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CORRELATION OF SERUM HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AND HOMOCYSTEINE LEVEL IN PATIENT WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Acute Myocardial Infarction (AMI), one of the primary manifestation of coronary heart disease, is a significat cause of death worldwide. Hyperhomocysteinemia, a risk factor for cardiovascular disease, is caused by nutritional or genetic disturbances in homocysteine metabolism. The role of hyperhomocysteinemia in altered lipid metabolism presumed holds the key to an increased risk of cardiovascular disease. Hyperhomocysteinemiacauses the reduction of serum High-Density Lipoprotein (HDL) cholesterol level by inhibiting hepatic synthesis of apo-A1 (significant apolipoprotein HDL). The aim of this study was to know the correlation between hyperhomocysteinemia and decreased HDL cholesterol levels for the management of cardiovascular disease risk factors. This research was an analytical study with cross-sectional design in 40 patients AMI who meet the inclusion and exclusion criteria and conduct blood test at the Central Laboratory of Hospital Dr. M. Djamil Padang and Biomedical Laboratory Faculty of Medicine Andalas University. The study was conductedin May 2016-Agustus 2017. Homocysteine level was measured by ELISA method. High-Density Lipoprotein level was performed by enzymatic colorimetric method. Data were analyzed by Spearman's correlation test. Research subjects were 40 people with male gender 30 (75%) and female 10 (25%), mean age 61.08 (11.09) year. The mean level of HDL cholesterol in patients with AMI is 41.93 ± 13.12 mg/dL. The mean level of homocysteine in patients with AMI is 25.36 ± 22.2 µmol/L. Spearman's correlation test showed a strong correlation between the levels of homocysteine and HDL cholesterol with r=-0.603 and p<0.01
.

Key words: High-density lipoprotein, homocysteine, acute myocardial infarction

INTRODUCTION

Cardiovascular disease is the leading cause of death worldwide. The World Health Organization (WHO) states that in 2012, out of 58 million deaths worldwide, approximately 31% (17 million) deaths were caused by cardiovascular disease and 7.4 million were due to coronary heart disease. Acute Myocardial Infarction (IMA) is one of the 5 major manifestations of coronary heart disease: stable angina pectoris, unstable angina pectoris, IMA, heart failure, and sudden death. IMA patients are estimated to be 1.5 million people with the deaths of about 500,000 patients annually in the United States.[1,2] The highest Case Rate Fatality (CRF) of IMA compared to other heart diseases was 16.6% in 2002 and 14.1% in 2003 based on hospital statistics in Indonesia.[3] The primary risk factors for the development of arterial atherosclerosis in IMA are dyslipidemia, diabetes mellitus, hypertension, smoking, and family history of coronary artery disease. Nearly most cardiovascular diseases can be prevented by avoiding behavioral risk factors. Various new risk factors have been studied, including total homocysteine levels in the blood.[1,4,5]

Homocysteine is a sulfur-containing amino acid, which is an intermediate in protein metabolism. Increased levels of homocysteine can be caused by a genetic defect that causes enzyme deficiency in homocysteine metabolism, or due to depletion of enzyme cofactors including cyanocobalamin vitamins (B12), folic acid (B9), and pyridoxine (B6).[6-8]

Increased levels of homocysteine have been shown to increase the risk of cardiovascular disease independently. Research conducted by Humphrey *et al*., concluded that an increase in serum homocysteine at 5 µmol/L would increase the risk of cardiovascular disease by about 20%. The role and mechanism of homocysteine as a risk factor for cardiovascular disease has not been fully understood. Several subsequent studies concluded that increased homocysteine increases the risk of cardiovascular disease through several mechanisms: Impaired endothelial function; Increased oxidative stress; Changes in lipid metabolism; Induction of thrombosis, but this relationship remains to be

proven.[9-11]

