

Original Article

Effect of Vitamin D Deficiency on Coronary Artery Stenosis

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ABSTRACT

Background: Vitamin D is a prohormone that has recently been reported to modulate the inflammatory process and probably atherosclerosis. There is conflicting evidence in favor of the impact of hypovitaminosis of vitamin D on coronary artery stenosis. The aim of this study was to evaluate the relationship between 25(OH) vitamin D and the extent and severity of coronary artery stenosis in sample of the Iranian population undergoing elective coronary artery angiography.

Methods: Patients undergoing elective coronary artery angiography were included in this case-control study. Significant coronary artery stenosis was defined as stenosis >60% of any major coronary artery and >50% for the left main artery as evaluated by quantitative coronary angiography.

Results: Hypovitaminosis D was observed in 60.2% of 224 patients. The patients were divided according to their vitamin D level (i.e., <10, 11–20, and 21–30) and also based on the percentage of their coronary artery stenosis (i.e., normal coronary artery, insignificant stenosis, and significant stenosis). A higher vitamin D level was associated with age. Hypovitaminosis D had no association with persistence, extent, and severity of coronary artery stenosis.

Conclusions: Hypovitaminosis D was not significantly associated with the incidence of diabetes mellitus, hypertension, and dyslipidemia. At present, the data regarding the causal link between vitamin D status and coronary artery stenosis are conflicting. These conflicting findings may be due to factors relating to the study designs, ethnicity, confounding factors, and other coronary artery disease risk factors. Further research is needed to determine whether this association does exist. (*Iranian Heart Journal 2015; 16(3): 38-44*)

Keywords: ■ Coronary artery stenosis ■ Cardiovascular disease ■ Vitamin D deficiency

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Vitamin D is not a real vitamin¹ but is a fat-soluble secosteroid produced in the skin as a result of sunlight exposure.² This prohormone causes optimal intestinal calcium absorption for bone mineralization. The most important compounds are vitamin D3 (or cholecalciferol) and D2 (or ergocalciferol). Both can be ingested from diet and supplements, but the major natural source of vitamin D is synthesis in the skin, which is dependent on sun exposure. The receptors of vitamin D are present in multiple tissues. A low level of vitamin D may have influence on different organs as well as the cardiovascular system. The prevalence of vitamin D deficiency is suggested to be about 30-50% in developing countries. Even in sun-rich countries, there are reports of the prevalence of vitamin D deficiency. The level of vitamin D is higher in summer. This level is also higher among men, individuals consuming supplements, and persons with fair skin. Time spent outdoors is known to be correlated with the level of vitamin D. Low vitamin D is more prevalent in patients with deep-skin pigmentation because vitamin D photosynthesis is ineffective in this group.³ The level of vitamin D does not always

decline in regions of high latitude. This paradox may be secondary to sun avoidance in hot regions and supplement usage in cloudy regions. There are different categorizations of the level of vitamin D, but a level <20 ng/mL is generally regarded as deficiency. Some observational studies and meta-analyses have suggested a possible link between vitamin D level and cardiovascular disease, but there are investigations that have found no such association.

In the present study, we sought to evaluate the influence of different levels of vitamin D on coronary artery stenosis.

METHODS

The present cross-sectional, case-control study was conducted on 224 patients who underwent elective coronary angiography in Rasool-e Akram and Shariati hospitals during a 6-month period. The study was approved by the Ethics Committee of Iran University of Medical Sciences. The study participants were men and women aged between 34 and 86 years admitted with a pre-diagnosis of coronary artery disease (CAD) for elective coronary angiography. Table 1 depicts the baseline characteristics of the participants.

Table 1. Baseline characteristics of the study population

Level of serum vitamin D (number of persons in each group)		Normal	Insufficient	Deficient	Very Deficient
Sex	male	48	28	38	20
	female	41	13	18	17
Age (y)	<50	10	15	10	12
	50-70	60	20	41	21
	>70	20	5	5	4
History of DM		27	12	15	10
History of DLP		56	24	35	22
History of HTN		67	23	38	27
Family history of CAD		12	12	11	9
History of C/S		40	23	21	12
Percentage of coronary artery stenosis	patent coronary artery	17	13	7	10
	insignificant stenosis (<60%)	20	8	13	6
	significant stenosis (>60%)	53	20	36	21

Abbreviations: DM, Diabetes mellitus; DLP, Dyslipidemia; HTN, Hypertension; C/S, Cigarette smoking.

