Original Article

Association of Serum Vitamin D with Acute Myocardial Infarction in Young Patients (≤40 Years)

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Abstract:

Background: Coronary heart disease (CHD) is the leading cause of death worldwide, with acute myocardial infarction (AMI) being the most severe manifestation. Recent evidence suggests that vitamin D deficiency (moderate/severe) is an important risk factor for coronary artery disease. **Objectives:** Considering paucity of the literature focusing young MI, the study was planned to assess the relation of different grades of low serum vitamin D with AMI in young patients admitted in a tertiary care hospital. **Methods:** This Hospital based case-control study was conducted in the department of cardiology in Dhaka Medical College Hospital (DMCH) over 1-year period. Patients with acute MI in young age (≤40 years) admitted in the CCU of DMCH were approached for inclusion in the study. Total 120 subjects (60 cases and 60 controls) were studied. Patients with acute MI were considered as cases and similar number of age and sex matched apparently healthy individual were included as controls. All study population were subjected to relevant investigations and detailed history along with socio-demographic data were collected. Serum vitamin D levels were categorized as severe vitamin D deficiency as a level <10ng/ml, moderate vitamin D deficiency at a level 10-20 ng/ml, vitamin D insufficiency as 21-29 ng/ml and a level of ≥30ng/ml was considered as normal. Serum 25(OH) vitamin D assay was performed for cases and controls using chemiluminescence immunoassay. Vitamin D status (normal/insufficiency vs moderate/severe deficiency) was studied among cases and controls. All necessary information were recorded in a pretested case record form. Statistical analyses were done by SPSS 22. **Results:** Mean age of cases and controls were 35.31±4.84 and 33.83±5.11 years respectively. Vitamin D deficiency (moderate/severe) was present in 86.7% cases and 46.7% controls and the difference was statistically significant (P<0.001). Among 60 cases of acute MI, 83% patients had acute ST segment elevated myocardial infarction and 17% patients had acute non-ST segment elevated myocardial infarction. Vitamin D deficient (moderate/severe) subjects were more likely to develop AMI than subjects who had normal/insufficient vitamin D levels in blood (OR 7.42, 95%CI 3.18-18.28, P<0.001). And among all the usual coronary risk factors, vitamin D deficiency (moderate/severe), Hypertension, Family history of premature CAD and smoking were significantly associated with increased incidence of acute MI (STEMI and NSTEMI) (P value<0.05 in all cases). **Conclusion:** Vitamin D deficiency (moderate/severe) is associated with increased incidence of acute MI in young age (≤40 years).

Keywords: Vitamin D; Myocardial infarction young

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Introduction:

Acute coronary syndrome is one of the leading causes of premature death in men and women despite unquestionable progress in the management and prevention of coronary artery disease.[1].

Hypovitaminosis D or low serum vitamin D is highly prevalent in the United States and worldwide. It has been estimated that around 1 billion people worldwide suffer from low serum vitamin D .[2] Although a consensus regarding the optimal level of serum 25(OH)D has not been established, most experts define severe vitamin D deficiency as a level <10ng/ml, moderate vitamin D deficiency as a level 10-20 ng/ml, vitamin D insufficiency as 21-29 ng/ml and a level of e"30ng/ml is considered as normal.[3] There is high prevalence of hypovitaminosis D among Indians despite the availability of abundant sunshine in large parts of India. This is true for both urban and rural populations and, in men and women, with reported population of prevalence of 70- 99%, with severe deficiency (<10 ng/ml) being reported as 62% in studies from Delhi.[4-7] Another review of vitamin D deficiency in Bangladesh showed prevalence of hypovitaminosis D in Dhaka among 16-40 years women being 12-17% and in Nandail 38-50%.[5]

Several mechanisms, direct and indirect, have been proposed for the association of vitamin D with CHD. Vitamin D could be related to CHD via increased blood pressure, impaired glycemic control or secondary hyperparathyroidism. An excess of PTH levels is known to promote atherosclerosis. PTH promotes myocyte hypertrophy and vascular remodeling. Hypovitaminosis D is known to up-regulate Renin Angiotensin Aldosterone System (RAAS) and lead to hypertrophy of smooth muscles and left ventricle, an adverse marker of cardiovascular event.[8] Consequently, low serum 25(OH) D has been associated with aberrant cardiac contractility, cardiomegaly, and increased ventricular mass due to myocardial collagen deposition.[9-10] Low serum Vitamin D also leads to endothelial dysfunction by creating a proinflammatory and prothrombotic environment. This promotes atheroma formation and atherosclerosis, the principal cause of myocardial infarction (MI).[11]