Hyperhomocysteinemia will lead to changes in lipid metabolism, which is thought to play an important role in the increased risk of cardiovascular disease. Most epidemiological data indicate that hyperhomocysteinemia is not associated with significant changes in total cholesterol, triglycerides and Low-Density Lipoprotein (LDL), but has a negative correlation with High-Density Lipoprotein (HDL) cholesterol. High-density lipoprotein cholesterol has several antiatherogenic abilities, the ability of cholesterol efflux from cells, antioxidants, antithrombotic, and anti-inflammatory. Hyperhomocysteinemia causes a decrease in serum HDL cholesterol concentration by inhibiting apo A-1 synthesis (apolipoprotein main HDL cholesterol) in the liver. Low-HDL cholesterol concentrations are found in patients with cardiovascular disease.[12,13]

Correlation between hyperhomocysteinemia and decreased HDL cholesterol levels is clinically important in the management of risk factors for cardiovascular disease. Clinicians do not consider homocysteine examination in most cases, so that patient therapy becomes ineffective. Clinicians still use traditional lipid risk factors (high LDL cholesterol and triglyceride levels and low HDL cholesterol) as the gold standard for underlying therapies.[14] An important aspect of reducing cardiovascular risk is by controlling serum total homocysteine concentrations as well as lipids. Possible management is to use a combination of anti-hyperlipidemic therapy with vitamin B for patient risk management. Keech *et al.* research on more than 9000 coronary patients with type 2 diabetes, fenofibrate only decreased 11% of coronary events, but homocysteine levels increased by almost 35% (from 11.2 to 15.1 μmol/L) at the end of the study. This finding may explain why the decrease in cardiovascular risk is less than expected.[15,16] Qujeq *et al*. found a significant negative correlation between serum homocysteine levels and HDL cholesterol levels in patients with myocardial infarction ($r = -0.93$, $p < 0.05$). Liao *et al.* found a negative correlation between homocysteine levels and serum HDL cholesterol levels in patients with coronary artery disease ($r = -0.54$). Mikael *et al*., the study concluded that there was a negative correlation between homocysteine levels and serum HDL cholesterol levels in patients with coronary artery disease ($r = -0.24$). Samara *et al*. also concluded a negative correlation between homocysteine levels and serum HDL cholesterol levels in ICU patients ($r = -0.42$). Abu Sedo found a negative correlation between homocysteine levels and serum HDL cholesterol levels in patients with cardiovascular disease ($r = -0.403$).

The aim of this study was to know the correlation between hyperhomocysteinemia and decreased HDL cholesterol levels for the management of cardiovascular disease risk factors.[17-21]

METHODS

The study was conducted in Mei 2016-August 2017 using a cross-sectional design, and samples were taken consecutively. Subjects consisted of acute myocardial infarction patients in the Department of Cardiology, Dr. M. Djamil Hospital Padang. Homocysteine and High-Density Lipoprotein (HDL) cholesterol assays were performed in all subjects. Level of homocysteine was performed by ELISA method. High-Density Lipoprotein level was performed by enzymatic colorimetric method.

Laboratory examinations were performed at the Central Laboratory of Hospital Dr. M. Djamil Padang and Biomedical Laboratory Faculty of Medicine Andalas University. Homocysteine examination was performed using Biotech ELISA Homocysteine Assay (Biotech) reagent, High-density lipoprotein cholesterol examination was performed using Pentra 400 Clinical Chemistry Analyzer (Horiba).

Statistical analysis was performed using SPSS ver 16.0. Data were analyzed by Spearman's correlation test.

RESULTS AND DISCUSSION

Research subjects were 40 people with male 30 (75%) and female 10 (25%), mean age 61.08 (11.09) year. Acute myocardial infarction classified into ST-Elevation of Myocard Infarction (STEMI) and Non-ST-Elevation of Myocard Infarction (NSTEMI). The mean level of HDL cholesterol in patients with AMI is 41.93 ± 1312 mg/dL. The mean level of homocysteine in patients with AMI was 25.36 ± 22.2 μmol/L. Spearman's correlation test showed a strong correlation between the levels of homocysteine and HDL cholesterol with $r=-0603$ and $p<0.01$.

