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Correlation of Homocysteine Levels With Folate Acid, Cyanocobalamine, and Pyridoxine Serum Levels In Acute Infark Miocard Patients

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Abstract. Cardiovascular disease is the cause of the highest mortality rate in the world. Acute myocardial infarction is one of the 5 major manifestations of coronary heart disease and the highest mortality rate in Indonesia. Hyperhomocysteinemia is one of the risk factors for the occurrence of acute myocardial infarction. The metabolism of homocysteine is influenced by folate acid, cyanocobalamin, and pyridoxine. Enzimsistationin-β-synthetase and cystationin-γ-liase that catalyze the transsulfuration of homocysteine are highly depended on pyridoxine. This study aims to determine the association of homocysteine with folate acid, cyanocobalamin, and pyridoxine serum levels in acute myocardial infraction patients. Cross-sectional design study with 25 samples of acute myocardial infraction patients are selected randomly. The research was conducted from July to December 2016 in Biomedical laboratory Andalas University. Homocysteine, folate acid, cyanocobalamin, and pyridoxine levels were examined by the ELISA method. Data is analyzed by the Pearson correlation test. The mean result of examination of homocysteine level was 23.17±9.2 nmol/mL, pyridoxine level 128.44 ± 34.02 pmol/L, cyanocobalamine level 188.79 ± 10.23 pmol/L and folate acid level 2.72 ± pmol/ L. Statistic analysis test found that there is a significant relationship of levels of homocysteine with pyridoxine (r = -0.530), but there is a very weak relationship with cyanocobalamine and folate acid (r = - 0.027 and - 0.003). There is a significant relationship of homocysteine levels with pyridoxine serum on acute myocardial infarction patients. And there is a very weak relationship of homocysteine levels with cyanocobalamine and folate acid.
Keywords: myocardial infarction, homocysteine, folate acid, cyanocobalamine, and pyridoxine

1. Introduction

Acute myocardial infarction is a health problem in the community and is the highest cause of death in Indonesia. The highest case fatality rate (CRF) is compared to other heart diseases, that is 16.6% in 2002 and 14.1% in 2003 based on hospital statistics in Indonesia [1]. Various new risk factors have been studied, including levels of total homocysteine in the blood [2,3].

Increased levels of homocysteine have been shown to increase the risk of cardiovascular disease independently [4]. The role and mechanism of homocysteine as a risk factor for cardiovascular disease is not fully understood. Several subsequent studies concluded that increased homocysteine increases the risk of cardiovascular disease through a mechanism of impaired endothelial function, increased oxidative stress, changes in pleated metabolism, induced thrombosis. However, this relationship must still be proven [5, 6, 7]. Homocysteine is an amino acid containing sulfur, which is an intermediate in methionine metabolism. Elevated levels of homocysteine can be caused by genetic defects that cause enzyme deficiency in homocysteine metabolism, or due to cofactor depletion of enzymes including cyanocobalamin, folate acid, pyridoxine [8,9].

The correlation between homocysteine levels and cyanocobalamin, folate acid and serum pyridoxine is important in the management of cardiovascular disease risk factors. In most cases, clinicians do not consider checking homocysteine so that therapy in patients becomes ineffective. An important aspect of reducing

cardiovascular risk is to control the total serum homocysteine concentration [10, 11]. The possible management is to use vitamin B for patient risk management. and long-term folate acid-based vitamin therapy is independently associated with reduced mortality in hyperhomocysteinemic patients with cardiovascular disease, and with a decrease in homocysteine concentration . In contrast, a study conducted found that supplementation with folate acid, vitamin B6 and B12 does not reduce the incidence of cardiovascular disease in high-risk women, although it can reduce homocysteine significantly [10, 12, 13].

This study was to determine the correlation of homocysteine levels with levels of cyanocobalamin, folate acid, and pyridoxine serum in IMA patients at the Dr.M.Djamil Hospital Padang.

2. Experimental Method

The study was conducted on 25 patients who had been diagnosed by a cardiologist at M. Djamil Hospital Padang as a patient with acute myocardial infarction. Informed consent was carried out for each patient. Patients receiving folic acid, cyanocobalamine and pyridoxine therapy were not included in the study.
The patient fasts 12 hours before the examination. Examination of levels of Homocysteine, folic acid, cyanocobalamin, and serum pyridoxine was carried out in the Biomedical laboratory of the Andalas University School of Medicine by ELISA method. Patients with normal ECG and ECHO and without angiographic findings were included as controls.
Data were analyzed by Pearson correlation test.

