Prospective study of hypovitaminosis D in acute coronary syndrome

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Abstract

Background: Hypovitaminosis D has emerged as one of risk factors in coronary atherosclerosis either independently or in association with other factors though the causal relationship is not established. Aims: We aimed at finding out the prevalence of vitamin D deficiency in patients with acute coronary syndrome and to study if any association exists between them. Methods: This was a prospective study carried out on 50 hospitalized patients from urban habitations with acute coronary syndrome at Dr. D Y Patil Medical College, hospital Pune (India) during Oct 2012 to Sept 2013. The vitamin D status and other risk factors were studied in these cases and compared with normal control group having 50 subjects without any co-morbidity. Results: 58 % males showed hypovitaminosis D. Vitamin D levels were significantly low (OR3. [8;0.97-15.21];95%CI) in cases with hypertension (65.79%) and 60.53% cases with diabetes mellitus (OR4.6[1.02-19.8] 95%CI). BMI more (Mean 26.9 ± SD 4.95) in cases with low vitamin D levels; but weakly significant (p=0.061). Postprandial hyperglycemia and hypercholesterolemia were inversely associated with vitamin D levels. Acute coronary syndrome had weakly significant association (p=0.093) with hypovitaminosis D in our patients. Conclusion: Vitamin D deficiency was weakly associated with acute coronary syndrome.

Keywords: Acute coronary syndrome, Hypovitaminosis D, Prevalence, Vitamin D deficiency.

INTRODUCTION

Reports from across the world indicate that hypovitaminosis D is widespread and is re-emerging as a major health problem globally [10]. The prevalence of Vitamin D deficiency in urban population is reported from 62-90 % in various ages in India [12].

Vitamin D deficiency has been linked to an increased risk of coronary artery disease (CAD) and cardiovascular (CV) death. Endothelial dysfunction plays an important role in pathogenesis of CAD and vitamin D deficiency is postulated to promote endothelial dysfunction [3].

Despite rising trends of CAD in Asians, only limited data are available on the relationship between vitamin D, CAD, and endothelial dysfunction. Indian patients with angiographic ally documented CAD frequently have vitamin D deficiency. Patients with lower 25(OH) D levels had higher prevalence of double- or triple-vessel CAD and diffuse CAD. Endothelial dysfunction as assessed by brachial artery FMD was also more frequently observed in those with low 25(OH) D levels [4].

Aims & Objectives

The present study was carried out to assess the prevalence of hypovitaminosis D in patients with acute coronary syndrome and association on between vitamin D deficiency and Acute Coronary Syndrome (ACS).

MATERIAL & METHODS

Total 50 cases were studied in a tertiary care hospital and Medical College in Western Maharashtra. All adult age >18 years admitted for acute coronary syndrome were eligible for this study. Patients were grouped according to their 25(OH) D levels within the total number of ACS cases and control subjects. The ACS group was studied as TnT positive and negative subpopulations as appropriate. The groups studied were those with vitamin D levels < or > 20 ng/Ml linked to presence of myocardial infarction and ischemia. ACS was identified on the basis of typical history of angina, ECG changes with or without elevated cardiac enzymes. Patients with history or presence of any of following were excluded from this study.
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- Chronic kidney disease (Creatinine ≥ 2mg/dl)
- Valvular Heart Diseases, Congenital Heart Diseases
- Liver Cirrhosis, Alcoholic Liver Disease
- Calcium and Vit D supplementation, use of corticosteroids, rifampicin
- Abnormal calcium levels (Normal reference range – 9 to 11 mg/dl)
- Pregnancy /Lactation

Control group had 50 age, sex matched normal subjects either relatives of patients or attendants without any co-morbidities.

All Patients underwent thorough history included time of onset of typical chest pain, nature of pain, increasing with exertion and associated symptoms like excessive sweating, breathlessness. History of smoking, Alcohol consumption, hypertension, diabetes mellitus and family history of IHD was recorded. A thorough clinical examination was carried out in each case with special reference to pulse, blood pressure, cardiovascular and respiratory examination for the presence of murmur, crepitations, S3 gallop.

