Vitamin D Deficiency As A Risk Factor For Myocardial Infarction

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Abstract:

The risk of coronary heart disease (CHD) has been repeatedly linked to vitamin D inadequacy. Recent findings indicate that vitamin D deficiency is a serious issue in India. However, there is a dearth of studies examining this connection among Indians. A total of 120 patients with MI and 120 age- and gender-matched healthy controls were studied at Venugram Hospital, Belagavi, India. Both groups were tested for clinical and biochemical markers of MI risk. Serum 25 (OH) vitamin D levels were measured using eCLIA in previously obtained samples from both patients and controls. Patients had lower median vitamin D levels, although vitamin D deficiency was widespread among both cases and controls. Patients more often suffered from diabetes, hypertension, and habitual use of tobacco products and alcohol. The values of both total and LDL cholesterol were also elevated. A multivariate logistic regression analysis found that those with severe vitamin D deficiency had an odds ratio of 4.5 times higher of experiencing a myocardial infarction. In this Indian study of patients with and without acute myocardial infarction, the levels of 25 (OH)D were significantly lower in the case group compared to the control group. Even though hypovitaminosis is common, it was obvious that severe vitamin D deficiency was associated with acute MI after controlling for other, more conventional risk factors.

1. Introduction

Reduced risk of cardiovascular disease is one of vitamin D's many benefits. Because vitamin D receptors are present in many cell types, including vascular smooth muscle cells and cardiomyocytes, it may have a role in regulating gene expression, controlling blood pressure, and influencing cell development and proliferation. [1] Cardiomyocytes, vascular endothelium, and vascular smooth muscle cells have all been shown to have vitamin D receptors, and the 1-α-hydroxylase enzyme necessary for the conversion to the active metabolite 1,25-dihydroxyvitamin D2 is expressed in cardiac myocytes and fibroblasts. Geographic and seasonal differences in mortality due to ischemic cardiopathy were observed in the early 1980s and 1990s. [2] “The first research to identify vitamin D as a preventive factor was a British one that found a negative correlation between sun exposure and death from ischaemic heart disease. The active metabolite of vitamin D is linked to the vitamin D receptor, which regulates many genes involved in fundamental processes that may be relevant for cardiovascular disease.” [3] These processes include cell proliferation, apoptosis, oxidative stress, membrane transport, and cell adhesion. The levels of the circulating form of vitamin D are inversely related with rise in mortality, and recent research have demonstrated that vitamin D deficiency is an independent risk associated with the incidence of cardiovascular disease. [4]

There is some evidence linking low plasmatic levels of vitamin D with an increased risk of cardiovascular disease, and there is also some evidence linking higher levels of 25-hydroxyvitamin D with a lower risk of cardiovascular disease in experimental models. However, the current body of

research is insufficient to draw any firm conclusions about the causality of these relationships. High-risk populations for vitamin deficiency include individuals who spend most of their time inside, such as pregnant women, breastfeeding moms, and the elderly. [5]

Despite advances in prevention and treatment, cardiovascular disease, including acute myocardial infarction (AMI) in particular, continues to be the primary cause of mortality and disability in affluent countries.[6] "In addition to the well-established risk factors for the development of AMI, new risk factors are emerging, and these new risk factors may have significant consequences for therapy in the near future." Among them, hypovitaminosis D has recently come to get a significant amount of attention. It is general information that the diets of a great number of individuals do not include sufficient amounts of vitamin D. [7] A lack of vitamin D has, for some time now, been associated with abnormalities in bone metabolism and calcium homeostasis. "Hypovitaminosis D is closely associated with major cardiovascular risk factors like diabetes, hypertension, and chronic kidney disease. [8] This fact, along with the discovery of nuclear vitamin D receptors (VDR) on vascular endothelial cells and cardiomyocytes, has made it possible for researchers to investigate the intriguing connection between hypovitaminosis D and cardiac disease."[9]

"The first findings of this study point to a possible connection between vitamin D insufficiency and the short-term and long-term prognosis of individuals who have AMI. [10] Vitamin D deficiency has been connected to the number of damaged coronary arteries, the severity of AMI outcomes, and the degree of cardiac remodeling in individuals who have AMI. This suggests that this condition raises the risk of both immediate and long-term cardiac difficulties." [11]

In this article, we talk about the relationship between hypovitaminosis D and AMI, its relevance in terms of prognosis, and the possible pathways that are responsible for this association. In the last part of this discussion, we will examine possible roadblocks as well as prospects for future study in this field. [12]

