Is low Vitamin D Levels A Risk Factor for Coronary Artery Disease

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ABSTRACT

Introduction: Coronary artery disease (CAD) among Indians has been shown to occur at an early age and is more aggressive, extensive and malignant. In India deaths due to CAD occur in 52.2% as compared to only 22.8% in the developed world. Evolving data is indicating that vitamin D deficiency is playing an important role in genesis of coronary risk. Hence, we proposed to study whether the low Vitamin D levels a risk factor for coronary artery disease.

Material and methods: This is a cross sectional study conducted in 252 subjects from Narayana Medical College and Hospital, Nellore, Andhra Pradesh. Among 252 subjects, 154 subjects were normal healthy controls (Group I) and 98 were angiographically proven CAD cases (Group II). Biochemical parameters such as Fasting plasma glucose, Fasting Insulin, 25 (OH) vitamin D, Lipid profile, iPTH, hs CRP were measured. HOMA IR and Atherogenic indices were calculated.

Results: The study findings suggest that among both the groups 84.0% were found to be vitamin D deficient and insufficient, only 16.0% are with vitamin D sufficient levels. HOMA IR was more in CAD subjects as compared to controls. However no statistically significant association was found between 25(OH) D and HOMA IR.

Conclusion: The present study findings suggests that lower vitamin D level is a risk factor for cardiovascular diseases but only in presence of other risk factors. However, supplementation of vitamin D among control subjects might be beneficial on cardiovascular outcomes.

Keywords: Coronary Artery Disease, Vitamin D Deficiency, Insulin Resistance, HOMA IR

INTRODUCTION

Coronary Artery Disease (CAD) is one of the leading causes of death in India.[1] The pathogenesis for CAD has gained new insights apart from inflammation and atherosclerosis. Many epidemiological studies have linked vitamin D deficiency and CAD, which may be due to the presence of Vitamin D receptors on various tissues such as pancreatic β cells, cardiomyocytes, endothelial cells and vascular smooth muscle cells.[2,3] Though various in vitro studies have proved that Vitamin D deficiency is the causative factor for CAD, no evidence in humans been provided substantially.[4] Various invitro trials proved that vitamin D can suppress the intracellular NF-κB pathway to decrease CAD progression. Although India has abundant sunshine, it is still an unresolved issue whether Vitamin D deficiency is involved in the pathogenesis of CVD or vice versa.[5,6,7] The prevalence of vitamin D deficiency (<30ng/ml) is also very high in Southeast Asia and India. The mechanism of Vitamin D deficiency leading to atherosclerotic vascular disease is complex. Mostly it might involve raised parathyroid hormone (PTH) levels leading to heightened renin–angiotensin–aldosterone system activity (RAAS), insulin resistance, and inflammation.[8] But there is lack of study data from Indian population regarding association of vitamin D deficiency with CAD, comparing the vitamin D levels between angiography proven CAD and normal individuals.[9,10] Hence this study has been designed to find the association of serum Vitamin D levels with multifactorial risk factors of CAD and whether serum Vitamin D can be used as risk profile marker for CAD.

MATERIAL AND METHODS

This cross sectional case - control study was conducted at Narayana Medical College & Hospital, Nellore, Andhra Pradesh. This study was reviewed and approved by institutional ethics committee and all participants were provided written informed consent. A questionnaire was given to participants to collect data on family history, Vitamin D intake, other diseases, medication history. Subjects on Vitamin D supplementation and renal disease were excluded. A total number of 252 subjects were included as study participants. Angiographically proven (>50% stenosis) CAD cases (n= 98) were recruited from the department of cardiology and healthy individuals (n=154) were considered as controls.

Fasting blood samples were collected to estimate plasma Glucose, serum calcium, Phosphorus, PTH, Insulin, ALP, Total Cholesterol, TGL, HDL, LDL, VLDL and hsCRP using commercial kits. Atherogenic indices were calculated.[11] Anthropometric parameters like Height, weight, BMI, systolic and diastolic blood pressure were measured by standardized techniques. Analysis of data was done by dividing controls as group I and cases as group II. All the biochemical and biological parameters were compared in both the groups. Vitamin D status was compared between the groups as sufficient (>30 ng/ml), Insufficient (20 -30ng/

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ml) and deficient (<20ng/ml).[12] Insulin resistance (HOMAIR >2.5) was measured and compared between the groups. HOMA- IR (mg/dl x mIU/L) = fasting glucose (mg/dl) x fasting insulin (mIU/L) /405.[13]