Association of hypovitaminosis D with coronary heart disease (CHD) has been reported in a large number of studies and reviews recently.[2, 12-14] There is also evidence of linking low serum vitamin D to early mortality, with vitamin D being considered as one of the possible treatable cardiovascular risk factors.[2,15-16]

However, there is no data on the association of low serum vitamin D with AMI in young (≤40 years) Bangladeshi

population. We therefore studied the association of this novel and potentially treatable risk factor of acute MI in our population. We analyzed fasting serum vitamin D level in cases of newly diagnosed young acute myocardial infarction (MI) patients and age and sex matched controls, to study the association of low serum vitamin D with AMI in Bangladeshi population.

Methods:

This case - control study was conducted at the Department of Cardiology, Dhaka Medical College Hospital, Dhaka, between May'2017 to April'2018. Serum 25-hydroxy [25(OH)] vitamin D measurement was performed at blood sample collected and then stored at -70[0]c in the biochemistry laboratory of BSMMU.

Newly diagnosed Patients with acute MI(STEMI and NSTEMI) in young age (≤40 years) admitted in the CCU of Dhaka Medical College Hospital, Dhaka , within the study period who fulfilled the other inclusion and exclusion criteria were taken as cases and age and sex matched healthy subjects with no history of Ischemic heart disease (IHD) and normal ECG were taken as controls. Study subjects having previous history of myocardial infarction/Unstable angina /Percutaneous Coronary Intervention (PCI)/Coronary Artery Bypass Graft (CABG) were excluded. Controls were matched to cases by age and sex with healthy subjects (doctors, medical students, nurses, other hospital staffs and patients attendants from DMCH, Dhaka) with no history of IHD and normal ECG findings. Cases and controls with cardiomyopathy, any valvular heart disease, congenital heart disease, pericardial disease, pregnancy, known liver, thyroid, renal diseases, malabsorption or malignancy, and those who were taking vitamin D supplement were excluded.CHD in the young is defined as CHD in patients (≤40 years) of age. The sample size for this study was calculated for a two sided significance of 0.05 and study power of 90%. The calculated sample size was 60 cases and 60 controls. Serum vitamin D was measured in both cases and controls by chemiluminescence immunoassay on blood samples collected and then stored at -70p c in the biochemistry laboratory of BSMMU . The ARCHITECT 25(OH) vitamin D assay was a chemiluminescent microparticle immunoassay for the quantitative determination of 25(OH) vitamin D in human serum and plasma. Statistical analysis of the data was done by Statistical Package for Social Science (SPSS) version 22.0. Confidence interval was considered at 95% level. The qualitative variables were expressed as frequency and percentage and the quantitative variables were expressed

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as mean with standard deviation. During analysis, student's t-test and chi-square test were used to analyze difference between baseline characteristics. Univariate and multivariate regression analysis were considered to evaluate the influence of potential risk factors. Risk measurement was done by odds ratio (OR). P-value <0.05 was considered statistically significant in all cases.25 (OH) vitamin D status was determined as the normal, insufficiency, deficiency and severely deficient state when the 25 (OH) vitamin D level was ≤30 ng/ml, 21-29 ng/ml, 10-20ng/ml and <10 ng/ml respectively. Multiple conditional logistic regression was used to investigate the relationship between MI and vitamin D deficiency controlling for other significant traditional risk factors including diabetes, hypertension, dyslipidaemia, tobacco use, obesity/overweight and family h/opremature CAD. Vitamin D status was taken as a binaryvariable (moderate/severe deficiency Vs normal/insufficient).

Results:

Study subjects were divided into two main categories depending on whether the patient had vitamin D level ≤ 20ng/ml (moderate/severe deficiency)or >20   ng/ml (normal/insufficiency) in blood. Vitamin D status among cases and controls and the association of different grade of serum vitamin D with AMI was studied.