The first studies on the subject were conducted in Denmark in 1978 and found that patients with angina or AMI had significantly lower levels of vitamin D in their blood than controls. According to the findings of a case control research conducted in 1990 between the winter and spring months, vitamin D levels were shown to be considerably lower in AMI patients when compared to the levels seen in controls. [13] ? "It was shown that the relative risk of AMI decreased from lower to higher quartiles of vitamin D levels, demonstrating that there is an inverse link between vitamin D and the risk of AMI." These rates have also been demonstrated to be accurate when applied to populations that are more recent. [14] "In the Framingham Offspring Study, which included 1,739 participants, those who had inadequate or insufficient levels of vitamin D were shown to have a cardiovascular risk factor that was two times higher than that of their healthy counterparts." [15]

Participants with levels > 15 ng/m and those with ≥ 10 ng/mL were at a greater risk of experiencing a first cardiovascular incident during the 5-year follow-up period than those without a history of coronary artery disease. This was determined by comparing participants with levels > 15 ng/m and those with levels 10 ng/mL. In a study of 18225 men called the Health Professionals Follow-up Study, researchers looked at the individuals' vitamin D levels over a period of 10 years and found that those with normal vitamin D levels had nearly half the risk of AMI compared to those with low vitamin D levels. [16] "This was true even after the researchers controlled for other cardiovascular risk factors. In a significant meta-analysis that compared the categories with the lowest to the highest levels of baseline circulating vitamin D concentration, researchers discovered an updated pooled relative risk of 1.52 for all cardiovascular events." These findings match the findings of the prior research. Therefore, there is an increasing body of data suggesting that a deficiency in vitamin D is a distinct risk factor for AMI. [17]

Prospective studies have demonstrated that vitamin D deficiency is frequent in AMI hospital inpatients, which is consistent with the results of these epidemiological investigations. [18] The levels of vitamin D in 96% of patients admitted to the hospital with acute coronary syndrome were found to be below 30

ng/mL, according to the findings of a research that was conducted at several centers and included 239 patients. These results have been substantiated by research, which found that 74% of AMI patients had an insufficient level of vitamin D, with 36% having a very severe deficiency. The median vitamin D blood content in a group of 206 AMI patients was 18.5 ng/mL, and 10% of the patients had a severe vitamin D deficiency. “Seven percent of the AMI patients were diagnosed with STEMI. One research reported that the prevalence of hypovitaminosis D in AMI patients was 89%, whereas another study found that the incidence was 68%.”[19]

“Low levels of vitamin D are not only a prevalent independent risk factor for AMI, but they are also associated with a worse outcome when AMI does occur. This is the conclusion that can be drawn from the first evidence of a possible independent association between severe deficiency of vitamin D and in-hospital mortality in patients with acute coronary syndromes. Those patients whose vitamin D levels were 10 ng/mL had a substantially higher in-hospital cardiovascular mortality rate, which was 24%, as compared to the other patients, who had a death rate of 4.9%.” [20] In a research that included 139 people who had been diagnosed with STEMI, hypovitaminosis D was shown to be related with an increased risk of dying while in the hospital. “The in-hospital mortality rates of patients with normal and low vitamin D levels were compared, however the experiment did not have enough participants to show a statistically significant difference between the two groups. [21] In AMI, there is now more data on the clinical effects of low levels of vitamin D.” It is now the most extensive study of its type, having examined the relationship between vitamin D levels and the risk of Acute Coronary Syndrome in a total of 1259 participants. In the final stages of their investigation, they found a correlation between low levels of vitamin D (7.3 ng/mL) and an increased risk of major cardiovascular issues. It is important to note that the link was observed to be strongest between readmissions to the hospital for either acute decompensated heart failure or subsequent acute coronary syndrome. [22]

2. Material and Methods

During the months of March 2020 and June 2022, researchers from the Department of Cardiology at Venugram hospital, Belagavi, India, performed the study. The research project was given the go light by Institute’s ethics Committee. Blood samples were maintained at —70 C cardiac- biochemistry laboratory for analysis of serum 25 hydroxy [25(OH)] vitamin D.

- **Plan of Research**

Individuals with a first-ever episode of acute myocardial infarction, aged 25 to 75, who gave informed permission were included in the research. Within the first 24 hours of hospitalization, patients were asked to fill out a questionnaire to determine their risk for MI, and a blood sample was taken from them while they were fasting. Electrocardiographic changes suggestive of a new MI were used to diagnose acute MI, along with the presence of characteristic symptoms. Participants were not included if they had a history of heart disease or cardiogenic shock that had been diagnosed more than 30 days previous to study participation.