STATISTICAL ANALYSIS

Data distribution was tested using Kolmogorov Smirnov test. Continuous variables are expressed as mean ± standard error of mean (SEM) and as frequency (number [%]) for categorical data. Comparison of means of biochemical parameters in the study groups were assessed using Independent samples t test. Pearson correlation analysis was performed to find correlation between 25 Hydroxy Vitamin D levels with insulin resistance**.** Statistical analysis was performed using Microsoft Excel spread sheets, SPSS software for windows version 25 (SPSS Inc., Chicago, IL, USA). A $P < 0.05$ was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study subjects are shown in Table 1. The mean age of CAD patients was more when compared with control group and was found to be statistically significant (p = 0.001). Among the two groups, males are more compared to females showing male preponderance in both the groups. Body mass index was more in control group compared to patients but was not statistically significant (p=0.535). In the present study the number of diabetics and hypertensives were lesser among CAD patients when compared to non-diabetics and non-hypertensives. Table 2 shows the biochemical parameters of the study subjects in both the groups. In the present study, FBS, fasting insulin, HOMA-IR and hs CRP levels were found to be higher in CAD patients when compared to controls which was found to be statistically significant (p < 0.001). Figure 1 is the vitamin D status based on cut off in

Parameters	Group I (n= 154)	Group II (n=98)	P value
Age (Years)	35.24± 11.73	50.15± 6. 49	0.001*
Male (%)	93 (53 %)	82 (47%)	0.657†
Female (%)	61 (79 %)	16 (21%)	0.001*
Body mass index	24.85± 4. 49	23.34± 1.98	0.535†
DM (n%)	-	23%	
HTN (n%)	-	07%	
* Significant at the 0.05 probability level. † NS- Not significant at the 0.05 probability level. Group I = Apparently healthy Controls; Group II = Coronary artery disease patient			

Table-1: Demographic and clinical characteristics in the study groups

Parameters	Group I (n= 154)	Group II (n=98)	P value
Fasting plasma glucose (mg/dl)	75.91 ±1.15	99.61 ±5.88	0.001*
Serum 25(OH) Vitamin D3 (ng/ml)	21.51 ± 0.65	23.25±0.90	0.367†
Fasting Insulin (µu/ml)	4.19±0. 43	20.01 ± 2. 45	0.001*
HOMA IR	0.83 ±0.10	4. 43±0.48	0.001*
TC (mg/dl)	187.10 ± 5.68	145.28± 4.42	0.154†
TGL (mg/dl)	165.88 ± 6.52	142.08± 6.36	0.010*
VLDL (mg/dl)	32.96± 1.31	28.41± 1.27	0.009*
HDL (mg/dl)	46. 34± 1.70	35.41± 1.26	0.126†
LDL (mg/dl)	79.30 ± 2.15	81.46± 2.90	0.546†
TC/ HDL ratio	4.10 ± 0. 04	4.18 ± 0. 04	0. 492†
TGL/ HDL ratio	4.03 ± 0.22	4.44 ± 0.24	0. 572†
LDL/ HDL ratio	2.30 ± 0.01	2.30 ± 0.01	1.000†
Non HDL	139.54 ± 4.13	109.87 ± 3.23	0.107†
Non HDL/ HDL ratio	3.10 ± 0.04	3.18 ± 0. 04	0. 492†
Log TGL/ HDL ratio	0.52 ± 0.02	0.58 ± 0.02	0. 477†
Serum PTH (pg/ml)	24.88 ±1.51	26.81 ±2.74	0.088†
Hs CRP (mg/L)	2.86 ±0.25	8.05 ± 0.22	0.001*
Group I= Apparently healthy Controls; Group II = Coronary artery disease patients; * Significant at the 0.05 probability level †NS - Not significant at the 0.05 probability level. TC: Total Cholesterol; TGL: Triglycerides; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; HDL: High density lipoprotein, PTH- Parathyroid Hormone			

Table-2: Biochemical parameters in control and CAD groups

Parameters	Non diabetic (n= 75)	Diabetic (n=23)	P value
Serum 25(OH) Vitamin D3 (ng/ml)	23.85±1. 42	21.32 ± 1.09	0.162†
HOMA IR	3.39 ±0. 43	7. 83± 1.26	0.002*
* Significant at the 0.05 probability level † NS- Not significant at the 0.05 probability level.			

