Correlation of vitamin D level and severity of coronary artery disease

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ABSTRACT

Introduction and Aim: Cardiovascular diseases are the leading cause of death worldwide. The prevalence of cardiovascular disease in India is continuously on the rise owing to the socioeconomic changes the country is undergoing. In order to minimise the mortality due to cardiovascular disease, early detection and control of modifiable risk factors is of utmost importance. We evaluated the correlation of vitamin D deficiency, one such possible modifiable risk factor, and the severity of CAD in patients at a hospital in Southern Karnataka. Unfortunately, relevant data regarding vitamin D deficiency in coronary artery disease pertaining to the Indian subcontinent is scarce. Thus, the results of our study can provide further evidence for the potential therapeutic benefit of Vitamin D in patients with cardiovascular risk factors, which in the long run can significantly reduce the morbidity and mortality of CAD.

Materials and Methods: A case-control study with 142 subjects was conducted in Kasturba Hospital. Based on coronary angiogram findings, cases were categorised as having single, double or multi vessel disease. Vitamin D level was quantified into 3 categories: normal (>30ng/ml), insufficient (20-30ng/ml) and deficient (<20ng/ml).

Results: Vitamin D deficiency was statistically significantly and inversely related to the number of vessels involved (multi vessel disease 83.3%, triple vessel disease 80%, double vessel disease 28.6% and single vessel disease 21.7%). The relationship between vitamin D levels and syntax scoring showed a negative correlation (-0.339). Multiple linear regression analysis showed that the severity of CAD was correlated to diabetes and vitamin D deficiency with p-value of 0.014.

Conclusion: Both our results and those of previous studies suggest that vitamin D could have a potential therapeutic effect in CAD.

Keywords: Both our results and those of previous studies suggest that vitamin D could have a potential therapeutic effect in CAD.

Introduction

Cardiovascular diseases are the leading cause of death worldwide. According to World Health Organization (WHO) fact sheet June 2021 update, 17.9 million people died from CVDs in 2019, constituting 32% of all global deaths. The Indian subcontinent constitutes 20% of the world’s population and has the highest incidence of cardiovascular disease (CVD) in the world. The prevalence of cardiovascular disease in India is continuously on the rise owing to the socioeconomic changes the country is undergoing. In order to minimise the mortality due to cardiovascular disease, early detection and control of modifiable risk factors is of utmost importance. According to the findings of our study, vitamin D deficiency is a probable modifiable risk factor for coronary artery disease (CAD). Currently, there is increasing evidence demonstrating that a deficiency of 25-hydroxyvitamin D is associated with a higher risk of cardiovascular morbidity ranging from myocardial infarction, cardiac failure to hypertension and metabolic syndrome. While several studies exist based on the western population, few studies have been done pertaining to the Indian population. The prevalence of vitamin D deficiency (<30ng/ml) is considerable in Southeast Asia and India, substantiating the need for further research in this field.

Vitamin D is postulated to have anti-inflammatory properties, inhibit vascular smooth muscle cell proliferation, regulate glucose metabolism and induce an anti-thrombotic state. Vitamin D deficiency is most commonly due to lack of sun exposure or dietary deficiency. Low vitamin D levels are associated with high levels of inflammatory markers, such as cytokines and interleukins. Vitamin D deficiency is also known to cause electrolyte imbalance and dysregulation of the renin–angiotensin–aldosterone system (RAAS) which can lead abnormalities of the vascular endothelium and eventually hypertension, stroke and CVD.

In our study, we evaluated the prevalence of vitamin D deficiency in CAD as well as the correlation of vitamin D deficiency and the severity of CAD in patients at a tertiary care hospital attached to Medical
College and University in Southern Karnataka. Unfortunately, relevant data regarding vitamin D deficiency in coronary artery disease pertaining to the Indian subcontinent is scarce. Thus, the results of our study provide further evidence for the potential therapeutic benefit of Vitamin D in patients with cardiovascular risk factors, which in the long run can significantly reduce the morbidity and mortality of CAD. Given that this study was conducted at a single centre, there are inherent biases. Multiple centre studies would be highly beneficial in eliminating these biases.

