Original Article

Serum Vitamin D levels in Acute Coronary Syndrome patients and its prognostic Significance

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ABSTRACT

Objectives : To assess the levels of Vitamin D in Acute Coronary Syndrome (ACS) and study the prevalence of Vitamin D deficiency in ACS as compared to healthy age and sex matched controls'.

Methods : A case-control study with 100 cases of ACS and 100 age and gender matched healthy controls was conducted at tertiary care hospital. Vitamin D levels were measured at the time of admission and cases were followed for their hospital course to observe for cardiac complications and death. The cases were divided into three groups according to vitamin D levels - severe deficiency (<10 ng/ml), moderate deficiency (10-19.99 ng/ml) and insufficiency (20-29.99ng/ml) for comparison.

Results : Vitamin D deficiency was present in 100% of cases and 95% of controls with severe deficiency present in 28% of cases and 13% of controls. Mean value in cases was 15.77± 6.49 ng/ml as compared to controls (19.68 ±7.05 ng/ml, p<0.0001). 82.1% cases with severe vitamin D deficiency developed in hospital cardiac complications as opposed to 29.6% cases with insufficient levels (p<0.001) In-hospital mortality was observed in 25% cases with severe deficiency and no mortality occurred in cases with insufficiency (p<0.0001). After adjusting for potential confounding variables through multivariate logistic regression, severe vitamin D deficiency remained an independent predictor of in hospital complications in ACS patients with an Odds risk of 4.19 (CI=1.02-17.11, p= 0.046). Also, there was no statistical difference in angiographic findings among the three groups of vitamin D.

Conclusion : Hence the study concluded that vitamin D deficiency is highly prevalent in both cases and controls with mean vitamin D levels lower in cases as compared to controls and severe vitamin D deficiency is independently associated with in-hospital cardiovascular complications.

Introduction :

Coronary heart disease (CHD) is the leading cause of death in India. According to Global Burden of Disease Study (2010), 24.8 % of all deaths in India are attributed to cardiovascular disease. Hence there is an emerging need to search for modifiable risk factors for CHD. Among the reversible risk factors, there is growing evidence to support association of Vitamin D deficiency and development of CHD.[1] Vitamin D receptors are present in a wide variety of tissues, including vascular endothelium, cardiomyocytes and lymphocytes. Vitamin D suppresses the reninangiotensin system[2], affects endothelial function[3] and could protect against atherosclerosis by its inhibiting effect on vascular smooth muscle cells proliferation. These effects may have direct relevance to cardiovascular disease. Because hypovitaminosis D is easily correctable, establishing the relationship between Vitamin D and the coronary heart disease becomes very important.

To plan preventive strategies for reduction in deaths related to coronary heart disease, information is needed about the current distribution of various risk factors associated with same. There is a paucity of evidences regarding some novel risk factors like levels of vitamin D in Indian population. There is limited statistics available about these events from developing countries. With this background, present study was conducted with following aim.

Aims and Objectives :

1. To study the prevalence of Vitamin D deficiency in acute coronary syndrome as compared to healthy age and sex matched controls.
2. To study the association of Vitamin D levels with in hospital mortality in acute coronary syndrome.
3. To study the association of Vitamin D levels with in hospital complications in acute coronary syndrome.

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Methods :

The study was conducted at Government Medical College, Nagpur during November 2015 to November 2017 after taking clearance from the institutional Ethics committee. The study design was a case control study. The sample size taken was 100 cases of acute coronary syndrome along with 100 age and gender matched healthy controls.

The inclusion criteria for cases was patients aged ≥ 20 years who were diagnosed to have acute coronary syndrome as per WHO criteria which included cases of ST elevation myocardial infarction, Non ST elevation myocardial infarction and unstable angina.

To include patients with non ST-segment elevation ACS, ≥ 1 of the 3 objective criteria had to be present

i) electrocardiographic changes consisting of transient ST-segment depression (≥ 0.05 mV) or T-wave inversion (≥ 0.1 mV);
ii) troponin change to a level beyond the threshold of the 99th percentile of a healthy reference population, with 10% coefficient of variability;
iii) previous documentation of coronary artery disease, defined as a definitive history of myocardial infarction or coronary obstruction ≥ 50% on angiography.

For inclusion of ST-segment elevation acute myocardial infarction, a persistent ST-segment elevation ≥ 0.1 mV in ≥ 2 contiguous leads or third-degree left bundle branch block with subsequent elevation of a serum marker of myocardial necrosis was required.

