Original Research Article

To evaluate the role of plasma vitamin D level as a prognostic marker and its relation to in-hospital complications in patients with acute coronary syndrome

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ABSTRACT

Background: Deficiency in 25-hydroxyvitamin D (25[OH] D), the main circulating form of vitamin D in blood, could be involved in the pathogenesis of acute coronary syndromes (ACS). To date, however, the possible prognostic relevance of 25 (OH) D deficiency in ACS patients remains poorly defined. The purpose of this study was to assess the association between 25 (OH) D levels, at hospital admission, with in-hospital complications in an unselected cohort of ACS patients.

Methods: We measured 25 (OH) D in 200 ACS patients at hospital presentation. Vitamin D serum levels >30 ng/mL were considered as normal; levels between 29 and 21 ng/mL were classified as insufficiency, and levels <20 ng/mL as deficiency. In-hospital complications were evaluated according to 25 (OH) D levels.

Results: In the study population 85 (42.5%) patients had normal 25 (OH) D levels, whereas 36 (18%) and 79 (39.5%) had vitamin D insufficiency and deficiency, respectively. The patients with vitamin D deficiency were associated with a higher risk for several in-hospital MACEs (major adverse clinical events) including mortality and it was statistically significant (P value < 0.05). The left ventricular function was more severely compromised in patients with vitamin D deficiency and it was statistically significant (P value < 0.05).

Conclusions: In ACS patients, severe vitamin D deficiency is independently associated with poor in-hospital outcomes. Whether low vitamin D levels represent a risk marker or a risk factor in ACS remains to be elucidated.

Keywords: Acute coronary syndrome, Risk factor, Vitamin D

INTRODUCTION

Beyond its fundamental role in bone metabolism and calcium homeostasis, vitamin D may influence several other medical conditions, including cardiovascular disease. Indeed, vitamin D receptors have been found in the myocardium as well as in vascular cells, and hypovitaminosis D, a common finding in many industrialized countries, has been independently associated with increased risk of developing acute myocardial infarction and heart failure.1,2 Moreover, vitamin D deficiency has been linked to conditions, such as hypertension, diabetes mellitus, metabolic syndrome, cardiac hypertrophy, and chronic kidney disease, that predispose to cardiovascular disease.3,4,5 More importantly, in heart failure patients, vitamin D supplementation has been shown to be associated with improved survival.6 Several studies have also demonstrated a survival benefit in end-stage renal disease patients treated with vitamin D, primarily related to a reduction in cardiovascular death.7 Thus, vitamin D seems to play an important role in cardiac function and in the development and progression of cardiovascular disease.
of coronary artery disease. Deficiency of vitamin D, or of 25-hydroxyvitamin D (25[OH] D), its main circulating form in the blood, has been recently reported to be common in patients with acute coronary syndromes (ACS), and preliminary studies indicate a possible association with prognosis.10

Very few studies, however, have investigated the association between vitamin D levels and clinical outcomes in ACS patients thus far.11,13 Therefore, convincing data demonstrating the possible impact of vitamin D insufficiency, or deficiency, on morbidity and mortality of ACS patients are still lacking. Notably, vitamin D has been demonstrated to suppress the renin-angiotensin system and to affect endothelial function, inflammatory processes, platelet function, insulin resistance, and blood pressure.3,14,16 All these effects are relevant during ACS, and related to patients’ clinical course. Moreover, low levels of vitamin D have been associated with ventricular dysfunction and cardiac remodeling after ACS, and with heart failure mortality and sudden cardiac death.11,17 Thus, both the short- and long-term outcomes of ACS patients could be significantly affected by vitamin D status.

The purpose of this study was to determine the clinical implications of 25 (OH) D levels in an unselected cohort of ACS patients at hospital admission, and their possible association with in-hospital morbidity and mortality. The present study was undertaken to observe plasma vitamin D level in patients with acute coronary syndrome. And to evaluate the role of plasma vitamin D level as a prognostic marker and its relation to In-hospital complications in patients with acute coronary syndrome.

