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ORIGINAL PAPER

# Association of Vitamin D with Risk Factors for Coronary Artery Disease

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## ABSTRACT

***Introduction:*** *Vitamin D safeguards cardiovascular health by reducing inflammation and susceptibility to atheroma. This study aimed to evaluate the association of coronary artery disease (CAD) and its risk factors like body mass index (BMI), glycated hemoglobin ($HbA_{1c}$), and lipid profile with vitamin D.*

***Methods:*** *Patients of both genders aged over 18 years, who underwent coronary angiogram for cardiac symptoms such as chest pain, breathlessness, palpitation, or syncope, were enrolled in the present study. Demographic and anthropometric data were collected. Glycated hemoglobin, lipid profile and 25-hydroxyvitamin D were measured. The severity of CAD was analyzed along with the SYNTAX scoring.*

***Results:*** *The study population was divided into three groups based on vitamin D levels: Group I (vitamin D level <20 ng/mL), Group II (20-30 ng/mL) and Group III (>30 ng/mL). There was a significantly higher number of patients with diabetes mellitus and triple vessel disease in Group I. On multivariable*

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*logistic regression, vitamin D had a significant odds ratio (OR) of 1.21 (1.03-1.43) for single vessel disease and 0.92 (1.13-1.43) for triple vessel disease. SYNTAX score had a significant OR of 0.697 (0.557-0.873) for single vessel disease and 1.27 (1.13-1.43) for triple vessel disease. There was a significant negative correlation between $HbA_{1c}$ and vitamin D (r =-0.269, p= 0.008). Vitamin D levels negatively correlated with triple vessel disease (r =-0.252, p= 0.013).*

***Conclusion:*** *Incidence of diabetes mellitus and levels of $HbA_{1c}$ were both higher among patients with vitamin D deficiency. Vitamin D deficiency was a risk factor for single and triple vessel disease.*

**Keywords**: vitamin D, coronary artery disease, body mass index, $HbA_{1c}$.

## ABBREVIATIONS

CAD=coronary artery disease
BMI=body mass index
$HbA_{1c}$=glycated hemoglobin
CVD=cardiovascular disease
TC=total cholesterol
HDL-C=high density lipoprotein-cholesterol
LDL-C=low density lipoprotein-cholesterol
VLDL-C=very low-density lipoprotein-cholesterol
RCTs=randomized controlled trials

## INTRODUCTION

Global health is greatly impacted by cardiovascular disease, which is identified by the World Health Organization as the leading global cause of death, with 7.3 million deaths being attributed to coronary artery disease (CAD) (1). The prevalence of CAD in India is estimated to be around 30 million in 2023. Smoking, dyslipidemia, elevated body mass index (BMI), increased high-sensitivity C-reactive protein and hyperhomocysteinemia are risk factors for CAD. Insulin resistance increases the risk of severe CAD in type 2 diabetes mellitus patients with inadequate glycaemic control (2). Metabolic syndrome, marked by factors like central obesity, dyslipidaemia, insulin resistance, high blood pressure and endothelial dysfunction, elevates cardiovascular risk and mortality by synergizing atherogenic factors. Vitamin D is essential for insulin release in response to elevated blood sugar, affecting glucose tolerance. Its deficiency reduces insulin secretion without impacting glucagon secretion (3). The hormonal function of vitamin D in regulating cell growth, migration, differentiation, immune response, inflammation and fibrosis may play a vital role from the early activation of endothelial inflammation to the susceptibility of atheroma (4). Vitamin D controls smooth muscle and cardiomyocyte growth, inhibits vascular smooth muscle cell proliferation via calcium influx, but risks calcification in renal failure (5). Vitamin D safeguards cardiovascular health by reducing inflammation, inhibiting smooth muscle cell growth, suppressing proatherogenic T lymphocytes, preserving endothelial function and shielding against glycation products (6). Total cholesterol (TC), LDL cholesterol (LDL-C) and triglycerides were also negatively correlated with 25(OH)D concentrations (7). Coronary calcification is correlated with vitamin D. Risk stratification for cardiovascular disease (CVD) based on vitamin D levels reveals an elevated risk with increasing concentrations (8).