3. Result and Discussion

The study was conducted from July to December 2016 on 25 patients with acute myocardial infarction from Dr. M. Djamil Hospital Padang.

Table 1. Homocysteine, folate asid,, cyanocobalamine and pyridoxine serum levels of acute myocardial infarction patients

No	Variable	Mean ±SD
1	Homosistein (nmol/ml)	23.17 ± 9.2
2	Pyridoxine (pmol/l)	128.44 ± 34.02
3	Cyanocobalamine (pmol/l)	188.79 ± 10.23
4	Folate Acid (ng/ml)	2.72 ± 0.91

The mean serum homocysteine levels obtained were 23.17 ± 9.2 nmol / ml. The same study conducted by Loscalzo et al., 2013 concluded that any increase in serum would increase the risk of cardiovascular disease about 20%. 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 (Senaratne et al., 2000; Obaidi et al, 2002; Nair K.G et al., 2002).

Table 2. Bivariate analysis of homocysteine with pyridoksine serum levels

	Mean ± SD	r	p
Homosistein (nmol/ml)	23.17 ± 9.2	-0.530	0.001
Pyridoxine (pmol/l)	128.44 ± 34.02		

There is a moderate correlation between homocysteine and pyridoxine serum with acute myocardial infarction.

Table 3. Bivariate analysis of homocysteine with Cyanocobalamine serum levels

	Mean ± SD	r	P
Homosisteine (nmol/ml)	23,17 ± 9,2	- 0,027	0,0061
Cyanocobalamine (pmol/l)	188,79 ± 10,23		

There is a very weak correlation between homocysteine and cyanocobalamine serum levels in patients with acute myocardial infarction.

Table 4. Bivariate analysis of homocysteine with folate acid serum levels

	Mean ± SD	r	p
Homosisteine (nmol/ml)	23,17 ± 9,2	-0,030	0,006
Folate acid (ng/ml)	2,72 ± 0,91		

There is a very weak correlation between homocysteine and serum folate acid levels in patients with acute myocardial infarction. In this study, 30% of patients with acute myocardial infarction had hyperhomocysteinemia.

Previous research conducted by Lin, T.K in 2002 concluded that severe deficiency of vitamin B12 and folic acid, respectively, experienced mild hyperomomysteinemia as much as 43.4% and 60.8%.
The results of the research conducted by Lonn E et al. in 2013 regarding the description of homocysteine with vitamin B6, B12 and folic acid in Systemic Lupus Erytematusus patients there was an increase of> 10 umol / l homocysteine in 71.8% of the sample, a decrease of 56.4% folic acid, vitamin B6 levels decreased by 46.2 % and 51.3% of the samples also experienced a decrease in vitamin B12 levels.
A meta-analysis of 25 randomized controls concluded that folic acid concentration 8 0.8 mg / day was needed to achieve a reduction in maximal homocysteine concentration, while folic acid concentrations of 0.2 mg / day and 0.4 mg / day were associated with a decrease in homocysteine concentrations of 60 % and 90%. Vitamin B12 (0.4 mg / day) causes a decrease in 7% homocysteine levels, (Yasaman Ghambai et al., 2016)

Homocysteine is an important endothelial aggression factor that causes endothelial dysfunction through a mechanism that leads to atherosclerotic plaque formation [11,15,16]. The mechanism of homocysteine causing endothelial dysfunction is by inhibiting endothelial cell growth, inducing an imbalance between O and NO with a decreased effect on vascular physiology; induces the expression of different adhesion molecules, and stimulates the formation of modified LDL particles, which play an important role in the etiology of atherosclerotic plaque formation [15, 17].

The removal system of homocysteine that is formed during metabolism in the body can be carried out in two ways, that are by converting to cysteine with a transulfuration reaction, and converting homocysteine back to methionine with a remethylation reaction, as shown in Figure 1 [8].

