

Original Article

Value of Vitamin D Deficiency in Predicting the Severity of Coronary Artery Disease in Type 2 Diabetes

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ABSTRACT

Background: The present study aimed to assess the relationship between vitamin D deficiency and the severity of coronary artery disease (CAD) in a sample of Iranian diabetic patients.

Methods: This cross-sectional study was performed on 169 consecutive diabetic patients suspected of CAD. The severity of CAD was defined based the number of involved coronary vessels. The serum vitamin D level was measured via immunoassay, and its serum level was categorized as normal (>30 ng/mL), insufficient ($20-30$ ng/mL), mildly-to-moderately deficient ($10-20$ ng/mL), and severely deficient (<10 ng/mL).

Results: There was no significant relationship between vitamin D deficiency and the number of involved coronary vessels ($P=0.423$), and nor was there any difference in the serum level of vitamin D in the individuals with CAD (24.84 ± 18.53 ng/dL) and those without CAD (22.37 ± 16.88 ng/mL) ($P=0.409$). Our multivariate logistic regression model showed that vitamin D deficiency could not predict the presence of CAD (OR=0.963, 95% CI: 0.666 to 1.392; $P=0.842$). Analysis of the area under the ROC curve indicated a low value for the measurement of the vitamin D level in discriminating CAD from the normal coronary status (AUC=0.533, 95% CI: 0.437 to 0.629; $P=0.496$).

Conclusions: Our study could not demonstrate a predictive role for vitamin D deficiency concerning the severity of CAD in type 2 diabetes. Among the different CAD risk factors, smoking and opium use were significantly correlated with vitamin D deficiency. (*Iranian heart Journal* 2018; 19(2): 57-64)

KEYWORDS: Coronary artery disease, Vitamin D, Diabetes, Risk factor

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Coronary artery disease (CAD) is now deemed the major cause of death the world over, especially in industrial countries. Potentially, the presence of various genetic, metabolic, and environmental risk factors can increase the risk of mortality and disability in affected patients.¹ In this regard, some metabolic and endocrinological factors have been identified to be allied to the progression and severity of CAD. Within the last few years, a significant association between deficiency in some vitamins and minerals and CAD has been found.²⁻⁴ An association between vitamin D deficiency and different cardiovascular risk factors and diseases has been extensively evaluated. In fact, some prospective and observational studies have addressed the possible linkage of vitamin D deficiency and the development of CAD and its risk factors.⁵⁻⁶ Thus, not only does vitamin D deficiency have a major role in bone metabolism, homeostasis regulation, and immune pathways but also the presence of vitamin D receptors on cardiomyocytes, endothelial cells, and vascular smooth muscle cells suggests the role of vitamin D in the vitamin D-mediated cardiovascular system.⁷⁻⁹ It has been shown that the cardiac muscle functioning depends on the circulating blood concentration of calcitriol.¹⁰ Calcitriol affects the growth, proliferation, and morphology of murine cardiomyocytes. In detail, treatment with calcitriol increases the expression of the cardiac muscle protein myotrophin. The link between vitamin D deficiency and the cardiovascular risk factors has been also shown.¹¹ According to the Framingham Offspring Study,⁵ individuals with low activated vitamin D are more frequently faced with the incidence of cardiovascular diseases such as myocardial infarction, coronary insufficiency, and heart failure than those with normal levels of vitamin D. Thus, treatment with vitamin D supplementation may reduce cardiovascular death and the length of hospitalization in patients with CAD; however, the association

between vitamin D deficiency and the severity of CAD—not least in cardiovascular risk subgroups such as diabetic patients—has remained uncertain. The present study aimed to assess the relationship between vitamin D deficiency and the severity of CAD in a sample of Iranian diabetic CAD patients.

