A study of 25 hydroxy cholecalciferol levels across different seasons in first time presenting acute myocardial infarction patients from rural background

Ranjith Kumar C[1], B Laxmikanth[2,*]

[1]Assistant Professor, Dept. of Biochemistry, S.V.S Medical College, Mahabubnagar, Telangana, [2]Associate Professor, Dept. of Biochemistry, Maheshwara Medical College& Hospital, Hyderabad, Telangana, India

***Corresponding Author:**
Email: drbachulaxmikanth@gmail.com

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Abstract

Introduction and Objectives: The main circulating form of vitamin D in blood is 25-hydroxy vitamin D (25[OH] D) has been known to be associated with the pathogenesis of acute coronary syndromes (ACS). Deficiency of 25[OH] D has been associated with cardiovascular risk and coronary artery disease. Therefore, it is of high importance to assess for 25(OH) D deficiency in acute myocardial infarction (AMI) to initiate treatment at the earliest. The serum levels of 25(OH) D in AMI patients across different seasons are unclear.

Materials and Methods: The serum levels of 25(OH) D were assessed in 50 subjects presented with first time myocardial infarction to Cardiology departments of SVS Medical College& Hospital. Patients were enrolled throughout the year of 2017 and their serum samples were analyzed using the TOSOH AIA 360. Group 1 consisted study period from February to May. Group 2 consisted study period from June to September. From October to December including January of 2017 considered as winter, named Group 3. Based on the vitamin D status, subjects were classified as normal (≥ 30 ng/ml), insufficient (20-30 ng/ml) and deficient (≤ 20 ng/ml) groups.

Results: Of the 50 enrolled patients, 60% were 25(OH) deficient and 18% were insufficient, for a total of 78% of patients with abnormally low 25 (OH)D levels. Vitamin D levels are statistically highly significant variation across the groups. ($p = 0.0000533$).

Conclusions: Our results suggested that the prevalence of Vitamin D deficiency was high in AMI patients presented in winter and summer seasons as compared to that of rainy season.

Keywords: 25 hydroxy cholecalciferol, Acute myocardial infarction, Troponin – I, CK-MB, Seasonal variation.

Introduction

Vitamin D deficiency has been reported to be highly prevalent, worldwide,[1] and has also been noted to be high in India.[2,3] The circulating levels of 25(OH)D is the active form of vitamin D which is found to be low in up to one half of the healthy population belonging to the middle and elderly age groups.[1,4–6] Among several, the main causes of low 25(OH) D levels include; limited cutaneous synthesis which is in turn due to inadequate sun exposure or pigmented skin and inadequate dietary intake. The characteristics of vitamin D deficiency include musculoskeletal system involvement and the growing evidence suggests that it affects vascular smooth muscle cell proliferation,[6] endothelium,[7] cardiomyocytes,[1,8] inflammation, vascular calcification, renin– angiotensin system (RAS),[9,10] blood pressure and left ventricular hypertrophy (LVH).[10–12] All of these may contribute to cardiovascular risk and myocardial infarction. In AMI patients, the vitamin D deficiency, its prevalence and associated pathophysiological manifestations have been reported previously.[13,14] However, there is a scarcity of studies on the effect of seasons on vitamin D levels (seasonal variations) in patients with myocardial infarction presenting for the first time. Therefore, this prospective study was undertaken to evaluate seasonal effects on Vit-D levels of first time presenting acute myocardial infarction patients.

Materials and Methods

This observational study was conducted between January 2017 to December 2017 at the Intensive Care and Cardiology Departments of SVS Medical College at Mahabubnagar, Telangana state, India. A total of 50 participants were recruited into this study. Through patient interviews and reviewing medical records, information regarding AMI; ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) have been obtained. The recruited subjects were stratified based on the seasons into three groups: Group 1 (Summer), Group 2 (Rainy) and Group 3 (Winter).

Participants were included in the study when their age was ≥20 years along with a biochemical evidence indicating elevated Creatine kinase-MB fraction and troponin-I suggestive of AMI. In addition, information on prolonged ischemic signs or symptoms and ECG changes were recorded. The exclusion criteria of this study involved; patients with kidney and hepatic diseases, serum creatinine >1.6 mg/dl, malignancy, and those on phenytoin or other medications that could influence vitamin D levels. Patients who are not

willing to give consent as well as those with missed vitamin D level were excluded.

