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Original Research Article

A study of association of vitamin D deficiency and coronary artery disease

Manoj Kumar*, Granth Kumar, Vijay K. Verma, Manish Gupta, Rajesh K. Gautam

Department of Medicine, Uttar Pradesh University of Medical Sciences, Saifai, Etawah, Uttar Pradesh, India

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***Correspondence:**
Dr. Manoj Kumar,
E-mail: mkumarrims@gmail.com

ABSTRACT

Background: Recently vitamin D has received great interests for its multiple effects on inflammatory system and potential role in atherothrombosis. Coronary artery disease (CAD) is one of the common causes of death and disability in developed countries. Experimental evidence points to the involvement of multiple factors in coronary plaque formation, including vitamin D. The study aimed to examine the association of coronary artery disease with vitamin D level.
Methods: 140 patients of CAD (coronary artery disease) and 101 age and sex matched control were enrolled in the study and 25-hyroxyvitamin D (25(OH)D) concentration was measured. All participants were evaluated for presence of conventional risk factors for coronary artery disease. Association of vitamin D level was established after adjusting other risk factors using logistic regression analysis.
Results: In our study vitamin D level is significantly lower in patient group (CAD patients) compared with control group (18.2±10.9 vs 28.8±21ng/mL). Vitamin D deficiency was present in 81.4% patient in CAD patients whereas 57.7% in control group. Vitamin D deficiency was found to be an independent predictor of CAD after adjusting effect of other risk factors like hypertension, diabetes, smoking, obesity, high blood cholesterol and level of physical activity with adjusted odds ratio (95% confidence interval) 2.695 (1.148-6.330).
Conclusions: In present study patients of coronary artery disease had significantly low level of vitamin D as compared to individual without coronary artery disease. Vitamin D deficiency was found to be an independent predictor of CAD after adjusting other risk factors emphasizing that vitamin D can be a potential risk factor for development of coronary artery disease.

Keywords: Antihyperlipedemic, Atherothrombosis, Hypercalcaemia, IMT

INTRODUCTION

Coronary artery disease (CAD) is one of the common causes of death and disability in developed countries, responsible for about one in every five deaths.[1] It is rapidly becoming a pandemic within the developing world as well where it involves a relatively younger population.[2] Great reduction in mortality has been achieved by improvement in myocardial revascularization techniques however, the results are still unsatisfactory in high-risk patients.[3,4] Therefore, more interests have been focused on the identification of new risk factors for coronary artery disease (CAD) and its prevention.[5] Calcium metabolism disorders, and especially vitamin D (25-hydroxy -cholecalciferol, 25-OHD3) deficiency, represent a rising problem, whose social and economic impact is growing due to ageing of the population. Recently Vitamin D has received great interests for its multiple effects on inflammatory system and potential role in atherothrombosis. Vitamin D deficiency has been related to endothelial dysfunction and enhanced risk of CVD.[6-8] In fact, vitamin D receptor

has been identified on the surface of smooth muscle cells, endothelial cells and myocardial cells, inflammatory cells controlling their proliferation and differentiation, and even in platelets, thus potentially influencing thrombosis.[9-11] Furthermore, independent association has been observed between vitamin D deficiency and cardiovascular risk factors, such as hypertension, diabetes mellitus, obesity, metabolic syndrome, Subclinical atherosclerosis [intima-media thickness (IMT)], and coronary calcification.[12-18] Vitamin D deficiency has also been associated with cardiovascular events, such as MI, congestive heart failure, sudden cardiac death and total mortality.[19-21] Several studies have been done to find association of vitamin D level with coronary artery diseases in different part of world with varying result. No study has been done in rural population of central India. So this study was conducted to investigate association of coronary artery disease with vitamin D level.

METHODS

This was a case-control cross sectional study that was conducted in Uttar Pradesh University of medical science from January 2016 to December 2016. 140 Patients known to have coronary artery diseases were included in the study in case group. Patients were considered to have confirmed coronary artery disease if they had previous episodes of ST elevation myocardial infarction (MI) or angiographically proven CAD. Control consisted of 111 age and sex matched relative or friends of patients in control group. All patients were clinically stable. Study was initiated after taking permission from institute ethical committee. Informed consent was taken from all participants before including in study. Exclusion criteria were the presence of neoplastic disease, heart failure, recent major surgical procedure, evidence of hypercalcemia and systemic inflammatory conditions, such as infection, liver, or kidney disease. The patients on vitamin D and calcium supplements were also excluded.