Table-3: Comparison of Vitamin D status among Non diabetic and diabetics in CAD group

cases and controls in total. Majority of the study subjects were found to have vitamin D levels < 20 ng/ml (44.0%) followed by 20-30 ng/ml (40.0%) and > 30 ng/ml (16.0%)

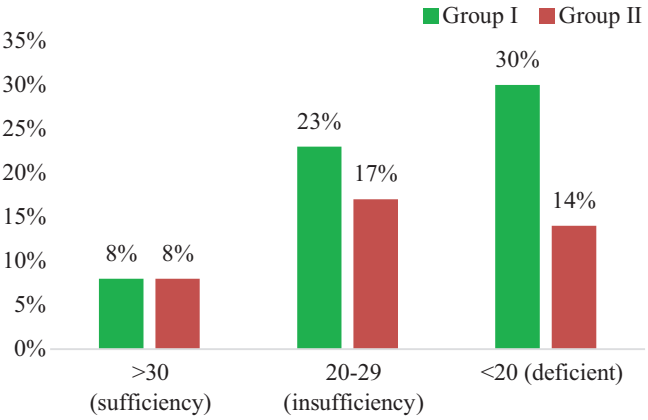

Figure-1: Vitamin D levels in control and CAD groups

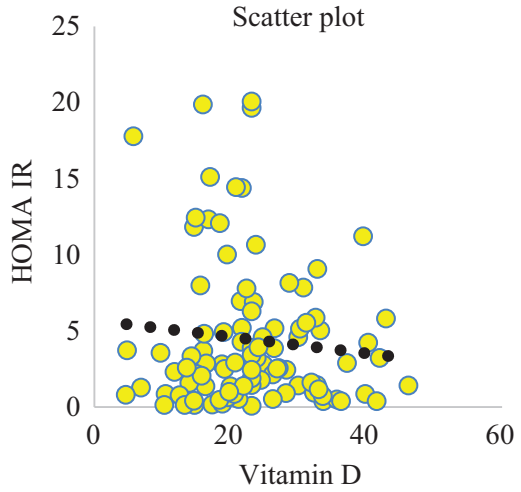

Figure-2: Scatter plot showing association between Vitamin D and HOMA IR

Parameter	r value	p-value
Fasting Insulin (µu/ml)	-0.075	0.468†
HOMA IR	-0.101	0.325†
TC (mg/dl)	- 0.118	0.067†
TGL (mg/dl)	- 0.016	0.797†
HDL (mg/dl)	- 0.125	0.047*
LDL (mg/dl)	- 0.109	0.085*
Serum PTH (pg/ml)	-0.014	0.825†
hs CRP (mg/L)	0.100	0.144†

r - Correlation coefficient * Significant at the 0.05 probability level. †Not significant at the 0.05 probability level.

Table-4: Pearson correlation analysis of 25 Hydroxy Vitamin D levels with insulin resistance in patients with Coronary artery disease

levels. Comparison of Vitamin D status among non-diabetic and diabetics in CAD group was shown in Table 3. HOMA-IR levels were found to be higher in diabetic CAD patients when compared to non diabetic CAD patients which was found to be statistically significant (p =0.002). Correlation analysis for 25 Hydroxy Vitamin D levels with insulin resistance was shown in Table 4 and figure 2. In the present study there was a inverse correlation of 25 Hydroxy Vitamin D levels with HOMA IR (r = -0.101, p = 0. 325) but was not statistically significant. Insulin Resistance status in group I & II was shown in table 5.

DISCUSSION

Evolving data indicates that vitamin D deficiency is playing an important role in genesis of coronary risk and CVD. In the MIDSPAN family study, with a median follow up of 14.4 years, plasma levels of vitamin D less than 15 ng/mL were associated with all-cause mortality, but not the risk of CV diseases.[14] Additionally, in a study involving 746 patients undergoing coronary angiography, no correlation was found between vitamin D levels (<20 ng/mL vs. >20 ng/mL) and the degree and severity of coronary artery disease.[15] In a large Middle Eastern study of 60,979 patients from 136 countries with year long sunlight, 82.5% of studied patients were found to have vitamin D insufficiency.[16] The prevalence of Vitamin D deficiency ranged from 40% to 99%, with most of the studies reporting a prevalence of 80%–90%, in consistent with this,our study findings project 84% of the study participants had Vitamin D insufficiency.[17,18] However, whether vitamin D deficiency represents a new cardiovascular risk factor and its supplementation can reduce the incidence of cardiovascular events is still unclear. Moreover, there are no data on Indian subjects linking vitamin D deficiency and insulin resistance with CAD. In the present study, serum 25(OH) vitamin D3 levels were found to be decreased in both CAD patients and control group but Vitamin D levels did not differ significantly between groups (p= 0.367). These findings are comparable to the studies who compared healthy participants with 128 acute MI or angina patients and reported similar 25(OH)D levels between both the groups. The results showed that vitamin D does not seem to protect against AMI and stroke.[19,20] These findings suggests that Vitamin D deficiency is not a risk factor for CAD, but an associated finding which has to be explored in terms of Visceral fat distribution.