While there are reports linking cardiovascular risk to vitamin D deficiency, there is a lack of information regarding the association of BMI, $HbA_{1c}$ and lipid profile with vitamin D. Therefore, our study aimed to investigate the correlation between vitamin D levels and CAD, along with associated risk factors such as BMI, $HbA_{1c}$ and plasma lipid levels. ❑

## METHODS

This is a hospital-based cross-sectional study conducted with the approval of the Institute Ethics Committee (CMCH & RC/IEC No.30 dated 11/4/2017). Patients of both genders aged over 18 years, who have undergone coronary angiography for cardiac symptoms such as chest pain, breathlessness, palpitation, or syncope, were enrolled in the study after obtaining their written informed consent. Patients who were taking vitamin D supplements, individuals with documented cardiac disease, chronic kidney disease, decompensated liver disease, hypoparathyroidism or hyperparathyroidism, as well as critically ill patients necessitating inotrope sup-

port, ventilator support, or hemodialysis were excluded from the study.

### Sample size

Considering a prevalence of 37% of vitamin D deficiency in CAD patients, and 95% confidence interval (CI) and 10% margin of error, the sample size is calculated at 90 (9). For this study, data from 96 patients have been included.

Baseline data along with clinical history were recorded and anthropometric measurements were taken. Blood samples were obtained after overnight fasting for biochemical analysis, including $HbA_{1c}$ (measured through the immunoturbidimetric method), lipid profile (serum TC measured by the cholesterol oxidase/peroxidase method, serum triglycerides by the glycerol-3-phosphate oxidase method, serum high density lipoprotein-cholesterol (HDL-C) by the direct enzymatic method, serum LDL-C by direct enzymatic method, and serum very low density lipoprotein-cholesterol (VLDL-C) calculated using the formula serum triglycerides/5). Additionally, the T-C/HDL-C ratio was calculated, and plasma total 25-hydroxyvitamin D was estimated through the electro-chemiluminescence immunoassay.

For patients with CAD, severity was determined as single, double and triple vessel disease. Additionally, SYNTAX scoring system was employed to evaluate complexity of coronary vessels such as bifurcation, thrombus, total occlusion, diffuse vessel involvement and calcification.

### Statistical analysis

SPSS version 21 was used for data analysis. Continuous variables were expressed as mean ± standard deviation (SD) and analysed by ANOVA. Categorical variables were expressed as percentage and analysed by chi-square test. Spearman and Pearson correlation was used to evaluate the relationship between variables. Multivariable logistic regression analysis was done to predict the risk factors for single, double and triple vessel disease. P value of less than 0.05 was considered significant. ❑

## RESULTS

The study population was divided into three groups based on vitamin D levels: Group I (vitamin D level <20 ng/mL, Group II (20-30 ng/mL) and Group III (>30 ng/mL).

The mean age of the study subjects was 57.53±11.33 years and 79% of them were males. About half the study population had a history of smoking and 16% a history of alcohol consumption. About 32% of patients had type 2 diabetes mellitus and 38% had a history of hypertension. The mean BMI of participants was 22.83±3.23 kg/m$^2$. There was no significant difference in age and gender between the three groups. Smoking was significantly higher in Group III, but there was no difference in alcohol consumption habits. There was a significantly higher number of patients with diabetes mellitus in Group I. There was no significant difference in height, weight, or BMI between groups (Table 1).

The mean $HbA_{1c}$ of the study population was 6.19±1.77 and it was significantly higher in Group I and Group II. Mean blood sugar at presentation was 159.68±73.48 mgs/dL, but no significant difference was noted among the three

**TABLE 1.** General characteristics of the study population

| Parameter | Total population (n=96) | Group I vitamin D levels <20 ng/mL (n=46) | Group II vitamin D levels 20-30 ng/mL (n=29) | Group III vitamin D levels >30 ng/mL (n=21) | *P* value |
|---|---|---|---|---|---|
| Age | 57.53±11.33 | 55.87±12.05 | 57.48±9.64 | 61.24±11.49 | 0.199 |
| Male | 76 (79.2) | 31 (67.4) | 25 (86.2) | 20 (95.2) | 0.018 |
| Female | 20 (20.8) | 15 (32.6) | 4 (13.8) | 1 (4.8) | |
| Smoking | 43 (44.8) | 16 (34.8) | 11 (37.9) | 16 (76.2)* | **0.005*** |
| Alcohol | 16 (16.7) | 8 (17.4) | 5 (17.2) | 3 (14.3) | 0.946 |
| Diabetes mellitus | 31 (32.3) | 18 (39.1)* | 11 (37.9)* | 2 (9.5) | **0.041*** |
| Hypertension | 37 (38.5) | 18 (39.1) | 10 (34.5) | 9 (42.9) | 0.830 |
| Height in cm | 162.27±7.18 | 161.48±7.99 | 163.55±7.06 | 162.24±5.28 | 0.482 |
| Weight in kg | 60.02±10.42 | 59.22±10.61 | 63.24±10.18 | 57.33±9.64 | 0.108 |
| BMI (kg/m$^2$) | 22.83±3.23 | 22.74±3.56 | 23.76±2.59 | 21.76±3.05 | 0.094 |