All the participant were queried for presence of cardiovascular risk factors such as age, sex, smoking status, physical activity, use of drugs, presence of diabetes and hypertension. The level of physical activity was assessed by a standard questionnaire (rapid assessment physical activity questionnaire) and the participants were divided to five categories according to the score they obtained by this questionnaire: without activity, low activity, light activity, moderate activity and appropriate activity.[22] Weight, height and the blood pressure of the participants were measured by the standard protocol. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). The blood pressure was measured two times with a five minute interval in sitting position from the right brachial artery. Then the mean blood pressure was calculated. Hypertension was considered as blood pressure ≥140/90 or the consumption of antihypertensive drugs.

All the participant were subjected to following investigation: complete blood count (CBC), fasting plasma sugar, post prandial plasma sugar (2 hour after 75gm of oral glucose), glycosylated haemoglobin (HbA1c), kidney function test (KFT) (serum urea and creatinine), liver function test (LFT) (serum bilirubin, albumin, SGOT, SGPT and alkaline phosphatase), 24 hour urinary protein, serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), fasting 25-hyroxyvitamin D (25(OH)D) and ultrasound whole abdomen, 12 lead electrocardiogram, treadmill test, echocardiography and coronary angiography (CAG) (if ECG and TMT were inconclusive). Vitamin D level were measured in the form of 25-hyroxyvitamin D (25(OH) D). Patients with 25-hyroxyvitamin D level <20ng/ml were considered vitamin D deficient. Participant were considered to have Diabetes if they met one of following criteria FBS levels ≥126 mg/dl or post prandial plasma sugar >200mg/dl or HbA1c >6.5% or on antidiabetic drugs. 25-hyroxyvitamin D was estimated by chemiluminescent immunoassay method. CBC was estimated using analyser Sysmex xp-100 (Transasia). LFT, KFT, and plasma Sugar were estimated using Randox Rximola clinical chemistry analyser. Direct estimation of TC, HDL-C levels and TG were done using Randox Rximola clinical chemistry analyser. Low and very low density lipoprotein cholesterols (LDL-C and VLDL-C) were calculated employing the Friedewald's formula.[23]

Statistical analysis

Continuous variable were expressed in mean and standard deviation. Categorical variable were expressed in absolute number and percentage. Comparison between continuous variable were done with unpaired ‘t’ test and comparison between categorical variable were done with chi- squired test. Relationship between individual factors with coronary artery disease was investigated using binary logistic regression. Independent association of risk factors were investigated using multivariate logistic regression. P-value<0.05 were considered significant.

RESULTS

Out of 141 patients in case group 77.86% were male and in control group out of 111 participants 79.28% were male. Mean age was 56.96 and 56.23 year in case and control group respectively. Baseline characteristics of participants are shown in Table 1. Hypertension, diabetes, smoking, obesity, high blood cholesterol and also the amount of physical activity was significantly different between the patients and the control group (P<0.05). 25-hyroxyvitamin D level and proportion of 25-hyroxyvitamin D deficient individuals in both group have been shown in Figure 1.

Proportion of vitamin D deficient individuals were significantly higher in the coronary artery disease group than control (P<0.05). Mean 25-hyroxyvitamin D level was also significantly lower in patients with CAD as compared to control (p<0.001).

Table 1: Base line characteristics of participants.

		Case	Case %	Control	Control %	P-value
Age		56.96±6.52		56.23±5.60		0.554
Sex (M:F)		(109:31)		(88:23)		
	male	109	77.86	88	79.28	0.785
	female	31	22.14	23	20.72	
Family history of CAD		34	24.29	11	9.91	0.003
History of smoking		63	45.00	12	10.81	<0.001
Physical activity	1	51	36.43	18	16.22	<0.001
	2	46	32.86	18	16.22	
	3	34	24.29	21	18.92	
	4	8	5.71	22	19.82	
	5	1	0.71	32	28.83	
diabetes		51	36.43	18	16.22	<0.001
hypertension		32	22.86	4	22.86 3.60	0.004
Total cholesterol (mg/dl)		244.42±56.82		212.41±32.02		
raised total cholesterol		50	35.71	11	9.91	<0.001
BMI(kg/m^2)		26.16±4.45		24.90±4.03		0.019
obesity		14	12.61261261	32	22.85714286	0.037
25-hydroxyvitamin D (ng/ml)		28.78±20.98		18.18±14.94		<0.001
vitamin d deficiency		114	81.43	64	57.66	<0.001

Relationship between risk factors and CAD has been shown in Table 2 as unadjusted or crude odds ratio or univariate regression analysis reveals crude odds ratio for the association between CAD and vitamin D deficiency as 3.2. Result of Multivariate regression analysis is shown in Table 3.

Table 2: Univariate Logistic regression analyses for the association of coronary artery diseases with various risk factors.

