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The Prevalence of Vitamin D Deficiency in Patients with Coronary Artery Disease and its Correlation with High Sensitivity C-Reactive Protein; A Report from Southern Iran

Laleh Mahmoudi [1], PharmD; Sara Asadi [1], PharmD; Alireza Moaref [2], MD; Omid Moradi [3], PharmD; Peyman Izadpanah [2,*], MD

[1] Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, IR Iran
[2] Cardiovascular Research Center, Shiraz University of Medial Sciences, Shiraz, IR Iran
[3] Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

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ABSTRACT

Background: Coronary Artery Disease (CAD) is the leading non-infectious cause of mortality in Iran. Inflammation plays an important role in CAD. Additionally, vitamin D deficiency is linked to a higher risk of cardiovascular mortality.

Objectives: This study aimed to evaluate the prevalence of hypovitaminosis D in patients with CAD and to determine the level of high-sensitivity C-Reactive Protein (hs-CRP) as the main inflammatory marker.

Methods: In this cross-sectional study, the prevalence of hypovitaminosis D was assessed in patients with CAD during 14 months. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences. The patients were evaluated regarding the level of 25-OH cholecalciferol via high-performance liquid chromatography and hs-CRP level via enzyme linked immunosorbent assay. The related demographics, medical history, and lipid profile were evaluated, as well. Insufficient and deficient levels of 25-OH vitamin D were defined as < 30 ng/mL and < 12 ng/mL, respectively. The patients with insufficient vitamin D levels were evaluated regarding the hs-CRP level, as the cardiac inflammatory marker. The correlation between vitamin D level and hs-CRP was also determined using a bivariate method reporting Pearson's correlation coefficient in the SPSS software (IBM Corp., version 25).

Results: In this study, hypovitaminosis D was reported in 257 (65.1%) out of the 395 patients with CAD. The mean age of the patients was 62.54 ± 8.81 years, and 77 ones (55.0%) were female. Vitamin D deficiency was more prevalent in the patients with hs-CRP levels > 3 mg/L (P = 0.003). In addition, a significant negative correlation was observed between vitamin D serum level and hs-CRP (R = -0.601, P < 0.001).

Conclusions: Vitamin D deficiency was prevalent in the patients with CAD, and decreased vitamin D levels were associated with increased hs-CRP levels. Hence, CAD patients should be evaluated regarding the vitamin D status.

1. Background

Cardiovascular Diseases (CVD) are the leading cause of death and disability in Iran (1). Although nutritional modifications and vitamins administration have been recommended to decrease the CVD risk, data in this regard are controversial (2). Vitamin D Receptors (VDR) are involved in the pathogenesis of Coronary Artery Disease (CAD) (3), and vitamin D deficiency may be associated with increased mortality from CVD (4). Vitamin D deficiency has been found to be associated with increased inflammation (5, 6), and systemic inflammation has a role in developing CAD (7). C-Reactive Protein (CRP) is the main inflammatory mediator in CAD (8), which is linked to an increase in the risk of adverse cardiovascular events and mortality (9). With regard to the immunomodulatory effects of vitamin D, studies have been performed to evaluate the link between vitamin D deficiency and CRP level (10), but the results have not been definitive. In particular, VDR polymorphisms have been shown to result in the variation in the effect of vitamin D in different populations (11).

*Corresponding author: Peyman Izadpanah, Cardiovascular Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
Cellphone: +98-9127055823,
Email: izadpanahpeyman52@gmail.com.

Table 1. Baseline demographics and clinical characteristics of the patients with Coronary Artery Disease (CAD) and hypovitaminosis D

Variable		Vitamin D deficiency (n=26)	Vitamin D insufficiency (n=114)	P-value
Age (years)		64.9±8.8	61.9±8.8	0.126
Gender	Male	10 (38.5%)	53 (46.5%)	0.458
	Female	16 (61.5%)	61 (53.5%)	
BMI (kg/m^2)		25.9±2.3	26.9±2.8	0.073
Past medical history	Hypertension	15 (57.7%)	56 (49.1%)	0.430
	Diabetes mellitus	11 (42.3%)	43 (37.7%)	0.664
	Dyslipidemia	9 (34.6%)	61 (53.5%)	0.082
	Positive family history of CVD	11 (42.3%)	42 (36.8%)	0.604
Habits	Smoking	8 (30.8%)	38 (33.3%)	0.802
Medication history	Statins	15 (57.7%)	77 (67.5%)	0.340
	Antiplatelet	21 (80.8%)	80 (70.2%)	0.277
Laboratory parameters	Cholesterol (mg/dL)	182.0±28.9	173.7±32.9	0.237
	LDL (mg/dL)	124.9±28.8	116.2±30.9	0.193
	HDL (mg/dL)	40.3±7.2	40.6±7.7	0.847
	Vit D (ng/mL)	8.3±1.9	19.1±3.6	<0.001

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; LDL, low density lipoprotein; HDL, high density lipoprotein; Vit D, vitamin D.

2. Objectives

Since the prevalence of vitamin D deficiency in Iran has been reported to vary from 30% to 90% in different populations (12), the present study aims to evaluate the prevalence of hypovitaminosis D in patients with coronary artery stenosis and to determine the effect of Vitamin D status on the level of high-sensitivity CRP (hs-CRP).