METHODS

This cross-sectional study was performed on 169 consecutive diabetic patients suspected of CAD, defined as the presence of a stenosis of greater than 50% of the diameter in at least 1 of the major coronary artery segments. In this regard and based on coronary angiography, the included patients were categorized as normal coronary or with single-, 2-, or 3-vessel involvement. The baseline characteristics and the clinical data of the participants—including demographics, anthropometric parameters (weight, height, and the body mass index), cardiovascular risk factors (current smoking, hypertension, hyperlipidemia, and opium addiction), and laboratory parameters (fasting blood sugar, hemoglobin A1c, lipid profile, and serum creatinine)—were collected from the hospital files. Diabetes mellitus was defined according to the criteria of the World Health Organization (WHO) as fasting plasma glucose levels of at least 7.0 mmol/l (126 mg/dL) or 2-hour plasma glucose levels of equal to or greater than 11.1 mmol/l (200 mg/dL). The serum vitamin D level was measured via immunoassay, and its serum level was categorized as normal (>30 ng/mL), insufficient (20–30 ng/mL), mildly-to-moderately deficient (10–20 ng/mL), and severely deficient (<10 ng/mL). The primary end point was to assess the relation between the severity of CAD and the severity of vitamin D deficiency. The secondary end point was to determine the best cutoff point for vitamin D to differentiate between normal and involved coronary vessels. The Ethics Committee of Kerman University of Medical Sciences approved the study research

proposal, and all the procedures were conducted in accordance with the standards of the World Medical Association's Declaration of Helsinki for research involving human subjects. Informed consent was obtained from all the study participants.

The results were presented as means $\pm$ standard deviations (SDs) for the quantitative variables, and they were summarized by absolute frequencies and percentages for the categorical variables. The continuous variables were compared using the *t* test and one-way ANOVA or the nonparametric Mann–Whitney *U* test or the Kruskal–Wallis test whenever the data did not appear to have normal distributions or when the assumption of equal variances was violated across the groups. The Pearson correlation test was applied to examine the association between the study measures. A multivariate logistic regression analysis was employed to assess the relationship between CAD and the level of vitamin D and the presence of baseline variables as confounders. The receiver operating characteristic (ROC) curve analysis was also applied to determine the predictive value of vitamin D measurement vis-à-vis the presence of CAD and also to determine the best cutoff value of this vitamin to discriminate CAD. For the statistical analyses, the statistical software SPSS, version 20.0, for Windows (SPSS Inc, Chicago, IL) was used. A *P* value of 0.05 or less was considered statistically significant.

RESULTS

The baseline characteristics and the clinical data of the study subjects adjusted for gender are depicted in Table 1. In total, the mean age of the patients was 57.32 ± 8.50 years and 42.6% were male. Comparisons of the baseline characteristics between the men and women showed higher prevalence rates of smoking and opium use in the men than in their female counterparts, while the means of the body mass index, cholesterol level, and low-density

lipoprotein level were higher in the female patients. The serum creatinine level was also high in the men when compared with the women. Overall, 16.6% of the suspected patients had a normal coronary status, while single-, double-, and triple-vessel disease was revealed in 15.4%, 15.4%, and 37.9% of the patients—respectively. There was a significant difference in the severity of CAD between the 2 genders inasmuch as the male patients suffered more severe CAD than did the women. As is presented in Table 2, among the baseline characteristics, only current smoking and opium use were positively associated with the severity of vitamin deficiency. On the other hand, the smokers and opium users had significantly lower levels of vitamin D. There was also no significant relationship between vitamin D deficiency and the number of involved coronary vessels (Table 2). The mean serum level of vitamin D in the patients with normal coronary was 22.34 ± 14.07 ng/mL, whereas the mean level of vitamin D in the patients with single-, double-, and triple-vessel diseases was 28.82 ± 27.25 ng/mL, 22.33 ± 16.00 ng/mL, and 21.82 ± 13.33 ng/mL—correspondingly—with no significant difference ($P=0.423$). In addition, no difference was found in the serum level of vitamin D between the individuals with CAD (24.84 ± 18.53 ng/dL) and those without CAD (22.37 ± 16.88 ng/mL) ($P=0.409$). Our multivariate logistic regression model (Table 3) illustrated that vitamin D deficiency could not predict the presence of CAD (OR=0.963, 95% CI: 0.666 to 1.392; $P=0.842$). According to the multivariate model, the male gender ($P=0.030$), advanced age ($P=0.013$), high body mass index ($P=0.033$), serum triglyceride level ($P=0.005$), and serum hemoglobin A1c ($P=0.004$) were the main correlates of CAD. The analysis of the area under the ROC curve (Fig. 1) indicated a low value for the measurement of the vitamin D level in discriminating CAD from the normal coronary status (AUC=0.533, 95% CI: 0.437 to 0.629; $P=0.496$).