Variables	Unadjusted	
	Odds ratio (95% CI)	p-value
Age	1.020 (0.979-1.063)	0.347
Sex	0.919 (0.500-1.688)	0.785
Family history of CAD	2.916 (1.401-6.067)	0.004
Smoking	6.750 (3.401-3.396)	0.000
Physical activity	0.444 (0.351-0.561)	0.000
HTN	2.993 (1.399-6.400)	0.005
hypercholesterolemia	5.051 (2.478-10.295)	0.000
diabetes	2.961 (1.607-5.454)	0.000
obesity	2.053 (1.035-4.074)	0.040
25-hydroxyvitamin D level	0.984 (0.977-0.991)	0.000
Vitamin D deficiency	3.220 (1.824-5.685)	0.000

After adjusting confounders with multivariate regression analysis, it was found that CAD is 2.7 times more common in Vitamin D deficient individual as compared to those with normal vitamin D level (p-value<0.02). Forest plot for adjusted odds ratio of each risk factors for coronary artery diseases has been shown in Figure 2.

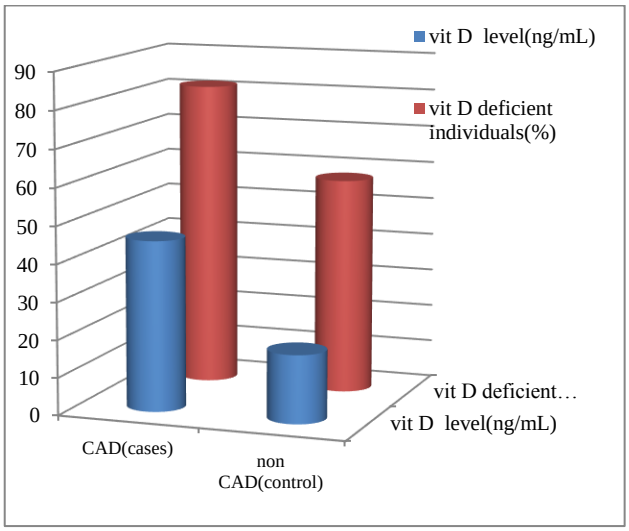

Figure 1: Vitamin d level and vitamin D deficiency in case and control.

DISCUSSION

Vitamin D deficiency is associated with coronary artery disease, and the actions of vitamin D are mediated by its binding to a specific nuclear Vitamin D receptor (VDR). VDRs are found in a variety of tissues including vascular smooth muscle cells, cardiomyocytes, and cells of the immune system.[24,25] It has been found that one of the functions of calcitriol, as well as other VDR ligands, is to impede the proliferation of vascular smooth muscle cells. A number of extra-renal tissues, including vascular smooth muscle cells, produce the enzyme CYP27B1, which transforms the primary circulating form of vitamin D, calcidiol to its active form, calcitriol. Eventually, calcitriol reduces platelet aggregation and thrombogenesis, likely through the activation of the VDR.[25,26]

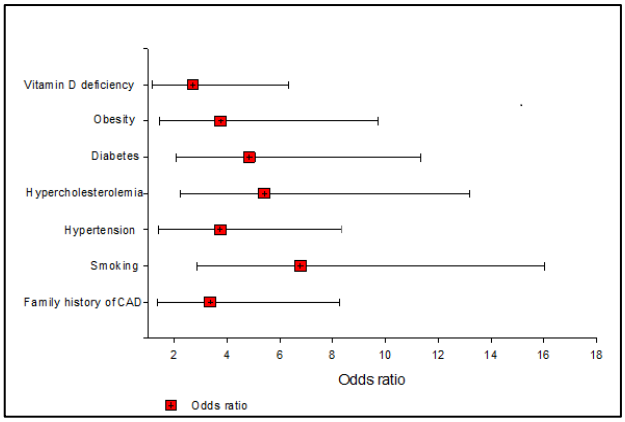

Figure 2. Forest plot showing adjusted odds ratio of each risk factors for coronary artery.

Table 3: Multivariate logistic regression analyses for the association of coronary artery diseases with various risk factors.

Variables	Adjusted		adjusted	
	Model 1*		Model 2#	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Family history of CAD	3.275 (1.337-8.024)	0.009	3.354 (1.363-8.256)	0.008
Smoking	6.467 (2.725-15.347)	0.000	6.776 (2.866-16.025)	0.000
Physical activity	0.443 (0.327-0.602)	0.000	0.448 (0.331-0.606)	0.000
Hypertension	3.707 (1.367-10.050)	0.010	3.732 (1.393-9.999)	0.009
Hypercholesterolemia	5.067 (2.082-12.331)	0.000	5.409 (2.220-13.178)	0.000
Diabetes	4.719 (2.003-11.118)	0.000	4.836 (2.063-11.335)	0.000
Obesity	3.755 (1.437-9.810)	0.007	3.750 (1.449-9.704)	0.006
25-hydroxyvitamin D	0.987 (0.976-0.997)	0.013	-	-
Vitamin D deficiency	-	-	2.695 (1.148-6.330)	0.023

*multivariate logistic regression with vitamin D taken as continuous variable. # Multivariate logistic regression low vitamin D taken as dichotomous variable.

