position β fibrinogen seems the most responsible to determine of fibrinogen serum level.¹⁶ Imran et al. reported an significant association between the polymorphism of β fibrinogen gene with serum fibrinogen level. Serum fibrinogen levels are high in patients with ischemic stroke.¹⁷ Inversely, Study of Myocardial Infarction Leiden reported high fibrinogen is not a risk for myocardial infarction service.^{18,19} Also, Koch et al reported on relationship haplotype gene chains α , β , and γ with myocardial infarction in 2 large control case studies.²⁰

Until now, scientific publications about the polymorphism of the β -455 G/A fibrinogen gene and serum fibrinogen levels and their effects on coronary artery stenosis are not present in Palembang-Indonesia. Based on the above description, the researcher is interested to conduct a research between polymorphism of fibrinogen gene and fibrinogen level on coronary disease with severity of stenosis associated with Gensini score.

Materials and Study Methods

This study used correlative analytic design with prospective approach without comparing group, was held in cardiac catheterization laboratory of internal medicine department and in microbiology department of General Hospital Muhammad Husin (GHMH) Palembang, starting July 2015-August 2016. The population of this study are all CAD patients undergoing cardiac catheterization and age > 30 years. This study excluded people with chronic kidney disease, malignancy, infection, pregnancy and lactation, and who are taking anticoagulant drugs. Based on the formula this study needs minimum sample is 31 orang. The selection of samples was done by consecutive sampling technique.

Gensini score is one of the scoring methods to examine the degree of coronary artery stenosis based on the results of coronary angiography. The calculation of these scores is based on the location of the anatomy of the arterial segment undergoing stenosis and the degree of narrowing of the affected lumen of the coronary artery. The degree of stenosis is divided into mild stenosis (0-15), moderate stenosis (16-30), and severe stenosis (31-72).

A 7 ml of blood sample was taken through radial or femoral artery shortly before the initiation of coronary angiography. Two cc of them was put into

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tube containing ethylene diamine tetra acetic acid (EDTA) for DNA extraction and for PCR, then DNA stored at -20 °C before the DNA isolation procedure is performed. The rest was not given anticoagulant for blood chemistry including fibrinogen. Serum fibrinogen levels were examined by ELISA (normal value: 150-450 mg / dl).

DNA isolation was performed by using Chelex-100 DNA extraction method using Phosphate Buffer Saline (PBS) pH 7.4; 0.5% Safonin in PBS; and chelex 20% in dd H₂O pH 10.5. Detection of gene polymorphism by cutting the primer PCR product by using the restrictive enzyme *Hae*III (MBI, Glen Burnie, MD, USA), where the 10 µl β-fibrinogen gene (amplicon) product is inserted into a digestive tube containing 0.2 µl enzyme *Hae*III in 1.2 µl 1/10 buffer I buffer buffer solution, then pure water (ddH₂O) until the mixed volume in the tube reaches 12 µl, and then incubated at 37 °C in water bath for 4 hours. To determine whether the restriction process is working properly or not, it is also used in the internal control of PCR products from individual samples known to have polymorphism. After incubation the restriction was separated electrophoresis in 2% agarose gel. Primer for PCR is intended to identify the following fragments: Gen β-fibrinogen -455G/A

Forward GAA CAT TTT ACC TTA TGT GAA TTA AGG and

Reverse GAA GCT CCA AGA AAC CAT CC.

The amplicon length for the β-fibrinogen -455G/A gene is 669 bp. The amplicon fragments was cut with the *Hae*III retractive enzyme (New England Biolabs, Ipswich MA, USA).

Processing and data analysis using SPSS for windows program. Data are presented in tables and graphs. The data is tested whether the distribution is normal or not, if the normal distribution then used *Pearson correlation test*, if the data distribution is not normal *Spearman correlation test*.

Ethical Clearance: This study was approved by ethics Committee of University of Sriwijaya - Indonesia.

Results

A correlative analytic study with a non-comparison prospective approach to see the correlation between the polymorphism of the fibrinogen β chain gene with serum fibrinogen level with the severity of coronary heart disease stenosis on 31 patients was obtained as follows.

