

# Association of Vitamin D Level with Severity of Angiographically Documented Coronary Artery Disease: Observations from Bangladeshi Patients

Ashraf Ur Rahman<sup>1,\*</sup>, Pradip Kumar Karmakar<sup>1</sup>, Sabrina Jabeen<sup>2</sup>, Shaila Nabi<sup>1</sup>, Ahad Mahmud Khan<sup>3</sup>, Saqif Shahriar<sup>1</sup>, Ifteqar Alam<sup>1</sup>, Shubhra Chakraborty<sup>1</sup>, Mohammad Abdul Matin<sup>4</sup>, S T M Abu Azam<sup>1</sup>

<sup>1</sup>Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Sher-e-Bangla Nagar, Dhaka, BANGLADESH.

<sup>2</sup>Icddr'b, Dhaka, BANGLADESH.

<sup>3</sup>Johns Hopkins University Bangladesh- Projahnmo, Dhaka, BANGLADESH.

<sup>4</sup>Upazila Health Complex, Parshuram, Feni, BANGLADESH.

## ABSTRACT

**Introduction:** Hypovitaminosis D may play unique role in the pathogenesis of Coronary Artery Disease (CAD), promoting accelerated atherosclerosis and subsequent cardiovascular events. Recent research has highlighted vitamin D deficiency as a novel cardiovascular risk marker, in addition to conventional and genetic risk factors. **Objective:** The objective of the study was to find out association between low vitamin D level and severity of coronary artery disease. **Material and Methods:** It was a cross sectional study carried out among 102 patients undergoing elective coronary angiography due to CAD in National Institute of Cardiovascular Diseases (NICVD), Bangladesh from May 2016 to April 2017. Serum 25-hydroxyvitamin D level of each patient was measured and categorized as deficient, insufficient and normal if the value were <20, 20 to <30 and ≥30 ng/mL respectively. Coronary Angiogram (CAG) was done during index hospitalization. The severity of the CAD was assessed by vessel score and Gensini score. **Results:** Out of 102 patients, 75 (73.5%) patients had vitamin D level <30 ng/ml, while 27 (26.5%) patients had normal level (≥30 ng/ml). Female patients had lower vitamin D level than male (Mean 20.4± 8.3 ng/ml vs 26.0± 10.1 ng/ml) ( $p=0.017$ ). Double or triple-vessel CAD were more frequent in those with 25(OH)D levels <30 ng/mL as compared to those with normal levels (≥30 ng/ml) ( $p<0.001$ ). Moderate to severe CAD (Gensini score ≥36) was found in 64.1% of patients with vitamin D insufficiency and 75.0% of patients with vitamin D deficiency ( $p<0.001$ ). Serum vitamin D level inversely correlated with both vessel score ( $r=-0.478$ ,  $p<0.001$ ) and Gensini score ( $r=-0.667$ ,  $p<0.001$ ). Multiple linear regression showed that vitamin D was associated with vessel score ( $\beta = -0.03$ , 95% CI = -0.05 to -0.02,  $p<0.001$ ) and Gensini score, Serum vitamin D levels, angiographic severity of CAD ( $\beta = -1.2$ , 95% CI = -1.6 to -0.8,  $p<0.001$ ) adjusting for diabetes mellitus, dyslipidemia and body mass index in the model. **Conclusion:** Serum vitamin D levels are inversely associated with angiographic severity of CAD. Low vitamin D level may be an emerging, independent and reversible cardiovascular risk factor.

**Key words:** Coronary artery disease, 25-hydroxyvitamin D, Vessel score, Gensini score.

## Correspondence

**Dr. Ashraf-Ur-Rahman**

Assistant Registrar, Department of Cardiology, National Institute of Cardiovascular Diseases (NICVD), Sher-e-Bangla Nagar, Dhaka-1207, BANGLADESH.

**Ph.no:**+88 02 9122560-74

**E-mail address:** tbspublication@gmail.com

**Submission Date:** 07-02-2019;

**Revision Date:** 08-03-2019;

**Accepted Date:** 31-03-2019.

**DOI:** 10.5530/jcdr.2019.2.10

## INTRODUCTION

In the quest to identify new predictors of Coronary Artery Disease (CAD) the focus has been shifted to vitamin D, given its association with various established risk factors for CAD like hypertension, diabetes, obesity, metabolic syndrome, congestive heart failure and prevalent coronary artery disease. Adequate levels of Vitamin D is important for optimal Cardiovascular (CV) function.<sup>1,2</sup>

