

IMPACT OF VITAMIN D DEFICIENCY ON CARDIOVASCULAR RISK FACTORS IN DIABETIC PATIENTS WITH CORONARY ARTERY DISEASE

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Abstract

Introduction: Diabetes mellitus (DM) is one of the major risk factors of coronary artery disease (CAD). The role of vitamin D deficiency (VDD) in CAD and its risk factors are highly conflicting. Hence, the current study was aimed to determine the relationship of VDD to cardiovascular risk factors among diabetics with established CAD. **Materials and Methods:** A cross-sectional study was conducted on 130 diabetic patients with established CAD, aged between 35 to 65 years of both sex. Serum lipid profile (enzymatic assay), HbA1c (High-pressure liquid chromatography), and 25 hydroxyvitamin D [Chemiluminescent Immunoassay (CLIA)] were estimated in the automated instrument. Study participants were categorized based on the vitamin D status as vitamin D sufficient (>30 ng/mL), insufficient (21-29 ng/mL), and deficient (< 20 ng/mL). **Results:** Among the 130 study participants, only 20.7% had sufficient vitamin D and the remaining 35.4% and 43.1% were vitamin D insufficient and deficient respectively. There was a significant increase in HbA1c (p-0.001), TC (p-0.031), LDL (p-0.014), TC/HDL (p-0.013), and non-HDL (p-0.017) in the VDD group in comparison with the sufficient group. A significant negative correlation of HbA1c was found with vitamin D with an r-value of -0.277 and p-value of 0.002. **Conclusion:** There was a significant increase in HbA1c, TC, LDL, TC/HDL, and non-HDL in the vitamin D deficient group compared to those with vitamin D insufficient and sufficient and a significant negative correlation of vitamin D with HbA1c.

Keywords: Cardiovascular risk factors, Coronary artery disease, Diabetes mellitus, Vitamin D

Introduction

Coronary artery disease (CAD) is now one of the most leading causes of death in both men and women around the world. Estimated prevalence rate in India over the past decades ranged from 1% to 13.2% and 1.6% to 7.4% urban populations and rural populations respectively.¹ Hence, there is a challenging need to identify novel modifiable risk factors in order to screen and prevent CAD. Vitamin D is a prohormone that has traditionally been thought to be necessary for skeletal metabolism. The identification of vitamin D receptors (VDR) on various other tissues had led to many studies showing non skeletal effect of vitamin D. Vitamin D deficiency (VDD) has got an impact on cardiovascular disease (CVD) directly and indirectly. The presence of VDR on endothelial cells, vascular smooth muscles elicits its vasoprotective effect, while deficiency of which leads to endothelial dysfunction, an early phase of atherosclerosis.^{2,3} VDD is also related to cardiovascular risk factors such as hypertension, obesity, insulin resistance and diabetes mellitus (DM), which explains its indirect role.⁴ Thus we aimed to determine the relationship of VDD to cardiovascular risk factors among diabetics with established coronary artery disease (CAD).

Methodology

Selection of participants

A cross-sectional study was conducted with prior informed consent on 130 diabetics with established CAD aged 35 to 65 years admitted to the cardiology section of a tertiary care hospital. Patients over the age of 65 and under the age of 35, as well as those with major concomitant non-CVD complications such as chronic kidney disease, chronic liver disease and malignancy, were excluded from the study.

Sample size calculation.

The sample size was calculated at 95% confidence interval and 80% power.⁵ Prior to the start of the study, institutional ethical clearance was obtained (IEC No.YEC-1/2019/106). The participants were enrolled in the study after providing prior written informed consent. Interviews were used to obtain information about socio-demographic characteristics and clinical history.

Clinical details

History of smoking and alcohol, duration of diabetes, concurrent history of hypertension, family history of CAD and DM were obtained by personal interview. Height and weight were measured using standard scale and body mass index (BMI) was calculated using the formula weight in Kg/ height in m². As per the World Health Organisation (WHO) criteria, the participants were categorised based on their BMI as normal weight (18-24.9 Kg/m²), overweight (25 - 29.9 Kg/m²) and obese (>30 Kg/m²).

Angiographic findings were checked from the records maintained in the cardiac department to confirm CAD. Biochemical laboratory investigations which includes lipid profile (enzymatic assay), and 25 hydroxy vitamin D [Chemiluminescent Immunoassay (CLIA)] were estimated in automated instrument-Vitros 5600 manufactured by Ortho Clinical Diagnostics, Johnson and Johnson and HbA1c (Principle - High pressure liquid chromatography) in Bio-Rad D-10 analyzer. The study participants were categorized as vitamin D sufficient (>30 ng/mL), insufficient (21-29 ng/mL) and deficient (< 20 ng/mL) as per the Current International Osteoporosis foundation guidelines for vitamin D.⁶ The Intra assay coefficient of 10.1% for mean concentration of 25 hydroxyvitamin D- 58.8 ng/mL for 80 observations.⁷Framingham risk score was calculated using an online dedicated software.

