The Association of Serum Vitamin D Levels and Short Term and 6-month Outcomes among Patients with Acute Coronary Syndrome

Mohsen Asadi Qomi [1], Sepehr Gohari [2], Hassan Ahangar [1,*], Ahmad Jalilvand [3], Seyed Jamal Moosavi [4], Koorosh Kamali [5], Mohammad Masoud Vakili [5], Tara Reshadmanesh [2]

[1] Department of Cardiology, Mousavi Hospital, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[2] School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[3] Department of Pathology, Mousavi Hospital, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[4] Cardiovascular Intervention Research Center, Rajaie Cardiovascular Medical and Research Center, Iran University of Medical Sciences, Tehran, Iran
[5] Department of Biostatistics, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

** Corresponding author: Hassan Ahangar, Department of Cardiology, Mousavi Hospital, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran. Tel: +98-9111512028, E-mail: ahanghar@zums.ac.ir*

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Abstract

Introduction: vitamin D affects the function of most of the cells in the body, including myocytes and endothelial cells, and also affects platelet function. This study aims to evaluate the relation between vitamin D deficiency and in-hospital and 6-month outcomes of patients with the acute coronary syndrome.

Methods: This was a prospective cohort study of patients admitted to Mousavi hospital with the diagnosis of acute coronary syndrome. A venous blood sample obtained from patients at the time of admission and 25-hydroxyvitamin D, lipid profile, and hs-troponin-I levels were measured. After coronary angiography, the severity of the coronary artery stenosis was calculated by the syntax score. Patients also evaluated in-hospital outcomes and even followed up for 6-month results.

Results: Totally, 204 patients were included in the study. The mean ± SD of age was 60 ± 11.6-year-old. The overall vitamin D deficiency was 80.9%. There was no association between vitamin D deficiency and in-hospital and 6-month mortality in patients with acute coronary syndrome (P = 0.824). There was a direct and statistically significant association between vitamin D levels and HDL cholesterol (P = 0.011). Twenty-eight percent of patients with negative hs-troponin-I and 14% with positive hs-troponin-I had normal vitamin D levels, which was statistically significant (P = 0.045).

Conclusion: This study does not demonstrate an association between vitamin D levels and in-hospital and 6-month outcomes in patients with the acute coronary syndrome.

INTRODUCTION

Ischemic heart disease is one of the leading causes of death and disability among cardiovascular diseases [1]. Despite significant advances in the treatment and prevention of coronary artery disease, the rate of mortality and disability is still increasing [2]. Calcitriol or 25-hydroxyvitamin D (25[OH]D), an active form of vitamin D, affects the function of most of the cells in the body via its receptor (VDR), including myocytes and endothelial cells, as well as smooth muscle cells in the vasculature [3]. Vitamin D has anti-coagulant effects by

increasing the amount of thrombomodulin and reducing the tissue factor [4]. Also, vitamin D has an impact on platelet function, suppresses inflammatory processes, and suppresses the renin angiotensin system [5]. In recent years, several studies have examined the relationship between the level of vitamin D and cardiovascular disease and its mortality [6]. In some of these studies, there was a significant relationship between low serum vitamin D level and cardiovascular disease, while in others, this relationship has not been proven [7]. The association between vitamin D deficiency and risk factors for atherosclerosis, including obesity, hyperlipidemia, glucose intolerance, metabolic syndrome, and hypertension, has been proven [8, 9]. Few studies have been conducted on the association between levels of vitamin D and acute coronary syndrome with different results [4, 10]. Given the limited studies available and the contradictory results in this regard, we aimed to evaluate the relationship between serum vitamin D levels and the in-hospital and 6-month outcomes in patients with the acute coronary syndrome.