Vitamin D<sub>3</sub>, “the sunshine vitamin,” is synthesized in the human epidermis via ultraviolet irradiation or it may be consumed in the form of oily fish or supplement.<sup>3</sup> The active form of vitamin D is Calcitriol (D<sub>3</sub>), which influences cellular growth, proliferation and apoptosis, oxidative stress, membrane transport, matrix homeostasis, cell adhesion and immune system functions and may regulate a large number of genes and healthy aging.<sup>4,5</sup> Vitamin D deficiency is considered a cardiovascular risk factor “non - classical”, which is very often unrecognized and untreated.<sup>6</sup> The low level of 25-hydroxy vitamin D [25(OH)D] has been shown to be associated with the prevalent Coronary Artery Disease (CAD) independently of other recognized cardiovascular risk factors.<sup>7</sup> Indoor lifestyle, sun avoidance strategies, obesity, diabetes mellitus, low HDL cholesterol, older age, distance from the equator, darker skin, winter season, air pollution, smoking, malabsorption, renal and liver disease and medications (anticonvulsants, glucocorticoids, antirejection medications and human immunodeficiency virus therapy) are the main mediators of Vitamin D insufficiency.<sup>8</sup> Due to longer biological half-life and higher concentra-

tions, 25(OH)D (D<sub>2</sub>) is considered to be the best indicator of vitamin D status.<sup>9,10</sup> Based on the existing data from laboratory studies, epidemiologic and experimental research and prevention trials, recent research has found linkage of inadequate vitamin D status with non-skeletal major chronic diseases, especially cardiovascular diseases.<sup>11</sup> Despite unconvincing results of vitamin D supplementation on mortality, poor vitamin D status was associated with cardiovascular and overall mortality.<sup>10</sup> Most experts define vitamin D deficiency as a calcidiol (D<sub>2</sub>) level of <20 ng/mL (50 nmol/L) and insufficiency as 21–29 ng/mL (51–74 nmol/L).<sup>12</sup> Vitamin D is sufficient if >30 ng/mL (75 nmol/L) and vitamin D intoxication is considered if >150 ng/mL (>375 nmol/L).<sup>13</sup> Zittermann *et al.*<sup>14</sup> found a vitamin D level of 30–35 ng/L as the best choice for risk reduction in cardiovascular mortality.

The prevalence of hypovitaminosis D is a global problem in all age groups, even in countries with good sun exposure all year round.<sup>15</sup> Almost one billion people in the world suffer from vitamin D deficiency or insufficiency.<sup>1</sup> In the National Health and Nutrition Examination survey 2005 to 2006 data, the prevalence of vitamin D levels <20 ng/ml (50 nmol/L) was 41.6 % in US adults. Despite adequate sunshine suboptimal vitamin D level is very common among the women of many southeast Asian countries including India and Pakistan.<sup>16,17</sup> In Bangladesh serum 25(OH)D <37.7nmol/l was seen in 50% of those in low income groups compared to 38% of high-income groups median. Lactating women have higher prevalence of hypovitaminosis D. Majority of Bangladeshi women wear

covered style of dress (like Burkha and Sari) which may negatively affect the Vitamin D status of many women in this part of the world.<sup>18</sup> The deficiency of Vitamin D suppresses inflammation via several biogenic pathways and stimulates systemic and vascular inflammation, which allows atherogenesis.<sup>3</sup> The development of hypertension is caused by the activation of the Renin Angiotensin Aldosterone system, which enables endothelial dysfunction associated with vitamin D deficiency.<sup>8</sup> Calcitriol regulates the genes involved in insulin production in the pancreas. Chronic Vitamin D deficiency also causes secondary hyperparathyroidism, increasing insulin resistance, impairing beta-pancreatic cell function and enabling the development of metabolic syndrome and diabetes mellitus.<sup>3</sup> Vitamin D is involved in regulation of growth and proliferation of smooth muscle cells and cardiomyocytes. Vascular smooth muscle cells and endothelial cells express receptors for Vitamin D, enabling conversion of calcidiol to calcitriol.<sup>9,19,20</sup> By acute influx of calcium into the cell, Vitamin D inhibits proliferation of vascular smooth muscle cells and increases calcification of smooth muscle cells.<sup>19</sup> Hypovitaminosis D is also associated with vascular stiffness, which is a known predictor of cardiovascular morbidity and mortality and a marker of subclinical atherosclerosis. Vitamin D deficiency was strongly associated with slow coronary flow, endothelial dysfunction and subclinical atherosclerosis, in patients with normal or near-normal coronary arteries at coronary angiography.<sup>21</sup> Several studies found increased risk of developing an acute myocardial infarction in individuals with Vitamin D levels lower than 30 ng/ml.<sup>22,23</sup> A significant association was found between circulating Vitamin D concentration and the risk of all-cause mortality, especially deaths due to CAD. The severity of coronary artery stenosis, assessed according to the Gensini score was associated with Vitamin D deficiency.<sup>24</sup> CAD is an increasingly important medical and public health problem and is the leading cause of mortality in Bangladesh. In addition to genetic and conventional risk factors; novel risk factor like hypovitaminosis D may play unique role in development of CAD.<sup>25</sup> People with deficient 25 (OH) D have higher risks of diabetes mellitus, obesity, hypertension, peripheral vascular disease, myocardial infarction, heart failure and ultimately mortality.<sup>26-28</sup> Low Vitamin D levels have been linked to inflammation, higher coronary artery calcium scores, impaired endothelial function and increased vascular stiffness.<sup>8</sup> Vitamin D deficiency can be considered to be an emerging cardiovascular risk marker. Despite of rising prevalence of coronary artery diseases among South Asian people, studies with angiographically documented coronary artery diseases and its association with Vitamin D level are very limited and reveal conflicting results. As per knowledge of the researcher no such study was found to be done in the context of Bangladesh. Therefore, this study was done to see the association in the country perspective of this country.