The exclusion criteria of the current study were comprised of unwillingness to

cooperate, previous or current use of vitamin D or calcium supplements, and chronic

kidney or liver disease. The patients were divided into 3 groups based on the result of coronary angiography: patent coronary artery, minimal CAD or insignificant stenosis (<60% lumen stenosis of any coronary artery), and significant stenosis (>60% stenosis of a major coronary artery). Blood samples were obtained on the same day of coronary angiography for the measurement of vitamin D level. Table 2 illustrates the categorization of the study population.⁴

Table 2. Categorization of vitamin D levels

Category	ng/mL	nmol/L
Sufficient	≥30	≥75
Insufficient	21-29	50-75
Deficient	10-20	25-50
Severe deficiency	≤10	≤25

Diabetes mellitus (DM) was defined as a fasting blood sugar level >126 mg/dL or the consumption of antidiabetic drug. Hypertension and dyslipidemia were defined as a blood pressure >140/90 mm Hg and total cholesterol >240 mg/dL or consumption of antihypertensive or antihyperlipidemic agents, respectively. The data were analyzed using Statistical Package for the Social Sciences (SPSS), version 17.5. A P value <0.05 was considered statistically significant.

RESULTS

The current study recruited 224 patients, comprising 135 (59%) men and 89 (39.4%) women aged between 30 and 82 years. The range of vitamin D level was between 2 and 114 ng/dL. Forty-seven (20.8%) patients had normal epicardial coronary artery, 47 (21.7%) had insignificant lesions, and the remaining 130 (57.5%) had significant lesions in at least 1 major coronary artery.

The prevalence of the significant stenosis of coronary arteries was not significantly allied to sex ($P=0.4$). In the lab analyses, 90 (39.8%) patients had normal levels of 25 (OH) vitamin D, 41 (18.1%) had insufficient levels, 56 (24.8%) had deficiency, and 37 (16.4%) had

severe deficiency. The prevalence of vitamin D deficiency had no correlation with gender ($P=0.21$), stenosis of any major coronary artery (left main artery [$P=0.93$], left anterior descending artery [$P=0.42$], left circumflex artery [$P=0.42$], and right coronary artery [$P=0.26$]). There was a lower incidence of vitamin D deficiency with increasing age, which was statistically significant ($P=0.01$). The level of vitamin D was not significantly different based on the existence of DM ($P=0.973$), dyslipidemia ($P=0.969$), hypertension ($P=0.19$), positive family history of CAD ($P=0.158$), or cigarette smoking ($P=0.149$). The prevalence of vitamin D deficiency was not significantly different between the patients with normal coronary arteries and those with insignificant and significant coronary lesions (0.889). Furthermore, there was no association between the significance of coronary artery stenosis and different levels of vitamin D ($P=0.355$).

DISCUSSION

Vitamin D is a prohormone that causes optimal intestinal calcium absorption for bone mineralization and has receptors in multiple tissues. It has been postulated that vitamin D deficiency can influence tissues other than the bone. There is extensive evidence to support that vitamin D receptors may influence the cardiovascular system at different sites. Nonetheless, recent research suggests that these receptors may not be present in all the target cells. There is, therefore, need for further clarification.¹ By exposure to ultraviolet-B from the sun, the first compound produced in the skin is vitamin D₃. Similar to vitamin D₃ or vitamin D₂, vitamin D also can be obtained from diet. Thereafter vitamin D binds to its receptors and is converted into 25(OH) vitamin D by the liver. Subsequently, by the influence of 1 α hydroxylase in the kidney, this compound is converted into 1, 25 dihydroxyvitamin D. It

should be borne in mind that $1\alpha(\text{OH})\text{ase}$ is present in other tissues; nevertheless, it has been speculated that kidney 1α hydroxylase significantly contributes to the circulatory level of $1, 25(\text{OH})$.⁵

Several mechanisms have been proposed for the impact of low vitamin D levels on the cardiovascular system. Chronic vitamin D deficiency causes hyperparathyroidism and acts on 3 pathways associated with parathormone excess:^{4,6} 1) increased insulin resistance, 2) activation of renin-angiotensin system (RAS), and 3) augmentation of inflammation. Another possible explanation is the inhibition of foam-cell formation and the suppression of macrophage cholesterol uptake in patients with type 2 diabetes.⁷ There is also a probable association with large high-density particles.⁸

The prevalence of vitamin D deficiency was estimated at about 85.47% in women and 75.34% in men in the year 2005 in Tehran according to a study conducted by Moradzadeh et al.⁹ The prevalence of vitamin D deficiency in developing countries was estimated at about 30-50% according to another study.¹⁰ One study showed that even in sunny regions, there is a widespread prevalence of vitamin D deficiency.¹¹ The prevalence of vitamin deficiency in the present study was about 60.2%, which is much lower than the incidence reported previously. This finding may be the result of the fortification of food with vitamin D.