All the participants provided written informed consent. Patient data included demographics such as; age, gender, marital status and education. Collected information on several confounders including; smoking status, alcoholism, previous angina, hypertension, diabetes mellitus, peripheral arterial disease, previous and family history on stroke, coronary artery disease and other chronic diseases affecting lung, kidneys and heart. Hypertension was defined as systemic BP ≥ 140 mm of Hg, diastolic BP ≥ 90 mm of Hg, or use of anti hypertensive therapy.[15] Criteria for diabetes mellitus were fasting glucose ≥ 126 mg/dl or use of insulin or hypoglycaemic medications.[16] Current smoking denoted regular use of cigarettes in the preceding year. The serum samples were obtained as soon as the patient got admitted to the hospital and before initiating medication (treatment). Data collected included, random plasma glucose, glycosylated hemoglobin (HbA1c), serum creatinine, CK-MB and troponin- I and 25 (OH) D levels. The patient classification has been performed as detailed in Table 1.

Table 1: The patient classification

	Group I (Summer)		**Group II (Rainy)**		**Group III (Winter)**		**Total**	
Enrolled patients	22		16		12		50	
Vit-D deficient (< 20 ng/ml)	17 (77.27%)	21 (95.45%)	3 (18.75%)	6 (37.5%)	10 (83.33%)	12 (100%)	30 (60%)	39 (78%)
Vit- D insufficient (20 -30 ng/ml)	4 (18.18%)		3 (18.75%)		2 (16.66%)		9 (18%)	
Vit- D normal (≥ 30 ng/ml)	1		10		0		11(22%)	
Mean value	16.60136		40.24250		16.80417			
Standard deviation	6.280692		21.802755		3.556156			

Tosoh AIA 360 Enzyme immunoassay principle based analyzer (Japan). According to the Endocrine Society guidelines and previously published recommendations, the following cut-off values were applied for classifying based on vitamin D status: subjects were classified as normal (≥ 30 ng/ml), insufficient (20-30 ng/ml) and deficient (≤ 20 ng/ml) groups.[17] Serum 25 (OH) D levels were analyzed using Kruskal Wallis Rank Sum test in R commander statistical software (version: 3.4.3, 30/11/2017). The local ethical committee approved the research.

Results

This study was conducted throughout a year 2017 at SVSMC. The mean age for the total population in deficient and insufficient groups was 56.97±12.78 and for sufficient group was 55.81±12.33. There were 39 (78%) males and 11(22%) females. Of which, 22% of patients (n=11), 18% of patients (n=9) and 60% of patients (n=30) had normal, insufficient and deficient levels of 25 (OH) D, respectively. Table 2 shows baseline clinical characteristics of acute coronary syndrome patients.

Table 2: The characteristics of patients enrolled into this study

Variable	**25 (OH) D value**		**P - Value**
	< 30 ng/ml	*≥ 30 ng/ml*	
	39 (78%)	*11(22%)*	
Age	56.97±12.78	55.81±12.33	0.7059
Men	31	8	0.6326
Women	8	3	
Smoking	13	6	0.3532
Alcohol	19	6	1.0
Diabetes Mellitus	27	8	0.9883
Hypertension	24	3	0.1286

As it is evident from Table 2, the study participants were not heterogeneous with respect to age or gender sub groups, smoking, alcohol, diabetes mellitus and hypertension status (Table 2). There was no statistical significance in terms of the prevalence of diabetes and hypertension in cases with lower levels of 25(OH) D. Whereas, there were more current smokers and alcoholics among cases with lower levels of 25(OH) D.

We tested for interaction across various factors to examine the association between 25(OH) D level and MI. We did not find statistical evidence of interaction by age, hypertension, diabetes mellitus alcohol use and smoking.

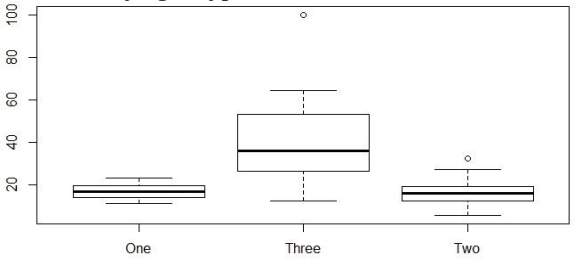

Fig. 1: Serum levels of Vitamin-D in different study groups

Vitamin D levels of AMI patients represented at different seasons at hospital admission were compared as different groups by using Kruskal-Wallis rank sum test, it revealed that rainy season/group 2 AMI patients had sufficient vit D values, those were significantly high, when compared to other seasons/groups AMI patient vitamin D values. As shown in Figure 1, Group 1 and Group 3 have shown very low levels of Vitamin-D. The insufficiency and deficiency of 25 (OH) D was high in summer (Group 1) and winter (Group 3) groups as noted to be 95.45% and 100%, respectively.