## MATERIALS AND METHODS

It was a cross sectional study carried out at National Institute of Cardiovascular Diseases (NICVD) from May 2016 to April 2017. The study protocol was approved by the Ethical Review Committee of NICVD. Total 102 Patients with Ischemic Heart Disease (IHD) undergoing Elective Coronary Angiography (CAG) were considered for inclusion in the study after the following exclusions: CKD (eGFR less than 60 mL/min per 1.73 m<sup>2</sup>), hepatic impairment, known malignant disease, patients on vitamin D or calcium supplementation, hyperparathyroidism or hypercalcemia and patients taking anticonvulsants, glucocorticoids or anti-HIV medications.

The questions were described in the native language to the participants. The participants had the right to be withdrawn from the study at any time. After taking informed written consent, meticulous history was taken and detailed clinical examinations were performed and recorded in semi-structured questionnaire. Risk factors profile including smoking,

hypertension, diabetes, dyslipidemia, alcohol intake and family history of CAD were noted. Body Mass Index (BMI) was measured and laboratory investigations were done which included serum Troponin I, serum Creatinine, random blood sugar, fasting lipid profile and serum calcium level. Transthoracic echocardiography was done on the day before coronary angiogram.

Serum 25-hydroxyvitamin D estimations were carried out by Immunit 2000 (DPC)/Vitros ECI System (J&J)/Abbott AxSym System Random Access Multibatch Immunoassay Analyzer. The level of 25 (OH) D  $\geq$ 30 ng/ml was considered as normal, 20 to <30 ng/ml was considered as insufficient and <20 ng/ml as deficient.

## Cardiac procedures

Coronary Angiogram (CAG) was done by conventional method in the index hospitalization. Interpretation of CAG was done by visual estimation by two cardiologists to assess the severity of coronary artery disease. Severity of coronary stenosis was graded according to the number of major epicardial vessel with significant stenosis (vessel score) and Gensini score.

## Vessel score

Significant CAD was defined as >70% stenosis in any of the three major epicardial coronary arteries or a left main coronary artery stenosis >50%. Angiograms revealing coronary artery stenosis <70% in major epicardial coronary arteries were termed non-obstructive CAD. Extent of coronary artery disease was defined as significant single, two or three vessel coronary artery disease.<sup>29</sup> Score ranges from 0 to 3 depending on the number of vessel involved. Left main coronary artery was scored as single vessel disease.<sup>30</sup>

## Gensini Score

A nonlinear score was assigned to each lesion based on the severity of stenosis as indicated by the reduction of lumen diameter. A multiplier was applied to each lesion score based upon its location in the coronary tree depending on the functional significance of the area supplied by that segment. The final Gensini score is the sum of the lesion scores. The score assesses 14 coronary artery segments, which are scored according to their anatomical importance (ranging from 0.5 to 5) multiplied by the score regarding the maximum degree of obstruction (score ranging from 1 to 32 for complete occlusion). The points of the 14 segments were summed to yield a final score.<sup>31</sup>

## Statistical analysis

Statistical Package for Social Sciences (SPSS) version 20 for windows was used to analyze the data. Descriptive statistics were computed. Chi-square test and Fisher's exact test were carried out to assess association of qualitative data. To compare the mean differences between the group's student's *t*-tests was done. Pearson correlation was done to see the association between two quantitative variables. Significant determinants identified from this analysis were studied and entered into a multiple regression model. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

### Demographic characteristics

The age of the patients ranged between 29 and 70 years with a mean of  $51.6 \pm 10.3$  years. Out of 102, 77 (75.5%) patients' age was 45 years or more. Among the patients, 80 (78.4%) were males and 22 (21.6%) were females. The mean age of male and female patients was  $52.7 \pm 10.4$  and  $47.4 \pm 8.6$  years, respectively.