Individuals without a history of cardiac disease or exertional chest pain and a normal ECG were used as controls and matched to cases in age and sex. Participants serving as controls were caregivers and family members of patients admitted to non-cardiac wards, caregivers and family members of cardiac patients who were unrelated to each other, and patients who were seen in non-cardiac outpatient clinics for conditions that were not associated with an increased risk of MI. Women who were pregnant or who had a history of liver, thyroid, or renal illness or cancer were not included in the case or control groups. In addition, if a participant's blood was drawn within 30 days of their matched case's blood, that participant was considered a control for the research.

Those with a systolic blood pressure of at least 140 mm Hg and a diastolic blood pressure of at least 90 mm Hg, or a history of current antihypertensive drug usage, were classified as having hypertension. Patients were considered to have diabetes mellitus (DM) if they had fasting plasma glucose levels of 126 mg/dl, postprandial plasma glucose levels of 200 mg/dl, or were using anti diabetic medication. People who have used tobacco in the previous six months and/or who have used tobacco consistently for more than six months were considered smokers/chewers. For the purposes of this study, a long-term

alcohol user was defined as someone who regularly used alcohol for at least six months before to the survey. Congenital heart disease among first-degree relatives less than 60 years of age was considered a positive family history. Nonwork-related physical activity was defined as any physical activity done for fun at least once a week. Most advanced degree earned was calculated.

- **Sample size calculation**

A power of 80% and a two-sided significance level of 0.05 were used to determine the required number of participants in this investigation. The sample size of 120 cases and 120 controls was determined using the odds ratio of 2.1 (15,16) and a control exposure of 50%.

- **Biochemical analysis**

Using glucose oxidase assay kits (RANDOX, UK), we quantified glucose levels. Serum samples were analyzed using commercially available kits (RANDOX, UK) for total cholesterol using the enzymatic CHOD-PAP technique. Serum HDL cholesterol levels were analyzed using a phospho-tungistic precipitating technique. Serum samples were analyzed for triglyceride concentration using a commercially available enzymatic GPO-PAP kit (RANDOX, UK). Analyses of serum 25 (OH) D levels were performed on samples kept at —70 C. On a Roche e 411 using a commercially available kit , we determined the 25 (OH) D concentration.

- **Statistical analyses**

Case and control statuses were used to compile statistical summaries of baseline participant characteristics. Independent t-tests were used to compare continuous variables between the case and control groups, while chi2 tests were used to compare categorical data. The levels of 25 (OH) vitamin D were compared between the case and control groups using the Manne Whitney U test. Counts and percentages are used to illustrate continuous variables like mean and standard deviation (SD) or median and interquartile range (IQR), whereas counts and percentages are used to illustrate categorical variables. If your 25(OH) vitamin D level is less than 10 ng/ml, you have a severe deficit. “Controlling for age, diabetes, hypertension, LDL cholesterol, smoking, central obesity, and education, multiple conditional logistic regression was performed to examine the association between MI and severe vitamin D insufficiency. We categorized people's vitamin D levels as either severely deficient or not severely deficient.” Once vitamin D exposure was log converted, the analyses were redone using it as a continuous variable.

3. Results

Table summarizes the similarities and differences between the cases and controls at the outset. Diabetic, hypertensive, and alcoholic patients were more common among the cases. The average waist-to-hip ratio, total cholesterol, and bad LDL cholesterol were all higher in this group as well. “Cases and controls did not vary with respect to age, family history of CHD, recreational physical activity, educational attainment, HDL cholesterol, or triglycerides. Cases had considerably lower median 25(OH) vitamin D levels than controls.

Table 1: Case and control characteristics

	Controls (n¼120)	Cases (n¼120)	p value
Age (Years)	52.1 ± 11.0	51.9 ± 11.4	0.8
Diabetes (%)	20.0%	40.0%	<0.001
Hypertension (%)	12.5%	34.2%	<0.001
Men (%)	88.3%	88.3%	1.0
Tobacco Use(%)	47.1%	62.2%	0.01
Any leisure physical activity (%)	39.5%	33.6%	0.4
Family History of CHD (%)	10.7%	21.8%	0.2
Alcohol Use (%)	26.1%	43.2%	<0.001
Waist Hip Ratio	0.92 ± 0.07	0.96 ± 0.06	<0.001
Total Cholesterol	177.5 ± 39.1	194.1 ± 62.8	0.01
Triglycerides	144.7 ± 84.4	156.8 ± 94.6	0.3
LDL Cholesterol	108.3 ± 38.5	123.7 ± 56.3	0.01
HDL Cholesterol	40.3 ± 10.4	39.1 ± 9.9	0.3
25 (OH)Vitamin D levels(ng/ml)	11.1 (6.5-18.3)	6.0 (3.9-9.0)	<0.001
Educated above Secondary level (%)	49.2%	57.1%	0.2