MATERIALS AND METHODS

A case control study with 142 subjects (71 cases and 71 matched controls) was conducted in Kasturba Hospital, a tertiary care centre in Manipal, India for a period of two years. The cases were diagnosed with CAD based on coronary angiogram findings. The study was approved by the Institutional Ethics Committee, Kasturba Medical College, Manipal and written informed consent was taken from each participant in the study. Relevant guidelines and regulations were adhered to while performing the study.

The age of the patients included in the study ranged from 18 to 65 years. Patients who were obese (BMI>30), on vitamin D supplements, known cases of chronic kidney disease, cholestatic liver disease, or a history of small bowel resection were excluded from the study. Additionally, patients on drugs like phenytoin, phenobarbital, carbamazepine, isoniazid and rifampicin were also excluded from the study as these drugs interfere with the absorption of vitamin D.

Detailed history and physical examination were undertaken for each subject. Age, sex, BMI, and blood pressure were documented. Lipid profile was done in the institutional laboratory by standard methods. The cases in the study were patients who were diagnosed with coronary artery disease by coronary angiogram. The angiography findings were categorised into single vessel disease(SVD), double vessel disease(DVD), triple vessel disease(TVD), or multi vessel disease(MVD). Controls had normal ECG and echocardiographic findings.

Serum 25-hydroxyvitamin D (vitamin D) was measured by Electrochemiluminescence immunoassay (ECLIA) in an overnight fasting blood sample of each of the subjects. Serum vitamin D levels were quantified as normal (>30ng/ml), insufficient (20-30ng/ml) or deficient (<20ng/ml) as per API guidelines.

Data analysis and interpretation were done using the SPSS 20 software. Data of normally distributed parameters have been calculated as mean ± standard deviation. Skewed data was presented as median ± standard deviation and was analysed using Mann-Whitney U test. Categorical variables were defined as percentages and analysed using Chi square test.

Syntax score was calculated from coronary angiogram report by using a syntax score calculator. Spearman’s correlation coefficient analysis was used to assess the relationship between vitamin D levels and syntax scoring. Multiple linear regression analysis was performed to identify the significant determinants of the syntax score using vitamin D, diabetes mellitus, hypertension, and dyslipidaemia as the covariates. A p-value of <0.05 was considered as statistically significant.

RESULTS

Baseline characteristics of the study population

The baseline demographic and clinical characteristics of the study population are illustrated in Table 1. Among the 71 cases diagnosed by angiography, 46 (64.7%) had single vessel disease, 14 (19.7%) had double vessel disease, 5 (7.1%) had triple vessel disease, and 6 (8.5%) had multiple vessel disease. Other factors such as mean age, BMI, lipid profile and vitamin D levels were not significantly different between the cases and controls (p values 0.60, 0.30, 0.64 and 0.0229 respectively).

Table 1: Baseline characteristics of cases and controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Cases (n=71)</th>
<th>Controls (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td></td>
<td>54.72±4.8</td>
<td>54.08±4.97</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Male</td>
<td>37 (52.1%)</td>
<td>35 (49.3%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>34 (47.9%)</td>
<td>36 (50.7%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Present</td>
<td>28 (39.4%)</td>
<td>21 (29.6%)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>43 (60.6%)</td>
<td>50 (70.4%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Present</td>
<td>32 (45.1%)</td>
<td>10 (14.1%)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>39 (54.9%)</td>
<td>61 (85.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Present</td>
<td>35 (49.3%)</td>
<td>18 (25.4%)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>36 (50.7%)</td>
<td>53 (74.6%)</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>3 (4.2%)</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>68 (95.8%)</td>
<td>70 (98.6%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>2 (2.8%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>69 (97.2%)</td>
<td>69 (97.2%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>27.8±3.6</td>
<td>25.6±3.3</td>
</tr>
<tr>
<td>Vitamin D (ng/ml)</td>
<td></td>
<td>24±15.18</td>
<td>27±12.14</td>
</tr>
</tbody>
</table>

Results are presented as number of subjects (%) or Mean ±SD; Median ±range (Vitamin D levels)

Vitamin D deficiency in cases and controls

71% cases were found to have low vitamin D levels, which includes vitamin D deficiency and vitamin D insufficiency. Among the cases, 32% had vitamin D deficiency, 39% had vitamin D insufficiency, and 28% had normal vitamin D levels. Among the controls, 16.9% had vitamin D deficiency, 42.25% had vitamin D insufficiency, and 40.84% had normal vitamin D levels. Though there is no statistically significant difference between the vitamin D levels in cases and controls, vitamin D deficiency was found to be more prevalent in cases (32%) and less prevalent in
controls (16.9%). From these results, we can postulate that vitamin D deficiency is more prevalent in people with CAD compared to people without CAD. Vitamin D deficiency may, thus, be considered as an independent risk factor for CAD as shown in Fig. 1.