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Table. 1. Baseline Characteristics

| Characteristic | n = 31 |
|------------------------|--------------|
| Sex, n (%) | |
| • Male | 20 (64,5%) |
| • Female | 11 (35,5%) |
| Age, year, mean ± SD | 56,52 ± 8,76 |
| Age group, n (%) | |
| • 30-39 yo | 2 (6,5%) |
| • 40-49 yo | 2 (6,5%) |
| • 50-59 yo | 14 (45,2%) |
| • ≥ 60 yo | 13 (41,8%) |
| Smoking habits, n (%) | |
| • Smoking | 13 (41,9%) |
| • Not smoking | 18 (58,1%) |
| Body Mass Index, n (%) | |
| • Underweight | 1 (3,2%) |
| • Normalweight | 11 (35,4%) |
| • Overweight | 19 (61,4%) |
| Diabetes Mellitus | |
| • Yes | 4 (12,9%) |
| • No | 27 (87,1%) |
| Hypertension | |
| • Yes | 11 (35,5%) |
| • No | 20 (64,5%) |

The CAD subjects in this study were more male (64.5%) with age above 50 years (87%). Nearly half of them were smokers (41.9%) and about 61.3% were overweight. By using *Shapiro-Wilk* normality test, the probability value of serum fibrinogen level and gensini score was <0,05 which means the data was not normally distributed, and so then calculation continued to see the Mean value of both variable.

Table 2. Distribution of serum fibrinogen level and Gensini score

| Correlation | N | Median (min- max) | Mean ± SD |
|----------------------------|----|-------------------|-----------------|
| S e r u m fibrinogen level | 31 | 288-711 | 420,16 ± 100,65 |
| Gensini score | 31 | 2,5-90 | 32,03 ± 26,72 |

Electrophoresis result of Gen β Fibrinogen promoter - 455 G / A

Fragments generated from electrophoresis are genotype -455 G/G homozygote resulting in fragments 488 and 181 bp, heterozygote -455G/A yields fragments 669, 488, 181 bp. Homozygote -455 A/A produces fragments 669 bp (uncut) (figure.1 below)

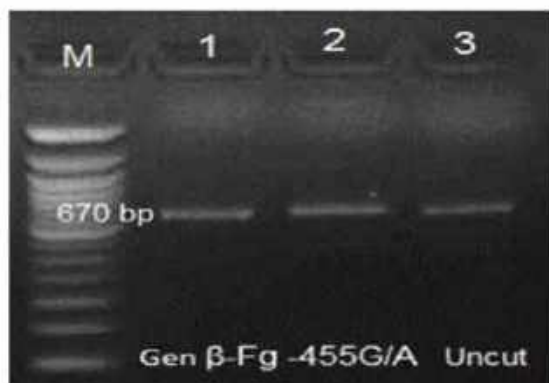


Figure. 1. Amplicon of Gen β -Fg-455G/A with size about 670 bp Homozygote wildtype G/G. M is a Marker. No 1, 2 and 3 are sample numbers.

In Figure 2 genotypes β Fg-455G/A genotypes were cut with restrictive enzyme HaeIII resulted in A/A mutant Homozygote fragments of 490 bp and 180 bp (sample no 1). Fragments Heterozygote G/A 670 bp, 490 bp and 180 bp (samples no 2 and 3).

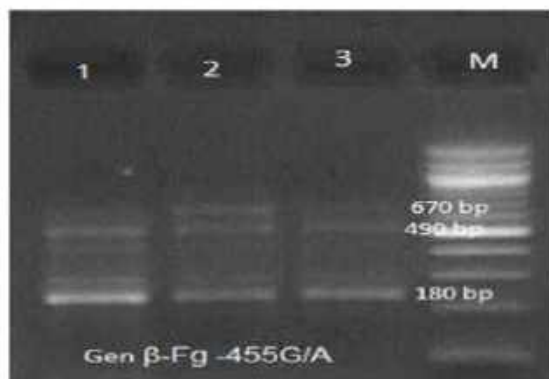


Figure.2. Amplicon Gen β Fg-455G/A is cut with the restriction enzyme HaeIII, M is the Marker.