Unstable angina was defined as chest pain occurring at rest (or with minimal exertion), lasting > 10 minutes; of relatively recent onset and / or more severe, prolonged or frequent than previous episodes.

Controls were matched to cases by age (within 5 years) and gender and were individuals who had no previous history of exertional chest pain or diagnosed heart disease and normal ECG. They were recruited from attendants or relatives of non-cardiac patients from non-cardiac wards or patients attending non-cardiac outpatient clinics for disorders unrelated to potential risk factors for Myocardial Infarction.

Exclusion criteria :

Patients with pre-existing liver disease, kidney disease (serum creatinine > 2 mg/dl), malignancy, thyroid disorder or those using drugs affecting Vitamin D levels (eg. corticosteroids, carbamazepine, phenobarbital, sodium valproate, gabapentin, isoniazid, mineral oil, calcitonin or Vitamin D supplements) were excluded from the study.

Investigations :

After undergoing detailed general and systemic examination, both cases and controls underwent the following investigations : 12 lead electrocardiogram, random blood sugar, CPK MB (only in cases), serum Vitamin D levels, kidney function test, liver function test, lipid profile, 2D-echocardiography (only in cases) and coronary angiography (only in cases). Serum vitamin D levels were estimated in fasting blood sample by chemiluminescent assay using standardized kit.

The cases were then divided into three groups based on vitamin D levels in accordance with NHANES III survey: severe deficiency (< 10 ng/ml); moderate deficiency (10 - 19.99 ng/ml) and insufficiency (20 - 29.99 ng/ml). A comparison was made between characteristics of cases and controls as well as among the above groups. The cases were followed till their hospital stay or mortality to document the complications. The complications were registered in the form of heart failure, cardiogenic shock, arrhythmias, heart block, post-infarct angina, fresh myocardial infarction, left ventricular dysfunction (Ejection Fraction <45%) and sudden cardiac death. Fresh MI was diagnosed in the event of persistent chest pain with subsequent increase in ST elevation or serial rise in cardiac biomarkers. The coronary angiography findings of cases were reported as single, double or triple vessel disease and if the block was < 70%, it was reported as insignificant block. GRACE score was calculated for cases to predict mortality risk by entering the variables : age, pulse, systolic blood pressure, serum creatinine, Killip class, cardiac arrest at presentation, cardiac

enzyme positivity and ST segment deviation into online calculators.

Statistical Analysis :

The data obtained was entered into Microsoft Excel Worksheet. Continuous variables were presented as Mean SD. Categorical variables were expressed in frequency and percentages. Continuous variables were compared statistically by independent t-test. Pearson's chi-square test was used for categorical variables. For small samples, fisher exact test was used whenever required. Multiple logistic regression analysis was performed to determine the relationship between severe vitamin D deficiency and in-hospital complications. $p < 0.05$ was considered as statistical significance. Statistical software STATA version 14.0 was used for data analysis.

Results :

Study population characteristics -

The baseline characteristics of cases and controls are shown in Table 1. The mean age of cases was 53.34 ± 9.32 years and that of controls was 54.04± 9.98 years (p=0.6115). The cases more frequently had diabetes (p<0.0001), hypertension (p<0.0001) and higher BMI (>25 kg/m2) as compared to controls (p=0.0002). The mean vitamin D levels in cases was 15.77± 6.49 ng/ml which was significantly lower than that in controls which was 19.68 ±7.05 ng/ml (p=0.0001). There was no significant difference in levels of HDL, LDL, triglycerides, total cholesterol, tobacco and alcohol consumption between cases and controls.

Distribution of vitamin D -

There was a significant difference in vitamin D levels among cases and controls ***(Table 2).*** Out of 100 cases, 28% showed severe deficiency whereas out of 100 controls, only 13% showed severe deficiency. None of the cases showed sufficient vitamin D levels, whereas 5 % of controls showed sufficient vitamin D levels. Thus, prevalence of severe deficiency in cases was found to be statistically significant (p<0.0001).

Serum vitamin D levels and in hospital complications -

It was found that 82.1% of cases with severe vitamin D deficiency developed complications as opposed to only 29.6% of cases with insufficient levels ($p < 0.001$) as shown in ***Table 3.*** The types of complications that occurred were heart failure in 16 patients, cardiogenic shock in 15 patients, heart block in 7 patients, arrhythmias in 7 patients, left ventricular dysfunction in 27 patients, post-infarct angina in 3 patients, fresh myocardial infarction in 2 patients and in-hospital mortality in 8 cases. In-hospital mortality was found in 25% of cases having severe deficiency, 2.2% of cases having moderate deficiency and none of the patients of insufficiency (p <0.0001). The GRACE score was also highest in cases showing severe deficiency (126.35 ± 29.16) as compared to insufficiency (85.70 ± 17.31; p<0.0001).