**Vitamin D and hypertension**

In our study, a total of 65 subjects had hypertension, among them 21 (58.3%) subjects with vitamin D deficiency had hypertension, 27 (48.2%) subjects with vitamin D insufficiency had hypertension, and 17 (34%) subjects with normal vitamin D levels had hypertension. There is no statistically significant correlation between vitamin D deficiency and hypertension (p value: 0.074).

**Vitamin D and diabetes mellitus**

In our study, a total of 63 subjects had diabetes, among them 20 (55.6%) subjects with vitamin D deficiency had diabetes mellitus, 22 (39.3%) subjects with vitamin D insufficiency had diabetes mellitus, and 21 (42%) subjects with normal vitamin D levels had diabetes mellitus. No statistically significant relation exists between vitamin D and diabetes mellitus (p value: 0.283).

**Vitamin D and lipid profile**

Fasting lipid profiles were analysed in both cases and controls and a total of 49 subjects were found to have dyslipidaemia. 12 (33.3%) subjects with vitamin D deficiency had dyslipidaemia, 24 (42.8%) subjects with vitamin D insufficiency had dyslipidaemia, and 13 (26%) subjects with normal vitamin D levels had dyslipidaemia. Analysis showed that no statistically significant relationship exists between vitamin D levels and dyslipidaemia (p value: 0.187).

**Vitamin D deficiency and coronary angiography categories**

As shown in Table 2, a statistically significant relationship was found to exist between coronary angiography categories and vitamin D levels with a p value < 0.001.

**Syntax scoring and vitamin D levels**

Bivariate analysis done by scatter plot (to correlate of vitamin D levels with severity of coronary artery disease with syntax scoring) shows that there is a negative correlation with a strength of -0.339. This is shown in Fig. 2.

![Fig. 1: Vitamin D levels in cases and controls. Vitamin D levels are represented in ng/ml](image1)

### Table 2: Relationship between vitamin D deficiency and coronary angiography categories

<table>
<thead>
<tr>
<th>Variable</th>
<th>MVD</th>
<th>TVD</th>
<th>DVD</th>
<th>SVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>6 (8.5%)</td>
<td>5 (7.1%)</td>
<td>14 (19.7%)</td>
<td>46 (64.7%)</td>
</tr>
<tr>
<td>Vitamin D Deficiency</td>
<td>5 (83.3%)</td>
<td>4 (80.0%)</td>
<td>4 (28.6%)</td>
<td>10 (21.7%)</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>1 (16.7%)</td>
<td>1 (20.0%)</td>
<td>3 (21.4%)</td>
<td>24 (52.2%)</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
<td>7 (50.0%)</td>
<td>12 (26.1%)</td>
</tr>
</tbody>
</table>

Results are presented as number of subjects (%)

![Fig. 2: Correlation between vitamin D levels and syntax score](image2)
Several variables were taken into consideration including 25(OH)D, T2DM, hypertension, and dyslipidaemia. This analysis revealed that 25(OH)D levels were significantly associated (p=0.014) and negatively correlated with.syntax scoring with Pearson correlation of -0.261 (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>-0.19</td>
<td>0.014</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.36</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>-0.115</td>
<td>0.217</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Currently, there is increasing evidence demonstrating that a deficiency of 25-hydroxyvitamin D is associated with a higher risk of cardiovascular morbidity ranging from myocardial infarction, cardiac failure, hypertension and metabolic syndrome (8). The current challenge is identifying the possible mechanisms that initiate and aggravate the development of atheromatous plaques, including the potential role of vitamin D deficiency (9). Cardiac myocytes and fibroblasts express VDR and CYP27B1. It has been identified that 1,2(OH)2D suppresses markers of cardiac hypertrophy, and deletion of the VDR specifically from the heart results in hypertrophy (10).