Serum fibrinogen levels in this population were determined by genotype AA, GA and GG, respectively. CAD patients with elevated fibrinogen levels are most commonly found in the AA genotype (48.4%), see table below.

Table 3. Distribution of Fibrinogen B Polymorphism Promoter -455G/A

| Characteristic | Serum fibrinogen level | | Total |
|-----------------|------------------------|--------|-------|
| | Increase | Normal | |
| Genotype | | | |
| • AA | 12 | 3 | 15 |
| • GA | 4 | 8 | 12 |
| • GG | 3 | 1 | 4 |
| Total | 19 | 12 | 31 |

Study Result Analysis

Analysis of the results of the study begins by looking for correlations between the polymorphism of the fibrinogen β chain gene with serum fibrinogen levels. Using *Chi-Square* test, there was a significant correlation between the two variables $p = 0.039$. (see table 4.4).

Table 4. The correlation between the polymorphism of the fibrinogen β chain gene with serum fibrinogen levels

| Characteristic | Serum fibrinogen level | | Total | p value |
|-----------------|------------------------|--------|-------|--------------|
| | Increase | Normal | | |
| Genotype | | | | |
| • AA | 12 | 3 | 15 | 0,039 |
| • GA | 4 | 8 | 12 | |
| • GG | 3 | 1 | 4 | |
| Total | 19 | 12 | 31 | |

The analysis then continued to look for correlation of serum fibrinogen level with degree of coronary artery stenosis based on gensini score of CAD patients, the results can be seen in table.4.5 below. It is already known that serum fibrinogen levels and Gensini score in this study were not normally distributed, so then the analysis is continued using Spearman / s rho test. The results of the analysis were found no significant correlation between serum fibrinogen level and coronary artery stenosis degree based on gensini score ($p = 0,447$), see table below.

Table 5. Correlation of serum fibrinogen levels with Gensini score

| Correlation | N | Median (Min-Max) | Mean \pm SD | p |
|------------------|----|------------------|---------------------|--------|
| Serum fibrinogen | 31 | 288-711 | 420,16 \pm 100,65 | 0,447* |
| Gensini score | 31 | 2.5-90 | 32,03 \pm 26,72 | |

*Uji Spearman's rho

The effect of serum fibrinogen level on gensini score was then analyzed by linear regression test to see any correlation between the two variables, found that the effect of serum fibrinogen level on gens score was only 4%.

In Chi Square test there was no significant correlation between polymorphism of fibrinogen β chain gene with degree of coronary artery stenosis ($p = 0,512$) (see table 4.6).

Table 6. Correlation between β Fibrinogen Chain Gene polymorphism with Gensini score

| Characteristic | Degree of Stenosis | | | Total | p value |
|-----------------|--------------------|----------|-----------|-----------|---------|
| | Severe | Moderate | Mild | | |
| Genotype | | | | | |
| AA | 6 | 3 | 6 | 15 | 0.512 |
| GA | 7 | 1 | 4 | 12 | |
| GG | 3 | 1 | 0 | 4 | |
| 18 Total | 16 | 5 | 10 | 31 | |

Discussion

This study was aimed to evaluate the correlation between polymorphism of β fibrinogen gene and serum fibrinogen level with severity of coronary artery stenosis in CAD patients who undergone coronary angiography at GHMH Palembang Indonesia.

Neither the Gensini score nor the serum fibrinogen levels were found to be abnormally distributed. In this study the average score of Gensini is 32.03 ± 26.72 in a range of 2.5 to 90. A total of 17 people (53.1%) obtained with severe stenosis degree, this number is more than those with mild degrees of stenosis and mild ie each of 5 people (15.6%) and 10 people (31.2%). In this study average serum fibrinogen level of CAD patients was 420.16 ± 100.65 mg/dl. Results of statistical analysis showed no significant correlation between serum fibrinogen level and coronary artery stenosis degree based on Gensini score ($p = 0.45$). Unlike the study results of Ahmed et al (2014) that reported a significant independent association between serum fibrinogen levels and the degree of coronary artery stenosis, and that the higher serum fibrinogen levels, the more severe the coronary artery stenosis. This study included only 31 people, unlike Ahmed et al who recruited 210 samples and divided them into 3 groups: fibrinogen levels <400 mg/dl, 400-600 mg/l and >600 mg/dl. In this study there was only 1 person with levels of 711 mg/dl (>600 mg/dl) and indeed with severe stenosis of the coronary arteries.¹¹