### Vitamin D level among the patients

Out of 102 patients, 75 (73.5%) patients had Vitamin D level <30 ng/ml, while 27 (26.5%) patients had normal level (≥30 ng/ml) (Table 1). Average serum Vitamin D level was 24.81± 9.95 ng/ml with minimum 6.20 ng/ml and maximum 63.60 ng/ml.

Table 2 shows the association between demographic characteristics and Vitamin D level. Age did not show any association with Vitamin D level. On average female patients had lower vitamin D level than male (20.4± 8.3ng/ml vs 26.0± 10.1ng/ml). It was statistically significant ( $p=0.017$ ).

### Cardiovascular risk factors

Table 3 shows association between cardiovascular risk factors and severity of coronary artery disease. In case of BMI, mean Gensini score was significantly higher in overweight patients in comparison to normal patients ( $p=0.019$ ). Similarly, diabetic patients and patients with dyslipidemia had more severe CAD as they had significantly higher vessel score and Gensini score ( $p < 0.001$ ).

Figure 1a shows 95% stenosis in proximal segment of Left Anterior Descending Artery (LAD) and Figure 1b shows 75% stenosis in proximal segment of Left Circumflex Artery (LCX) of the same patient. So, this study patient had DVD and Gensini score was 50 indicating severe CAD while the patient had Vitamin D deficiency (16.30 ng/ml).

### Vitamin D level and severity coronary artery disease

Table 4 shows serum vitamin D level and severity of CAD where if serum vitamin D level is lower; then vessel involvement and Gensini score are higher for patients. There is an inverse relationship between them. Major proportion of patients (52.8%) with Vitamin D <20 ng/ml had double vessel disease. 41.0% ( $n=16$ ) patients had DVD in the group having vitamin D level 20-<30 ng/ml. Most of the ( $n=5$ , 62.5%) TVD cases were found in the group <20 ng/ml, while rest 37.5% ( $n=3$ ) TVD cases were within the group having Vitamin D level 20-<30 ng/ml. All of these were statistically highly significant ( $p < 0.001$ ).

Gensini score was categorized into two classes. Persons having score <36 had absent or mild CAD and those with score ≥ 36 had moderate to severe CAD.<sup>32</sup> Major proportion (75%) of patients with vitamin D deficiency and 64.1% with vitamin D insufficiency showed Gensini score ≥36. All the patients with normal vitamin D level (≥30 ng/mL) had Gensini score <36 which was statistically highly significant ( $p < 0.001$ ).

Figure 2 shows correlation between serum vitamin D level and vessel score ( $r = -0.478$ ,  $p < 0.001$ ) where serum vitamin D level inversely correlated with vessel score ( $r = -0.478$ ,  $p < 0.001$ ).

Figure 3 shows correlation between serum vitamin D level and Gensini score ( $r = -0.667$ ,  $p < 0.001$ ) where serum vitamin D level is inversely correlated with Gensini score ( $r = -0.667$ ,  $p < 0.001$ ).

Multiple linear regression was constructed with diabetes mellitus, dyslipidemia, BMI and vitamin D as independent variable and Vessel score and Gensini score as the dependent variable (Table 5). The analysis revealed that vitamin D was associated with vessel score ( $\beta = -0.03$ , 95% CI= -0.05 to -0.02,  $p < 0.001$ ) adjusting for diabetes mellitus and dyslipidemia and Gensini score ( $\beta = -1.2$ , 95% CI= -1.6 to -0.8,  $p < 0.001$ ) adjusting for diabetes mellitus, dyslipidemia and body mass index in the model.

### DISCUSSION

Our study demonstrates that low vitamin D level increased the risk of CAD and the association between angiographic severity of CAD and vitamin D deficiency remained significant even after adjustment for significant cardiovascular risk factors such as diabetes, dyslipidemia and higher BMI.

Vitamin D insufficiency and deficiency were very common among our study population. We found that 73.5% patients undergoing CAG had either vitamin D insufficiency or deficiency. Akin *et al.*<sup>24</sup> revealed in their study that 83% of the patients had vitamin D level less than 30 ng/mL which is similar to our findings. Another study also found higher proportion (93%) of vitamin D deficiency and insufficiency.<sup>33</sup> To the best of our knowledge, this is the first study to assess the relationship of serum

**Table 1: Distribution of Vitamin D level of the study population.**

Vitamin D level (ng/ml)	Frequency	Percentage
≥30	27	26.5
20-<30	36	35.3
<20	39	38.2
Total	102	100.0