In southern India, although the prevalence of CAD is high, there is a paucity of studies establishing the relationship of vitamin D deficiency with CAD. Further, not many studies showed a significant relationship between vitamin D levels and CAD. Hence, we conducted this study to obtain additional data in this area, which will play an integral role in the development of a potential therapy for CAD. We have described the relationship between vitamin D and several factors.

The significance of the relationship between age and vitamin D levels is controversial. One study showed that there was no significant heterogeneity observed between age group and vitamin D deficiency (11). On the other hand, Raina et al., demonstrated that vitamin D levels decreased with age (12). However, Nair et al., found that children and young- and middle-aged adults are at equally high risk for vitamin D deficiency and insufficiency worldwide (13). In our study, vitamin D deficiency was more prevalent in adults between 40 and 60 years of age. This may be attributed more time spent indoors, decreased physical activity and the small sample size.

The effect of gender on vitamin D is still not fully understood. One study showed that the Vitamin D levels were lower in females compared to males(14). However, a study conducted by Hagenau et al., showed that the differences by gender were more significant in the infant age group as compared to an older age group (15). Furthermore, in a study conducted by Liew et al., results showed no discernible difference in 25(OH)D levels between genders(5). In our study, 31.9% females and 19.7% males were found to have vitamin D deficiency, which is possibly due to the greater time spent by women indoors.

The prevalence of vitamin D deficiency appears to be higher in those with diabetes mellitus compared to those without as described by a study by Karur et al., (11). In our study, 55.5% of vitamin D deficient subjects had diabetes mellitus, 39.28% of vitamin D deficient subjects had diabetes mellitus, 42% of normal vitamin D level subjects had diabetes mellitus. Although there is no statistically significant correlation between vitamin D deficiency and diabetes mellitus (p value = 0.283), an increased frequency of vitamin D deficiency was observed in the subjects with diabetes mellitus. This can be explained by the pre-existing association between diabetes mellitus and vitamin D (vitamin D deficiency reduces insulin secretion; 16).

Hypertension has been known to be associated with vitamin D deficiency. Kota et al., demonstrated that systolic blood pressure, diastolic blood pressure, and mean arterial pressure was higher among cases of vitamin D deficiency, which was postulated to be due to the relationship between vitamin D deficiency and the renin-angiotensin-aldosterone system (RAAS; 17). Other studies demonstrated that there is an increased risk for CAD in vitamin D deficient patients with associated hypertension(18). In our study, 58.3% of vitamin D deficient subjects had hypertension, 48.2% of vitamin D insufficient subjects had hypertension and 34% with normal vitamin D levels had vitamin D deficiency. Though there is no statistically significant relationship between vitamin D and hypertension (p value=0.074), the prevalence of hypertension is more in vitamin D deficiency group. This can be attributed to the already established relationship between vitamin D and RAAS.

Dyslipidaemia is another factor that has been associated with vitamin D deficiency. In a cohort of 3788 subjects, Jiang et al., found that serum 25(OH)D is an inversely relationship with LDL cholesterol and triglycerides levels, and direct relationship with HDL cholesterol levels(19). In our study, 33.33% of the vitamin D deficient subjects had dyslipidaemia, 42.8% of the vitamin D insufficient subjects had dyslipidaemia, and 26% of the subjects with normal vitamin D levels had dyslipidaemia. Analysis showed that there is no significant correlation between vitamin D deficiency and dyslipidaemia (p value-0.187), probably due to the small sample size.

**Notes:**

1. Pearson correlation of
2. | Significance of each variable with syntax score
3. Table 3: | Variable | Beta value | P value |
4. | Vitamin D | -0.19 | 0.014 |
5. | Diabetes mellitus | 0.36 | 0.001 |
6. | Hypertension | 0.15 | 0.14 |
7. | Dyslipidaemia | -0.115 | 0.217 |

**DOI:** https://doi.org/10.51248/v42i5.1911
Our main aim was to study the relationship between vitamin D deficiency and CAD. The vitamin D levels in the cases demonstrated a skewed distribution with a median of 24 and a range of 15.18, while the vitamin D levels of the controls had a median of 27 and a range of 10.14. Analysis revealed that there is no statistically significant relationship between the case and control groups with a p value of 0.229. The small sample size, severity of Vitamin D deficiency in the cases and varying levels of vitamin D levels in the Indian population may attribute to the skewed distribution.

