Original Article –

Correlation of Vitamin D level with severity of Coronary Artery Disease(CAD) in patients of Acute Coronary Syndrome(ACS) in a Tertiary Care Centre in Western India

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Abstract

Background : Vitamin D deficiency (VDD) is a widespread problem in developing countries. Recent studies have shown association of Vitamin D deficiency with atherosclerosis and Coronary artery disease. This study was conducted to assess the relationship between Vitamin D and the severity of coronary artery disease (CAD) in patients undergoing coronary angiography.

Materials and methods: Consecutive patients who underwent coronary angiography for acute coronary syndrome or effort angina were included in a descriptive cross-sectional study and their Vitamin D level was measured. CAD was defined as at least one vessel stenosis >50% on coronary angiography. Vitamin D levels were correlated to the CAG findings as to the severity and number of vessels involved and also to the traditional CAD risk factors

Results: Vitamin D Deficiency was noted in 70.72% of the population in the study. Patients were classified as normal Vitamin D level(> 30ng/ml), Vitamin D insufficiency (20-30ng/ml) and Vitamin D Deficiency (<20ng/ml). Vitamin D levels had inversely correlated with significant coronary artery disease both for number of vessels involved and severity ($p<0.001$) and dyslipidemia($p=0.009$). No significant association was found between VDD and other risk factors such as age, sex , hypertension, diabetes mellitus and smoking.

Conclusion : Vitamin D deficiency was noted in majority of the patients undergoing CAG and was found to be significantly associated with the prevalence and severity of CAD. However studies involving larger population are needed to evaluate whether supplementation with vitamin D may help in prevention of atherosclerosis and further development of CAD.

Keywords *Vitamin D, Coronary artery disease, Coronary angiography*

Introduction

Presently Cardiovascular disease is the leading cause of mortality in India and this has reached epidemic proportions.[1]In addition to the traditional risk factors of age, hypertension, diabetes mellitus etc, vitamin D Deficiency(VDD) is increasing being recognized to be associated with coronary artery disease and cardiovascular mortality and now considered as a risk factor for coronary atherosclerosis.[2, 3]Also studies have shown that Vitamin D deficiency is associated with other cardiovascular comorbidites like diabetes mellitus, hypertension, dyslipidemia, obesity, peripheral vascular disease and heart failure.[4, 5]It has been shown that vitamin D deficiency affects vascular function,

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accelerates atherosclerosis by plaque formation and progression and stimulation of systemic and vascular inflammation by upregulation of proinflamatory cytokines like TNF, IL-6 and upregulation of anti inflammatory cytokine IL-10.[6, 7]Also Vitamin D has been found to have a role in inhibition of vascular calcification and its deficiency can lead to increased risk of calcified coronary atherosclerotic lesions[8]

Vitamin D is a fat soluble vitamin which acts like a prohormone and mediates its functions by binding to the nuclear receptor (Vitamin D Receptor).[9]Vitamin D is synthesized in the skin as a pro-hormone on exposure to UltraViolet(UV-B) rays from sunlight as Ergocalciferol (Vitamin D2) and also absorbed in a small extent from the Gasterointestinal tract from food in form of Vitamin D3 (Cholecalciferol)and can be supplemented as Vitamin D3 in medication. All of these forms are activated in the liver to 25(OH)D, and further hydroxylated in the kidney to 1,25-dihydroxyvitamin D[1,25$(OH)_2$D]. the 25(OH)D is a stable form not affected by level of calcium, phosphate and Parathyroid hormone and has a half-life of 2–3 weeks and hence can be used as measure of vitamin D level in blood [10].The optimal range is reported as 25-80 ng/ml while Vitamin D insufficiency is reported as < 30 ng/ml and Vitamin D Deficiency(VDD) as < 20 ng/ml.[11] The prevalence of vitamin D deficiency is higher in the developing countries with some studies showing upto 50% of population having VDD. Risk factors for development of Vit D deficiency are (i)decreased intake due reduced sun exposure and malnutrition (ii) decreased absorption due to celiac sprue, inflammatory bowel disease (iii) metabolic factors like liver and kidney disease, nephritic syndrome and antiepilepsy medications.[11]

We conducted this study to determine the association of Vitamin D levels with severity of coronary artery disease in patients undergoing coronary angiogram and to establish correlation of Vitamin D Deficiency with conventional cardiac risk factors like Smoking, Hypertension, Dyslipidemia, Diabetes Mellitus and family history of CAD in patients.