Mean age of cases and controls were 35.31±4.84 years

33.83±5.11 years respectively (P>.05). There was no statistically significant difference (P >0.05) regarding the gender incidence in chi-square test. Male female ratio was 2.08:1 among the whole subjects.

In this study majority of both cases (86.7%) and controls (46.7%) had vitamin D deficiency (moderate) (Table II). Twenty percent (20%) of cases had severe deficit in vitamin D level whereas none of the control group had severe deficit of vitamin D. On the other hand, 10% of the controls had normal vitamin D level and none of the cases had normal level of vitamin D. In case group, the mean serum vitamin D level was 14.75±4.99 ng/ml, ranging from 6.00 to 26.30ng/ml. In control group, the mean serum vitamin D level was 21.05±6.00ng/ml, ranging from 11.00 – 31.00ng/ml. The difference was statistically significant (P <0.001)(Table-I). Vitamin D deficient (moderate/severe) subjects were more likely to develop AMI than subjects who had normal/insufficient vitamin D levels in blood (OR 7.42, 95%CI 3.18-18.28, P<0.001). (Table III)

Smoking, HTN, F/H of premature CAD and vitamin D deficiency (moderate/severe) were found to be significantly (p<0.05) associated with AMI in young (≤40 years) patients; other risk factors (DM, Dyslipidaemia and overweight/obese) were not found to be significantly (p>0.05) associated with AMI risk in young (≤40 years) patients. A subject with vitamin D deficiency (moderate/severe) compared to a not deficient subject (normal/insufficient) was 8.81 (95% CI 2.874 to 27.023) times

Table I

Comparison of serum 25(OH) Vitamin D level in cases and controls (n=120).

Serum 25-(OH) Vitamin D level (ng/ml)	Case (n=60)		Control (n=60)		P value
	n	%	n	%	
Normal (≥30)	0	0	6	10	0.01[s]
Insufficient (21 – 29)	8	13.3	26	43.3	<0.001[s]
Moderately deficient (10 – 20)	40	66.7	28	46.7	0.03[s]
Severely deficient (< 10)	12	20	0	0	<0.001[s]
Mean ±SD	14.75±4.99		21.05±6.00		<0.001[s]
Range (min – max)	6.00 – 26.30		11.00 – 31.00		

Table-II

Vitamin D status (normal/insufficiency vs moderate/severe deficiency)
among cases and controls (n=120).

Serum 25-(OH) Vitamin-D Status	Case(n=60)		Control(n=60)		P value
	n	%	n	%	
Deficient (moderate/severe)	52	86.7	28	46.7	<0.001[S]
Normal/ Insufficient	8	13.3	32	53.3	

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Table-III
Risk measurement of serum 25(OH) vitamin D level for AMI in young (≤40 years) patients (n=120)

Serum 25-(OH) Vitamin-D Status	Case (n=60)		Control (n=60)		Odds Ratio (OR)	95% CI for OR	P value
	n	%	n	%			
Deficient (moderate/severe)	52	86.7	28	46.7	7.42	3.18-18.28	<0.001[S]
Normal/ Insufficient	8	13.3	32	53.3			

Table-IV
Risk measurement of different risk factors for AMI in young (≤40 years) patients (n=120) (Multiple logistic regression model)

Risk factors	Regression coefficient (β)	Odds Ratio (OR)	95% CI for OR	P value
Vitamin D deficiency(moderate/severe)	2.176	8.81	2.874-27.023	<0.001[S]
Smoking	1.013	2.76	1.030-7.364	0.04[S]
Dyslipidemia	0.782	2.19	0.791-6.040	0.13[NS]
HTN	1.762	5.82	1.681-20.161	0.005[S]
DM	1.268	3.55	0.974-12.969	0.06[NS]
F/H of premature CAD	1.711	5.53	1.225-25.009	0.02[S]
Overweight/Obese	0.818	2.27	0.865-5.932	0.10[NS]

more likely to have AMI.

Discussion:

This study was intended to find out the association between serum vitamin D level and AMI in young (≤40 years) patients.