METHODS

This was an observational study. All consecutive ACS patients, including both ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) patients, admitted to the Intensive Cardiac Care Unit of Cardiology department, MLN Medical College, Allahabad, Uttar Pradesh, India between January 2015 to December 2015 were included in the study.

230 patients admitted with acute coronary syndrome were selected for the study. Out of this 200 were selected after exclusion. Patients with renal or hepatic disease, malignancy, those on phenytoin or other medications that can affect vitamin D level, and patients who refused or unable to give consent, as well as those with missed vitamin D level were excluded. 100 age and sex matched control subjects were selected from patients in other wards matched in every possible aspect except for the disease under study. The local ethical committee approved the research.

A written informed consent was taken. Baseline clinical characteristics including socio-demographic data, diabetes mellitus, hypertension, history of coronary syndrome, family history of coronary artery disease, and smoking history were obtained. The diagnosis of acute coronary syndrome was based on history, raised level of cardiac enzymes, and electrocardiographic (ECG) changes. Blood samples were collected for admission plasma sugar, HbA1c, liver and renal function tests, serum electrolytes including calcium and magnesium and high sensitive CRP. Lipid profile was measured after 12 hours fast. The estimated glomerular filtration rate was calculated according to the Modification of Diet in Renal Disease (MDRD) formula.18 The left ventricular ejection fraction (LVEF; echocardiogram) was measured in all patients within 24 hours from hospital admission.

In all patients a venous blood sample (3.5ml) was drawn at hospital admission and biological measurement of 25 (OH) D was done in all enrolled patients. Architect 25-OH vitamin D assay (Abbott Diagnostics, Wiesbaden, Germany), with a limit of detection of 7ng/ml, was used for serum 25 (OH) D measurement. According to published data, and to the US Endocrine Society guideline recommendations, we used the following cut-off values for classifying vitamin D status: >30ng/mL were considered normal vitamin D levels; between 29 and 21 ng/mL were classified as vitamin D insufficiency, and<20 ng/mL as vitamin D deficiency.19 All patients received standard medical treatment and coronary revascularization on the basis of the current standards of care recommended by published guidelines.

The primary end point of the study was death of patient during hospitalization. In-hospital major adverse clinical events (MACEs) (major bleeding (requiring blood transfusion), acute pulmonary edema (with or without the need for mechanical ventilation), cardiogenic shock, clinically significant tachyarrhythmias (ventricular fibrillation, sustained ventricular tachycardia, and atrial fibrillation) and bradyarrhythmias requiring pacemaker implantation, and acute kidney injury) were evaluated as secondary end points.

In this study the chi square test (χ² test) for independent samples was used for data analysis, with data presented as mean±SD unless otherwise specified. Pearson’s correlation was applied and P-value <0.05 considered significant.

RESULTS

Patient characteristics

A total of 200 Acute coronary syndrome patients were studied. Table 1 shows baseline clinical characteristics of acute coronary syndrome patients. Mean age was 61±12 years. There were 143 (71.5%) males and 57 (28.5%) females. In the study group 136 (68%) patients had STEMI and 64 (32%) patients had NSTEMI. Out of them, 85 (42.5%) patients had normal 25 (OH) D levels at hospital admission, whereas 79 (39.5%) and 36 (18%)
had vitamin D insufficiency and deficiency, respectively. No difference in this proportion was observed between STEMI and NSTEMI patients. Table 2 shows risk factors for acute coronary syndrome.