During hospitalization, complete blood count, urine, fasting & post prandial blood glucose, blood urea, serum creatinine, liver function tests, chest x-ray, ECG, CPK MB, Troponin-T (TnT) and 2D echo were done. Venous blood sample sent for vitamin D2 estimation by radioimmunoassay. Hypovitaminosis D was defined as < 20 ng/ml.

Statistical Analysis

The statistical software primer of biostatistics version 6 was used to calculate p values. Chi square test and t test were used to determine the significance level among two groups.

RESULTS

The comparison of parameters showing age, sex between patients with hypovitaminosis and normal group did not reveal significant observation. Mean age was 55.67 years with Vitamin D level with ≥20ng/ml and 57.34 with Vitamin D level with <20ng/ml. 58 % males showed hypovitaminosis D. Vitamin D levels were low in cases suffering from hypertension (65.79%) and diabetes mellitus (60.53%), but the significance was weak. The risk factors for ACS and relation with vitamin D levels is depicted in table-1.

High postprandial blood sugar (Mean 172.87±SD 47) showed significantly less vitamin D levels (p=0.029) in our patients. High serum total cholesterol (Mean188.58±SD30.38) and triglyceride (Mean 188.58±SD30.38) were significantly associated (p=0.007 & < 0.001) with low serum vitamin D levels in study group (Table 2).

Acute coronary syndrome and Hypovitaminosis D did not have significant association in our patients (table-3).

Table 1: Showing risk factors in ACS group and vitamin D levels

<table>
<thead>
<tr>
<th>Risk factors for ACS</th>
<th>Vitamin D Levels</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20ng/ml</td>
<td>≥20ng/ml</td>
</tr>
<tr>
<td></td>
<td>n=38</td>
<td>n=12</td>
</tr>
<tr>
<td>Hypertension OR3.8(0.97-15.21) 95%CI</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>Diabetes Mellitus OR4.6(1.02-19.8) 95%CI</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Tobacco chewing</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Family history</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Body Mass Index(BMI)&gt;30</td>
<td>16</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2: Showing relation of various parameters in acute coronary syndrome and Vitamin D levels and control subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ACS group</th>
<th>Control group</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Vitamin D status</td>
<td></td>
<td>Vitamin D status</td>
</tr>
<tr>
<td></td>
<td>&lt;20ng/ml n=38</td>
<td>≥20ng/ml n=12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (Yrs)</td>
<td>57.3</td>
<td>10.4</td>
<td>55.7</td>
</tr>
<tr>
<td>BG(F)(mg/dl)</td>
<td>137.2</td>
<td>44.8</td>
<td>114.6</td>
</tr>
<tr>
<td>BG (PP)(mg/dl)</td>
<td>172.8</td>
<td>47.1</td>
<td>141.3</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>188.5</td>
<td>30.4</td>
<td>161.2</td>
</tr>
<tr>
<td>HDL-C(mg/dl)</td>
<td>52.5</td>
<td>12.6</td>
<td>48.7</td>
</tr>
<tr>
<td>LDL-C(mg/dl)</td>
<td>132.5</td>
<td>25.1</td>
<td>118.5</td>
</tr>
<tr>
<td>Triglycerides(mg/dl)</td>
<td>188.5</td>
<td>30.4</td>
<td>122.3</td>
</tr>
</tbody>
</table>
DISCUSSION
Vitamin D levels were low in cases with hypertension and diabetes mellitus. BMI was higher in cases with low vitamin D levels in our study. However, the strength of significance was weak.

It is suggested that the possible correlation between low vitamin D and cardiac events is due to metabolic, procoagulant and inflammatory changes and is not independently related to premature myocardial infarction. This suggests that hypovitaminosis D either is an epiphenomenon or increases the risk of ACS by promoting established risk factor mechanisms that predispose to atherothrombosis. Hypovitaminosis D in our study, vitamin D deficiency being common in patients with T2DM, has been shown to be associated with endothelial dysfunction and subclinical atherosclerosis.