Both reactions use vitamins and folate acid as cofactors. At high protein intakes, and there is not enough folate acid, pyridoxine and cyanocobalamine to digest, homocysteine levels can increase in the blood [8, 18]. The main pathway for homocysteine is transsulfuration to cysteine. This mechanism occurs when methionine is high in the blood. The first reaction is condensation between homocysteine and serine to cystathionine. This reaction is catalyzed by the enzyme cystathionine-β-synthetase and requires pyridoxine as a cofactor. Cystathionine is then hydrolyzed to cysteine and α-ketobutyrate with the help of the enzyme cystathionine-ase-liase. The oxidative decarboxylation reaction will convert α-ketobutyrate to propionyl-CoA, which will be converted into succinyl-CoA in the Krebs cycle. Subsequent catabolism of cysteine produces taurine and inorganic sulfate, which will be excreted in the urine [8, 19]. The second pathway, which is methionine resynthesis from homocysteine, occurs when the methionine level is low in the blood [8]. The mechanism of this methionine synthesis is through a reaction catalyzed by methionine synthetase and beta-homocysteine methyl transferase (BHMT). Methionine synthetase requires

sianocobalamin and N5-methyl tetrahydrofolate (THF). The reaction catalyzed by this enzyme causes a relationship between homocysteine and a 'one carbon unit' metabolism. N5-methyl THF is synthesized from N5-10-methylene THF through a reaction catalyzed by N5-10-methylene THF reductase (MTHFR). This reaction requires adenine nicotinamide dinucleotide hydrogen (NADH), which is regulated by SAM as a negative regulator and SAH as a positive regulator [20, 21, 22].

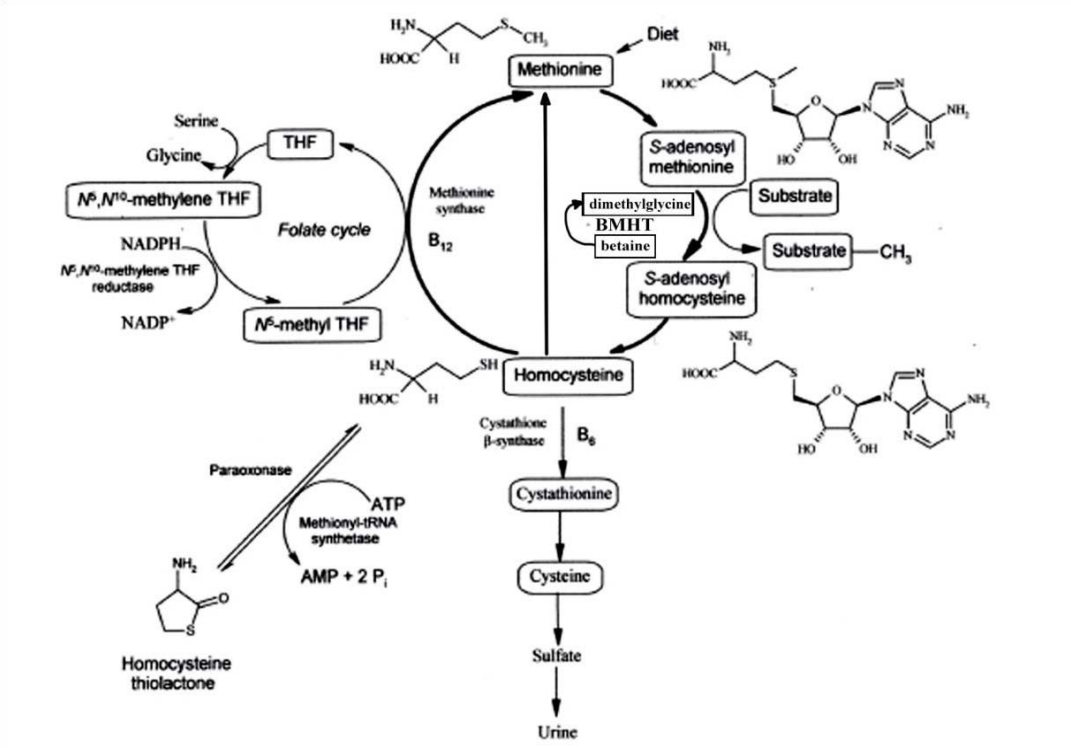

Figure 1. Homocysteine metabolism [8].

4. Conclusion

This study has shown there is a significant relationship of homocysteine levels with pyridoxine serum levels on patients with acute myocardial infarction and very weak relationship with cyanocobalamine and folate acid

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