**Table 1: Baseline clinical characteristics of acute coronary syndrome patients (n = 200).**

<table>
<thead>
<tr>
<th>Character</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range (years)</td>
<td></td>
</tr>
<tr>
<td>21-40</td>
<td>45 (22.5%)</td>
</tr>
<tr>
<td>41-60</td>
<td>94 (47%)</td>
</tr>
<tr>
<td>61-80</td>
<td>61 (30.5%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>143 (71.5%)</td>
</tr>
<tr>
<td>Females</td>
<td>57 (28.5%)</td>
</tr>
<tr>
<td>Type of MI</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>136 (68%)</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>64 (32%)</td>
</tr>
</tbody>
</table>

In this study smoking was the most common single risk factor for ACS and it was present in 34 (17%) patients. 44(22%) patients had multiple risk factors while 32(16%) patients had no known risk factor for ACS. Table 3 shows that vitamin D deficiency was present in 39.5% of patients as compared to 26% in control population and insufficient vitamin D levels were present in 18% of patients as compare to 11% in control population.

**Association between vitamin D and in-hospital outcomes**

Table 4 shows that the overall in-hospital mortality in all study patients was 14.5% (n = 29). The patients with vitamin D deficiency were associated with a higher risk for several in-hospital MACEs, including mortality and it was statistically significant (P value < 0.05). Table 5 shows that left ventricular function was more severely compromised in patients with vitamin D deficiency and it was statistically significant (P value < 0.05).

**Table 2: Coronary risk factors among the study group (n = 200).**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>15 (7.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (15%)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>26 (13%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>34 (17%)</td>
</tr>
<tr>
<td>Obesity</td>
<td>19 (9.5%)</td>
</tr>
<tr>
<td>Two or more risk factors</td>
<td>44 (22%)</td>
</tr>
<tr>
<td>None</td>
<td>32 (16%)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Coronary heart disease is a leading cause of mortality and morbidity worldwide and elderly people are at special risk. Vitamin D deficiency is not uncommon, and it is associated with cardiovascular risk. The present study, aimed at investigating the role of vitamin D in a consecutive, non-selected cohort of ACS patients,
demonstrated an independent association between its severe deficiency and in-hospital clinical outcomes. Multiple lines of evidence suggest a link between vitamin D and cardiovascular disease. Epidemiological studies reported that the rates of coronary artery disease, diabetes, hypertension, as well as of vitamin D deficiency, increase in proportion to increasing distance from the equator.\textsuperscript{20} Cardiac death has also been reported to be at its highest during periods of decreased sunlight exposure (i.e., winter months).\textsuperscript{21} Moreover, observational studies, small clinical trials, and meta-analyses indicate that vitamin D therapy may reduce cardiovascular events and mortality.\textsuperscript{4,22,23} Although these data from apparent healthy subjects support a role of vitamin D deficiency as a new potential cardiovascular risk factor, there is still paucity of information regarding the implications of vitamin D deficiency in ACS and its possible association, or causal relationship, with morbidity and mortality. Clinical interest derives from the fact that vitamin D deficiency can be readily determined by blood testing and treated by supplementation. In particular, a single oral ultra-high dose of vitamin D has been shown to restore normal 25 (OH) D levels within 2 days in critically ill patients, without causing adverse effects, thus providing the basis of an easy-to-administer dosing regimen for prospective intervention trials in acute cardiovascular settings.\textsuperscript{24}  

In another study, Correia et al reported a possible independent association between vitamin D deficiency and in-hospital cardiovascular mortality.\textsuperscript{12} Again, in this study the sample size was relatively small (n=206), STEMI patients were underrepresented (7% of all patients), and deaths for complications occurring after bypass surgery were also considered. Therefore, no definite conclusion can be drawn at this time on in-hospital clinical relevance of vitamin D deficiency. Thus far, the largest study evaluating vitamin D and prognosis in ACS patients was that by Ng et al.\textsuperscript{13} They found an association between the lowest vitamin D quartile (<7.3 ng/mL) and long-term major adverse cardiovascular outcomes in 1259 patients. Notably, the association was predominantly with nonfatal adverse outcomes, such as re-hospitalization for ADHF (Acute decompensated heart failure) or for another ACS, rather than mortality.  