Patient characteristics and in-hospital complications -

The cases having complications had higher age (57.17 ± 9.58; p=0.0002), higher percentage of patients with past history of IHD (24.4%; p=0.037), higher GRACE score (118.84 ± 29.68; p<0.0001) and greater percentage of patients with severe vitamin D deficiency (51.1%; p=0.002) as shown in ***Table 4.*** After using logistic regression analysis for above variables ***(Table 5),*** severe vitamin D deficiency remained an independent predictor of in-hospital complications with an odds ratio of 4.19(CI=1.02-17.11, p = 0.046). Age, sex and past history of Ischemic Heart Disease lost statistical significance whereas GRACE score remained significantly associated with occurrence of in-hospital complications (odds ratio = 1.07, CI = 1.02-1.13, p = 0.004).

Serum vitamin D levels and coronary angiography findings -

Single vessel disease occurred in 42.8%, 33.3% and 44.4% of patients with severe, moderate and insufficient Vitamin D levels respectively (p=0.786), double vessel disease in 21.4%, 31.1% and 33.3% of patients with severe, moderate and

insufficient vitamin D levels respectively (p=0.570), triple vessel disease in 25%, 20% and 14.8% of patients with severe, moderate and insufficient vitamin D levels respectively (p=0.640) whereas insignificant block was found in 10.7%, 15.5% and 7.4% of patients with severe, moderate and insufficient vitamin D levels respectively (p=0.572). Thus there was no association between vitamin D levels of cases and their angiographic findings ***(Table 6).***

Table 2 : **Distribution of Vitamin D levels in cases & controls**

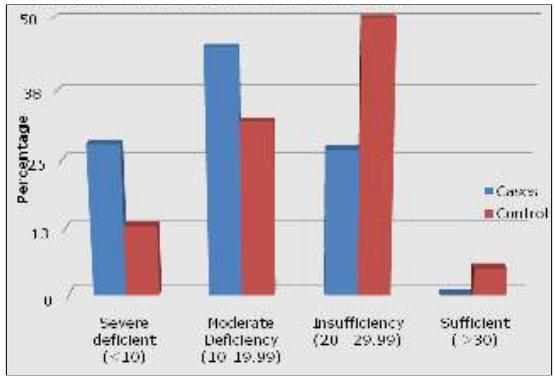

Table 1 : **Characteristics of Cases and Control**

Variables	Cases (n=100)	Control (n=100)	p-value
Age in years	53.34 ± 9.68	54.04 ± 9.78	0.6115,NS
Gender(M/F)	65/35	65/35	1.0000,NS
Diabetes	47	19	<0.0001, HS
Hypertension	55	12	<0.0001, HS
Tobacco	45	33	0.082, NS
Alcohol	15	13	0.684, NS
BMI(kg/m2)	24.51± 3.80	22.59± 3.32	0.0002, HS
Triglycerides(mg/dl)	142.18 ±41.26	131.22± 42.10	0.0642, NS
Total Cholesterol(mg/dl)	173.3 ±43.39	167.07± 26.39	0.2214, NS
HDL Cholesterol(mg/dl)	42.98± 9.06	41.04 ±5.36	0.0671, NS
LDL Cholesterol(mg/dl)	111.42± 23.41	108.41± 24.21	0.3171, NS
Vitamin-D(ng/ml)	15.77± 6.49	19.68 ±7.05	0.0001, HS

BMI = Body mass index. HDL = High density lipoprotein. LDL = low density lipoprotein

Table 3 : **Association of vitamin-D deficiency with in hospital complications**

S No.	Variable	Vitamin-D levels (ng/ml) <10 Severe Deficiency (n=28)	10-19.99 Moderate deficiency (n=45)	20-29.99 insufficiency (n=27)	TOTAL	Chi2-value	p-value
In hospital complications		23 (82.1%)	14(31.1%)	8(29.6%)	45	21.6921	<0.001, HS
1	Heart Failure	9(32.1%)	5(11.1%)	2(7.4%)	16(35.5)	7.7125	0.021, S
2	Cardiogenic shock	10(35.7%)	4(8.9%)	1(3.7%)	15(33.3%)	13.4433	0.002, HS
3	Heart Block	3 (10.7%)	4 (8.9%)	nil	7 (15.5%)	2.8723	0.238, NS
4	Arrhythmia	5 (17.9%)	1 (2.2%)	1 (3.7%)	7 (15.5%)	7.0986	0.029, S
5	LV dysfunction	13 (46.4%)	8 (17.7%)	6 (22.2%)	27 (60%)	7.6168	0.022,S
6	Fresh MI	2 (7.1%)	nil	nil	2 (4.4%)	5.2478	0.073, NS
7	Post infarct Angina	nil	2 (4.4%)	1 (3.7%)	3 (6.6%)	1.2346	0.539, NS
8	In hospital Mortality	7 (25%)	1 (2.2%)	nil	8 (17.7)	15.3835	<0.0001, HS
9	GRACE Score	126.35±29.16	98.11± 23.67	85.70 ±17.31		F=21.37	<0.0001,HS

