Prevalence of Low Circulatory Vitamin D Levels in Patients with Acute Myocardial Infarction - A Cross Sectional Study from a Tertiary Care Centre in Kozhikode, Kerala

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ABSTRACT

BACKGROUND

Vitamin D deficiency continues to be an unrecognized health disorder globally while ischemic heart disease (IHD) is the leading cause of premature mortality. Many recent studies have found high rates of cardiovascular diseases among patients with low vitamin D levels. Due to limited randomized control trials, it is reasonable to screen acute myocardial infarction (AMI) patients for vitamin D deficiency. Thus, the study aims to find out as to whether vitamin D deficiency is a risk factor for AMI and evaluate the association between their troponin I and vitamin D levels.

METHODS

In this cross-sectional study, cases included patients admitted with myocardial infarction in the medicine wards or ICU while controls were age and sex matched apparently healthy subjects. Detailed history was taken about duration of the illness and other significant medical illness. Serum troponin I (Trop I) levels and electrocardiogram (ECG) reports were assessed. Serum samples for 25-hydroxyvitamin D [25(OH)VitD] estimation by electrochemiluminescence method, were collected from both cases and controls. Statistical analysis was performed using SPSS version 22.0 software.

RESULTS

The mean 25(OH)VitD levels were found to be significantly lesser in cases [20.98 ± 6.29 ng/ml] as compared to controls [27.13 ± 10.50 ng/ml], further decreased in ST-elevation myocardial infarction (STEMI) (17 %) subjects [15.70 ± 4.43 ng/ml] as compared to non-ST elevation myocardial infarction (NSTEMI) (83%) [22.06 ± 6.10 ng/ml]. There exists a significant moderate negative correlation [ρ = -0.46] between troponin I levels and 25(OH)VitD levels in AMI.

CONCLUSIONS

Vitamin D deficiency hence can be a risk factor for development of myocardial infarction. But already established risk factors confounds to state it as an independent risk factor.

KEYWORDS

Acute Myocardial Infarction, 25-Hydroxyvitamin D, Troponin I, ST-Elevation myocardial infarction, Non-ST Elevation myocardial infarction

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BACKGROUND

Myocardial infarction (MI), the most common form of ischemic heart disease (IHD), has the highest morbidity and mortality in the world imposing heavy burden on the health system.[1] According to the reports published by Global burden of disease in the year 2017, IHD was ranked the first among leading causes of early deaths. The current prevalence rate of 1,655 per 100,000 population is expected to exceed 1,845 by the year 2030.[2] In developed countries like the United States, age-adjusted prevalence of heart disease and coronary heart disease are 11.8% and 7.2% respectively.[3] The major risk factors among South Asians for coronary artery disease (CAD) are related to lifestyle changes, smoking, alcohol, metabolic syndrome and psychosocial factors that necessitates implementation of adequate preventive measures.[4] Altered nutrition due to deficient in vital nutrients is also linked to spurt of CAD and other age-related degenerative diseases.[5] Likewise, emerging studies have shown that vitamin D deficiency is increasingly being associated with CAD mortality and morbidity.[6]

Vitamin D deficiency continues to be an unrecognized nutritional disorder in many populations around the world. Among the heliophobic Indian population, >90% of apparently healthy persons have subnormal vitamin D levels.[7] Several studies have shown a high prevalence (50 – 97%) of vitamin D deficiency in tropical and subtropical regions of India and other South Asian countries, despite abundant sunlight.[8]

Vitamin D concentration in serum depends upon oral intake through diet or supplements and the synthesis of Vitamin D_3 in the subcutaneous tissue by ultraviolet (UV) B radiation.[9] α-hydroxylase and vitamin D receptor (VDR) is expressed in most of the human cells.[10,11] α-hydroxylase converts inactive vitamin D to active vitamin D or known as 1,25-dihydroxy vitamin D [$1,25(OH)_2$VitD].[9] This $1,25(OH)^2$ VitD complexes with high affinity receptor VDR and in association with retinoid X receptor (RXR) transcriptionally regulates genes which have important role in growth, immunity and cardiovascular homeostasis.[9] An intermediate, 25-hydroxycholecalciferol [25(OH)VitD], is synthesized in a step prior to $1,25(OH)_2$VitD, which is the stable form in serum and is commonly measured for estimating vitamin D.[12] Decreased concentration of vitamin D influences vascular smooth muscle cell proliferation, endothelium and cardiomyocytes inflammation and vascular calcification.[13]