Another possible explanation for such correlation has been suggested to be due to a strong association between low vitamin D levels and the slow coronary flow phenomenon. In addition, this has been shown to be associated with atherothrombosis. In a meta-analysis of 18 RCTs of over 57,000 participants, the summary relative risk for all-cause mortality was reduced by 7% with vitamin D therapy. Another meta-analysis of eight RCTs showed a statistically non-significant reduction in CVD risk. Hence the association between vitamin D deficiency and ACS is controversial.

Vitamin D levels were also low in cases suffering from hypertension and diabetes mellitus. BMI was high in cases with low vitamin D levels in our study. However, age sex matched controls also presented with hypovitaminosis D in our study, vitamin D deficiency being common in normal population in India.

Vitamin D and diabetes has been studied in 2 cohort studies earlier. Knekt P et al (2008) investigated the relation of serum vitamin D with type 2 diabetes incidence using pooled data from these 2 cohorts. Authors have concluded that the results support the hypothesis that high vitamin D status provides protection against type 2 diabetes.

BMI was significantly more in cases with low vitamin D levels in a study conducted in 2008. Giovannucci E et al assessed prospectively whether plasma 25-hydroxyvitamin D (25(OH)D) concentrations are associated with risk of coronary heart disease. Body mass index, alcohol consumption and physical activity were significantly associated with vitamin D levels.

Our study showed hypovitaminosis in patients with fasting as well as post prandial hyperglycemia and the postprandial values were significantly associated with vitamin D deficiency. In 2011, Thorand B, et al. studied the association between serum 25-hydroxyvitamin D (25(OH)D) and incident type 2 diabetes showed significant inverse association was observed between serum 25-OHD and incidence of type-2 diabetes after adjustment for diabetes risk factors and season. Authors concluded that Vitamin D status is inversely related to type 2 diabetes risk and our data suggest that this association may be partially mediated by subclinical inflammation. Our study revealed that hypovitaminosis D is associated with hyperglycemia, significantly so with post prandial than fasting.

In 2001; the relation between serum level of 25-hydroxyvitamin D3 and IHD in a case-control study involving 143 patients with either angiographic evidence of coronary artery disease or patients with acute myocardial infarction was explored. Serum levels of 25-hydroxyvitamin D3, calcium, inorganic phosphate, total cholesterol, low density lipoprotein and triglycerides were elevated in a higher proportion of patients compared to controls. Their study showed serum levels of 25-OH-D3 >222.5 nmol/l in 59.4% of cases compared to 22.1% in controls (p < 0.001). Similarly, prevalence of vitamin D deficiency in patients with T2DM with/without CVD, to correlate it with anthropometric and metabolic parameters and to determine the predictors of vitamin D deficiency was studied in 2013. Severe vitamin D deficiency was noted in 16.1% healthy subjects, in 21.6% patients with T2DM and in 26.9% patients with T2DM and CHD. Patients with T2DM who were vitamin D deficient had increased weight, waist circumference, cholesterol, triglyceride levels when compared with patients with T2DM who had sufficient vitamin D level. 25(OH)D levels correlated with BMI and waist circumference in all subjects, but did not correlate with metabolic parameters (lipids, HbA1c). Body weight, waist circumference and BMI were the best predictors of vitamin D level in their study.

Vitamin D could impact glycemic control in terms of the inverse relation of vitamin D with HbA1C%, and at the same time poor glycemic control could impact vitamin D status in uncontrolled diabetic patients.