LV dysfunction = left ventricular dysfunction (EF<45%). GRACE Score = Global Registry of Acute Coronary Events Score

Table 4 : **Clinical parameters of cases with in hospital complications**

Parameters		In hospital complications		p-value
		Yes (n=45)	No (n=55)	
Age in years		57.17 ± 9.58	50.2 ± 8.74	0.0002, HS
Sex (M/F)		24/21	41/14	0.027, S
Diabetes		23(51.1%)	24(43.6%)	0.456,NS
Hypertension		24(53.3%)	31(56.3%)	0.762, NS
Past H/O of IHD		11(24.4%)	5(9.1%)	0.037, S
Tobacco		19(42.2%)	26(27.3%)	0.614,NS
Alcohol		7(15.5%)	8(14.5%)	0.888, NS
BMI(kg/m2)		24.62 ±3.82	24. ± 3.82	0.8010,NS
Triglyceride(mg/dl)		143.75 ± 40.56	140.89 ± 42.16	0.7317, NS
Total cholesterol(mg/dl)		167.88 ± 46.48	177.72 ± 40.58	0.2617, NS
LDL(mg/dl)		109.8 ± 22.41	112.74 ± 24.33	0.5342, NS
Vitamin D Deficiency (ng/ml)	<10	23(51.1%)	5(9.1%)	0.002, HS
	10-19.99	14(31.1%)	31(56.3%)	
	20-29.99	8(17.8%)	19(34.5%)	
GRACE score		118.84 ± 29.68	89.43 ± 19.03	<0.0001, HS

IHD - Ischemic heart disease. BMI - Body Mass Index. LDL - Low density lipoprotein.
GRACE score - Global Registry of Acute Coronary Events score.

Table 5 : **Association of severe vitamin D deficiency with in hospital complications after adjustment for potential confounding factors**

Variable	Adjusted Odds Ratio	95% Confidence Interval	p-value
Vitamin D deficiency	4.19	1.02 17.11	0.046, S
Age	0.89	0.79 1.00	0.060, NS
Sex	1.74	0.58 5.21	0.322, NS
Past h/o IHD	2.66	0.57 12.39	0.212, NS
GRACE score	1.07	1.02 1.13	0.004, HS

IHD - Ischemic heart disease. GRACE score - Global Registry of Acute Coronary Events score

Table 6 : **Association of vitamin D levels with Coronary Angiography findings**

	VITAMIN D levels (ng/ml)				
CAG FINDINGS	<10 (n=28)	10-19.99 (n=45)	20-29.99 (n=27)	Chi square value	p-value
SVD	12 (42.8%)	15 (33.3%)	12 (44.4%)	3.1802	0.786 NS
DVD	6 (21.4%)	14 (31.1%)	9 (33.3%)	1.1232	0.570 NS
TVD	7 (25%)	9 (20%)	4 (14.8%)	0.8912	0.640 NS
NS	3 (10.7%)	7 (15.5%)	2 (7.4%)	1.1218	0.572 NS

CAG = Coronary angiography. SVD = Single vessel disease. DVD = double vessel disease. TVD = triple vessel disease.
NS = not significant (block < 70%).

Discussions :

Experimental and epidemiological studies have suggested that vitamin D related arterial damage might be involved in the onset of atherosclerosis and that intake of vitamin D may be a risk factor for coronary heart disease. However, the evidence for a causal association is sparse and the hypothesis is controversial.[5]

The present study revealed a high prevalence of vitamin D deficiency in both cases and controls. None of the cases and only 5% controls showed sufficient vitamin D level. Insufficiency was found in 27% cases and 50% controls, moderate deficiency in 45% cases and 32% controls whereas severe vitamin D deficiency was present in 28% cases and only 13% of controls.