**Table 2: Demographic characteristics of the patients and serum Vitamin D level**

Characteristics	Serum Vitamin D level, n (%)				Mean± SD	p-value <sup>a</sup>
	<20 ng/ml	20-<30 ng/ml	≥30 ng/ml	Total		
<b>Age of the patients</b>						
<45 years	9 (36.0)	10 (40.0)	6 (24.0)	25 (100.0)	25.4±11.3	0.947
≥45 years	27(35.1)	29(37.7)	21 (27.3)	77 (100.0)	24.6±9.6	
<b>Sex of the patients</b>						
Male	26 (32.5)	29(36.3)	25 (31.3)	80 (100.0)	20.4± 8.3	0.017
Female	10(45.5)	10(45.5)	2 (9.1)	22 (100.0)	26.0± 10.1	
<b>Total</b>	<b>36(35.3)</b>	<b>39(38.2)</b>	<b>27 (26.5)</b>	<b>102 (100.0)</b>	<b>24.8±10.0</b>	

**Table 3: Association between cardiovascular risk factors and severity of coronary artery disease**

Cardiovascular risk factors	Number	Vessel score (Mean± SD)	p value	Gensini score (Mean± SD)	p-value <sup>a</sup>
<b>Age</b>					
<45 years	25	1.3±0.9		28.2±18.5	
≥45 years	77	1.3±0.8	0.878	30.9±22.6	0.586
<b>Sex</b>					
Male	80	1.4±0.8		29.4±20.0	
Female	22	1.2±0.9	0.479	33.0±25.7	0.485
<b>Body mass index</b>					
Normal	68	1.3±0.9		27.0±22.2	
Overweight	34	1.5±0.7	0.239	36.7±17.7	<b>0.019</b>
<b>Smoker</b>					
No	36	1.3±0.9		31.6±23.2	
Yes	66	1.4±0.8	0.687	29.3±20.0	0.597
<b>Hypertension</b>					
No	37	1.2±0.9		28.5±22.3	
Yes	65	1.4±0.9	0.380	31.2±20.8	0.534
<b>Diabetes mellitus</b>					
No	41	1.0±0.8		18.4±18.1	
Yes	61	1.6±0.8	<b>0.001</b>	38.2±19.5	<b>&lt;0.001</b>
<b>Dyslipidemia</b>					
No	42	0.9±0.8		19.0±18.6	
Yes	60	1.6±0.8	<b>&lt;0.001</b>	38.0±19.6	<b>&lt;0.001</b>
<b>Family history of IHD</b>					
No	57	1.3±0.9		27.6±21.0	
Yes	45	1.4±0.9	0.294	33.5±21.3	0.160
<b>Alcohol intake</b>					
No	98	1.4±0.9		30.6±21.3	
Yes	4	1.3±0.9	0.827	26.8±22.2	0.742
<b>Total</b>	<b>102</b>	<b>1.3±0.9</b>		<b>30.2±21.2</b>	

<sup>a</sup>Student's *t*- test

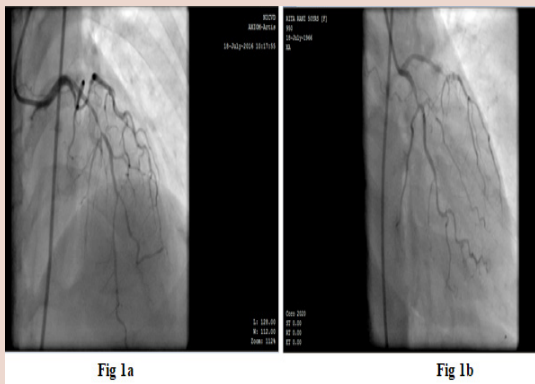
**Table 4: Serum vitamin D level and severity of coronary artery disease**

Vitamin D level (ng/mL)	Vessel involvement				p-value <sup>a</sup>	Gensini score		p-value <sup>b</sup>
	None n (%)	SVD n (%)	DVD n (%)	TVD n (%)		<36 n (%)	≥36 n (%)	
<20	2 (5.6)	10 (27.8)	19 (52.8)	5 (13.9)	<0.001	9(25.0)	27(75.0)	<0.001
20-<30	6(15.4)	14(35.9)	16(41.0)	3 (7.7)		14(35.9)	25(64.1)	
≥30	10 (37.0)	15 (55.6)	2 (7.4)	0 (0.0)		27 (100.0)	0 (0.0)	
<b>Total</b>	<b>18 (17.6)</b>	<b>39 (38.2)</b>	<b>37 (36.3)</b>	<b>8 (7.8)</b>		<b>50 (49.0)</b>	<b>52 (51.0)</b>	

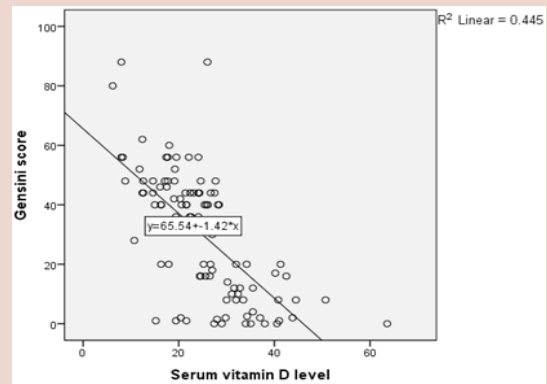
<sup>a</sup>Fisher's Exact test, <sup>b</sup>Chi-Square test