Discussion

The risk of coronary heart disease increases in elderly people and is a leading cause of mortality and morbidity. The deficiency of Vit-D deficiency is well documented and is known to be associated with increased cardiovascular risk. Our results suggested that there is a high prevalence of vitamin D deficiency and insufficiency in AMI patients in summer and winter seasons compared to the AMI counterparts presented in rainy seasons.

Because of a lesser exposure to direct sunlight in summer and winter seasons, vitamin D synthesis may be less.[18] Interestingly, cardiovascular mortality rates have been reported to be high during decreased exposure to sunlight in winters.[19] Further, 25(OH) D deficiency has shown to be of higher prevalence in the winter months.[14] Unlike these previous observations, the MI risk has been found to be decreased with raised vitamin D3 levels observed in a rainy season.[20] Our results are well in support of a previous report by Scragg et al.,[20] Previous evidence suggests that individuals with vitamin D deficiency are at higher risk of ischemic heart disease.[18,20,21] Edward et al., established that risk of MI is relatively increased in cases with deficient levels of 25(OH)D, independent of plasma lipid levels.[21]

We observed no statistical significance with respect to age and sex among groups with < 30 ng/ml and ≥ 30 ng/ml of Vitamin-D. Similar results were reported by Edward et al.[21] The present study results are in accordance with previous studies in support of a hypothesis stating 'increased exposure to sunlight is protective against coronary heart disease'. Protective role of vitamin D in CVD may involve multi-factorial mechanisms. Among several contributors; the vascular smooth muscle proliferation, suppression of vascular calcification, dys-regulation of pro-inflammatory and anti-inflammatory cytokines and impaired regulation of the renin-angiotensin system are important.[22] In a randomized controlled trial (RCT)[23] of either UV-B or UV-A administered through tanning booths, UV-B, which increased 25(OH)D levels by 162% has been proven to be effective in reducing 24-hour ambulatory blood pressure (by –6/–6mmHg, *P*< .001), whereas UV-A was showed to be not effective on 25(OH)D levels or blood pressure. In another RCT,[24] on individuals with low Vit-D status (< 20 ng/mL; mean, approximately 10 ng/mL), supplementation with 800 IU of vitamin D has resulted in an increase in serum 25(OH)D of 72% (*P*<.01), a decrease in systolic blood pressure of 9.3% (*P*=0.02) and a decrease in diastolic blood pressure of 8.5% (*P* = 0.10).

Calcification is known as a common feature of atherosclerosis and all angiographically significant lesions are reported to be calcified.[25] Levels of 1,25-dihydroxyvitamin D have been shown to be inversely associated with vascular calcification.[26] Calcification of coronary arteries has been associated with increased risk of MI[27] suggesting that vitamin D may affect MI risk through its effects on vascular calcification.

Other mechanisms could also account for or contribute to the association between 25(OH)D and MI risk. Vitamin D deficiency, possibly combined with low calcium intake has been reported to be associated with impaired fasting glucose and hence a possible risk of type 2 diabetes mellitus[28-31] which may in turn contribute to CVD risk.

It is noteworthy that, 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.[32]

A study by Ng et al[33] evaluating vitamin D and prognosis of ACS patients, an association between the lowest vitamin D quartile (<7.3 ng/mL) and long-term major adverse cardiovascular outcomes was reported. Importantly, patients with 25 (OH) D deficiencies had a

3-fold higher mortality risk even after adjustment for important independent variables associated with cardiovascular mortality. This is further evident from the findings of Halkin et al., and Saltzman et al.[34-36]

Skin pigmentation has a vital role in vitamin D production. Therefore, individuals with darker skin produce less vitamin D with the same ultraviolet B radiation as compared to fairer skin individuals.[37] This explains the higher prevalence of vitamin D deficiency in our cohort as all the study subjects were Indians with dark skin. The main limitations of this study are; lack of an adequate control group with normal levels of Vitamin D, and it is a single center study.

In conclusion, Vit-D deficiency and insufficiency are acting as cofactors to ACS (acute coronary syndrome) proved in most of studies. This study established the seasonal effect on Vit-D levels in AMI patients. In winter and summer seasons, the Vit-D prevalence is high compare to rainy season. By supplements and follow-ups the Vit-D in risk groups, especially at winter and rainy seasons, myocardial infarction incidents can be prevented to some extent. And, food fortification with vitamin D may also be helpful in decreasing economic burden in treating cases of ACS.

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