Table 1. Baseline characteristics and the clinical data of the study population

Characteristic	Total	Men	Women	P value
Age, y	57.32 ± 8.50	58.40 ± 9.57	56.52 ± 7.55	0.155
BMI, kg/m ²	26.84 ± 4.59	25.99 ± 4.33	27.47 ± 4.70	0.039
Insulin use	25 (14.8)	9 (12.5)	16 (16.5)	0.469
Diabetes duration, y	5.87 ± 5.70	5.70 ± 5.99	6.00 ± 5.50	0.733
Hypertension	125 (74.0)	52 (72.2)	73 (75.3)	0.657
Current smoking	24 (14.2)	22 (30.6)	2 (2.1)	< 0.001
Opium addiction	47 (27.8)	30 (41.7)	17 (17.5)	0.001
Serum creatinine, mg/dL	1.05 ± 0.22	1.13 ± 0.21	0.99 ± 0.21	< 0.001
Serum triglyceride, mg/dL	157.31 ± 1.03	161.99 ± 134.81	153.83 ± 72.26	0.642
Serum cholesterol, mg/dL	169.58 ± 44.33	157.06 ± 47.52	178.87 ± 39.56	0.001
Serum HDL	36.92 ± 9.76	33.99 ± 7.91	39.09 ± 10.45	< 0.001
Serum LDL	100.75 ± 36.78	93.10 ± 38.41	106.42 ± 34.63	0.021
HbA1c, %	7.71 ± 1.65	7.83 ± 1.58	7.61 ± 1.70	0.402
Coronary artery status				
Normal coronary	28 (16.6)	6 (8.3)	22 (22.7)	0.001
Trivial coronary involvement	25 (14.8)	9 (12.5)	16 (16.5)	
Single-vessel disease	26 (15.4)	8 (11.1)	18 (18.6)	
Two-vessel disease	26 (15.4)	12 (16.7)	14 (14.4)	
Three-vessel disease	64 (37.9)	37 (51.4)	27 (27.8)	

BMI, Body mass index; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; HbA1c, Serum hemoglobin glycated hemoglobin

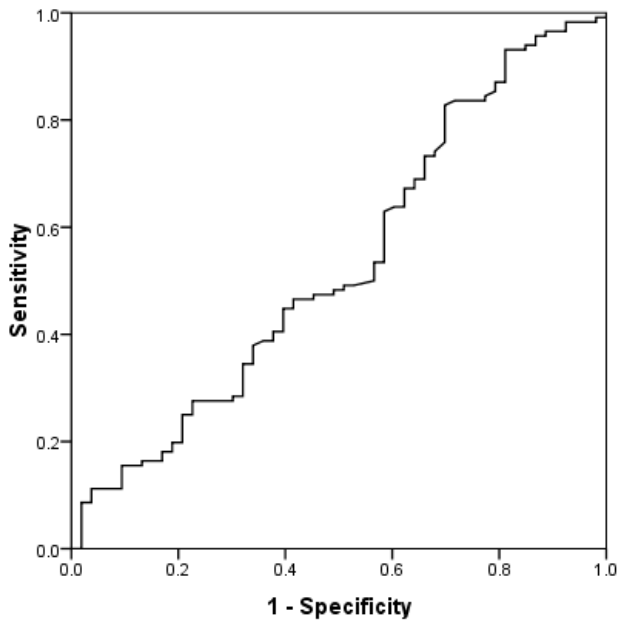
Table 2. Association between the vitamin D status and the cardiovascular risk profile

