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RESEARCH ARTICLE

Association between Homocysteine Level and Vitamin D Deficiency with Acute Coronary Syndrome in Indonesia

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ABSTRACT:

Background: Acute coronary syndrome (ACS) is an acute subset of coronary heart disease that requires immediate treatment. ACS is at a high prevalence in Indonesia. Homocysteine is another product of methionine metabolism. Hyperhomocysteinemia is known to cause ACS through several mechanisms, namely inducing oxidative stress, endothelial injury, and increased likelihood of plaque rupture. Vitamin D is a hormone needed by the body that comes from food or is produced through the metabolism of Vitamin D. Vitamin D functions as an anti-inflammatory, anti-thrombotic and anti-atherosclerotic agent. This study aimed to analyze the relationship between homocysteine level and Vitamin D deficiency with acute coronary syndrome incidence. **Methods:** This study was a cross-sectional, observational analysis study with 90 subjects. Subjects were enrolled into two groups; patients with ACS and patients with health control based on age. All subjects were selected from Universitas Airlangga Hospital, Surabaya. Serum homocysteine level and Vitamin D deficiency were calculated using an enzyme-linked immunosorbent assay (ELISA). The relationship between serum homocysteine level and **Results:** Ninety subjects were obtained in this study. The mean age was 62.1±10.9 years (among patients with ACS) and 60.1±10.3 years (healthy persons), with 55.6% male patients. The traditional risk factors i.e., diabetes, hypertension, and dyslipidemia were 62.2%, 91.1%, and 75.6%, respectively. The Chi-square analysis results showed homocysteine level and ACS obtained a contingency coefficient of 0.270 (p = 0.008) and Vitamin D with ACS had a contingency coefficient of 0.468 (p = < 0.001). **Conclusions:** There was a weak association between homocysteine level and ACS and a moderate association between Vitamin D deficiency and ACS.

KEYWORDS: Acute coronary syndrome, Homocysteine, Vitamin D.

INTRODUCTION:

Acute coronary syndrome (ACS) is at a high prevalence in Indonesia.

The Indonesian Ministry of Health recorded that cardiovascular diseases including ACS were found in more than 11.5 million people. This number is the highest among the prevalence of other non-communicable diseases[1].

Acute coronary syndrome is the term used for describing symptoms of ischemic chest pain. Acute coronary syndromes include several types, such as unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI)[2-4]. The main symptom of

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acute coronary syndrome is chest discomfort, which appears suddenly as pain, pressure, tightness, and burning[5-8].

Hyperhomocysteinemia and Vitamin D deficiency are associated with an increased risk of developing acute coronary syndromes[9]. Homocysteine is an amino acid that contains a sulfhydryl formed during the metabolism of methionine to cysteine[10,11]. Hyperhomocysteinemia is reported to be influenced by several factors, including a methionine-enriched diet which may increase the metabolism of methionine to homocysteine[12-14]. Homocysteine levels of more than 15 mmol/mL were significantly associated with an increased risk of acute coronary syndrome[15].

Furthermore, Vitamin D is a necessary nutrient consumed from food or produced through Vitamin D metabolism[16]. The body needs sufficient Vitamin D because it has several systemic effects, including anti-inflammatory, anti-thrombotic, and anti-atherosclerotic effects as heart protection[17,18]. Vitamin D deficiency can interfere with this process and human health. Research explains that Vitamin D deficiency is a risk factor for cardiovascular disorders[15,19,20], specifically the incidence of acute coronary syndrome in humans[17].

With the impacts of Hyperhomocysteinemia and Vitamin D deficiency, this study analyzed the association between homocysteine level and Vitamin D deficiency with ACS.

METHODS:

This study was part of an observational cross-sectional study conducted at the Universitas Airlangga Hospital between October 2021-March 2022. The research protocols of this study were approved by the Universitas Airlangga Hospital Ethics Committee (Reference number 067/KEP/2022).

This study involved 90 subjects sampled sequentially from subjects who experienced acute coronary syndrome and health control. There were 45 samples each in control (health control) and experiment groups (acute coronary syndrome). Subjects were selected based on their history of medical records. The inclusion criteria for the subjects were those age> 18 years who were diagnosed with acute coronary syndrome. While subjects who had undergone organ transplantation, chemotherapy, radiotherapy, stroke, or taking vitamins B6, B12, and folic acid were excluded.

Subjects were matched with health complaints experienced, and they were grouped based on age and sex. Other risk factors for acute coronary syndrome, such as hypertension, diabetes mellitus, chronic kidney disease, and dyslipidemia, were gathered from their medical records.

The sample size for this study was calculated at a significance level of 0.05 and a type II error of 20 %. Based on previous studies with a correlation coefficient of 0.445, the minimum sample size was 37 subjects. Meanwhile, this study used a bigger sample size which was 90 subjects. Serum homocysteine level and Vitamin D deficiency were measured using an enzyme-linked immunosorbent assay (ELISA). The brand of the ELISA kit used was *BT Lab*. Blood samples were taken to identify serum homocysteine level and Vitamin D deficiency and stored at -40^{0}C.