MATERIAL AND METHODS

This study was a prospective, cohort study of all patients with acute coronary syndrome admitted in the cardiac care unit (CCU) in Mousavi hospital in Zanjan, between September 2016 and September 2017. The study was conducted under the principles of the declaration of Helsinki and approved by the ethics committee of Zanjan University of medical sciences (ZUMS.REC.1395.206). All the patients provided written informed consent. The inclusion criteria were: (1) age between 45-75 years; (2) patients with U.A (unstable angina), STEMI(S-T segment elevation myocardial infarction), or non-STEMI who underwent coronary angiography. The exclusion criteria were: (1) patients with the history of myocardial infarction; (2) patients with the history of CABG (coronary artery bypass graft) or PCI (percutaneous coronary intervention); (3) history of malignancy; (4) Patients undergoing dialysis; (5) Patients with a life expectancy of fewer than six months; (6) Lack of access to the patient during the follow-up. At the time of admission, a venous blood sample was obtained from the patients. The lab tests including 25[OH]D using ARCHITECT 25-OH Vitamin D (Abbnott, USA), high sensitive Troponin-I using ARCHITECT STAT High Sensitive Troponin-I (Abbnott, USA), blood glucose, lipid profile, and urine albumin to creatinine ratio were done. Regarding the manufacturer datasheet, the hs-troponin-I levels more than 34.2 ng/ml in male patients and 15.6 ng/ml in female patients were considered as positive. According to the vitamin D levels, Patients were divided into three groups: sufficient (vitamin D level ≥ 30 ng/ml), mildly deficient (20 ng/ml ≤ vitamin D level < 30 ng/ml), and severely inadequate (vitamin D level< 20 ng/ml) [11]. The occurrence of arrhythmias, acute pulmonary edema, and mortality of the patients during admission, plus the data from the lab tests of the two groups, was recorded in the predesigned checklist. Angiographic data were calculated based on the syntax score. Two skilled cardiologists recalculated the syntax scores to confirm the accuracy of the results obtained from the first score calculation. The cardiologists were blinded to each other to calculate the syntax scores. Then patients were followed up for six months after the discharge. Patients' follow up included their health status and re-hospitalization because of the acute coronary syndrome, arrhythmia, and mortality.

Statistical Analysis

All data were transferred into IBM SPSS statistics version 22 software and undergone statistical analysis. In data analysis, the Mann-Whitney test was used to compare the means of vitamin D and the occurrence of pulmonary edema and arrhythmias as early complications during admission, and re-hospitalization with cardiovascular causes as a late complication during six months. Chi-square test was used to determine the relationship between vitamin D level and HDL (high-density lipoprotein) cholesterol, LDL (low-density lipoprotein) cholesterol, blood glucose, triglyceride, albumin to creatinine ratio, and also syntax score. Also, the Chi-square test was used to evaluate the variables, including hs-troponin-I status, pulmonary edema, and arrhythmia during hospitalization and re-hospitalization during six months in three groups of patients based on vitamin D level. Kruskal-Wallis test was used to determine the relationship between the severity of vitamin D deficiency with HDL cholesterol, LDL cholesterol, blood glucose, triglyceride, and albumin to creatinine ratio, as well as syntax score. The significance of the relationship was shown with the odds rate (95% CI).

RESULTS

Based on the inclusion criteria, a total of 257 consecutive ACS patients were included in the study. Thirty-eight patients due to lack of vitamin D samples, 13 patients due to lack of access to them for a six-month follow-up, and two patients due to malignancy were excluded from the study. Finally, data from 204 patients were analyzed. One hundred and fifty-four patients (75%) were men, and 50 (25%) were women. The mean ± SD of age was 60 ± 11.6-year-old. The mean ± SD of vitamin D level was 22.57 ± 13.8 ng/ml. Of the 204 patients admitted with a diagnosis of acute coronary syndrome, 165 patients (80.9%) suffered from vitamin D deficiency. Of these, 138 patients (83.6%) had a mild deficiency, and 27 (16.4%) had severe lack. The baseline laboratory and angiographic results are shown in Table 1. The hospital course complications and follow up are shown in Table 2.

The Mann-Whitney test did not show a significant difference between two groups in terms of means of

vitamin D in men and women as well as hs-troponin-I status (P = 0.085 and P =0.204 respectively).

Table 1. Demographic, Laboratory Results, and Syntax Score of the Patients

	Values
Age	60 ± 11.6
Male Gender	154 (75)
Risk Factors	
No	48 (23.5)
Smoking	64 (31.3)
HTNd	95 (46.5)
DMe	63 (30.8)
Vitamin D (ng/ml)	22.6 ± 13.8
Triglyceride (mg/dl)	132.2 ± 73.6
LDLa cholesterol (mg/dl)	88.9 ± 31.3
HDLb cholesterol (mg/dl)	37.3 ± 9.9
Blood glucose (mg/dl)	160.6 ± 81.8
Albumin/Creatinine ratio	0.32 ± 1.09
Syntax score	15.05 ± 9.53
Positive Hs-troponin Ic	129 (63.2)

Data in the table are presented as No. (%) or Mean ± SD.
LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Hs-troponin I: High sensitive Troponin-I; HTN: Hypertension; DM: Diabetes Mellitus.