BMI=body mass index

**TABLE 2.** Biochemical parameters of the study population

| Parameter | Total population (n=96) | Group I vitamin D levels <20 ng/mL (n=46) | Group II vitamin D levels 20-30 ng/mL (n=29) | Group III vitamin D levels >30 ng/mL (n=21) | *P* value |
|---|---|---|---|---|---|
| Mean $HbA_{1c}$±SD | 6.19±1.77 | 6.41±1.80 | 6.52±1.84 | 5.24±1.22 | 0.018* |
| Random blood sugar | 159.68±73.48 | 169.98±86.09 | 162±77.54 | 133.9±55.26 | 0.190 |
| Total cholesterol | 138.75±34.31 | 140.35±35.64 | 136.41±36.49 | 138.48±29.21 | 0.891 |
| LDL | 86.99±26.18 | 88.76±30.11 | 85.24±25.21 | 85.52±17.69 | 0.820 |
| HDL | 32.05±8.03 | 31.3±7.43 | 32.34±8.33 | 33.29±9.05 | 0.632 |
| TGL | 131.59±63.67 | 135.65±69.95 | 138.69±68.16 | 112.9±35.52 | 0.311 |
| VLDL | 26.69±12.52 | 27.65±13.39 | 28.17±13.82 | 22.52±7.16 | 0.225 |
| TC/HDL | 4.42±1.27 | 4.57±1.39 | 4.28±1.22 | 4.29±1.06 | 0.551 |
| TGL/HDL | 4.38±2.46 | 4.65±2.78 | 4.59±2.43 | 3.48±1.47 | 0.167 |
| Vitamin D | 21.36±12.39 | 11.15±5.6 | 24.41±2.47 | 39.52±7.13 | 0.000* |

$HbA_{1c}$=glycated hemoglobin; LDL=low density lipoprotein; HDL=high density lipoprotein; TGL=triglycerides; VLDL=very low-density lipoprotein; TC=total cholesterol

**TABLE 3.** Syntax score and angiographic findings of the study population

| Parameter | Total population (n=96) | Vitamin D levels <20 ng/mL (n=46) | Vitamin D levels 20-30 ng/mL (n=29) | Vitamin D levels >30 ng/mL (n=21) | *P* value |
|---|---|---|---|---|---|
| Syntax score | 19.24±13.44 | 20.63±14.44 | 15.66±11.34 | 21.14±13.49 | 0.228 |
| Angiographic findings | | | | | 0.017* |
| Normal | 4 (4.2) | 1 (2.2) | 3 (10.3) | - | |
| Single vessel disease | 23 (24) | 8 (17.4) | 6 (20.7) | 9 (42.9) | |
| Double vessel disease | 20 (20.8) | 7 (15.2) | 10 (34.5) | 3 (14.3) | |
| Triple vessel disease | 49 (51) | 30 (65.2)* | 10 (34.5) | 9 (42.9) | |