Characteristic	Normal Vitamin D	Insufficient Vitamin D	Mild-to-Moderate Vitamin D Deficiency	Severe Vitamin D Deficiency	P value
Male gender	16 (34.0)	18 (50.0)	25 (47.2)	13 (39.4)	0.423
Age, y	59.97 ± 8.49	57.11 ± 8.92	55.87 ± 8.72	56.12 ± 7.03	0.078
BMI, kg/m ²	28.30 ± 4.52	26.71 ± 4.38	27.19 ± 4.92	25.70 ± 4.43	0.088
Insulin use	7 (14.9)	4 (11.1)	7 (13.2)	7 (21.2)	0.666
Diabetes duration, y	6.93 ± 5.42	5.37 ± 5.77	4.65 ± 5.64	6.62 ± 5.78	0.263
Hypertension	35 (74.5)	22 (61.1)	42 (79.2)	26 (78.8)	0.235
Current smoking	3 (6.4)	3 (8.3)	10 (18.9)	8 (24.2)	0.010
Opium addiction	8 (17.0)	9 (25.0)	18 (34.0)	12 (36.4)	0.028
Serum creatinine, mg/dL	1.11 ± 0.22	1.01 ± 0.21	1.01 ± 0.17	1.05 ± 0.28	0.129
Serum triglyceride, mg/dL	152.08 ± 76.85	153.47 ± 135.65	165.75 ± 111.56	155.38 ± 85.86	0.913
Serum cholesterol, mg/dL	171.00 ± 39.31	169.61 ± 43.58	175.21 ± 52.96	158.47 ± 35.79	0.398
Serum HDL	39.45 ± 12.25	36.06 ± 6.41	34.66 ± 9.37	37.87 ± 8.79	0.085
Serum LDL	100.02 ± 34.20	99.75 ± 31.17	107.44 ± 43.79	92.11 ± 32.96	0.307
HbA1c, %	7.45 ± 1.57	8.14 ± 1.96	7.41 ± 1.33	7.61 ± 1.47	0.120
Coronary artery status					
Normal coronary	9 (19.1)	8 (22.2)	3 (5.7)	8 (24.2)	0.646
Trivial coronary involvement	6 (12.8)	4 (11.1)	9 (17.0)	6 (18.2)	
Single-vessel disease	11 (23.4)	6 (16.7)	5 (9.4)	4 (12.1)	
Two-vessel disease	5 (10.6)	6 (16.7)	11 (20.8)	4 (12.1)	
Three-vessel disease	16 (34.0)	12 (33.3)	25 (47.2)	11 (33.3)	

BMI, Body mass index; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; HbA1c, Serum hemoglobin glycated hemoglobin

Table 3. Main determinants of the presence of coronary artery disease

Variable	P value	Odds Ratio	95% Confidence Interval	
			Lower	Upper
Vitamin D deficiency	0.842	0.963	0.666	1.392
Male gender	0.030	0.333	0.123	0.898
Age	0.013	1.072	1.015	1.133
Body mass index	0.033	0.908	0.831	0.992
Duration of diabetes	0.349	1.045	0.953	1.144
Insulin injection	0.766	1.207	0.350	4.161
Hypertension	0.280	0.609	0.248	1.496
Current smoking	0.542	0.645	0.158	2.633
Opium use	0.874	0.927	0.365	2.354
Serum creatinine	0.303	0.350	0.048	2.580
Serum triglyceride	0.005	0.993	0.988	0.998
Serum cholesterol	0.069	1.011	0.999	1.024
Serum hemoglobin A1c	0.004	1.520	1.144	2.020

ROC Curve**Figure 1.** Receiver operating characteristic (ROC) curve analysis to assess the predictive value of vitamin D in discriminating coronary artery disease from the normal coronary status