Most people can meet their vitamin D needs via sunlight. Still, the level of synthesis varies by the color of the skin.¹² A growing number of studies point to vitamin D deficiency as a risk factor for cardiovascular disease.^{13,14,4}

Vitamin D insufficiency may be associated with an increased risk of CAD in general, but uncertainties still exist beyond published reports. Several studies have found a strong association between low circulatory levels of vitamin D and cardiovascular disease.

Scragg et al.¹⁵ reported a relationship between serum vitamin D level and risk of myocardial infarction. One study conducted on Indian

patients found significantly higher prevalence of double- and triple-vessel CAD and diffuse CAD in patients with vitamin D deficiency.¹⁶ A study performed by Chen et al.¹⁷ confirmed the results of that article and reported that low vitamin D levels had a significant association with the severity of coronary artery stenosis. A study by Mozos and Marginean¹⁸ reported an association between low vitamin D levels and vascular inflammation, endothelial dysfunction, formation of foam cells, and proliferation of smooth muscle cells. In contrast, one study found no association between $25(\text{OH})$ vitamin D levels and coronary artery calcification or severely obstructive stenosis.¹⁹ One study published in the Journal of American Medical Association (JAMA) showed that low vitamin D levels were linked to a greater risk of heart disease in whites and Chinese, but not in blacks and Hispanics, and concluded that vitamin D levels tended to be lower among people from other racial and ethnic minority groups and that some of these populations had higher rates of heart disease. However, after correcting for other risk factors for heart disease, the researchers did not find an association between low vitamin D and cardiovascular events in their black and Hispanic participants.²⁰

In the present study, we assessed the prevalence of low vitamin D levels and the relationship between low vitamin D levels and coronary artery stenosis. We found no convincing evidence in favor of an association between serum vitamin D levels and coronary artery stenosis. This may be due to the race or ethnicity of the Iranian population.

Ibhar et al.¹⁰ concluded that the cause-effect relationship between vitamin D levels and CAD was complicated by the fact that low vitamin D levels might be a result of cardiovascular disorder rather than the cause of the disease. Sunlight exposure maintains vitamin D levels and ambulatory subjects with normal outdoor exercise activities are likely to have higher vitamin D levels and a

lower likelihood of cardiovascular disease. We also did not find that the patients with DM had lower levels of vitamin D deficiency than their nondiabetic peers ($P=0.973$). Kulie et al.²¹ suggested that vitamin D might play a role in the hemostasis of glucose metabolism and development of types 1 and 2 DM. Another mechanism proposed by other investigators is that vitamin D receptors have an immunomodulatory effect. In some populations, the development of type 1 DM is associated with polymorphism in vitamin D receptors.^{22,23} Martin and Campbell²⁴ found that vitamin deficiency in their study population led to reduced insulin secretion by calcium effect on insulin secretion. These earlier observational studies raised the suggestion that low vitamin D levels contribute to DM. Nevertheless, because they were not designed to investigate cause and effect, they could not prove it and were able to establish only a link. A more recent study challenged claims that low vitamin D levels could cause type 2 DM.²⁵ This large genetic study concluded that there was no evidence that a person with a low level of vitamin D might be prone to develop type 2 DM. The authors investigated the link between levels of vitamin D and risk of developing DM by examining the gene that controls the blood level of vitamin D and found no evidence of a link between the risk of developing DM and the different gene variants that control the blood level of vitamin D. Our study results are not comparable with the studies on vitamin D status and type 2 DM in younger and older populations which claim an association between DM and vitamin D levels.^{26,27,28} We did not find any significant association between vitamin D levels and incidence of hypertension or dyslipidemia ($P=0.19$ and $P=0.969$, respectively). Stephen G. Rostand³ postulated that there might be an association between vitamin D deficiency and increased prevalence of hypertension in the African-American population. Whereas some cross-sectional studies have shown an

association between low vitamin D and higher incidence of systolic blood pressure, larger observational studies have demonstrated a weaker — yet similar v association. These dissimilarities may be due to differences in population studies and unmeasured confounders.²⁹

CONCLUSIONS

Hypovitaminosis D was observed in 60.2% of the population undergoing elective coronary angiography in the present study. Vitamin D deficiency was not significantly associated with the prevalence, extent, and stenosis of any major coronary artery. In addition, hypovitaminosis D was not significantly associated with the incidence of DM, hypertension, and dyslipidemia. At present, the data regarding the causal link between vitamin D status and coronary artery stenosis are conflicting. It may be due to the factors relating to the study designs, ethnicity, confounding factors, and other CAD risk factors. Further investigations are needed to determine whether this association does exist.

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