**TABLE 4.** Multivariable logistic regression analysis for prediction of coronary artery disease

| Parameters | Single vessel disease | | Double vessel disease | | Triple vessel disease | |
|---|---|---|---|---|---|---|
| | *P* value | OR (CI) | *P* value | OR (CI) | *P* value | OR(CI) |
| Age | 0.090 | - | 0.375 | - | 0.216 | - |
| Sex | 0.120 | - | 0.926 | - | 0.332 | - |
| BMI | 0.05 | - | 0.414 | - | 0.066 | - |
| Diabetes mellitus | 0.426 | - | 0.836 | - | 0.088 | - |
| Hypertension | 0.08 | - | 0.673 | - | 0.744 | - |
| Smoking | 0.154 | - | 0.779 | - | 0.087 | - |
| Alcohol | 0.085 | - | 0.857 | - | 0.744 | - |
| HbA1c | 0.15 | - | 0.258 | - | 0.052 | - |
| Random blood sugar | 0.133 | - | 0.708 | - | 0.788 | - |
| Total cholesterol | 0.054 | - | 0.146 | - | 0.699 | - |
| LDL | 0.387 | - | 0.156 | - | 0.465 | - |
| HDL | 0.027 | - | 0.295 | - | 0.717 | - |
| TGL | 0.690 | - | 0.601 | - | 0.890 | - |
| VLDL | 0.638 | - | 0.457 | - | 0.498 | - |
| TC/HDL | 0.025* | 310.67 (2.09-462) | 0.420 | - | 0.983 | - |
| TGL/HDL | 0.611 | - | 0.997 | - | 0.411 | - |
| Vitamin D | 0.019* | 1.21 (1.03-1.43) | 0.951 | - | 0.026* | 0.92 (0.85-0.99) |
| Syntax score | 0.002* | 0.697 (0.557-0.873) | 0.119 | - | 0.000* | 1.27 (1.13-1.43) |

$HbA_{1c}$=glycated hemoglobin; LDL=low density lipoprotein; HDL=high density lipoprotein; TGL=triglycerides; VLDL=very low-density lipoprotein; TC=total cholesterol

groups. The lipid profile was within normal range among the groups, except for reduced HDL-C levels. The study population had a mean level of vitamin D of 21.36±12.39 (Table 2). The mean SYNTAX (19.24±13.44) did not significantly differ between groups. On angiography, 51% of patients had triple vessel disease and the majority of them (65.2%) were in Group I (Table 3).

On multivariable logistic regression, vitamin D had a significant OR of 1.21 (1.03-1.43) for single vessel disease and 0.92 (1.13-1.43) for triple vessel disease. SYNTAX score had a significant OR of 0.697 (0.557-0.873) for single vessel disease and 1.27 (1.13-1.43) for triple vessel disease (Table 4).

There was a significant negative correlation of $HbA_{1c}$ with the vitamin D level (r = -0.269,