In the present study, fasting insulin and HOMA-IR levels were found to be higher in CAD patients when compared to controls which were found to be statistically significant (p < 0.001). Among group II (Cases) 91.0% were having HOMAIR >2.5, 79.0% of subjects had insufficient vitamin

Parameters	Group I (n= 154)	Group II (n=98)	P value
HOMA IR < 2.5	118 (76 %)	75 (24%)	0.001†
HOMA IR > 2.5	36 (9 %)	23 (91%)	0.001*

Group I = Apparently healthy Controls; Group II = Coronary artery disease patients; *Significant at the 0.05 probability level †NS-Not significant at the 0.05 probability level.

Table-5: Insulin Resistance status in group I & II

D level, which indicates that insulin resistance is one of the leading cause and marker for CAD. Normally, vitamin D may have a beneficial effect on insulin action either directly by stimulating the expression of insulin receptors and thereby enhancing insulin responsiveness for glucose transport, or indirectly via its role in regulating extracellular calcium and ensuring normal calcium influx through cell membranes and intracellular cytosolic calcium in insulin-responsive tissues such as skeletal muscles and adipose tissues.[21,22] Rajasree et al. in their study reported a higher prevalence of elevated vitamin D and calcium levels in CAD patients than controls and proposed the hypothesis of vitamin D-mediated arteriolar calcification leading to atherosclerosis.[23] Hence by our study findings, the deficient /insufficient vitamin D levels and raised HOMAIR in CAD group signifies that vitamin D levels may have role on insulin action, may be at the receptor level, because we cannot directly prove the association with HOMAIR. This needs a large scale invitro and also clinical trials to prove this association. Moreover, more studies are required to assess whether hypovitaminosis D is associated directly with acute MI among patients with T2DM and to investigate the clinical implications of this association in the prevention and management of cardiovascular events such as acute MI.[24,25] However recommend to measure serum vitamin D levels for all T2DM patients and to treat it if it was deficient to decrease the relative risk of acute MI. Few observational studies found association between vitamin D levels and metabolic parameters. However, there are studies presenting the lack of any impact of vitamin D on metabolic parameters associated with insulin resistance in patients and healthy subjects.[26,27] Therefore deeper understanding of vitamin D molecular involvement in processes related to insulin signaling may result in new therapeutic strategies preventing from development of insulin-resistance-associated disorders in Coronary artery disease patients. By our findings it is proved that there is significant percentage of Vitamin D deficiency in both cases and controls. So, we cannot attribute vitamin D deficiency to CAD. Future epidemiological studies are needed to define a cut off of 25(OH) D levels in Indians.

CONCLUSIONS

Taken together, observations of the present study suggest that hypovitaminosis of vitamin D is not a risk factor for cardiovascular outcomes in Coronary artery disease patients. However, the present study findings suggests that vitamin D may have an important role in regulating glycemic control, which might contribute to beneficial effect on cardiovascular outcomes. Henceforth, supplementation of vitamin D might be beneficial on cardiovascular outcomes among patients without coronary artery disease.