Statistical analysis

The statistical package for the social science, version 22 (SPSS Inc., Chicago, IL) was used for the statistical analysis. The normality distribution of the data was analysed by Kolmogorov-Smirnov test. The continuous variables were expressed as mean and standard deviation and categorical variables were expressed as frequency and percentage. Parameters which are not normally distributed were expressed as median and interquartile range. To compare the study parameters between groups, the Kruskal Walli's test and Anova test were used for non parametric and parametric data respectively. Categorical variables were compared using Chi square test. Spearman and Pearson correlation were used for correlational analysis of non parametric and parametric variables respectively.

Results

As per the inclusion criteria, 130 diabetic patients with CAD were included in the study. The mean age of the study participant was 54.09 ±7.28. Only 20.7% had sufficient vitamin D and the remaining 35.4% and 43.1% were vitamin D insufficient and deficient respectively. The baseline characteristics of the study participants were shown in Table 1. Out of 130 study participants, 94(71.2%) and 38 (28.8%) were male and females respectively and the mean age of the population was 54 ±7.28. 44 (33.8%) and 29 (22.3%) were smokers and alcoholics respectively. The mean vitamin D was 22.87 ±8.70. Table 2 shows the comparison of baseline characteristics of the study participants in three groups categorized based on the vitamin D levels. The non parametric test of statistical significance were applied as the study data were not normally distributed, which showed a significant increase in HbA1c ($p = 0.001$), TC ($p = 0.031$), LDL ($p = 0.014$), TC/HDL ($p = 0.013$) and non HDL ($p = 0.017$) in vitamin D deficient group in comparison with sufficient group. The non parametric correlational analysis of vitamin D with cardiovascular risk factors displayed in Table 3 shows, negative correlation of vitamin D with BMI, HbA1c, TC, LDL, HDL, TC/HDL and non HDL. However, the correlation was statistically significant only with HbA1c with r value of -0.277 and p value of 0.002. The prevalence of categorical cardiovascular risk factors in three groups categorized based on the vitamin D levels was shown in Figure 1. There was an increase in prevalence of HTN, family history of DM and obesity and overweight in vitamin D deficient group compared to deficient and sufficient group.

Table 1 Demographic and baseline characteristics of study population

Parameter	Whole study group
Age (years)	54 ±7.28
#Male Gender	93 (71.5)
#HTN n(%)	66 (50.7)
#Family h/o CAD n(%)	43 (33.7)
#Family h/o DM n(%)	58 (44.7)
#H/o Smoking n(%)	44 (33.8)
#H/o Alcohol n(%)	29 (22.3)
#Over weight and obese	50 (38.4)
BMI (kg/m ²)	24.36 ± 3.59
[§] HbA1c (%)	9.2 (3.9)
[§] TC (mg/dL)	167 (64)
[§] LDL (mg/dL)	100 (47)
[§] HDL (mg/dL)	35 (11)
[§] TC/HDL	5.16 (2.38)
[§] Non HDL	132 (63)
[§] FraminghamRisk score	25(14)
Vitamin D (ng/mL)	22.87 ± 8.70

CAD- Coronary artery disease, BMI- Body mass index, HbA1c- Glycated hemoglobin, TC- Total cholesterol, LDL- Lowdensity lipoprotein, HDL- High density lipoprotein.[§]Expressed as median and interquartile range, #Categorical variables expressed as frequency and percentage

Table 2 Comparison of study variables between the groups based on vitamin D status

	Vitamin D Sufficient (n-27)	Vitamin D insufficient (N-46)	Vitamin D deficiency (n=57)	P Value
\$Age (years)	57.148 ± 8.23	52.56 ± 5.54	53.7 ± 7.67	0.015
WC (cm)	91.41 ± 9.96	91.69 ± 8.27	91.75 ± 9.16	0.993
BMI (kg/m²)	25.1 ± 2.97	23.91 ± 3.4	24.78 ± 3.98	0.387
\$HbA1c (%)	8.51 ± 1.79	9.16 ± 2.14	10.75 ± 2.96	0.001*
\$TC (mg/dL)	163.85 ± 39.42	187 ± 40.69	174.48 ± 46.37	0.031*
\$LDL (mg/dL)	94.68 ± 38.16	115.10 ± 33.7	105.36 ± 37.86	0.014*
\$HDL (mg/dL)	34.88 ± 8.24	32.60 ± 7.64	34.51 ± 12.15	0.645
\$TC/HDL	4.82 ± 1.15	6.06 ± 2.2	5.41 ± 1.59	0.013*
\$Non-HDL	128.96 ± 35.54	154.39 ± 39.61	139.96 ± 41	0.017*
Framingham risk score	25 ± 8	24 ± 7	19 ± 8	0.2
Vitamin D (ng/mL)	36.02 ± 4.67	25.63 ± 2.72	15.23 ± 3.99	0.000