Due to rising prevalence of acute myocardial infarction (AMI) and vitamin D deficiency in India there is a definitive need to assess their association. However, the interrelation between AMI and Vitamin D deficiency is poorly understood in Southeast Asia. In this study we aim to the find the association between MI and Vitamin D deficiency in a tertiary care centre located in the Kozhikode district of Kerala state.

METHODS

Study Design
Comparative cross-sectional study.

Duration of Study
12 months; October 2019 to September 2020.

Study Population
In our study cases were defined as the patients diagnosed with AMI and admitted in the medicine wards or ICU of Government Medical College Hospital, Kozhikode, Kerala. Age and sex matched healthy controls were selected among the bystanders. Group 1 included 47 patients admitted with myocardial infarction and in group 2 we included 47 age and sex matched healthy controls. Detailed history was taken about duration of the illness and other significant medical illness. Inclusion criteria for patients included cases from both sexes diagnosed with myocardial infarction in the age group above 18 years and admitted in wards and ICU of General Medicine department. Exclusion criteria for the patients included any acute illness other than myocardial infarction, known renal disease, endocrine disorder, vitamin D supplementation, pregnant ladies and lactating mother. Inclusion criteria for controls included both sexes of age above 18 years who were apparently healthy with no prior illnesses or co-morbidities. Exclusion criteria for the controls included any acute illness other than myocardial infarction, known renal disease, endocrine disorder, vitamin D supplementation, pregnant ladies and lactating mother. Informed consent was taken from all cases and controls.

Specimen and Study Parameters
Blood samples were collected by venipuncture from both group 1 and group 2 subjects. Subsequently serum was extracted. Troponin I was used as the cardiac marker for AMI and was estimated in both the groups. Vitamin D status was determined by measuring serum 25(OH)VitD from both the study groups. Electrocardiogram (ECG) findings and serum renal function test was assessed in both groups.

Reagents and Instrumentation
Troponin I was assayed using three-site sandwich immunoassay using direct chemiluminometric technology in Siemen's immunoassay system.[14] Here the binary lite reagent includes a polyclonal goat anti-troponin I antibody labelled with acridinium ester and two biotinylated mouse monoclonal anti-troponin I antibodies which bind to troponin I in the sample. The biotin contained in the immune complex then binds to streptavidin-labelled magnetic particles. This assay measures troponin I concentrations up to 50 ng/ml with a minimum detectable concentration (analytical sensitivity) of 0.006 ng/ml.

25(OH)VitD was estimated by electro-chemiluminescence binding assay in Cobas e-411 fully automated electrochemiluminescence analyzer.[15] In this method a complex consisting of ruthenium labelled vitamin D binding protein and 25-hydroxyvitamin D is formed initially. After adding streptavidin-coated microparticles and biotinylated 25-hydroxyvitamin D, unbound ruthenium labelled vitamin D binding proteins become occupied. A complex consisting of ruthenylated vitamin D binding protein

and biotinylated 25-hydroxy vitamin D is formed and becomes bound to the solid phase by interaction between biotin and streptavidin. The reagents have a detection range of 3 to 100 ng/ml. Values below the limit of detection were reported as < 3 ng/ml and values above the limit of detection were reported as >100 ng/ml.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows, Version 22.0 was used to perform statistical analysis. Descriptive analysis of all the explanatory parameters was done using frequency and proportions for categorical variables, while mean & standard deviation (SD) was used for continuous variables. Mann Whitney Test was used to compare the mean 25-hydroxyvitamin D levels between the case and control groups. Similarly, the mean 25-hydroxyvitamin D and troponin levels were compared among the cases. The relationship between vitamin D and troponin I was analyzed using Spearman's correlation test. The level of significance (p-value) was set at $p < 0.05$.