Table 2. The Hospital Course Complications and Follow up of the Patients

	Values
Arrhythmia	
Negative	182 (89.2)
Atrial	10 (4.9)
Ventricular	12 (5.9)
Pulmonary edema	26 (12.7)
Re-hospitalization	33 (16.2)
In-hospital death	3 (1.5)
Death during follow up	0 (0.0)

Data in the table are presented as No.(%).

Also, There was no significant difference between the vitamin D levels according to the occurrence of pulmonary edema, arrhythmias, re-hospitalization with cardiovascular causes (P = 0.305, P = 0.392, P = 985, respectively) (Table 3).There was a significant direct correlation between vitamin D and HDL cholesterol levels (P = 0.011). However, there was no meaningful relationship between vitamin D level and LDL cholesterol, blood glucose, triglyceride, albumin to creatinine ratio, and also syntax score (P > 0.05). In patients with negative hs-troponin-I (unstable angina), 21 (28%) had sufficient vitamin D level, 46 (61.3%) were mildly deficient, and 8 (10.7%) were severely inadequate. In patients with positive hs-troponin-I (STEMI or non-STEMI), 18 (14%) had sufficient vitamin D level, 92 (71.3%) were mildly deficient, and 19 (14.7%) were severely inadequate. There was a significant difference between the two groups (positive and negative hs-troponin-I) according to the vitamin D status (P = 0.045). The frequencies of the occurrence of the arrhythmia, pulmonary edema, and re-hospitalization according to the vitamin D levels are shown in detail in Table 4.

There were no significant differences between vitamin D status and the occurrence of arrhythmia and pulmonary edema (early complication) and re-hospitalization (late complications) (P = 0.787, P = 0.939, P = 0.961, respectively). The mean ± SD of Syntax score in the three groups according to the vitamin D status was 15.80 ± 11.75 ng/dl in the normal group, 14.92 ± 8.78 ng/dl in mildly deficient and 15.16 ± 9.68 ng/dl in severely small groups. There was no significant relationship between the severity of vitamin D deficiency with the calculated syntax score (P = 0.939), as well as the other variables, including HDL cholesterol, LDL cholesterol, blood glucose, triglyceride, and albumin to creatinine ratio (P > 0.05) (Table 5).

Of the patients studied, only 3 (1.5%) died during the hospitalization period. There was no significant relationship between vitamin D levels and the mortality during hospitalization period (P = 0.824). None of the patients died during six months follow up.

Table 3. Comparison of Vitamin D level in Complicated and Non-complicated Patients during the Hospital Course and Six Months Follow Up

	Vitamin D		P-value
	Mean ± SD [a]	Median ± IQR [b]	
Hs-troponin-I			0.214
Positive	21.16 ± 12.12	19.8 ± 12.2	
Negative	28.69 ± 16.13	20.4 ± 18.9	
Arrhythmia			0.392
No	22.53 ± 14.13	19.7 ± 14.4	
Atrial	26.19 ± 12.3	21.8 ± 15.3	
Ventricular	20.08 ± 9.69	20.7 ± 11.7	
Pulmonary edema			0.305
No	22.44 ± 14	19.7 ± 14.4	
Yes	23.45 ± 12.69	21 ± 10.3	
Re-hospitalization			0.985
No	22.81 ± 14.3	19.8 ± 14.4	
Yes	21.31 ± 10.4	20.7 ± 13.8	

[a, b] Data in the table are presented as Mean ± Standard Deviation and Median ± Interquartile Range.
Hs-troponin-I: High sensitive Troponin-I

Table 4. Comparison of Severity of Vitamin D Deficiency in Complicated and Non-complicated Patients during the Hospital Course and six Months Follow Up.