We found that diabetes was seen in higher number of cases (60.53%) who had vitamin D deficiency state, which was similar to Wang TJ et al in 2008. The risk of cardiovascular disease in relation to vitamin deficiency was studied by them. The study showed graded increase in cardiovascular risk across categories of 25-OH D, with multivariable-adjusted hazard ratios of 1.53 (95% CI: 1.00 to 2.36) for levels 10 to <20 ng/ml and 1.80 (95% CI: 1.05 to 3.08) for levels <10 ng/ml. Our study showed hyperlipidaemia; particularly total cholesterol and triglycerides) was associated with hypovitaminosis D. In a recent report from Indian subjects, low levels of 25-hydroxyvitamin D were independently associated with dyslipidemia. Hence 25-hydroxyvitamin D deficiency endangers this population for an early onset of cardiovascular and cerebrovascular diseases. Although this association is emerging clearly, studies on the effect of vitamin D supplementation on reducing dyslipidemia are contradictory and unclear. Zahra et al measured 25 (OH) D serum levels in 57 patients that were diagnosed with coronary artery disease in 2012. Authors concluded that low levels of 25 (OH) D are associated with prevalent coronary artery disease independent of other cardiovascular risk factors.

Table 3: Showing association between type of ACS and vitamin D levels

<table>
<thead>
<tr>
<th>ACS TYPE</th>
<th>Vitamin D level, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;20ng/ml</td>
<td>≥20ng/ml</td>
</tr>
<tr>
<td>Infarction (OR 0.25, [0.7-0.99] 95%CI)</td>
<td>10 (59%)</td>
<td>7 (41%)</td>
</tr>
<tr>
<td>Ischemia</td>
<td>28 (88%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>12</td>
</tr>
</tbody>
</table>

Chi Sq 2.862, df=1, p =0.091
Lee et al. [17] assessed 25 (OH)D levels in 239 patients in a multicenter prospective study and found a high (96%) prevalence of vitamin D deficiency in patients with acute myocardial infarction.

Another study in published 2014, authors found that out of the 314 enrolled patients, 212 (67.5%) were 25(OH) D deficient and 50(16%) were insufficient, for a total of 83.5% of patients with abnormally low 25(OH) D levels. They did not have significant heterogeneity among age or gender sub groups but 25 (OH) D deficiencies was more frequently seen in those with lower socioeconomic status, lower activity levels, presence of diabetes, hypercholesterolemia (LDL), hypertriglyceridemia and in smokers. Roy A et al. (2015) reported that severe vitamin D deficiency is associated with risk of acute MI even after adjusting for the known risk factors of acute MI [19].

In the Khalili et al. [20], reported a significant inverse relationship between serum levels of matrix metalloproteinase-9 evaluated 72 hours after hospital admission, and vitamin D. The authors also reported a possible correlation between hypovitaminosis D and increased mortality.

In their study, Ross A et al. [21] have investigated the significance of vitamin D levels <16ng/mL in relation to outcome. Below 16 ng/mL vitamin D behaved as an independent predictor for total death both in the univariate and multivariable analysis. As vitamin D deficiency was found to be an independent risk factor at levels below 16ng/mL.

Strengths and Limitations
In comparison to previous observational studies we enrolled subjects with and without myocardial infarction. We did not correct vitamin D levels for parathyroid hormone (PTH), but we do not regard this to be of great importance, as previous data would indicate that only very low values of vitamin D will influence the level of PTH [22]. As this is an observational study, unknown confounders are likely to be missed.

CONCLUSION
Our study revealed that Hypovitaminosis D is patients with acute coronary syndrome as well as normal population is commonly seen and is associated in a weakly significant manner. However, the prevalence of vitamin D deficiency in study groups is subject to type 2 error due to sample size. It is concluded that our patients with Hypovitaminosis D did not have statistically significant risk acute coronary syndrome either in association with other risk factors or independently. Our patients within ACS group with low vitamin D levels did not have significant difference in presentation as ischemia or infarction of myocardium.

Conflict of interest
Authors declare that there is no conflict of interest in undertaking this study and the study is un funded.

Authors’ Contribution
AAB -Concept and Design, Final approval
BV -Review of manuscript
SVD & VSR -Collection and compilation of data, literature search
SAB -Quality control of laboratory services.

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