The prevalence of vitamin D insufficiency varied significantly between the two groups. In both the patients and controls, vitamin D insufficiency was quite common." 79.2 % of cases and 47.7% of controls had a 25(OH) vitamin D level below 10 ng/ml, which is considered to be a severe deficit. Only 1.7% of patients and 4.2% of controls had adequate vitamin D levels.

Table 2: Vitamin D Levels: A Comparison of Cases and Controls.

	Severe deficiency (<10 ng/ml)	Deficiency (10e<30 ng/ml)	Sufficient (≥30 ng/ml)
Cases (n¼120)	95 (79.2%)	23 (19.2%)	2 (1.7%)
Controls (n¼120)	56 (46.7%)	59 (49.2%)	5 (4.2%)
p value	<0.001		

When controlling for other factors shown to be statistically and clinically important, a 4.5-fold increased risk of MI was identified in those with severe vitamin D insufficiency. "After transforming vitamin D exposure onto a logarithmic scale, the connection remained when the study was redone.

Table 3: Logistic regression analysis reveals an association between vitamin D insufficiency and acute myocardial infarction after controlling for confounding factors.

Variable	Adjusted odds ratio (95% C.I)	p value
Vitamin D deficiency		
(≥10 ng/dl	1	<0.001
<10 ng/dl	4.5(2,2, 9.2)	
Central Obesity ((≥0.90 for men& (≥0.85 for women)		
No	1	0.006
Yes	2.8 (1.3, 6.0)	
Diabetes Mellitus		
No	1	0.02
Yes	2.3 (1.1, 4.7)	
Hypertension		
No	1	0.07
Yes	2.1 (0.9, 4.7)	
Tobacco use		
No	1	0.06
Yes	1.9(0.9, 3.8)	
LDL Cholesterol		
<130	1	0.7
≥130	1.1 (0.6, 2.3)	
Alcohol use		
No	1	0.12
Yes	1.7 (0.8, 3.4)	
Education		
Secondary and below	1	0.25
Above Secondary	1.5 (0.8, 2.9)	

4. Discussion

According to the results of this case control study of incident acute MI, vitamin D insufficiency, and especially severe deficiency, is quite common in Belagavi (Karnataka). Vitamin D levels were found to be significantly lower in cases than in controls. Even after accounting for other risk factors for acute myocardial infarction, severe vitamin D insufficiency is still linked with an increased risk of this devastating condition.

Consistent with past research from India, this one indicated a significant rate of vitamin D insufficiency. Despite having much higher vitamin D levels than urban respondents, vitamin D deficiency was shown to be as common in rural South Indians as it was in urban subjects." [23] "Another study conducted found that over 90% of healthy adults over the age of 50 had insufficient vitamin D levels , with 62% having a severe deficiency (serum 25(OH) vitamin D 10 ng/ml) and 6.8% having vitamin D insuffi ciency (serum 25(OH) vitamin D levels 20-30 ng/ml)." [24] A comparable high frequency of vitamin D insufficiency was found in a research conducted in the Indian state of Andhra Pradesh. [25] In metropolitan areas, about 90% of men and 94% of women have vitamin D levels below the minimum recommended level of 30 ng/ml. The percentages for men and women living in rural regions were 84% and 99%, respectively. Vitamin D insufficiency is common among Indians due to their dark complexion, insufficient direct skin contact to sunshine, and the absence of vitamin D in the typical Indian diet.

Recent research emphasizes vitamin D's positive impact on heart health. The risk of ischemic heart disease was found to be 40% higher in people with low vitamin D, 64% higher in people with myocardial infarction, 57% higher in people with premature death, and 81% higher in people with fatal

ischemic heart disease/myocardial infarction, according to a large population-based study reported. [26] "Meta-analyses of 18 research published together indicated that those in the lowest vs highest quartile of 25(OH) vitamin D level had a 39% and 46% higher risk of ischemic heart disease and premature mortality, respectively. Large-scale randomized trials, such as the VITAL research, are now underway, however it is not yet known if vitamin D supplementation has any positive effects on cardiovascular health."