3. Patients and Methods

This cross-sectional study was conducted on the patients aged ≥18 years diagnosed with CAD who were admitted to Al-Zahra Heart Center, a tertiary educational hospital affiliated to Shiraz University of Medical Sciences, from October 2019 to November 2020. The study was performed in accordance with the declaration of Helsinki and was approved by the board of Ethics Committee.

The diagnosis of CAD was confirmed by coronary angiography. Then, the patients were evaluated in terms of the 25-OH cholecalciferol level using High-Performance Liquid Chromatography (HPLC). The 25-OH cholecalciferol levels >30 ng/mL, <30 ng/mL, and <12 ng/mL were categorized as sufficient, insufficient (13), and deficient (14), respectively. The exclusion criteria for hs-CRP evaluation were 1) sufficient 25-OH cholecalciferol levels, 2) vitamin D supplementation in the previous month, 3) having a history of coronary artery bypass graft surgery or myocardial infarction in the previous three months, autoimmune diseases, chronic kidney disease (creatinine clearance <60 mL/min/1.73 m2), and liver failure (child-Pugh class C), and 4) receiving anti-inflammatory medications, except for aspirin and statins. Demographics, laboratory parameters regarding the lipid profile, history of comorbidities, habitual history, and past medication history were recorded. The level of hs-CRP was measured by the Enzyme Linked Immunosorbent Assay (ELISA) method (Pars Azmun, Private held, Tehran, Iran).

The statistical analysis was done using the SPSS software (IBM Corp., version 25, NY: IBM Corp). Categorical variables were reported as frequency (percentage) and were analyzed using chi-square test. Continuous variables were reported as mean ± Standard Deviation (SD) and were analyzed using independent sample t-test and Mann-Whitney U test for parametric and non-parametric variables, respectively. A bivariate correlation model using Pearson's correlation coefficient, reporting R and p-value, was used to evaluate the potential correlation between the levels of vitamin D and hs-CRP. A p-value less than 0.05 was considered statistically significant. The reverse power calculation for the significance of the difference in increased hs-CRP levels in patients with vitamin D insufficiency and deficiency was performed using Pearson's chi-squared test (two-sided) via STATA, version 14 (StataCorp, Texan, USA).

4. Results

In this study, 14 months after the evaluation of 395 patients with confirmed coronary stenosis, hypovitaminosis D was observed in 257 patients (65.1%). From the 257 patients with hypovitaminosis D, 140 were included. The mean age of the patients was 62.54±8.81 years, and 77 ones (55.0%) were female. Besides, 53 patients (37.9%) had a positive family history of CAD. Other related baseline demographics and clinical characteristics have been presented in Table 1.

Considering the laboratory evaluations, the mean vitamin D level was 17.10 ± 5.38 ng/mL. The vitamin D level was less than 12 ng/mL in 26 patients (18.6%). Additionally, the mean hs-CRP level was 3.4 ± 0.9 mg/L, and 88 patients (62.9%) had hs-CRP levels ≥ 3 mg/L. Increased level of hs-CRP was more prevalent in the patients with vitamin D deficiency. In this regard, 23 patients (88.5%) with elevated hs-CRP levels had vitamin D deficiency compared to 65 ones (57%) without elevation in hs-CRP levels (P = 0.003). The results also indicated that vitamin D serum level had a significant reverse correlation with the increase in hs-CRP levels (R = -0.601, P < 0.001).

The reverse power was calculated for 140 patients (114 patients with vitamin D insufficiency and 26 ones with vitamin D deficiency) assuming α=0.05 and increased hs-CRP proportion of 0.570 and 0.885 in the patients with vitamin D insufficiency and deficiency, respectively. The power was reported as 0.919.

5. Discussion

Previous studies have demonstrated that patients with vitamin D deficiency are at an increased risk of adverse cardiac events (15, 16). In the present study, the prevalence of hypovitaminosis D was 65%. Considering such a high prevalence, this population is at risk and should be evaluated in this regard. Previously, the prevalence of vitamin D insufficiency and severe deficiency was found to be even higher in patients with CAD in Iran (98%) (17). By recognizing the importance of screening for vitamin D deficiency and increasing supplementation during the past decade, the prevalence of hypovitaminosis D has decreased. Nonetheless, as the prevalence of hypovitaminosis D is still high amongst patients, they should be evaluated and provided with a sufficient amount of vitamin D.

The current study findings demonstrated that decreased vitamin D levels were significantly linked to an elevation in hs-CRP levels. Additionally, elevated hs-CRP levels were considerably more prevalent in patients with vitamin D levels less than 12 ng/mL. This finding is more interesting when taking the previous findings into account. Accordingly, in patients with CAD and increased levels of hs-CRP > 3 mg/L, there was a higher risk of cardiac events in future (18) as well as a 2.4-fold increase in the risk of peri-procedural myocardial infarction (19).

In conclusion, vitamin D deficiency was associated with a higher inflammatory state, which could increase the risk of adverse cardiac events. Thus, all patients with CAD are recommended to be examined regarding the vitamin D status. Supplementation should also be considered as needed.

5.1. Ethical Approval

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5.2. Informed Consent

Written informed consent forms were obtained from the patients.

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Authors' Contribution

LM: administration, study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, and study supervision; SA: statistical analysis, drafting of the manuscript, and acquisition of data; AM: technical support and critical revision of the manuscript for important intellectual content; OM: drafting of the manuscript and statistical analysis; PI: study concept and design, acquisition of data, administrative and material support, critical revision of the manuscript for important intellectual content, and study supervision.

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