RESULTS

The first group encompassed 47 AMI patients of which there were 31 males (66%) and 16 females (34%) and the mean age of this group was 55.38 years. The second group that served as the control included 47 age and sex matched apparently healthy individuals free of these events. There were 32 males (68%) and 15 females (32%) in the control group and the mean age of this group was 53 years. Majority of the cases were males and high proportion of the AMI that was observed in this study was NSTEMI (non-ST elevation myocardial infarction).

There were 83% of NSTEMI cases (n = 39) and 17% of STEMI (ST-elevation myocardial infarction) cases (n = 8) based on the ECG report. Serum 25(OH)VitD levels were significantly lower in cases (20.98±6.29 ng/ml) as compared to controls (27.13±10.50 ng/ml) and the p value was 0.003. (Table 1). Among the cases, 44.7% (n = 21) of subjects had deficiency while in control group it was 29.8% (n = 14). Normal levels of 25(OH)VitD, was observed in 27.7% of controls (n = 13) and in only 6.4% (n = 3) of cases. (Table 1).

Serum 25(OH)VitD were significantly lower in STEMI (15.70 ± 4.43 ng/ml) as compared to NSTEMI (22.06 ± 6.10 ng/ml, p = 0.001) cases (Figure 1, Table 2). Reciprocally, troponin I was higher in STEMI (4.44 ± 1.66 ng/ml, p = 0.009) in comparison to NSTEMI (1.98 ± 1.43 ng/ml) cases (Figure 1, Table 2).

Spearman's correlation test was used to assess the relationship between troponin I & 25(OH)VitD levels in AMI and a significant moderate negative correlation (ρ=-0.46) between serum troponin I & 25(OH)VitD levels was observed in cases (Table 3). Simple linear regression analysis to predict the troponin I levels by 25(OH)VitD levels shows that for every 1 ng/ml decrease in 25-OH vitamin D levels, the troponin I levels will significantly increase by 0.15 units in cases ($p < 0.001$).

This variability between troponin I and 25(OH)VitD levels in case group is explained by an R^2 of 31% (Table 4). The Scatterplot for depicting the relationship between troponin I and 25(OH)VitD levels, shows the trend line indicating a downward trend reflecting the negative correlation between them. (Figure 2).

Parameter		Group 1 (Cases)	Group 2 (Controls)	p-value
Age (years) Mean age		55.38±9.46	53±6.50	0.12
Sex	Males	31 (66.0%)	32 (68.1%)	0.83
	Females	16 (34.0%)	15 (31.9%)	
Mean	25(OH)VitD (ng/ml)	20.98±6.29	27.13±10.50	0.003
25(OH)VitD	Normal	6.4% (n=3)	27.7% (n=13)	
	Insufficiency	48.9% (n=23)	42.6% (n=20)	
	Deficiency	44.7%(n=1)	29.8% (n=14)	

Table 1. Vitamin D Levels in AMI Cases as Compared to Apparently Healthy Controls. [AMI: Acute Myocardial Infarction; 25(OH)VitD :25-Hydroxyvitamin D]

Parameter	Group 1 (Cases)		P-Value
	STEMI (n=8)	NSTEMI (n=39)	
25(OH)VitD (ng/ml)	15.70±4.43	22.06±6.10	0.001
Troponin I (ng/ml)	4.44±1.66	1.98±1.43	0.009

Table 2. Vitamin D and Troponin I levels in STEMI and NSTEMI Cases. [NSTEMI: Non-ST-Elevation Myocardial Infarction; STEMI: ST-Elevation Myocardial Infarction; 25(OH)VitD : 25-Hydroxyvitamin D]

Variable	Values	25(OH)VitD
Troponin I	n	47
	p-value	0.001
	rho (ρ)	-0.46

Table 3. Spearman's Correlation Test to Assess the Relationship between Troponin I & 25(OH)VitD Levels in AMI. [AMI: Acute Myocardial Infarction; 25(OH)VitD: 25-Hydroxyvitamin D]

Group	Independent Variable	Unstandard Coefficients Beta	Error Standard Error	t	P-Value	R^2
Case	Constant	5.61	0.74	7.556	<0.001	0.31
	25(OH)VitD	-0.15	0.03	-4.510	<0.001	