**Table 5: Multiple regression of severity of coronary artery disease.**

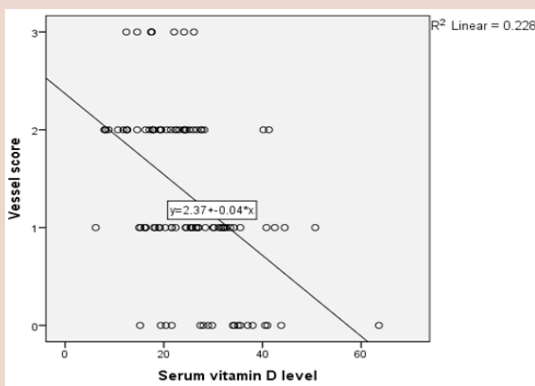
Variables	Vessel score			Gensini score		
	β	95% CI	p value	β	95% CI	p value
Serum vitamin D level, ng/mL	-0.03	-0.05 to -0.02	<b>&lt;0.001</b>	-1.2	-1.6 to -0.8	<b>&lt;0.001</b>
Diabetes mellitus	0.03	-0.39 to 0.442	0.902	4.7	-3.9 to 13.4	0.279
Dyslipidemia	0.33	-0.08 to 0.74	0.116	3.7	-4.8 to 12.3	0.390
Body mass index	-	-	-	3.9	-2.7 to 10.6	0.243



**Figure 1a and Figure 1b:** CAG shows 95% stenosis in proximal LAD and 75% stenosis in proximal LCX of a study patient.



**Figure 3:** Correlation between serum vitamin D level and Gensini score ( $r = -0.667, p < 0.001$ ).



**Figure 2:** Correlation between serum vitamin D level and vessel score ( $r = -0.478, p < 0.001$ ).

25(OH)D level with CAD severity among the Bangladeshi population. The high prevalence of vitamin D deficiency is a reflection of generalized hypovitaminosis D in our country.

In our study female patients had significantly lower Vitamin D level than male. Dijkstra *et al.*<sup>34</sup> also found that women often have lower levels of 25(OH) D levels than men. Potential causes include differences in body fat composition, inadequate dietary intake, childbearing and menopause. As Bangladesh is a predominantly Muslim society the practice of purdah (a covered- up style of dress) is very common in women of different socio-economic classes. Lack of sun exposure may predispose to reduced endogenous synthesis of vitamin D in women.

The conventional risk factors of CAD include smoking, diabetes, hyperlipidemia and hypertension.<sup>35</sup> Severity of CAD assessed by vessel score and Gensini score showed significant association with diabetes mellitus, dyslipidemia and overweight in this study. However, we did not observe any associations between CAD and established risk factors like smoking and hypertension. It might be due to small sample size of this study.

In our study, a significant inverse association between serum 25(OH)D levels and the severity of CAD was found. Double or triple vessel CAD were more frequent in those with low 25(OH)D levels as compared to those with normal levels. Syal *et al.*<sup>33</sup> also found in their study that vitamin D deficiency had higher frequency of double or triple-vessel CAD and higher mean number of coronary vessels involved. Salla *et al.*<sup>36</sup> also found low Vitamin D levels in higher proportions in patients with single, double or triple vessel involvement. Though Dhibar *et al.*<sup>37</sup> found that the

frequency of Vitamin D deficiency was higher in patients with normal coronary artery as compared to the patients with CAD, it was statistically insignificant. However, Alsancak *et al.* in their study with 746 patients failed to demonstrate significant relationship between serum Vitamin D levels and the severity and extent of coronary artery disease.<sup>38</sup> Vitamin D insufficiency was associated with increased arterial stiffness and endothelial dysfunction in healthy humans. It was recently demonstrated that Vitamin D supplementation significantly improves endothelial function, both in patients with diabetes and in healthy Vitamin D insufficient adults.<sup>39</sup> In Heart and Soul Study done on 946 participants with stable cardiovascular disease in San Francisco, California with prospective median follow up for 8 years for cardiovascular events revealed that low 25-hydroxy Vitamin D levels remained independently associated with cardiovascular events.<sup>40</sup> Another study by Akin *et al.*<sup>24</sup> also found a significant inverse association between serum 25(OH)D levels and the severity of CAD assessed by Gensini score.

This study has a number of limitations. First, as it is cross-sectional study, conclusions regarding causality may not be possible. Secondly, serum 25(OH)D levels vary with geography, seasonality, latitude and altitude presumably as a result of sunlight exposure. Therefore, a single measurement of Vitamin D may not reflect lifetime status. Finally, the sample size in our study was relatively small which made valid analyses of the statistical data difficult.