DISCUSSION

The present study could not demonstrate an association between vitamin deficiency and both presence and severity of CAD in suspected patients. On the other hand, vitamin D deficiency could not predict severe CAD from the normal coronary status. This nonsignificant relationship may be explained by some points. First, although some previous studies have demonstrated the predictive value of vitamin D deficiency in relation to CAD—to the best of

our knowledge, the current study is the first of its kind to describe the predictive value of the vitamin D level and CAD severity in diabetic patients. In fact, the role of vitamin D and its receptors in the cardiomyocytes, endothelial cells, and vascular smooth muscle cells to progress CAD may be independent of changes in this vitamin in diabetic patients. Thus, future studies should be performed to further describe the pathophysiological effects of vitamin D deficiency on CAD in diabetic patients. Second, it has been demonstrated that both vitamin D metabolism and its interaction with vitamin D-

specific receptors are influenced by some genetic patterns which may be different in diabetic patients. More genetic research is required to shed sufficient light on this issue. Some authors have found no relationship between vitamin D deficiency and the arterial wall properties in CAD. Siasos et al¹² reported no difference between their subjects concerning vitamin D deficiency, insufficiency and sufficiency in flow-mediated dilation (FMD), augmentation index AI, and pulsed-wave velocity in the arteries. Verdoia et al¹³ showed that vitamin D did not influence the angiographic features of coronary lesions but was associated with a higher prevalence rate of left main lesions. Degerud et al¹⁴ demonstrated that the plasma 25(OH)D3 level was not associated with the 1-year progression of CAD in statin-treated patients. In a review by Schnatz and Manson,¹⁵ it was shown that most vitamin D supplementation trials had failed to demonstrate improvement in CAD and, therefore, the evidence remained inconclusive—highlighting the need for rigorous randomized trials of higher vitamin D doses with cardiovascular events. Further, most of the previous studies with a focus on the general population or nondiabetic patients have shown a significant association between vitamin D deficiency and the presence of CAD. In a study by Chen et al,¹⁶ the serum 25(OH)D level was associated with the risk of CAD in single and multiple regression models. Seker et al¹⁷ indicated that the plasma level of vitamin D was associated with the extent and complexity of CAD and, thus, might play a role in the pathogenesis and severity of coronary atherosclerosis. Moreover, some longitudinal studies have demonstrated increased cardiovascular mortality and morbidity associated with vitamin D deficiency.¹⁸ Low vitamin D levels have been linked to inflammation, higher coronary artery calcium scores, impaired endothelial function, and increased vascular stiffness. Syal et al.,¹⁹

indicating that Indian patients with documented CAD frequently suffered from vitamin D deficiency, reported that those with lower 25(OH)D levels had a higher prevalence rate of double- or triple-vessel CAD and diffuse CAD. The contradictory results regarding the association between vitamin D deficiency and CAD severity may be due to differences in geographical patterns, genetic susceptibilities, study designs, and inclusion criteria for selecting study populations.

Several studies have shown the effects of smoking on vitamin D deficiency. Cutillas-Marco et al²⁰ indicated that smoking was associated with an increased risk of hypovitaminosis D due to a reduced vitamin D intake in smokers. Morabia et al²¹ showed that the current smokers in their investigation had lower dietary intakes of calcium and vitamin D than did those who never smoked. Some other studies have succeeded in showing an association between opium addiction and bone loss owing to calcium and vitamin D deficiency.²² Both smoking and opium use can trigger vitamin D deficiency by negatively affecting individuals' appetite.

In summary, our study could not demonstrate a predictive role for vitamin D deficiency as regards the severity of CAD in type 2 diabetes. Among the different CAD risk factors, smoking and opium use were significantly correlated with vitamin D deficiency. Accordingly, smokers and opium addicts are susceptible to vitamin D deficiency. Be that as it may, the other CAD risk factors were not associated with CAD and its severity. Given the paradoxical results in the previous studies, our findings may be specific to our population and as such need further investigation.

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