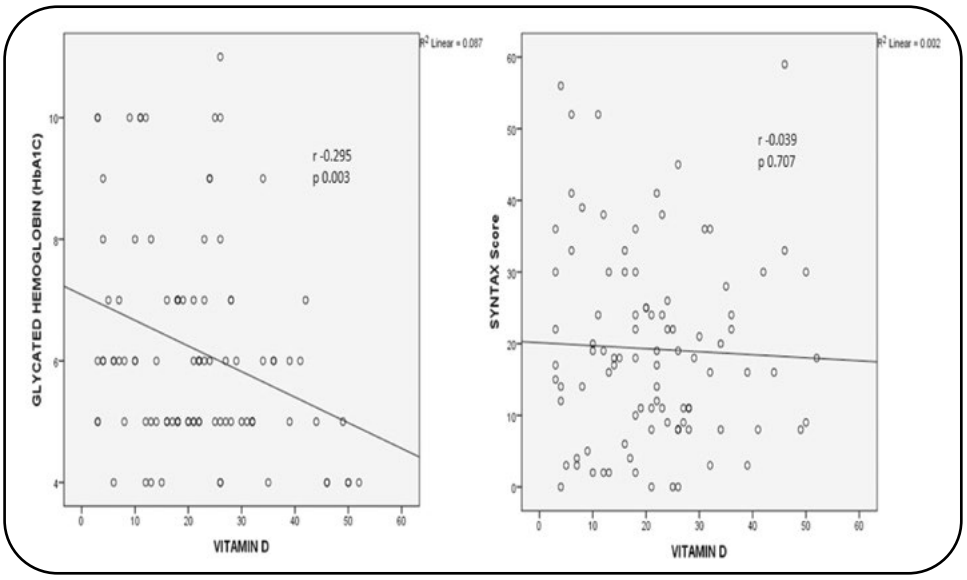


**FIGURE 1.** Correlation between glycated hemoglobin ($HbA_{1c}$), SYNTAX score and vitamin D

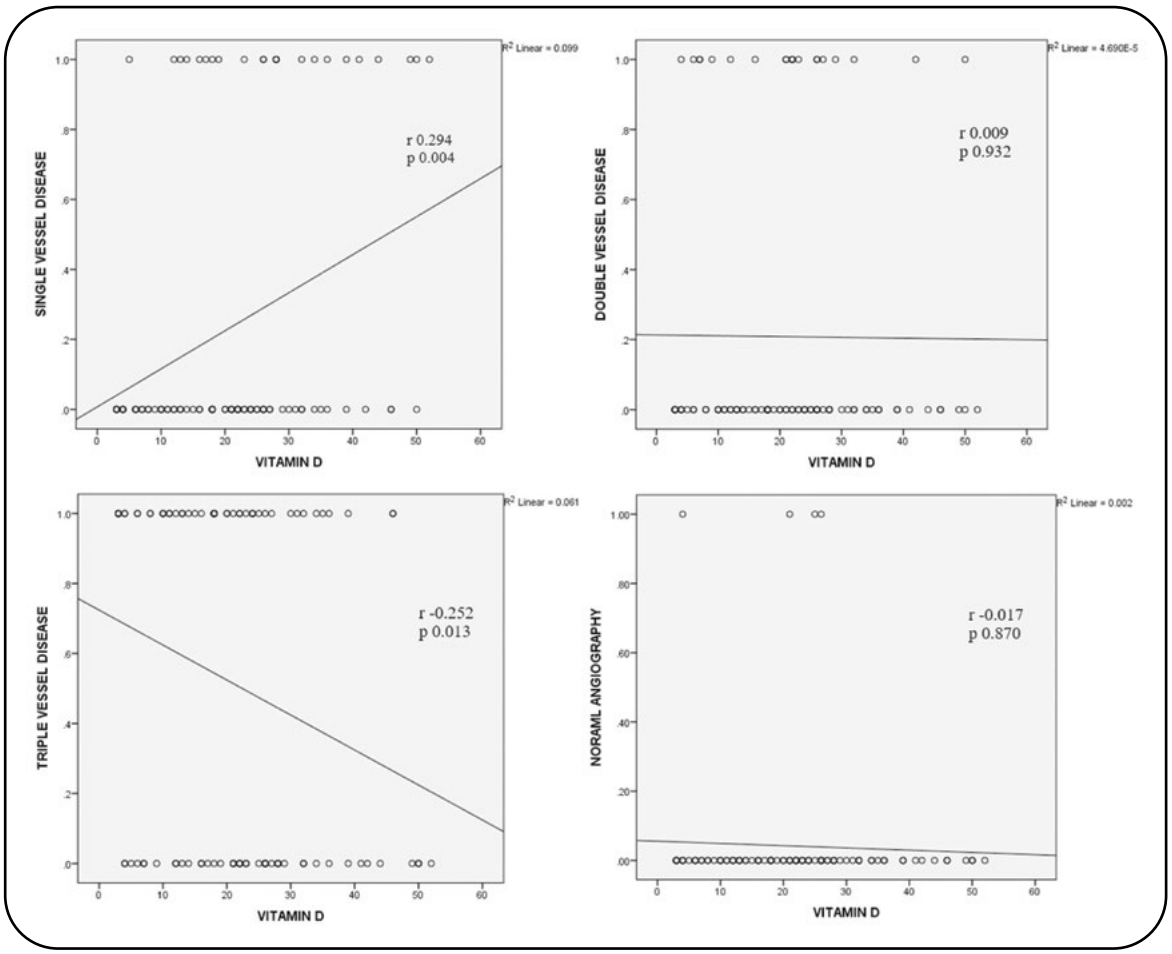


**FIGURE 2.** Correlation of angiographic findings and vitamin D

p= 0.008). SYNTAX score was negatively but insignificantly correlated with vitamin D level (r=-0.039, p=0.707) (Figure 1). Vitamin D levels had a significant negative correlation with triple vessel disease (r =-0.252, p= 0.013) (Figure 2). ❑

## DISCUSSION

The present study involved assessing vitamin D levels in patients undergoing a coronary angiogram. Additionally, measurements were taken

for BMI, $HbA_{1c}$ and lipid profile. SYNTAX scoring was done after the angiogram procedure.

The study population had a mean age of 57.53±11.33 years, with 79% of them being males. This aligns with findings from other studies that show an occurrence of CAD typically after the age of 50, with a subsequent increase in prevalence (10). There was a higher number of males compared to females, which is in agreement with the well-established fact that men are more susceptible to CVD than women, with the latter being protected from cardiovascular morbidity to some extent, at least until menopause. A medical history of habit of smoking and alcohol consumption escalates the risk, particularly in males (11).