"Patients with 25(OH) vitamin D levels >89 ng/ml had an elevated risk of ischemic heart disease compared to those with lower levels, according to the only case control research from India on the connection of vitamin D with CHD. This study was conducted among South Indians in Trivandrum. [27] Neither the relationship between vitamin D insufficiency and MI nor the very high cut-off selected for this research are typical." This research accepted that even intense and continuous exposure to UVB sunshine is not hazardous, but it did warn that eating plenty of vitamin D-rich foods could be harmful. "Nonetheless, several case control studies have shown a link between low vitamin D levels and MI. Men with vitamin D insufficiency (25(OH) vitamin D levels 15 ng/ml) were shown to have a higher risk of MI compared to men with 25(OH) vitamin D levels >30 ng/ml in a nested case-control analysis of the Health Professional Follow-Up Study (HPFS)."[28]

"In the United States, a prior case-control study found a similar negative connection between 25(OH) vitamin D levels and risk of acute myocardial infarction. Those with adequate 25(OH) vitamin D levels (>30 ng/ml) were shown to have a reduced risk of MI than those with vitamin D insufficiency, even after accounting for known co-variates. This research was conducted in Pakistan.". found similar results in 100 patients from North India having coronary angiography; those with low vitamin D levels had more severe coronary artery disease and endothelial dysfunction. [29]

Several direct and indirect mechanisms have been proposed to explain the link between vitamin D and CHD. Vitamin D may influence CHD risk in many ways. These include blood pressure, glucose regulation, and PTH. Since elevated PTH levels have been linked to an increased risk of atherosclerosis, low vitamin D levels and elevated PTH levels may both have a role in the development of coronary heart disease. Deficiency in vitamin D is associated with an increase in the activity of the renin angiotensin aldosterone system (RAAS) and the development of hypertrophic changes in the heart's smooth muscles and left ventricle.22,23 Vitamin D deficiency may also contribute to type 2 diabetes via its impact on pancreatic b-cell function, insulin resistance, and inflammation.24,25 Vitamin D's effects on cardiac myocyte remodeling, as well as cardiac relaxation and contractility, have been shown to have a more direct role in animal investigations.26,27 Anti-inflammatory cytokine (IL-10) is up-regulated while pro-inflammatory cytokines (TNF-a, IL-6) are down-regulated by vitamin D.[30]

An increased risk of MI was also shown to be connected with alcohol usage, which is an intriguing discovery. "The results of a case-control study of acute myocardial infarction (MI) and another case-control research of India's industrial population both corroborate this link.

Several things work in favor of this research." [31] Cases were selected via chance, eliminating the potential for protopathic bias, which is frequent in case control studies of chronic illnesses due to the existence of preclinical disease before to study beginning and the subsequent alteration of risk variables. Although the controls were gathered at the same time and place as the study participants, they were limited by their hospital setting.

Phenotyping was performed extensively on both patients and controls. However, the research had a number of flaws, the case-control study design being among them. No data on nutrition or skin color was provided, and the information on physical activity was sketchy at best. Although the exposure rate in controls was greater than expected, this study's sample size limits its usefulness. While this is the most recent evidence between Vitamin D with MI/CHD in Indians, larger, more powerful studies including participants from numerous places throughout the country are required. Women are also underrepresented in this analysis.

Due to the observational nature of the research, we cannot draw any conclusions on the cause of severe vitamin D insufficiency. "Unfortunately, this is the present state of all vitamin D investigations, and until the outcomes of properly planned and powered randomized control trials are published, causation cannot be established. Archival blood samples were used for the analysis. As a steroid, however, 25(OH) vitamin D is very stable. Previous research has shown the long-term stability of 25(OH) vitamin D in preserved samples, up to 24 years."

5. Conclusion

Patients with acute MI and controls from Belagavi, India were found to have significantly lower blood 25 (OH) vitamin D levels than cases, indicating a very high rate of vitamin D insufficiency. Vitamin D deficiency was associated with increased risk of acute myocardial infarction (MI), and this association persisted even after adjustment for more established risk factors. Larger cross-sectional and cohort studies are required to corroborate this link, and more research is needed from India. At the same time, it is important to educate the public about vitamin D insufficiency and the need of getting enough of it to prevent skeletal and maybe cardiovascular injury.

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