Material and Methods

This was a cross sectional prospective study of 263 patients who underwent Coronary Angiography during a 3-month period at a tertiary care hospital in Western India. These included patients were of either gender and aged 18 to 75 yearswho underwent Coronary Angiography either for Acute Coronary Syndrome (Acute ST Elevation MI, Non-ST Elevation MI or Unstable Angina) or for Stable Effort Angina (symptomatic on medication). Patients who have liver or kidney disease, parathyroid disease, pregnancy, osteomalecia or taking drugs which affected Vitamin D metabolism were excluded from the study. Written and informed consent was taken from patients and their relatives for enrolment in the study.

Patients underwent CAG in the coronary Cath lab(PHILIPS FD-10) and interpretation of CAG was done by senior interventional cardiologist as to the number of vessels involved, severity of stenosis and calcification. The patients were divided into 3 groups based on the result of coronary angiography: Normal coronaries, non critical stenosis (<50% lumen stenosis of any coronary artery), and significant stenosis (>50% stenosis of a major coronary artery).Depending on number of vessels involved they were classified into Normal coronaries, single vessel disease (SVD), double vessel disease (DVD) or Triple Vessel Disease(TVD). In addition to routine investigations all these patients underwent Vitamin D [25-(OH)D] level measurement in the Biochemistry Department by an autoanalyzer . A level of Vitamin D > 30ng/ml was considered as normal, 20-30 ng/ml as insufficient and < 20ng/ml as deficient. Diabetes Mellitus, Hypertension, Dyslipidemia were defined based on standard definitions.

For quantitative variables under different groups undergoing CAG statistically analysis was done by using Mann-Whitney test. For qualitative variables chi square test was used. The data were analyzed using SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp and inference was drawn. A P value <0.05 was considered statistically significant.

Results

In our study of 263 patients who underwent CAG and Vitamin D level estimation, Vitamin D Deficiency was found in 186 (70.72%)patients, Vitamin D Insufficiency was found in 45(17.11%) patients while normal Vitamin D level was found in 32(12.16%) patients. There were 184 males (69.96%) and 79 females (30.03%) in the study population. Severe Vitamin D Deficiency (<20ng/ml) was found in 70.10% males and 72.15% females.

No statistical significant correlation was found between VDD and gender(p=0.732)

On evaluation of Vitamin D level with age, it was found that in the young(<30yrs) VDD was 50% while in > 30 years VDD was 74.43% and it was statistically significant (p=0.0018). (Table 1)

Table 1: Correlation of Vitamin D status and age

Age	Vit D <20ng/ml	Vit D 20-30ng/ml	VitD >30ng/ml	Total
<30 years	20	12	8	40
30-60years	155	23	20	198
>60years	11	10	4	25
Total	186	45	32	263

The level of Vitamin D was corelated with conventional risk factors for CAD like hypertension, Diabetes mellitus, Dyslipidemia and Smoking. 140 patients were hypertensive out of which 96(68.57%) had VDD, while 90(73%) of non hypertensives had VDD and this was not statistically significant (p=0.431).(Table2) Similarly on evaluation of VDD with Diabetes mellitus, 163 patients were found to be diabetic, out of which 114(69.93%) had VDD while 72(72%) non diabetics had VDD. The difference was not statistically significant(p=0.72). (Table3)

Table 2: Correlation between Vitamin D status and hypertension

Hypertension	Vit D <20ng/ml	Vit D 20-30ng/ml	VitD >30ng/ml	Total
Yes	96	28	16	140
No	90	17	16	123
Total	186	45	32	163

Table 3 : Correlation between Vitamin D status and diabetes mellitus

Diabetes Mellitus	Vit D <20ng/ml	Vit D 20-30ng/ml	VitD >30ng/ml	Total
Yes	114	32	17	163
No	72	13	15	100
Total	186	45	32	163