Today, the growth suppressant and immune-modulatory effects of calcitriol are of important interest because of their potential use in the management of disorders, including acute coronary syndrome(ACS) and atherosclerosis where the principal pathological mechanisms are unrestrained cell growth and remodelling in the vascular wall.[25,30] Inflammation is also a key factor driving the processes of plaque formation, progression, and rupture in patients with ACS. An inflammatory subset of monocytes and macrophages has been reported to selectively concentrate in atherosclerotic plaques and produces pro-inflammatory cytokines. Calcitriol, involved in the regulation of body calcium homeostasis, promotes the differentiation of immature myeloid precursor cells into monocytes and macrophages. Crucially, calcitriol has long been shown to possess immune-regulatory properties and may inhibit key steps in this inflammatory process.[31-33]

In present study 25-hyroxyvitamin D level is significantly lower in patient group compared with control group (18.2±10.9 vs 28.8±21ng/mL). Vitamin D deficiency was present in 81.4% patient in case group whereas 57.7% in control group. Vitamin D deficiency was found to be an independent predictor of CAD after adjusting effect of other risk factors like hypertension, diabetes, smoking, obesity, high blood cholesterol and level of physical activity with adjusted odds ratio (95% confidence interval) 2.695 (1.148-6.330). This observation was similar to study done by Verdoia et al who noticed in their study of 1484 patients that vitamin D deficiency was significantly associated with higher prevalence of CAD [adjusted OR (95%CI)=1.32(1.1-1.6), P=0.004] and severe CAD [adjusted OR (95%CI)=1.18(1-1.39), P=0.05].[34] Similar observation was noticed in a study on 100 patients undergoing CAG done by Syal et al who found that the mean 25(OH) D level was 14.8±9.1ng/mL; vitamin D deficiency was present in 80% and only 7% had optimal 25(OH) D level.[35] Raina et al also observed that CAD patients had significantly low 25-hyroxyvitamin D level than control (15.53 vs 40.95ng/mL).[36] They also observed that vitamin D level

decreases among cases with age. The higher the age, the lesser is the vitamin D level. Seker et al observed in their study on 209 patients of stable CAD and 102 healthy control that vitamin D level of patient group is lower compared with control group 13.1±8.9 vs 9.4±5.0ng/mL and vitamin D level is independently associated with extent and complexity of CAD assessed with SYNTAX scores (β=-0.396, P<0.001).[37] Similarily Shanker et al reported that in 287 patients with CAD, vitamin D levels were significantly lower than in matched healthy controls, with patients in the first vitamin D quartile having a 2.54 times greater risk of CAD than those in the fourth quartile.[38] More recently, Goleniewska et al evaluating 130 patients with ST-elevation myocardial infarction, identified vitamin D levels as independent predictors of multi vessel CAD at multiple stepwise logistic regression.[39] In present study 25-hyroxyvitamin D level was significantly lower in smokers than non-smoker (p<0.001) and 25-hyroxyvitamin D level was positively correlated with level of activities which was supported by other studies as well. In a study conducted by Brot et al it was observed that dietary vitamin D intake, non-smoking, and physical activity (in men) were significantly associated with higher concentrations of serum 25-hydroxyvitamin.[40]

In a study conducted by Rolim et al total cholesterol (β=−0.36, p<0.01) and BMI (β=−0.21, p=0.04) was independently associated with levels of 25-hydroxyvitamin D.[41] Like earlier studies negative relationship was found between body mass index, systolic blood pressure, total cholesterol, age and vitamin D level in present study. However this relationship unlike earlier studies was not found to be significant. This may be due to small sample size of study population.

Limitations

Blood samples were drawn only once in our study population. A single measurement of 25-hydroxyvitamin D may not reflect lifetime vitamin D status. Small study group limited power of some analyses.

CONCLUSION

In present study patients of coronary artery disease had significantly low level of vitamin D as compared to individuals without coronary artery disease. Vitamin D deficiency was found to be an independent predictor of CAD after adjusting other risk factors emphasizing that vitamin D can be a potential risk factor for development of coronary artery disease. However in present study sample was small. So further study is needed on large sample so that the result may extrapolated on general population.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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