	Vitamin D			P-value
	Normal	Mild deficiency	Severe deficiency	
Hs-troponin-I				0.045
Positive	18 (14)	92 (71.3)	19 (14.7)	
Negative	21 (28)	46 (61.3)	8 (10.7)	
Arrhythmia				0.787
No	35 (19.2)	123 (67.6)	24 (13.2)	
Atrial	3 (30)	6 (60)	1 (10)	
Ventricular	1 (8.3)	9 (75)	2 (16.7)	
Pulmonary edema				0.939
No	34 (19.1)	121 (68)	23 (12.9)	
Yes	5 (19.2)	17 (65.4)	4 (15.4)	
Re-hospitalization				0.961
No	33 (19.3)	115 (67.3)	23 (13.5)	
Yes	6 (18.2)	23 (69.7)	4 (12.1)	

Data in the table are presented as No. (%).
Hs-troponin-I: High sensitive troponin-I

Table 5. Comparison of the Syntax Score and Laboratory Findings Based on the Severity of Vitamin D Deficiency

	Vitamin D						P-value
	Normal		Mild deficiency		Severe deficiency		
	Mean ± SD [a]	Median ± IQR [b]	Mean ± SD	Median ± IQR	Mean ± SD	Median ± IQR	
HDL (mg/dl)	38.95 ± 10.8	36 ± 12	37.34 ± 9.7	37 ± 13	34.74 ± 9.6	33 ± 7	0.253
LDL (mg/dl)	83.31 ± 31.4	79 ± 54	89.75 ± 30.2	85 ± 42	93.52 ± 36.8	94 ± 58	0.457
Triglyceride (mg/dl)	127.51 ± 84.6	105 ± 108	135.3 ± 70.6	120 ± 92	124.7 ± 74.5	113 ± 77	0.415
BG (mg/dl)	144.6 ± 52.6	132 ± 75	158 ± 80.4	132 ± 76.5	199.2 ± 111	146 ± 140	0.162
Syntax score	15.8 ± 11.75	15.5 ± 14.5	14.9 ± 8.78	14 ± 10	15.16 ± 9.68	12 ± 15.5	0.939
Albumin/ Creatinine ratio	0.183 ± 0.17	0.128 ± 0.15	0.34 ± 1.3	0.137 ± 0.16	0.373 ± 0.56	0.18 ± 0.11	0.203

[a, b] Data in the table are presented as Mean ± Standard Deviation and Median ± Interquartile Range.
HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BS: Blood Glucose.

DISCUSSION

In this study, 204 patients with the acute coronary syndrome, including acute myocardial infarction unstable angina, were evaluated. Finally, it was found that about 81% of patients had some degrees of Vitamin D deficiency. No significant relation observed between vitamin D level and variables such as hs-troponin-I status and short term outcomes. There was also a statistically significant correlation between the level of vitamin D and HDL cholesterol levels. Also, there was a significant difference between the hs-troponin-I and levels of vitamin D.

In the study of the prevalence of vitamin D deficiency among patients with acute coronary syndrome, De Metrio et al. reported that about 70% of patients with the acute coronary syndrome had a mild deficiency, and 19% had severe deficiency [5]. The results of this study were closely related to our results. In our study, patients had similar levels of vitamin D regardless of positive or negative hs-troponin-I levels. Correia et al. argued that levels of vitamin D did not correlate with hs-troponin-I levels [12]. As already mentioned, after dividing patients into three groups based on the vitamin D level, it was found that patients with negative hs-troponin-I are more likely to have normal levels of vitamin D. In other words, the rate of normal vitamin D level in patients with acute myocardial infarction is lower. These results suggest that the level of vitamin D in patients with acute coronary syndrome could be evaluated as an acute phase agent. Leong et al. reported that patients with normal levels of vitamin D had higher levels of hs-troponin-I [4]. The reason for this difference is probably due to the different methods of hs-troponin-I test, which in our study patients divided into two groups of positive and negative hs-troponin-I. Still, in the study of Leong, the hs-troponin-I was expressed quantitatively. However, Naesgaard et al. found no relationship between vitamin D level and hs-troponin-I in patients with the acute coronary syndrome [13]. In our study, vitamin D level was not significantly associated with atrial fibrillation or ventricular arrhythmias. In a long-term follow-up study, it was found that atrial fibrillation was not associated with vitamin D levels [14]. But in a similar prospective study, vitamin D deficiency was significantly associated with atrial fibrillation in the long term follow up [8]. In a similar study with the present study, only one study examined vitamin D deficiency with the short-term and one-year outcomes of patients with acute coronary syndrome. It was found that during hospitalization, deficiency, or normal levels of vitamin D did not affect arrhythmias such as atrial fibrillation, ventricular tachycardia, and Brady-arrhythmias requiring pacemaker insertion [5]. One of the goals of this study was to examine the relationship between lipid profiles and vitamin D levels. In this study, there was a significant positive correlation between vitamin D levels and HDL cholesterol levels. The level of vitamin D was higher in those with high HDL cholesterol but did not show significant association when patients divided into three groups based on vitamin D level. There was no significant correlation between vitamin D and LDL