## CONCLUSION

This study demonstrates that serum Vitamin D levels are inversely associated with angiographic severity of coronary artery disease. A high prevalence of hypovitaminosis D was found in Bangladeshi patients with angiographically documented CAD. Our results suggest that low Vitamin D levels may be an emerging and independent cardiovascular risk factor. The findings of this study may motivate future larger trials to determine whether Vitamin D interventions can prevent the development of cardiovascular diseases.

## ACKNOWLEDGEMENT

The authors appreciate all the respected colleagues of department of cardiology and cath lab staffs of NICVD. We also acknowledge all the patients who participated in the study.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**BMI:** Body Mass Index; **CAD:** Coronary Artery Disease; **CAG:** Coronary Angiography; **DVD:** Double Vessel Disease; **IHD:** Ischemic Heart Disease; **NICVD:** National Institute of Cardiovascular Diseases; **TVD:** Triple Vessel Disease; **25(OH)D:** 25-hydroxy Vitamin D.

## SUMMARY

This cross sectional study looked for association between low Vitamin D level and severity of coronary artery disease among 102 patients undergoing elective coronary angiography due to CAD at NICVD, Dhaka. Vitamin D level of each patient was measured and categorized as deficient, insufficient and normal if the value were <20, 20 to <30 and ≥30 ng/mL respectively. Following CAG, the severity of the CAD was assessed by vessel score and Gensini score. Our study demonstrates that low Vitamin D level increased the risk of CAD and serum Vitamin D level inversely correlated with both vessel score ( $r=-0.478$ ,  $p<0.001$ ) and Gensini score ( $r=-0.667$ ,  $p<0.001$ ). The association between angiographic severity of CAD and Vitamin D deficiency remained significant even after adjustment for significant cardiovascular risk factors such as diabetes, dyslipidemia and higher BMI.