REFERENCES

1. Gomar FS, Quilis CP, Leischik R, Lucia A., Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med. 2016; 4: 256.
2. Kristen LJ, Michel C, Gary LP, Ashley EW, Douglas RS. 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. Hypertension. 2011;57:63–69.
3. Ai S, He Z, Ding R, et al. Reduced vitamin D receptor on circulating endothelial progenitor cells: a new risk factor of coronary artery diseases. J Atheroscler Thromb 2018; 25:410–21.
4. Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? J Am Coll Cardiol. 2008;52:1949–56.
5. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008;117:503-5
6. Karur S, Veerappa V, and Nanjappa MC. Study of vitamin D deficiency prevalence in acute myocardial infarction. IJC Heart & Vessels. 2014;3:57–59.
7. Akhtar T, Aggarwal R, Sachin K. Serum Vitamin D Level in Patients with Coronary Artery Disease and Association with Sun Exposure: Experience from a Tertiary Care, Teaching Hospital in India. Advances in Medicine, 2019;1-5
8. Aggarwal R, Akhthar T, Jain SK. Coronary artery disease and its association with Vitamin D deficiency. J Midlife Health. 2016;7:56–60
9. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, et al. Systematic review: vitamin D and cardiometabolic outcomes. Ann Intern Med. 2010;152:307–14.
10. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D, Srinivasarao PV, Sarma KV, et al. High prevalence of low dietary calcium, high phytate consumption, and Vitamin D deficiency in healthy South Indians. Am J Clin Nutr. 2007;85:1062–7.
11. Jafar TH Chaturvedi N and Papps G. Prevalence of Overweight and Obesity and their Association with Hypertension and Diabetes Mellitus in an Indo- Asian Population. CMAJ 2006; 175:1071-7.
12. Dawson-Hughes B, Mithal A, Bonjour JP, Boonen S, Burckhardt P, Fuleihan GE, et al. IOF position statement: Vitamin D recommendations for older adults. Osteoporos Int. 2010;21:1151–4.
13. Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. Diabetes Care. 1997;20:1087–92.
14. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of Vitamin D deficiency: An endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–30.
15. Alsancak Y, Cengel A, Akyel A, Ozkan S, Sezenoz B, Unlu S, et al. Relationship between serum vitamin D levels and angiographic severity and extent of coronary artery disease. European Journal of Clinical Investigation. 2015;45:940-948.
16. Rodriguez G, Starr AZ, Czernuszewicz GZ, Manhas A, Alhariri A, Willerson JT, et al. Determinants of plasma vitamin D levels in patients with acute coronary syndromes. Eur J Clin Invest 2011; 41:1299–1309.
17. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, WellinitzB, Kinkeldei J, Boehm BO,WeihrauchG, Maerz W. Independent association of low serum

25- hydroxyl vitamin D levels with all cause and cardiovascular mortality. Arch Intern Med 2008; 168: 1340-49.
18. Tepper S, Shahar DR, Geva D, Avizohar O, Nodelman M, Segal E, et al. Identifying the threshold for vitamin D insufficiency in relation to cardiometabolic markers. Nutrition, Metabolism, and Cardiovascular Diseases
19. Babu US, Calvo MS. Modern India and the Vitamin D dilemma: Evidence for the need of a national food fortification program. Mol Nutr Food Res. 2010;54:1134–47
20. Aparna P, Muthathal S, Nongkynrih B, Gupta SK. Vitamin D deficiency in India. J Family Med Prim Care. 2018;7:324-330.
21. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004; 79: 820-25.
22. Szymczak-Pajor I, Śliwińska A. Analysis of Association between Vitamin D Deficiency and Insulin Resistance. Nutrients. 2019;11:794.
23. S. Rajasree, K. Rajpal, C. C. Kartha et al. Serum 25-hydroxyvitamin D3 levels are elevated in South Indian patients with ischemic heart disease. European Journal of Epidemiology. 2001; 17:567–571.
24. Fahrleitner A, Dobnig H, Obernosterer A, Pilger E, Leb G, Weber K, et al. Vitamin D deficiency and secondary hyperparathyroidism are common complications in patients with peripheral arterial disease. Journal of General Internal Medicine. 2002;17:663-669.
25. Pilz S, Tomaschitz A, Drechsler C, Ritz E, Boehm BO, Grammer TB, et al. Parathyroid hormone level is associated with mortality and cardiovascular events in patients undergoing coronary angiography. European Heart Journal. 2010;31:1591-1598.
26. Deleskog A, Piksasova O, Silveira A, Samnegård A, Tornvall P, Eriksson P, et al. Serum 25-hydroxyvitamin D concentration, established and emerging cardiovascular risk factors and risk of myocardial infarction before the age of 60 years. Atherosclerosis 2012; 223:223–229.
27. Murr C, Pilz S, Grammer TB, Kleber ME, Meinitzer A, Boehm BO, et al. Vitamin D deficiency parallels inflammation and immune activation, the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. Clin Chem Lab Med 2012;50:2205-12.

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