Table 4. Simple Linear Regression Analysis to Predict the Troponin I Levels by 25(OH)VitD Levels in AMI. [AMI: Acute Myocardial Infarction; 25(OH)VitD: 25-Hydroxyvitamin D]

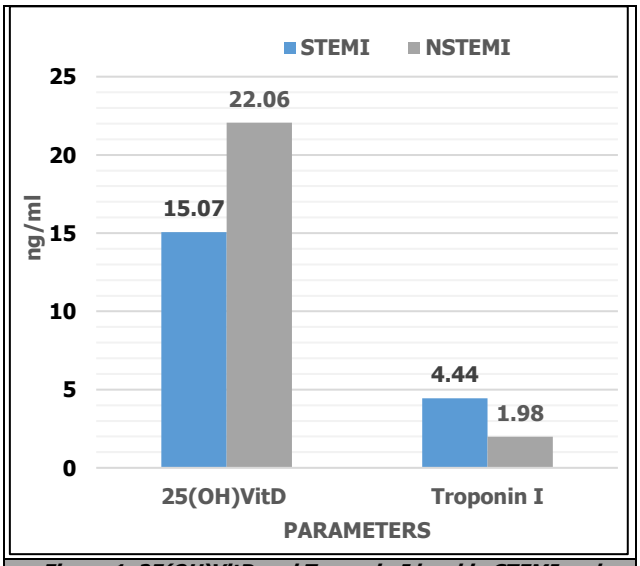

Figure 1. 25(OH)VitD and Troponin I level in STEMI and NSTEMI. [AMI: Acute Myocardial Infarction; NSTEMI: Non-ST-Elevation Myocardial Infarction; STEMI: ST-Elevation Myocardial Infarction; 25(OH)VitD : 25-Hydroxyvitamin D]

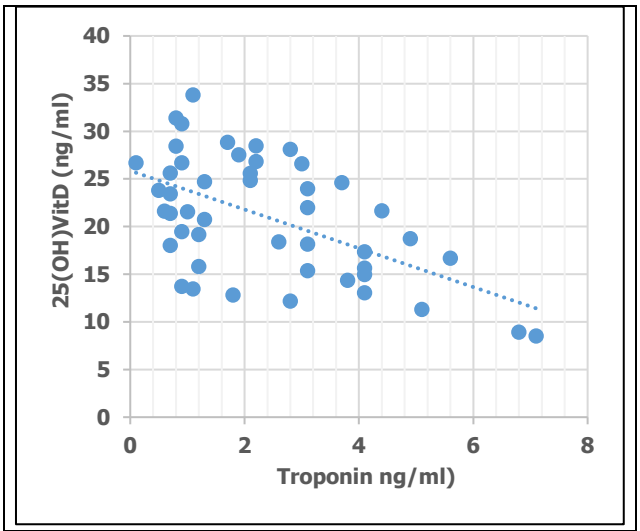

Figure 2. Scatterplot Depicting the Relationship between Troponin I and 25(OH)VitD Levels. [25(OH)VitD : 25-Hydroxyvitamin D]

DISCUSSION

Even though dietary sources like seafoods, vegetable oils, cereals and milk are good sources of vitamin D, mostly it is obtained through cutaneous synthesis by the action of ultraviolet-B rays.[13] However, there is high prevalence of hypovitaminosis D in Indian population. In order to decrease the deficiency manifestations, a panel of endocrinologists have laid new guidelines on daily allowance of vitamin D and have recommended 1000 - 2000 IU daily for adult population in India.[7]

The vitamin D axis plays an important role in regulation of renin-angiotensin system (RAS), blood pressure and left ventricular hypertrophy which are key determinants associated with increased risk for developing CAD.[13] Calcitriol, the active form of vitamin D plays a vital role in preventing vascular calcification by regulation of vascular matrix proteins and calcium influx.[13] Due to the synthesis of proteins related to vitamin D function such as vitamin D receptor (VDR) and 1α-hydroxylase within the cardiomyocytes, endothelial cells and vascular smooth muscle cells, calcitriol has potential significance in regulation of cardiovascular system and thereby cardiovascular disorders.[16] Raljević et al in a cross-sectional study involving 155 subjects reported that VDR polymorphisms involving T/T genotype of the BsmI (rs1544410) and the G/G genotype of the Taq1 (rs731236) but not Fok1 (rs2228570), is increasingly associated with AMI.[17] Vitamin D deficiency is associated with increased mortality and morbidity in AMI due to higher post-ischemic complications and cardiac remodeling.[6,18]