However, from our results, vitamin D deficiency was more prevalent in the case group (32%) in comparison with the control group (16.9%). Furthermore, 71% of the cases had low vitamin D levels (which includes vitamin D deficiency and insufficiency). This finding suggests that vitamin D may be considered as an independent risk factor for CAD.

Several studies demonstrated that majority of the patients with myocardial infarctions were found to have vitamin D deficiency or insufficiency (11, 20). Furthermore, in a study by Liew et al., on a sample of 275 patients, vitamin D mean in patients with CAD was 57.0 ± 1.73 versus 70.1 ± 2.46 nmol/L in patients without CAD (p < 0.01) (5). In a study conducted by Syal et al., on the Indian population, out of 100 patients undergoing CAG, 80% were found to have vitamin D deficiency and only 7% had normal vitamin D levels (21). Similarly, Verdoia et al., demonstrated that the mean vitamin D level was 14.8 ± 9.1 ng/mL and the prevalence of vitamin D deficiency and CAD were significantly related (22). In multivariate analysis of the Framingham offspring study, it was found that the risk of cardiovascular events like acute myocardial infarction (AMI), heart failure, and angina was 1.62 times higher in patients with vitamin D levels <15 ng/mL (<37.5 nmol/L) when compared to those with levels ≥15 ng/mL (8). All these above studies further strengthen the possibility of vitamin D being an independent risk factor for CAD.

Based on the coronary angiogram findings, the disease was categorized into Single vessel disease(SVD), Double vessel disease(DVD), Triple vessel disease(TVD) and Multi vessel disease(MVD). Amongst these categories, vitamin D deficiency was found to be more prevalent in TVD/MVD as compared to DVD/SVD.

The relationship between vitamin D deficiency and Syntax score was first described by Chen et al., In a multivariate linear regression analysis, he found that vitamin D levels showed a negative correlation with syntax score (23). Our study also revealed that a statistically significant relationship existed between number of vessels involved and serum vitamin D levels (p value < 0.001).

Results similar to ours were seen in several studies. First, Baktir et al., found a significantly lower vitamin D level in the high syntax scoring group compared to the low syntax scoring group (21+8 vs. 16.7+6.8). A multiple linear regression analysis confirmed this relationship (coefficient beta: −0.217, p=0.029) (2). Second, Liew et al., demonstrated significantly lower vitamin D levels in TVD patients when compared to SVD patients (50.6 ± 2.84 nmol/L vs 61.3 ± 3.16, p=0.01) and DVD patients (50.6 ± 2.84 vs 59.0 ± 2.99 nmol/L, p= 0.07) using a one-way ANOVA test (5). Third, in a study conducted by Sogomonian et al., the percentage of coronary artery occlusion was found to have an inverse relationship with vitamin D levels (7).

On the other hand, Raina et al. demonstrated that there was no statistically significant relation between the disease severity and vitamin D level (12). Our study revealed that 25(OH)D levels (p=0.014) were significantly associated with severity of the Syntax score, and were negatively correlated with syntax scoring with Pearson correlation of -0.261.

The limitations of our study include the small sample size and the fact that it is a single centre study. Several confounding factors including season were not taken into account. Nevertheless, our findings can be a stepping stone in the development of a potentially modifiable risk factor for CAD. In addition, vitamin D levels can be used for risk stratification. These benefits can greatly reduce the morbidity and mortality associated with CAD, especially in the Indian subcontinent, where the prevalence of CAD is very high.

CONCLUSION

In our study, vitamin D deficiency was found in 71% of the cases with CAD and had a direct relationship with the severity of the disease (number of vessels involved). Vitamin D deficiency was found to be more prevalent in MVD/TVD, and less prevalent in DVD/SVD. Bivariate analysis between Syntax scoring and vitamin D showed that a negative correlation exists between them, with a weak strength of correlation. Multiple linear regression analysis revealed vitamin D as an independent risk factor for CAD (p=0.01). This relationship could be the basis for the potential therapeutic benefit of Vitamin D in patients with CAD, particularly pertaining to the South Indian population.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES


DOI: https://doi.org/10.51248/v42i5.1911