CAD- Coronary artery disease, BMI- Body mass index, HbA1c- Glycated hemoglobin, TC- Total cholesterol, LDL- Low density lipoprotein, HDL- High density lipoprotein. \$Kruskal Walli’s test used for comparison *P< 0.05 considered statistically significant.

Table 3 Correlation of vitamin D with cardiovascular risk factors

Parameters	Correlation	P value
Age	0.079	0.378
BMI	-0.089	0.316
^s HbA1c	-0.277	0.002*
^s TC	-0.090	0.314
^s LDL	-0.079	0.377
^s HDL	-0.043	0.627
^s TC/HDL	-0.080	0.367
^s Non-HDL	-0.087	0.331
Framingham Risk score	0.282	0.001*

BMI- Body mass index, HbA1c- Glycated hemoglobin, TC- Total cholesterol, LDL- Low density lipoprotein, HDL- High density lipoprotein. \$Spearman correlation done *P< 0.05 considered statistically significant.

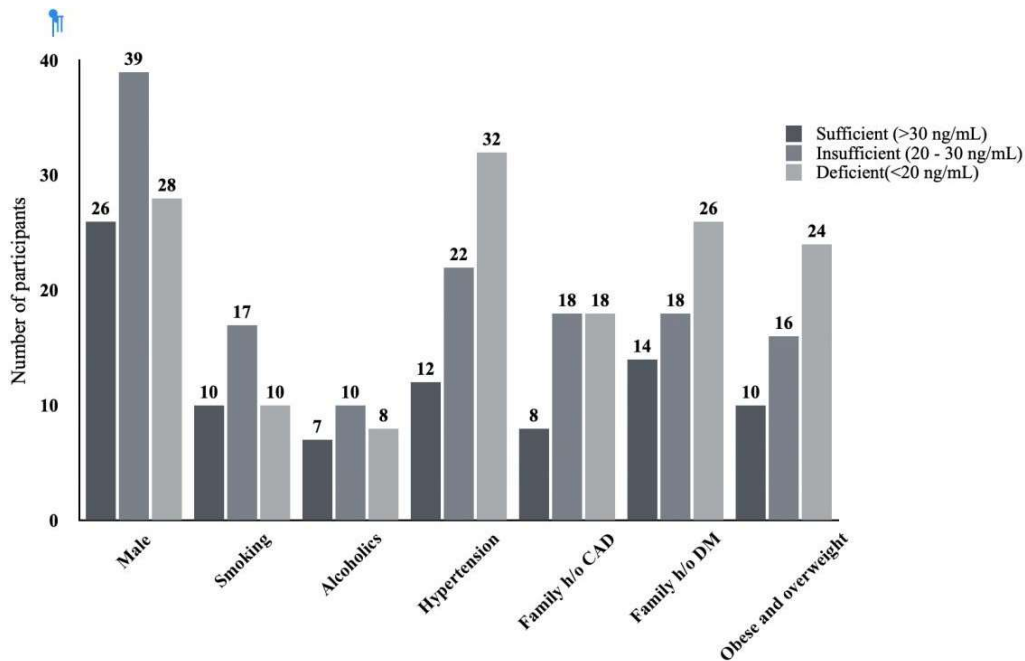


Figure 1 Prevalence of CVD risk factors in groups based on vitamin D levels

Discussion

The present study aimed at determining the impact of VDD to cardiovascular risk factors in a diabetic patients with CAD, revealed a statistically significant difference in HbA1c, TC, LDL, TC/HDL and non HDL among the groups categorized based on the vitamin D status (Table 2), and significant inverse correlation of vitamin D with HbA1C (Table 3). The mean vitamin D level was found to be as low as 22.87 ± 8.70 (Table 1). According to Knezevic Pravecek *Met al.*,⁸ acute coronary syndrome (ACS) patients had low levels of vitamin D, and the diabetic patients had the lowest level. While lowered 25 hydroxy vitamin D was evidenced among CAD patients in multiple studies, literature evidence in relation of vitamin D with various CVD risk factors in a diabetic CAD patients remains sparse. Prevalence of hypertensive and combined obese and overweight subjects were found as 32(50%) and 24(48%) respectively in the VDD group compared to vitamin D sufficient and insufficient (Figure 1). The prevalence of CAD is more than double among diabetic patients with VDD when compared with those having sufficient vitamin D.⁹