Our cross-sectional study shows that the risk for occurrence of AMI putatively increases with reduced circulatory 25(OH)VitD levels. In our study we found that the mean 25(OH)VitD levels were found to be significantly lower in cases as compared to controls. Moreover, in the STEMI patients which comprised of 17% of subjects, 25(OH)VitD levels were significantly lower in comparison to NSTEMI patients that were 83% of the total subjects. We also observed a negative correlation between troponin I levels and 25(OH)VitD levels within AMI subjects. Furthermore, vitamin D deficiency is seen in 44.7% of cases and 29.8% of the control subjects which reflects its prevalence in the general population.

Roy et al. in their case-control study reported higher prevalence of vitamin D deficiency [25(OH)VitD < 30 ng/ml] in MI (Myocardial infarction) with median levels lower in cases as compared to controls (6 ng/ml and 11.1 ng/ml respectively; $p < 0.001$).[19] There was increased occurrence of diabetes mellitus, hypertension, higher waist hip ratio, increased serum cholesterol and low density lipoprotein (LDL), tobacco use and alcohol consumption in these cases. Multivariate logistic regression analysis has shown that subjects having severe vitamin D deficiency [25(OH)VitD <10 ng/ml] had increased risk of getting MI [odds ratio (OR)=4.5, 95% CI=2.2-9.2].[19] In the study conducted by Karur et al. on 314 AMI patients, 212 (67.5%) had deficient 25(OH)VitD levels and 50 (16%) had insufficient 25(OH) VitD levels.[20] In patients with lower socioeconomic status, sedentary lifestyle, diabetes mellitus, high LDL cholesterol, high triglycerides and smoking habits, decreased 25(OH) VitD levels were frequently observed. Mohammad et al. in his case-control study observed vitamin D was more deficient in cases than controls (57.7% and 51%, respectively) but there was no statistical significance ($p = 0.6$).[21] However, they found that vitamin D deficiency was strongly associated with diabetes mellitus in cases.

Safaie et al in their prospective case control study on 88 patients with acute coronary syndrome (ACS) reported vitamin D deficiency in 59.1% of the cases. Their study also observed a higher prevalence of vitamin D deficiency in STEMI patients (77.5%) as compared to NSTEMI (47.7%). The logistic regression analysis of their study revealed that the status of vitamin D deficiency (Odd ratio: 8.1, 95% CI: 2.3 – 28.2; $p = 0.001$) and history of previous MI (Odd ratio: 7.9, 95 % CI: 1.5 – 42; $p = 0.015$) are the main predictors of STEMI.[22] In a cohort study on 206 AMI patients (7% with STEMI) by Correia et al., the average serum vitamin D concentration was 20 ± 8.2 ng/ml, of which severe deficiency was reported in 10% of the subjects.[23] The mortality rate was significantly higher at 24% in vitamin D deficient patients when compared to non-deficient patients which was 4.9%.

In a recent study Akter et al. reported significantly lower levels of vitamin D levels in STEMI ($p = 0.001$) and NSTEMI ($p = 0.004$) in comparison to controls subjects. Their study suggested that vitamin D deficiency could be an individual risk factor for the development of AMI.[24] Cannistraci et al., conducted a large-scale study on 2270 cases from different geographic locations across the both the hemisphere and also multi-ethnic population whether the circadian variation of STEMI onset is altered in summer season.[25] In the study it was observed that the difference between numbers of diurnal and nocturnal STEMI was significantly decreased during summer season. They stated that during summer months the average day light hours are more and diurnal STEMI episodes had an inverse relationship to serum 25(OH)VitD levels. This suggests the importance of higher

day light hours that can putatively reduce the incidence of diurnal STEMI by modulating serum vitamin D levels.