In a study conducted by Marwaha RK et al[5], vitamin D deficiency was found in 91.2% individuals, including severe vitamin D deficiency in 62% and vitamin D insufficiency in additional 6.8% of the population. Similar observations were observed by Roy A et al[4] in myocardial infarction patients (79.21%) and healthy controls (46.71%).

In the present study, the cases had higher prevalence of diabetics (47.00%), hypertensives (55.00%) and had higher BMI as compared to controls. Similar results were found by Roy A et al[4].

In the present study, out of 100 cases of acute coronary syndrome, 45 developed in hospital cardiac complications including mortality. The incidence of in hospital complications increased across the groups of vitamin D levels i.e. out of 45% cases developing complications, 29.6% had insufficient vitamin D levels, 31.1% had moderate deficiency and 82.1 % had severe deficiency.

Among complication, Left Ventricular Dysfunction (27.00%), heart failure (16.00%), Cardiogenic Shock (15.00%), Arrhythmia (7.00%), Heart block (7.00%), fresh Myocardial Infarction (2.00%), Others (8.00%). the complications significantly associated with severe vitamin D deficiency were heart failure (p=0.021), cardiogenic shock (p=0.002), arrhythmia (0.029) and LV dysfunction (p=0.022). Similar observations were found by Ng LL et al[7], DeMetrio M et al[8] and Correia LC et al[9]

In the present study, severe vitamin D deficiency had the highest association with in hospital complications (p <0.001) and after adjusting for the relevant confounding factors, severe vitamin D deficiency remained an independent predictor of in hospital complications including mortality with an Odds ratio of 4.19.

This was also confirmed by De Metrio M et al[8] who observed that the lowest quartile of vitamin D (< 9 ng/ml) was associated with the highest risk for several in-hospital complications (p=0.001) and lowest quartile of vitamin D remained significantly associated with re-hospitalization for ADHF, with a hazard risk of 2.72 (95% CI 1.14 6.75; p = 0.02) after adjustment for potential confounding factors

In the present study, out of 100 cases, eight patients showed in hospital mortality in the form of sudden cardiac death; out of which seven had severe vitamin D deficiency and one had moderate deficiency. Thus severe vitamin D deficiency had a statistically significant association with in hospital mortality (p<0.0001).

Correia LC et al[9] also observed in-hospital cardiovascular death in patients with severe vitamin D deficiency (=10 ng/ml) to be 24%, as compared to 4.9% in the remaining patients (relative risk 4.3, 95% CI 1.8 to 10, p =0.001). After adjustment for potential confounders, severe vitamin D deficiency was associated with cardiovascular mortality with an odds ratio of 14 (95% CI 1.2 to 158, p = 0.03).

Pilz S et al[10] also observed that during a median follow up of 7.7 years, patients with severe vitamin D (<25 nmol / liter) deficiency had hazard ratio of 2.84 (CI 1.20- 6.74) for death due to heart failure and sudden cardiac death as compared to hazard ratio of 5.05 (CI 2.13-11.97), in persons with optimal vitamin D (=75 nmol / liter).

In the present study, no relationship was found between vitamin D categories and the coronary angiography findings. Similar observations were reported by Pilz S et al[10] and Goleniewska B et al[11], who demonstrated that the 25 (OH) D concentrations between patients with single- and multi-vessel CAD did not differ significantly (10.2 vs. 11.4 ng/mL, p = 0.62).

Conclusions :

There is high prevalence of vitamin D deficiency in cases of acute coronary syndrome as well as healthy controls with mean vitamin D levels lower in cases as compared to controls. There is a significant

association between vitamin D deficiency and in hospital cardiac complications and mortality and it has linear relationship with degree of vitamin D deficiency. The study demonstrated no significant difference in coronary angiographic findings among the three groups of vitamin D deficiency.

Limitations :

The findings of current study should be deduced keeping in view the subsequent limitations. This is a single centre study and the sample size taken is very small. Also, there is a poor representation of women in this study. The study just establishes an association of vitamin D with in hospital complications including mortality. It does not establish whether vitamin D is a risk marker or a risk factor for occurrence of complications in ACS patients. Many factors that affect vitamin D status (e.g. diet, latitude, season, sunlight exposure, skin colour, serum albumin etc.) were not taken into account and may have influenced, at least in part, our results.

Strengths :

Present study was conducted in tertiary care centre, in which most of sophisticated investigations are available. The careful and meticulous data collection was one of the our strengths.

Clinical Implication

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 but requires confirmation in interventional trials with vitamin D supplementation. However, elucidating the effects on outcomes may require large adequately powered clinical trials. Larger studies with greater power from multiple centres and from different parts of India are needed.

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