Our study supports the close association between low vitamin D levels at hospital presentation and worse prognosis in ACS patients. Indeed, patients with 25 (OH) D deficiency had a 3-fold higher mortality risk, even after adjustment for important independent variables associated with mortality in ACS. This was also evident in studies of Halkin A et al and Saltzman AJ et al.\textsuperscript{25-27} Notably, patients with STEMI and NSTEMI had a similar vitamin D status and portrayed a comparable mortality risk. Thus, our results strengthen the evidence of a close association between low vitamin D levels and poor outcome, and they pave the way for studies based on pharmacologic supplementation of vitamin D in selected high-risk ACS patients, namely those with severe vitamin D deficiency, in order to improve their prognosis.  

The possible causal relationship underlying the association between vitamin D status and outcomes in ACS remains to be elucidated. Mechanisms by which vitamin D deficiency may confer an increased cardiovascular risk, directly or indirectly leading to hyperparathyroidism, include renin-angiotensin-system activation and disorders of insulin synthesis, secretion, and sensitivity, that influence glycemic control and may favor the onset of diabetes.\textsuperscript{3,6,14,28} Of note, low blood 25OH-D concentrations have been associated with an increased risk of both macrovascular and microvascular disease events in type 2 diabetes.\textsuperscript{29} However, in our study, the prognostic implications of vitamin D were confirmed also after adjustment for diabetes.  

Other potential consequences of vitamin D deficiency involve exacerbation of atherogenesis, inflammation, acceleration of arterial calcification, cardiac remodeling and systolic dysfunction, higher risk of restenosis following PCI, and influence on lipid levels.\textsuperscript{9,15-17,20-32} Additionally, vitamin D deficiency has been associated with endothelial dysfunction, which is, in turn, linked to an increased risk of cardiovascular events.\textsuperscript{33,34} In particular, the endothelium mediates vascular tone control, platelet aggregation, endothelium permeability, and neoangiogenesis; thus, its dysfunction may exacerbate coronary thrombosis and vasoconstriction occurring during ACS.\textsuperscript{35-37}  

Finally, in our study, patients with lower vitamin D levels had higher high-sensitivity C-reactive protein values, suggesting a possible link between low vitamin D levels and inflammation. However, controversial data exist on this possible relationship, as recently reported by Eren et al. who found no association between calcidiol levels and inflammatory markers in ACS.\textsuperscript{38} Indeed, frail patients with high cardiovascular risk burden, because of their health status may spend more time indoors and have less sun exposure, leading to vitamin D deficiency. Although a clear evidence that patients with cardiovascular disease have lower levels of 25(OH)D, a similar association exists for a large number of other medical conditions, like cancer, multiple sclerosis, and psychiatric diseases, supporting the concept that vitamin D is simply a general marker of health.\textsuperscript{39}  

Overall, all these features, associated with older age, higher cholesterol and triglycerides levels, and less aggressive coronary reperfusion strategy, may contribute to explain the worse outcome of ACS patients with vitamin D deficiency in our study. Whether vitamin D serves as a risk factor or as a risk marker in ACS, however, cannot be deduced from our study, and future investigation is warranted to clarify this issue.
CONCLUSION

The study demonstrated the presence of an association between vitamin D deficiency and poor in-hospital outcomes in patients with ACS. The correction of vitamin D deficiency and maintenance of an optimal status may be a promising approach for acute treatment and secondary prevention of ACS that requires confirmation in interventional trials with vitamin D supplementation.

Limitations of the study were first, we included a population admitted to a single center. Second, the study population was possibly underpowered to detect a significant difference in in-hospital mortality. Third, our data are only hypothesis generating, because they do not provide evidence to support a causal relationship, and they require confirmation in suitably designed clinical trials. Finally, many factors that affect vitamin D status (eg, latitude, season, sunlight exposure, skin color, vitamin D intake, serum albumin, etc.) were not taken into account in our study, and may have influenced, at least in part, our results.

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