Laboratory tests conducted on the study sample were HDL cholesterol and serum homocysteine levels. The results of the examination can be seen in Table 2. The mean HDL level of the research sample was 41.93 (13.12) mg/dL with the lowest level of 12 mg/dL and the highest level of 78 mg/dL. The mean of homocysteine level of the research sample was 25.36 (22.2) μmol/L with the lowest level was 5.399 μmol/L and the highest level was 94.755 μmol/L.

Table 1. The characteristics of subjects

Variable	n (%)	Mean (SD)
Sex		
Male	30 (75)	
Female	10 (25)	
Age (year)		61.08 (11.09)
AMI classification		
STEMI	25 (62.5)	
NSTEMI	15 (37.5	

*Mean ± SD, SD: standard deviation

Table 2. High-density lipoprotein cholesterol and homocysteine level

Variable	Mean (SD)
High-Density Lipoprotein (HDL) cholesterol (mg/dL)	41.93 (13.12)
Homocysteine (µmol/L)	25.36 (22. 2)

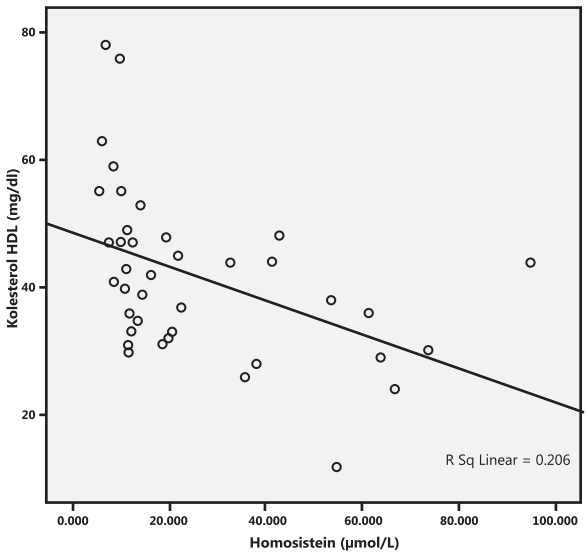

Figure 1. Correlation of homocysteine and HDL cholesterol level, r=-0.603

The sample of the study was 40 people with males sex (75%) more than females (25%). This result was consistent with the study of Ahmadi *et al.*, which examined the epidemiology of IMA in Iran obtained an average prevalence of IMA higher in males (72.4%) than in females (27.6%). Another study by Qujeq *et al.*, on total homocysteine relationships with AMI patients, showed 53% of males and 47% of females. Al-Obaidi *et al.* study on the increase of homocysteine in AMI patients: 78% patients were males and 22% were females.[9,17,22]

Acute myocardial infarction is mostly found in males over females. It is associated with the effect of estrogen on females who have atheroprotective effects so that IMA and other atherosclerotic complications are rare, especially in premenopausal females.[23] Another risk factor that can affect smoking habit in most males is smoking more than females.[24]

The mean age of the IMA patients in this study was 61.08 (11.09) years with the age range 40-94 years. Al-Obaidi *et al.* research obtained the mean age of IMA patients 61.8 (0.74) years. The incidence of IMA increases dramatically with increasing age. Research Qujeq *et al.* obtained the mean age of IMA patients 48.65 (3.81) years with age range 29-73 years.[9,17]

Age increment is associated with elevated risk factors in an advanced age such as elevated blood pressure, serum diabetes mellitus cholesterol, and decreased physical activity.[25,26] Age has a major effect, although atherosclerosis is progressive but will not lead to clinical manifestations until age > 50 years. In the adult population aged 40-60 years, IMA incidence increased to five-fold.[24]