Table 1: Categories of homocysteine (Hcy) level[8]

Hcy level	Descriptions
<= 15 mmol/mL	Normal
> 15 mmol/mL	High

Tabel 2: Categories of vitamin D (Vit D) level[10]

Vit D level	Descriptions
>= 30 ng/mL	Sufficient
20 – 29 ng/mL	Deficient
< 20 ng/mL	Severe Deficient

A summary of subject characteristics from two groups was drawn. The Chi-square test was then performed to identify serum homocysteine level and Vitamin D deficiency. The significance was determined based on the p-value < 0.05. The strength of the relationship was analyzed using the contingency coefficient test. The categories of homocysteine level and Vitamin D deficiency used for both groups can be seen in Tables 1 and 2.

RESULT:

Ninety subjects met the criteria of this study. The mean age of the subjects was 62.1±10.9 years in subjects with ACS and 60.1±10.3 years in healthy subjects. The youngest patient was 40 years old, and the oldest was 85. Male was the most dominant sex of the research subjects.

Table 3: Baseline characteristic (n=90)

Characteristics	Value (%)	
	ACS (n=45)	Healthy (n=45)
Age (mean)	62.1±10.9	60.1±10.3
Sex (n)		
Male	25 (55.6)	25 (55.6)
Female	20 (44.4)	20 (44.4)
Diagnosis (n)		
STEMI	12 (26.7)	-
NSTEMI	26 (57.8)	-
UA	7 (15.5)	-
Healthy	-	45 (100)
Diabetes (n)		
Yes	28 (62.2)	36 (80.0)
No	17 (37.8)	9 (20.0)
Hypertension (n)		
Yes	41 (91.1)	35 (77.8)
No	4 (8.9)	10 (22.2)
Dyslipidemia (n)		
Yes	34 (75.6)	28 (62.2)
No	11 (24.4)	17 (37.8)

The diagnosis of ACS was dominated by NSTEMI (57.8%), then STEMI (26.7%), and UA (15.5%). Most subjects who experienced ACS also suffered from diabetes mellitus, hypertension, and dyslipidemia.

Based on the Chi-square test results, the association between homocysteine level and ACS obtained a contingency coefficient of 0.270 and a p-value of 0.008. While the association between Vitamin D deficiency and ACS obtained a contingency coefficient of 0.468 and a p-value of < 0.001 (Table 4).

Table 4. Association of homocysteine and vitamin D deficiency with ACS

Variable	ACS	Healthy	*p*
Homocysteine level			
Normal	28	39	0.008
High	17	6	
Vitamin D level			
Sufficient	8	21	< 0.001
Deficient	14	22	
Severe Deficient	23	2	

DISCUSSION:

As seen in Table 3, the subjects who experienced ACS were dominated by men (55.6%), and their mean age of them was 62.1±10.9 years. The findings are consistent with a study conducted at 192 hospitals where 82,196 patients experienced ACS in China from 2014 to 2018. It showed that 74.4% of the patients were male, and the mean age of the patients was 63.1±12.5 years[21].

Traditional risk factors that can increase the likelihood of ACS include diabetes mellitus[22], hypertension[23], and dyslipidemia[24]. A person with at least one of these risk factors possibly has a greater risk of experiencing ACS[25]. This current study found that the patients had diabetes mellitus (62.2%), hypertension (91.1%), and dyslipidemia (75.6%). These results are directly proportional to previous studies in Indonesia. They showed that most of the patients suffered from diabetes mellitus (53.3%)[26], hypertension (68.4%), and dyslipidemia (68.4%)[27].

This study analyzed the association between homocysteine levels and Vitamin D deficiency with ACS. A weak association was found between homocysteine level and ACS. These results are supported by research conducted in Africa which showed similar results[28]. In another study, more than 15 mmol/mL of homocysteine level was significantly associated with an increased risk of acute coronary syndrome[15]. Having hyperhomocysteinemia will increase free radicals to trigger oxidative stress and endothelial dysfunction[29]. Endothelial dysfunction will increase the chances of atherogenesis, causing the formation of atherosclerotic plaques[30].

Moreover, this current study delineated a moderate association between Vitamin D deficiency and ACS. This finding indicates that low Vitamin D levels are associated with the incidence of ACS. Research in Saudi Arabia also reported similar findings[17]. Vitamin D is known to have several systemic effects, including anti-inflammatory, anti-thrombotic, and anti-atherosclerotic effects as cardiac protection. In addition, Vitamin D has been shown to increase nitric oxide, inhibit platelet and leukocyte aggregation and adhesion processes, reduce oxidative stress in the endothelium, affect vascular muscle, prevent the release of pro-inflammatory cytokines, modulate immune responses, and restrain vascular smooth muscle cell proliferation and migration. Lack of Vitamin D also will reduce the protective effect on the heart[17,31-33].

CONCLUSION:

There was a weak association between homocysteine level and ACS and a moderate association between Vitamin D deficiency and ACS.

CONFLICT OF INTEREST:

All authors declare no conflicts of interest in this study.

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