cholesterol and triglyceride. In various studies, the results are very different in this regard. In some studies, items of the lipid profile were significantly related to the vitamin D level, and in others, they were unrelated [15-17]. The use of anti-lipid drugs, different timing for measuring lipid profile, and the different diet of the patients can explain these differences. Previous studies suggest that high blood sugar levels in patients with acute myocardial infarction are associated with worse clinical outcomes [18]. Also, it is reported that vitamin D deficiency is associated with insulin resistance [19]. Regarding this issue, another goal of this study was to investigate the relationship between non-fasting blood glucose and vitamin D levels, which did not showed significant correlation. However, in the study by Leong et al., It was reported that with increasing vitamin D levels, non-fasting blood glucose decreased significantly [4]. Albuminuria is one of the known risk factors for the development of cardiovascular diseases. On the other hand, vitamin D deficiency may interfere with the pathogenesis of protein excretion in the urine [20]. In a systematic review study, the use of an active form of vitamin D, along with other commonly used drugs, reduced the proteinuria in people with chronic kidney disease [21]. In our study, there was no significant correlation between albumin to urine creatinine ratio and vitamin D levels. One of the important goals of our study was to investigate the relationship between the level of vitamin D and the severity of coronary artery disease in patients with the acute coronary syndrome, which has been studied in various studies. In the Goleniewska study, the severity of coronary artery disease in patients with myocardial infarction was determined using the Gensini scoring system. Finally, there was no significant relationship between the severity of coronary artery disease and vitamin D levels [22]. De metrio et al. did not find a significant correlation between vitamin D level and syntax score in the outcome of patients with the acute coronary syndrome [5]. In our study, using the syntax scoring system, it was found that there was no statistically significant correlation between the severity of coronary involvement and vitamin D levels. However, Dziedzic et al. showed a significant relationship between the severity of the coronary involvement and vitamin D levels, using the CASSS scoring system [23]. The type of study design, target population, and the difference in the systems for calculating the severity of coronary artery involvement could be the probable causes of the difference in the results of various studies. In this study, three patients died during admission, and 27 patients with a mean vitamin D level of 20 ng/dl were re-hospitalized. However, vitamin D levels did not significantly correlate with mortality and re-hospitalization. So far, several studies have been conducted on the relationship between vitamin D and cardiovascular death and But there is no cohesion in the results of studies. A systematic review by Miller et al. concluded that vitamin D levels ranging from 15 to 70 ng/dl had no relation to increased cardiovascular mortality [24]. But De metrio et al. showed that there is a significant relationship between vitamin D level and hospitalization mortality and re-hospitalization [5]. Also, Correia et al. also argued that in-hospital deaths in patients with vitamin D deficiency are higher than those with normal levels of vitamin D [12]. Small sample size, exclusion of patients with previous history of myocardial infarction and entry of patients with a maximum age of 75 years were the notable differences with the two studies mentioned, which can reduce the relative mortality in our subjects and could be an explanation for the lack of relevance of vitamin D levels to the mortality and re-hospitalization.

Limitations

The major limitation of this study was that due to the small study population, mortality, as an essential cardiovascular outcome did not occur during six months, follow up and the statistical analysis could not be done for this variable. Also, the results regarding the in-hospital mortality cannot be reliable as the result of low incidence.

CONCLUSION

In conclusion, the results of this study showed that a large proportion of patients with the acute coronary syndrome, especially those with acute myocardial infarction, suffer from vitamin D deficiency. The studies that have been conducted so far on the relationship between vitamin D levels and short and long-term complications of the acute coronary syndrome have also shown controversial results. The present study did not show a significant correlation between vitamin D levels and in-hospital and 6-month implications of patients with the acute coronary syndrome. Further studies are suggested to evaluate the relevance of vitamin D levels with some factors such as coronary calcification, lesion length, etc. Also, in future studies, longer follow-up and vitamin D testing at different intervals is recommended to ensure that the serum vitamin D levels remain stable.

Conflict of Interest

None declared.

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