In our study 197 patients had dyslipidemia out of which 150 (76.14%) had VDD while 36 patients with normal lipid profile had VDD(54.54) and this correlation was found to be statistically significant (p=0.009)(Table4). Meanwhile there were 151 patients with history of smoking out of which 101 had VDD(51.41) while 85 non smokers(42.58) had VDD (p=0.11) which was statistically non significant

Table 4 : Correlation between Vitamin D status and dyslipdemia

Dyslipidemia	Vit D <20ng/ml	Vit D 20-30ng/ml	VitD >30ng/ml	Total
Yes	150	30	17	197
No	36	15	15	66
Total	186	45	32	163

The correlation of CAG findings of CAD severity with respect to the Vitamin D level was also evaluated. Number of patients with normal coronaries were 16(6.08%), single vessel disease(SVD) was 81(30.74%), with double vessel disease(DVD) was 123(46.76%) and triple vessel disease was 43(16.43%). Out of patients with normal coronaries 2 patients (12.5%) had Vitamin D Deficiency, patients with SVD 57(70.37%) had VDD, patients with DVD 91(73.98%) had VDD while in patients with TVD 36(83.72%) had VDD. On statistical analysis it was found that for each level of severity of CAD it was inversely related to the level of Vit D and was statistically significant for patients with TVD($p<0.001$) Patients with normal Vitamin D levels had less severe coronary artery disease compared to the ones with vitamin D level <20ng/ml.(Table 5). This is represented graphically with the graph showing the percentage of patients with CAD compared to the Vitamin D levels and shows the severity of CAD is inversely related to the level of Vitamin D in these patients (Figure 1)

Table 5 : Correlation between Vitamin D status and Coronary Artery Disease

No. of coronary vessels involved	Vit D <20ng/ml	Vit D 20-30ng/ml	VitD >30ng/ml	Total
Normal (0)	2	8	6	16
SVD(1)	57	16	8	81
DVD(2)	91	17	15	123
TVD(3)	36	4	3	43
Total	186	45	32	263