Among cases 86.7% were deficient (moderate/severe) in vitamin D which is significantly more compared to controls (46.7%, P<0.001). Among control group only 10% subjects had normal vitamin D level. But, among cases there was not a single patient who had normal level of vitamin D. Till date no study has determined the vitamin D status in both young (≤40 years) adult men and women of Bangladesh. In this respect a high proportion of vitamin D deficient (moderate/severe) men (controls) in this study is a unique and important finding. A greater proportion of men among cases having hypovitaminosis D can be explained by the fact that a greater proportion of men being hospitalized for myocardial infarction than women.[17]

Several studies were carried out to determine the vitamin D level in adult women in the country,in one study vitamin D deficiency was found in 38% women and in another study vitamin D deficiency (<25nmol/l) was found in 16% female garments workers and a high prevalence of vitamin D insufficiency 88.5% was also noted .[18-19] In this study 30% women had vitamin D deficiency.

In 2017, at Sylhet MAG Osmani Medical College a study was done regarding association of 25-hydroxycholecalciferol with acute myocardial infarction. In that studyvitamin D was found to be significantly reduced in AMI patients when compared with that of controls which were 28.50±16.68 ng/ml in cases and 38.32±16.47 ng/ml in controls, P=0.011.[20]

In an Indian study, Karur and colleagues included AMI patient from all ages and found 83.5% vitamin D deficiency or insufficiency .[21] In our study we found that all (100%) patients of young (≤40 years) AMI patients had either insufficient vitamin-D level (13.3%) or moderate/ severely deficient vitamin-D level (86.7%). In the study by Roy *et al.* severe deficiency of vitamin D was found in 79.2% cases and 46.7% controls.[8] But, this study found severe deficiency in 20% cases and none of the control.

Ng et al., 2013[22] demonstrated that 74% of AMI had low vitamin D levels and 36% of them had severe deficiency. In this study 86.7% of AMI had vitamin D deficiency (moderate/severe deficiency) level and among them 20% had severe deficiency.

In this study serum 25(OH) vitamin D level in AMI was found to low in cases (14.75±4.99 ng/ml) than in controls (21.05±6 ng/ml)This findings were supported by the

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findings of Rath et al., 2016.[23]

Risk measurement of serum 25(OH) vitamin D level for AMI showed that vitamin D deficient (moderate/severe) patients had significantly higher odds of developing AMI than those who have insufficient/normal vitamin D level OR 7.42, 95%CI 3.18-18.28, P<0.001). When other risk factors were adjusted the OR increased to 8.81 (95% CI 2.874- 27.023, p <0.001). This in agreement with findings of studies done in India, Pakistan, and USA .[8,24-25]

In the multiple logistic regression analysis by taking AMI as dependent variable and risk factors for AMI as independent variable Roy et al., 2015[8], showed that vitamin D deficiency increased risk of AMI. In that study, vitamin D deficiency, obesity, DM, HTN, smoking and dyslipidaemia had odds ratio (OR) 4.5, 2.8, 2.3, 2.1, 1.9 and 1.1 respectively. In this study showed that serum vitamin D deficiency (moderate/severe), smoking, HTN and F/H of premature CAD were significantly (P <0.05) associated with AMI risk in young (d"40years) patients with Odds ratio 8.81, 2.76, 5.83 and 5.53 respectively. Whereas DM, Dyslipidaemia and overweight/obesity were not (P >0.05) (Table IV).

Vitamin D deficiency (moderate/severe) causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, and inflammation .[2] Combination of these factors contributes to the increased risk of cardiovascular events in vitamin D deficiency(moderate/severe). Therefore, large scale studies are needed to evaluate the cardiovascular benefits of vitamin D supplementation.

Conclusion:
Substantial evidence suggests that a large portion of different populations have suboptimal levels of vitamin D, which may adversely affect the cardiovascular (CV) system, and may affect the incidence of AMI. Vitamin D deficiency (moderate/severe) was significantly associated with acute MI incidence.

Limitations :
The study population was confined to the Cardiology Department of DMCH. Therefore, the results of the study may not reflect the exact picture of the country. Only one of the emerging risk factors (serum vitamin D) was studied. Follow up of the patients for longer duration was beyond scope

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