## REFERENCES

- Holick MF. Vitamin D deficiency. *New England Journal of Medicine*. 2007;357(3):266-81.
- Zittermann A. Vitamin D and disease prevention with special reference to cardiovascular disease. *Progress in Biophysics and Molecular Biology*. 2006;92(1):39-48.
- Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency: An important, common and easily treatable cardiovascular risk factor?. *Journal of the American College of Cardiology*. 2008;52(24):1949-56.
- Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kieftede-Jong JC, et al. Vitamin D and risk of cause specific death: Systematic review and meta-analysis of observational cohort and randomised intervention studies. *BMJ*. 2014;348:g1903.
- Norman P, Powell J. Vitamin D and cardiovascular disease. *Circulation Research*. 2014;114(2):379-93.
- Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2008;11(1):7-12.
- Siadat ZD, Kiani K, Sadeghi M, Shariat AS, Farajzadegan Z, Kheirmand M. Association of vitamin D deficiency and coronary artery disease with cardiovascular risk factors. *Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences*. 2012;17(11):1052.
- Kunadian V, Ford GA, Bawamia B, Qiu W, Manson JE. Vitamin D deficiency and coronary artery disease: A review of the evidence. *American Heart Journal*. 2014;167(3):283-91.
- Judd S, Tangpricha V. Vitamin D deficiency and risk for cardiovascular disease. *Circulation*. 2008;117(4):503.
- Zittermann A, Prokop S. The role of vitamin D for cardiovascular disease and overall mortality. *Sunlight, Vitamin D and Skin Cancer*: Springer. 2014;106-19.
- Wang L, Ma J, Manson JE, Buring JE, Gaziano JM, Sesso HD. A prospective study of plasma vitamin D metabolites, vitamin D receptor gene polymorphisms and risk of hypertension in men. *European Journal of Nutrition*. 2013;52(7):1771-9.
- Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *The American Journal of Clinical Nutrition*. 2006;84(1):18-28.
- Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *The American Journal of Clinical Nutrition*. 2008;87(4):1080S-6S.
- Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: A meta-analysis of prospective cohort studies. *The American Journal of Clinical Nutrition*. 2011;95(1):91-100.
- Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem?. *The Journal of Steroid Biochemistry and Molecular Biology*. 2014;144:138-45.
- Atiq M, Suria A, Nizami SQ, Ahmed I. Maternal vitamin-D deficiency in Pakistan. *Acta Obstetrica Et Gynecologica Scandinavica*. 1998;77(10):970-3.
- Goswami R, Gupta N, Goswami D, Marwaha RK, Tandon N, Kochupillai N. Prevalence and significance of low 25-hydroxyvitamin D concentrations in healthy subjects in Delhi. *The American Journal of Clinical Nutrition*. 2000;72(2):472-5.
- Islam M, Lamberg-Allardt C, Kärkkäinen M, Outila T, Salamatullah Q, Shamim A. Vitamin D deficiency: A concern in premenopausal Bangladeshi women of two socio-economic groups in rural and urban region. *European Journal of Clinical Nutrition*. 2002;56(1):51.
- Davies MR, Hruska KA. Pathophysiological mechanisms of vascular calcification in end-stage renal disease. *Kidney International*. 2001;60(2):472-9.
- O'Connell TD, Berry JE, Jarvis A, Somerman M, Simpson R. 1, 25-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. *American Journal of Physiology-Heart and Circulatory Physiology*. 1997;272(4):H1751-H8.
- Oz F, Cizgici AY, Ofiaz H, Elitok A, Karaayvaz EB, Mercanoglu F, et al. Impact of vitamin D insufficiency on the epicardial coronary flow velocity and endothelial function. *Coronary Artery Disease*. 2013;24(5):392-7.
- Goleniewska B, Kacprzak M, Zielińska M. Vitamin D level and extent of coronary stenotic lesions in patients with first acute myocardial infarction. *Cardiology Journal*. 2014;21(1):18-23.
- Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. *Archives of Internal Medicine*. 2008;168(11):1174-80.
- Akin F, Ayça B, Köse N, Duran M, Sari M, Uysal OK, et al. Serum vitamin D levels are independently associated with severity of coronary artery disease. *Journal of Investigative Medicine*. 2012;60(6):869-73.
- Islam AM, Majumder A. Coronary artery disease in Bangladesh: A review. *Indian Heart Journal*. 2013;65(4):424-35.
- Melamed ML, Muntner P, Michos ED, Uribarri J, Weber C, Sharma J, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. *Arteriosclerosis, thrombosis and vascular biology*. 2008;28(6):1179-85.
- Dobnig H, Pilz S, Schrnagl H, Renner W, Seelhorst U, Wellnitz B, et al. Independent association of low serum 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Archives of Internal Medicine*. 2008;168(12):1340-9.
- Schierbeck LL, Jensen TS, Bang U, Jensen G, Køber L, Jensen JEB. Parathyroid hormone and vitamin D markers for cardiovascular and all-cause mortality in heart failure. *European Journal of Heart Failure*. 2011;13(6):626-32.
- Chaitman BR, Bourassa MG, Davis K, Rogers WJ, Tyras DH, Berger R, et al. Angiographic prevalence of high-risk Coronary Artery Disease in Patient Subsets (CASS). *Circulation*. 1981;64(2):360-7.
- Sullivan DR, Marwick TH, Freedman SB. A new method of scoring coronary angiograms to reflect extent of coronary atherosclerosis and improve correlation with major risk factors. *American Heart Journal*. 1990;119(6):1262-7.
- Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol*. 1983;51:606.
- Ling S, Shu-zheng L. Association between non-alcoholic fatty liver disease and coronary artery disease severity. *Chinese Medical Journal*. 2011;124(6):867-72.
- Syal SK, Kapoor A, Bhatia E, Sinha A, Kumar S, Tewari S, et al. Vitamin D deficiency, coronary artery disease and endothelial dysfunction: observations from a coronary angiographic study in Indian patients. 2012.
- Dijkstra S, Van BA, Janssen J, DeVleeschouwer L, Huysman W, Akker EVD. High prevalence of vitamin D deficiency in newborn infants of high-risk mothers. *Archives of Disease in Childhood*. 2007;92(9):750-3.
- Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, et al. Prevalence of conventional risk factors in patients with coronary heart disease. *JAMA*. 2003;290(7):898-904.
- Salla SP, Patchipala R, Paidi S. Relationship between Serum Vitamin D Level and Angiographic Severity in Coronary Artery Disease. *Journal of Evidence Based Medicine and Healthcare*. 2017;4(22):1260-5.
- Dhibar DP, Sharma YP, Bhadada SK, Sachdeva N, Sahu KK. Association of vitamin D deficiency with coronary artery disease. *JCDR*. 2016;10(9):OC24.
- 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(9):940-8.
- Al Mheid I, Patel R, Murrow J, Morris A, Rahman A, Fike L, et al. Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. *Journal of the American College of Cardiology*. 2011;58(2):186-92.
- Welles CC, Whooley MA, Karumanchi SA, Hod T, Thadhani R, Berg AH, et al. Vitamin D deficiency and cardiovascular events in patients with coronary heart disease: data from the Heart and Soul Study. *American Journal of Epidemiology*. 2014;179(11):1279-87.

**Cite this article :** Rahman AU, Karmakar PK, Jabeen S, Nabi S, Khan AM, Shahriar S et al. Association of Vitamin D Level with Severity of Angiographically Documented Coronary Artery Disease: Observations from Bangladeshi Patients. *J Cardiovascular Disease Res*. 2019; 10(2): 52-7.