Cardiovascular disease, exacerbated by hypertension, stands as the primary cause of morbidity and mortality in patients with diabetes. In our study, 38% of subjects had a history of hypertension, with 32% of them having been diagnosed with type 2 diabetes mellitus. The impact of diabetes and hypertension on the cardiovascular system significantly intersects, primarily driven by both microvascular and macrovascular diseases (12).

In our study, the average BMI was 22.83±3.23 kg/m$^2$, falling within the normal to overweight range for Asians. A substantial percentage of CAD patients in our cohort were either overweight or obese. The interaction of high BMI with hypertension exhibited a detrimental additive effect (13). Hyperlipidemia remains the predominant risk factor for CAD (14). In our study, the lipid profile of these patients was generally normal, except for low HDL-C. Research indicates that an increase in HDL-C is associated with a lower risk of cardiac mortality, whereas a decrease in HDL-C is linked to an elevated risk of significant adverse cardiac events and cardiac death (15). It is widely recognized that HDL-C plays a pivotal role in the development of cardiovascular mortality and morbidity, and targeting HDL-C can contribute to risk reduction (16, 17). Furthermore, studies have demonstrated that the risk of coronary heart disease was diminished when HDL-C levels surpassed 90 mg/dL in men and 75 mg/dL in women (18).

Glycated hemoglobin has been associated with severe CAD, aligning with findings in our study. Previous research has also utilized $HbA_{1c}$ as a predictive biomarker for CAD in individuals without diabetes, aiding in the assessment of both the likelihood and severity of CAD (19, 20). In our study, Group I exhibited a significantly higher prevalence of diabetes, leading to elevated $HbA_{1c}$ levels among subjects. Moreover, it has been observed that genetic variations related to vitamin D may contribute to a predisposition for poor glycemic control and the development of type 2 diabetes (21, 22). Nevertheless, several randomized controlled trials (RCTs) have demonstrated that vitamin D supplementation did not enhance insulin release in individuals with prediabetes and those who are otherwise healthy (23, 24). In the current study, a notable negative correlation between $HbA_{1c}$ and vitamin D levels is identified, which is consistent with previously reported findings (22, 25). It is hypothesized that vitamin D may play a role in influencing insulin release, suggesting the importance of regular monitoring and potential supplementation for diabetes patients (25).

Several studies support a higher incidence of CAD in vitamin D-deficient individuals with hyperlipidemia and DM (26, 27). Hypovitaminosis D increases the risk of developing hypertension, coronary artery disease, sudden cardiac death, or cardiac failure (13). Regardless of cardiovascular risk factors, low levels of 25(OH) vitamin D are associated with an increased incidence of CAD (28). In our study, a higher incidence of triple vessel disease was observed in the vitamin D deficient group. Vitamin D had a significant OR of 1.21 (1.03-1.43) for single vessel disease and 0.92 (1.13-1.43) for triple vessel disease. Vitamin D levels were negatively correlated with single vessel and triple vessel disease. Vitamin D levels had no association with double vessel disease in our study; this may be due to small number of double vessel disease in the current study compared to single or triple vessel disease. Mehta *et al* found a negative association between vitamin D deficiency and triple vessel disease (80%), double vessel disease (28.6%) and single vessel disease (21.7%) (29). Morgan *et al* identified a significant inverse correlation between maximal luminal stenosis and 25-OH vitamin D levels (30). An Iranian study noted a negative correlation between the coronary artery calcium score and serum vitamin D level, concluding that vitamin D insufficiency was linked to coronary artery calcification and severity of coronary artery stenosis (31).

Derived from risk assessment categories in various studies and expert consensus, the SYNTAX score was developed as an angiographic tool to assess the complexity of CAD (32). Cerit *et al* found

no association between serum vitamin D levels and the SYNTAX score similar to our study (33). While Mehta *et al* reported a negative correlation between vitamin D levels and SYNTAX scores in their study (29). We found that, on multivariable logistic regression, SYNTAX score had a significant OR of 0.697 (0.557-0.873) for single vessel disease and 1.27 (1.13-1.43) for triple vessel disease.

### Study limitations

This study was conducted in a single centre with a restricted sample size. The fact that only the South Indian population was included may limit the external validity of our findings. However, we have analysed vitamin D levels with angiographic evidence of CAD, which was the major strength of our study. ❑

## CONCLUSION

Patients with vitamin D deficiency had more incidences of diabetes mellitus and high $HbA_{1c}$ levels. Vitamin D deficiency was a risk factor for single and triple vessel disease. Further multicentric studies are warranted in this line. ❑

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