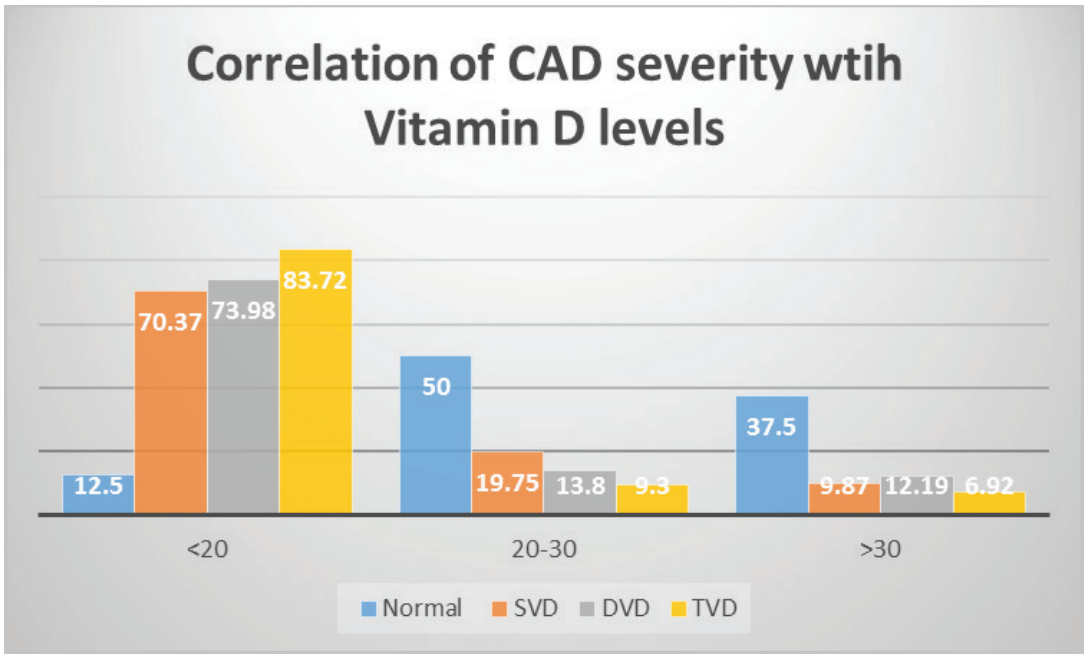

Figure 1. Percentage of patients with CAD corelated to the vitamin D levels

Discussion

There have been numerous studies in recent times highlighting the association of Vitamin D deficiency with higher incidence of CAD.[12-14]In fact these studies suggest that Vitamin D deficiency can act as an independent risk factor for CAD.[15, 16]Considering the limited data available from this part of India regrading Vitamin D level in patients with CAD this study was undertaken to corelate the risk of Vitamin D Deficiency with the severity of CAD along with their Coronary Angiogram findings.

In our study of 263 patients who underwent CAG, Vitamin D deficiency was detected in 70.72% patients. This number is similar to previous values in studies conducted in India.[17]The main finding of our study is a significant association between measured low Vitamin D level and the prevalence of severe CAD. Furthermore, as evident in figure 1 patients with Vitamin D Deficiency had significant coronary artery disease as compared to those who had normal Vitamin D level ($p<0.001$).This is in sync with studies by Chenet al, Danik et al etc have showed that low level of Vitamin D is associated with CAD.[13, 15, 18, 19] . Also angiographically it has been shown that the patients with low Vitamin D levels have higher number of coronary artery involvement. [16] In our study too VDD was present in more patients with SVD(70.37%), DVD(73.98) and TVD(83.72) and higher number of coronaries involved as compared to patients with normal Vitamin D levels.(Figure 1) Higher rate of Coronary Artery Calcification was also observed in our study indicating higher plaque burden in patients having VDD.

No significant difference between gender and Vitamin D level was noted in our study($p=0.732$). Previous studies have however shown Vitamin D level to be lower in females compared to males[20] and this was attributed to females staying indoor, purdah and ghunghat practices, malnutrition and frequent pregnancies and lactation making them more Vitamin D deficient.

We found Vitamin d deficiency more in the elderly compared to the younger population ($p=0.018$). This was also seen in previous studies where VDD was observed in elderly and posutulated that with advancing age the ability of skin to synthesize Vitamin D decreases as well as they may have reduced renal and hepatic metabolism which affects the pathways of its synthesis. [10, 13]

In our study we found no significant correlation of Vitamin D levels with relation to Hypertension($p=0.431$) and patients with Diabetes ($p= 0.72$). Some studies have shown that Vitamin D level are lower in patients with

hypertension[13, 19, 21] and Diabetes [19, 22, 23]. Smoking inhibits Vitamin D induced translocation of VDR from the nucleus to the cell membrane, VDD has been observed in previous studies in smokers[24] our study found no significant correlation between smoking and VDD(p=0.11). We found dyslipidemia to be significantly corelated with Vitamin D deficiency(p=0.009). This has been observed in previous studies by Rolf et al, [25] Vitamin D deficiency affecting calcium absorption, Triglyceride metabolism, insulin resistance, disruption of lipoprotein metabolism leading to dyslipidemia have been postulated[26]

Limitations

This study was conducted on 263 patients and findings should be confirmed in large sample studies before being generalized. This was an observational study and the association of Vitamin D with CAD can't be postulated as a causal factor for the same and needs experimental and randomized control trials to evaluate this hypothesis further. This was a hospital-based cohort study from a single centerand not a population based study and findings cannot be generalized for the entire population

Conclusion

The field of interventional cardiology has progressed at a fast rate with newer techniquesof stenting techniques and pharmacological advances with dual antiplatelets and statins but still progression of atherosclerosis remains uncontrolled especially in high risk patients. Though conventional risk factors like Diabetes, Hypertension, smoking, dyslipidemia are given importance in the workup of CAD, new risk factors like low vitamin D level are not being recogonized and also it can be corrected much easily compared to other traditional risk factors. Our study shows VDD is widespread in India and also has a significant correlation to CAD. More widespread studies involving multiple centres and more patients should be undertaken to study the association further and steps for correction of Vitamin D deficiency in the population should be undertaken.

Ethical Clearance- Observational study and no intervention done in human subjects - institutional review committee was informed and study cleared.

Source of Funding- Self

Conflict of Interest – Nil

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