The mean HDL cholesterol level of the study subjects was 41.93 (13.12) mg/dL with the lowest levels of 12 mg/dL and the highest concentration of 78 mg/dL. The mean HDL cholesterol level in this study was similar to that of Samara *et al.* getting a mean of HDL 40.9 (10.78) mg/dL. Based on the NCEP criteria, HDL cholesterol levels <40 mg/dL (<1.033 mmol/L) is a risk factor for coronary heart disease, HDL cholesterol ≥ 40 mg/dL (≥ 1.033 mmol/L) desirable, whereas HDL cholesterol ≥ 60 mg/dL (≥ 1.550 mmol/L) has the ability to protect against heart disease.[21] This study obtained HDL cholesterol levels <40 mg/dL as much as 45%, HDL cholesterol ≥ 40 mg/dL as much as 47.5% and HDL cholesterol ≥ 60 mg/dL as much as 7.5%. Based on these criteria the mean HDL cholesterol level of the study subjects (40.9 (10.78) mg/dL) can still be classified as desirable but lacked protection capability.[20]

Mean homocysteine level of the study subjects was 25.36 (22.2) µmol/L with the lowest level of 5.399 µmol/L and the highest grade of 94.755 µmol/L. Alam *et al.*, suggests these levels are classified as mild hyperhomocysteinemia (homocysteine> 15-30 µmol/L).[25] This result was following the research of Brattstrom and Wilcken, who found mild homocysteine elevations appear in 20-30% of patients with atherosclerotic disease. Previous studies had shown that hyper-homocysteinemia was associated with an increased risk of cardiovascular events.[10] An elevated serum homocysteine of 5 µmol/L will increase the risk of cardiovascular disease by about 20%.[11] Increased homocysteine increases the risk of cardiovascular disease through several mechanisms namely

impaired endothelial function, increased oxidative stress, changes in lipid metabolism, and the induction of thrombosis.[10,13] The number of research samples with normal homocysteine level was 21 people (52.5%). Normal homocysteine levels indicate that no metabolic metabolism is present, either in synthesis or in excretion.

Fourteen of the 21 (67%) study samples with normal homocysteine levels had normal HDL cholesterol (> 40 mg/dL). The results of this study found a strong negative correlation between HDL cholesterol levels with serum homocysteine (r = -0.63) (p <0.01). This finding suggests the possibility of a decrease in serum HDL cholesterol levels may be used to assess hyperhomocysteinemia in acute myocardial infarction patients so that risk management can use a combination of anti-hyperlipidemic and vitamin B therapy.[15,26] Hyperhomocysteinemia decreases serum HDL cholesterol concentrations by inhibiting apoA-1 synthesis (primary apolipoprotein HDL) in the liver.[23,27] Homocysteine can reduce the expression of apoA-1 through loss of alpha peroxisome proliferator receptors (PPARα), mediating the apoA-1 transcription.[13] Hyperhomocysteinemia may also cause a decrease in the transcription of apoA-1 by the effects of other regulatory factors, such as increased nuclear factor κB (NF-κB) signals that decrease the transcription of apoA-1, alter DNA methylation, as well as reduced LCAT enzyme activity.[10,27] Qujeq *et al*. found a significant negative correlation between serum homocysteine levels and HDL cholesterol levels in patients with myocardial infarction (r = -0.93, p <0.05). Liao *et al*. found a negative correlation between homocysteine levels and serum HDL cholesterol levels in patients with coronary artery disease (r = -0.54). Some of the study samples had high homocysteine levels but were not followed by a decrease in HDL cholesterol or vice versa, presumably because of the influence of anti hyperlipidemic drugs that may affect HDL cholesterol levels. The impact of anti hyperlipidemic drugs cannot be fully controlled because exclusion criteria are obtained from medical records only. Foods can also affect levels of homocysteine (a diet rich in methionine, betaine, choline, vitamin B, folic acid, coffee, tea, and alcohol) that exceeds the recommended daily intake. This study took a sample, of fasting blood so it is expected to minimize the influence of food on the results of the research.

CONCLUSION AND SUGGESTION

Homocysteine level and HDL cholesterol in AMI patients have a strong negative correlation. Further research is needed on other parameters that cause increased homocysteine such as enzyme cofactor depletion including cyanocobalamin vitamins (B12), folic acid (B9), and pyridoxine (B6). Further study is also needed on apolipoprotein-A1 to determine the correlation of homocysteine levels with serum apolipoprotein-A1 levels.

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