Welles et al. found after a median follow-up of 8.0 years among 946 participants following adjustment for sociodemographic factors, season of blood measurement, health behaviours and comorbid conditions, that cardiovascular events were independently associated with 25(OH)VitD levels below 20 ng/ml.[26] In the study conducted by Ng et al. on 1259 acute coronary syndrome patients for assessing their prognosis with serum vitamin D concentration observed that the lowest vitamin D quartile (< 7.3 ng/ml) was associated with long-term major adverse cardiovascular events.[27] Similarly, Deleskog et al. in their case-control study of MI in patients above 60 years of age, documented decreased 25(OH)VitD, concentration in cases than controls.[28]

Anderson et al in their analysis observed that vitamin D deficiency is associated with increased prevalence of cardiovascular risk factors such as diabetes, hypertension, and hyperlipidaemia as well as cardiovascular diseases and stroke.[29] Lee et al. found that in 239 patients who were enrolled in a 20-hospital prospective myocardial infarction registry, 179 (75%) were 25(OH)VitD deficient and 50 (21%) were insufficient.[30] A nested case-control study conducted by Giovannucci et al in large cohort of 18,225 male health professionals aged between 40 to 75 years, during a 10 years follow-up found that men deficient in 25(OH)VitD (≤ 15 ng/ml) were at increased risk of developing MI.[31] Vitamin D deficiency is associated with many health-related issues, including non-skeletal manifestations. The association between decreased serum vitamin D concentration with cardiovascular diseases and its risk factors has been studied in both animal and human subjects.[32]

Vitamin D status can be rapidly determined by testing serum 25(OH)VitD and can be corrected by supplementation. Studies and trials on the effect of vitamin D supplementation on cardiovascular risk factors are conflicting with inconsistent results. In an experimental study on 56 male MI model Wistar rats, it was found that vitamin D_3 supplementation along with aerobic-resistance exercise training significantly improved their functional performance indicated by higher cardiac ejection fraction.[33] Rats receiving both the intervention also showed under-expression of TGF-β (transforming growth factor-β1), smad 2/3 (mothers against decapentaplegic homolog 2/3) and collagen I/III which enhance cardiac function and attenuate myocardial fibrosis. Thus, vitamin D_3 along with aerobic exercise training can potentially reduce the morbidity related to AMI by modulating cardiac physiology and pathological fibrotic changes. On the contrary in a meta-analysis by Barbarawi et al. that included 21 randomized control trails found that there was no significant association between vitamin D supplementation and reduction in major adverse cardiovascular events, MI, stroke, CVD mortality or all-cause mortality.[34] The study pointed that there is possibly no role of vitamin D supplementation in providing cardiovascular protection. Wu et al. reported that vitamin D supplementation for 6 months in post-MI period significantly reduced the levels of inflammatory marker C-reactive protein (CRP) and decreased SYNTAX score, which is a scoring system for measuring the severity of coronary artery disease.[35] These findings show that the causative relationship between vitamin D deficiency, vitamin D supplementation and post-MI outcome need to be studied in detail.

The high prevalence of vitamin D demands for greater sample size which is limited in our study. The data on dietary patterns and sun light exposure was not collected in this study. There was also absence of control group that is adequate with normal vitamin D levels. The already established risk factors for MI confounds to state vitamin D deficiency as an independent risk factor. Large cross sectional and cohort studies with multivariate regression analysis including all the risk factors for MI are required to establish vitamin D deficiency as an independent risk factor. This would help in determining whether vitamin D supplementation in persons with deficiency could be beneficial for primary or secondary prevention of cardiovascular events. If successful, supplementation with easy and low-cost vitamin D can impact our health positively.

CONCLUSIONS

Our study established an association between vitamin D deficiency and myocardial infarction based on the serum levels of 25-hydroxyvitamin D and troponin I. The mean 25-hydroxyvitamin D levels were found to be significantly lesser in cases as compared to controls. Moreover, 25-hydroxyvitamin D was profoundly decreased among ST-elevation myocardial infarction cases compared to non-ST elevation myocardial infarction subjects. A significantly moderate negative correlation between serum levels of troponin I and 25-hydroxyvitamin D was observed in patients admitted with myocardial infarction. We also found that vitamin D deficiency exists among 44.7% of cases and 29.8% of controls respectively, which reflects its prevalence in the general population.

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