Fibrinogen is a plasma soluble glycoprotein composed of 1482 amino acids with molecule weight (MW) of 340 kDa, 2 carbohydrate clusters with BN 10 kDa, and several Ca^{+} bonds with high affinity. Fibrinogen plays a role in physiopathological processes in the body, including inflammation, atherogenesis and thrombogenesis. Low fibrinogen levels can cause hemostasis disorders such as bleeding, while high levels affect the function of hemereologi. In atherotrombogenesis, fibrinogen infiltration into the walls of blood vessels, increases blood viscosity, increases trombocyte aggregation

and forms thrombus. Fibrinogen also acts as an acute phase protein that promotes degranulation of platelet.¹¹ Its levels will increase two to tenfold in response to stimuli.

Chi Square test result obtained significant correlation between polymorphism of fibrinogen β chain gene with serum fibrinogen level ($p = 0.039$). The results of this study are in accordance with the research of Liu in Ch³⁵ which proves the existence of polymorphism of beta fibrinogen -455 G/A gene with increased levels of fibrinogen. Dögen's research found the same result in which there is a fibrinogen content relationship with polymorphism of fibrinogen genes. Studies 41 ie Muat and Behague found that the polymorphism of the -455G/A fibrinogen gene led to an increase in fibrinogen levels on which coronary atherosclerotic progression was based.

Polymorphism is a gene mutation that does not cause changes in protein structure but results in variation in the function of the protein. Polymorphism can result from a change of base on a promoter, an exon or an intron. Polymorphism does not manifest clinically but can determine susceptibility to disease. Polymorphisms are found in populations with frequencies greater than 1%. Several studies have revealed the influence of genetic factors on plasma fibrinogen levels, genetic influences varying from 20% to 35% on plasma fibrinogen levels. The influence of genetic control supports the view that high plasma fibrinogen levels are a primary risk factor for atherothrombotic disorders. This study proved the existence of polymorphisms of Fibrinogen gene -455 G/A, A/A and G/G.

This study concluded there was no significant relationship between polymorphism of fibrinogen β chain gene with degree of coronary artery stenosis which obtained $p = 0.512$ ($p > 0.05$). Dögen's research found the same thing where there is no influence between polymorphism of fibrinogen genes and the risk of myocardial infarction. In contrast to the Tosetto study showing that the polymorphosis of the -455 G/A gene represents an initial risk of atherosclerosis seen in carotid artery plaque. Bozdemir proved that the beta-fibrinogen gene polymorphism -455G/A plays a role in the occurrence of left atrial thrombus and spontaneous echo contras. Similar results with this study also found in the Blake study, mutations of the fibrinogen gene have no effect as risk factors for cardiovascular disease. Koch's study found no association of variations in fibrinogenic genes 39 h myocardial infarction. Several other risk factors play a role as risk factors for coronary heart disease. This

is the case in *Hastuti et al.*, And *Molagheghi's* study that risk factors such as age, sex, lipid profile, smokers and diabetes play a greater role than fibrinogen.

Conclusion

Although this study succeeded to prove that serum fibrinogen level was determined by polymorphisme fibrinogen gene β -455 G/A, but there are no significant correlations between polymorphisme fibrinogen gene β -455 G/A and serum fibrinogen level with severity of coronary artery stenosis in CAD patients. This study suggest to study other candidate gene to look for other cardiac risk beside this fibrinogen.

Conflict of interest statement

We declare that we have no conflict of interest.

Authors' Contribution:

Data gathering and idea owner of this study: Taufik Indrajaya, Yudhi Fadilah

Study design: Taufik Indrajaya, Yudhi Fadilah, Mediarty, Yuwono, Ali Ghanie

Data gathering: Taufik Indrajaya, Yudhi Fadilah, Mediarty, Yuwono,

Writing and submitting manuscript: Taufik Indrajaya, Yuwono, Ali Ghanie

Editing and approval of final draft: Taufik Indrajaya, Yudhi Fadilah, Mediarty, Yuwono

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