DM is one of the major risk factors of CAD, due to enhanced prothrombotic and pro-inflammatory status which leads to atherosclerosis.¹²VDD exhibits an increase in insulin resistance there by leading to compromised control over blood glucose.^{13,14}.Zhao H *et al.*,(2020), found a significant negative correlation between 25(OH) D and HbA1c ($r = -0.259, p = 0.00$) which supports the current study.¹⁵ In a double blinded RCT by Madar *et al.*, there was no improvement in HbA1c, lipid and fructosamine in those with low vitamin D status after oral vitamin D supplementation for 3 months.¹⁶ Nevertheless, the randomised controlled trial (RCT) by Upreti V *et al.*,(2018), with 6 months of vitamin D supplementation, the case group with type 2 diabetes mellitus and hypovitaminosis D showed significant decrease in mean FPG levels (131.4 to 102.6 mg/dl; $p = 0.04$), HbA1c levels (7.29% to 7.02% ; $p = 0.01$), and PPPG levels (196.2 to 135.0 mg/dl; $p < 0.001$).¹⁷

Dyslipidemia in DM is a principle denominator promoting atherosclerosis which leads to macrovascular complications.¹⁸ 97% of diabetics are dyslipidemic, which in turn correlates with atherosclerosis.¹⁹ An association between low vitamin D and dyslipidemia has been identified which can be attributed to the impact of vitamin D on beta-cell function, which leads to insulin resistance, disruption of lipoprotein metabolism, and ultimately, increased TG and decreased HDL cholesterol levels.^{20,21} Studies indicate that increase in calcium absorption decrease the synthesis and secretion of TG.²² The current study showed significant difference in TC, LDL, TC/HDL and non HDL across the groups categorised based on the vitamin D status. Our findings are supported by study conducted by Tripathy *et al.*, which showed significant correlation of VDD with dyslipidemia but no correlation found with conventional CVD risk factors such as age, sex, smoking and family history, DM, and HTN.²³ Chaudhuri *et al.* also observed an independent association VDD with dyslipidemia.²⁴ Al Quaziz *et al.*, found a significant association of VDD with low HDL in men and high TG in women.²⁵

Obese people are found to be VDD as 25 (OH) vitamin D gets sequestered in the subcutaneous fat, which results in its decrease in circulating level.²⁶ A negative correlation of vitamin D was seen with body mass index (Table 3), though not significant. A cross-sectional study conducted among community dwelling healthy seniors found an inverse association of 25(OH)D with fat mass.²⁷ However, RCT studies show contradicting results. Wamberg *et al.*,²⁸ found no effect of vitamin D on body fat and adipose tissue but Salehpouret *al.*,²⁹ found a positive effect of vitamin D on fat mass reduction assessed by Bioelectrical Impedance Analysis. These differences may be due to difference in dose of vitamin D supplemented and the sample size.

Vitamin D is found to have a role in maintaining blood pressure by reducing renin secretion which ultimately leads to decrease in activity of renin-angiotensin-aldosterone system (RAAS).³⁰ Jorde *et al.*³¹ demonstrated an association between reduced serum vitamin D levels and hypertension. However, whether vitamin D supplementation could prevent the onset of hypertension in the future is not identified. Kota *et al.*³² evidenced that individuals with inadequate vitamin D had elevated systolic blood pressure, diastolic blood pressure, and mean arterial pressure. National Health and Nutrition Examination Survey (NHANES) on 7228 participants during the time period 2003-2006 revealed an inverse association between vitamin D level and blood pressure.³³

Conclusion:

A significant negative association exist between the lipid profile and HbA1c with vitamin D level in diabetic patients with CAD. Therefore, vitamin D might have an indirect role in the pathogenesis of CAD which highlights the importance of its adequacy in a diabetic population. Thus, screening and dietary supplementation in case of vitamin D deficiencies might be beneficial in halting the progression of diabetic complications.

Limitations

As our study was a cross sectional study, temporal association between cause and effect cannot be identified. Use of non diabetic individuals as the control group gives a better picture of the alterations in vitamin D levels and its relation with cardiovascular risk factors.

Future Scope of the Study

Further longitudinal studies in a larger sample size are desirable to confirm these results. A case control study, with non-diabetic as a control group will help in providing the risk ratio of diabetic population verse non-diabetic population to cardiovascular risk factors.

Compliance with Ethical Standards

Conflict of Interest -The authors declare that they have no conflict of interest

Informed Consent-Informed consent was obtained from all individual participants included in this study.

Code of ethics All procedures conducted in the current study involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its ethical standards.

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