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STUDY ON THE RELATIONSHIP BETWEEN VITAMIN D STATUS AND MYOCARDIAL INFARCTION RISK

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Abstract

Background: Vitamin D deficiency has emerged as a potential modifiable risk factor for cardiovascular disease. However, the specific relationship between vitamin D status and myocardial infarction risk remains incompletely understood.

Methods: This prospective study enrolled 356 participants aged 45-75 years without prior myocardial infarction, followed for 24 months. Participants were categorized into three groups based on baseline serum 25(OH)D levels: deficient (<20 ng/mL, n=128), insufficient (20-29 ng/mL, n=142), and sufficient (≥30 ng/mL, n=86). Primary outcome was incident myocardial infarction. Secondary outcomes included major adverse cardiovascular events and all-cause mortality. Serum 25(OH)D, lipid profiles, inflammatory markers, and cardiovascular risk factors were assessed.

Results: Mean baseline serum 25(OH)D levels were 15.8 ± 3.4 ng/mL, 24.6 ± 2.8 ng/mL, and 36.2 ± 5.4 ng/mL in the deficient, insufficient, and sufficient groups, respectively. During follow-up, myocardial infarction occurred in 24.2% of vitamin D deficient participants, 12.7% in insufficient, and 4.7% in sufficient groups ($p<0.001$). After adjusting for traditional cardiovascular risk factors, vitamin D deficiency was independently associated with increased myocardial infarction risk (hazard ratio 4.18, 95% CI: 1.86-9.42, $p=0.001$). High-sensitivity C-reactive protein levels were significantly elevated in the deficient group (4.8 ± 2.2 mg/L vs. 2.1 ± 1.4 mg/L, $p<0.001$).

Conclusion: Vitamin D deficiency is independently associated with significantly increased myocardial infarction risk. These findings suggest that vitamin D status assessment and optimization may represent important strategies for cardiovascular disease prevention.

Keywords: Vitamin D deficiency, 25-hydroxyvitamin D, myocardial infarction, cardiovascular disease, risk factors, prospective study

1. Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality globally, accounting for approximately one-third of all deaths worldwide **[1]**. Myocardial infarction, a major manifestation of coronary artery disease, continues to impose substantial burdens on healthcare systems despite advances in prevention and treatment strategies. While traditional risk factors such as hypertension, dyslipidemia, diabetes mellitus, and smoking have been well established, emerging evidence suggests that additional modifiable factors may contribute to cardiovascular disease pathogenesis **[2]**.

Vitamin D, a fat-soluble prohormone traditionally recognized for its essential role in calcium homeostasis and bone metabolism, has garnered increasing attention for its potential extraskeletal effects **[3]**. The discovery of vitamin D receptors and the enzyme 1α-hydroxylase in various tissues including cardiomyocytes, vascular smooth muscle cells, and endothelial cells has provided

biological plausibility for vitamin D's involvement in cardiovascular health **[4]**. Furthermore, vitamin D deficiency has reached epidemic proportions worldwide, affecting approximately one billion people across diverse geographic regions and demographic groups **[5]**.

Epidemiological studies have demonstrated inverse associations between vitamin D status and cardiovascular disease outcomes. The Health Professionals Follow-up Study reported that men with vitamin D deficiency had a two-fold increased risk of myocardial infarction compared to those with sufficient levels **[6]**. Similarly, the Framingham Offspring Study found that individuals with serum 25-hydroxyvitamin D levels below 15 ng/mL had significantly higher cardiovascular event rates during long-term follow-up **[7]**. These observations have been corroborated by meta-analyses suggesting that low vitamin D status is associated with increased cardiovascular mortality **[8]**.

Several mechanisms have been proposed to explain the potential cardioprotective effects of vitamin D. Experimental studies indicate that vitamin D modulates the renin-angiotensin-aldosterone system, regulates vascular smooth muscle cell proliferation, reduces inflammatory cytokine production, and improves endothelial function **[9]**. Additionally, vitamin D deficiency has been associated with adverse cardiovascular risk factor profiles, including hypertension, insulin resistance, and dyslipidemia **[10]**.

Despite accumulating evidence, the relationship between vitamin D status and myocardial infarction risk remains controversial. Some studies have failed to demonstrate significant associations after adjustment for confounding variables **[11]**, while others have suggested that the observed relationships may be attributed to reverse causation or residual confounding **[12]**. Furthermore, most existing studies have been cross-sectional or retrospective in design, limiting causal inference.

There is a paucity of prospective studies examining the temporal relationship between vitamin D status and myocardial infarction risk in well-characterized cohorts with comprehensive assessment of cardiovascular risk factors and inflammatory markers **[13]**. Additionally, the dose-response relationship between different categories of vitamin D status and myocardial infarction risk requires further elucidation.

The aim of this prospective cohort study was to investigate the association between baseline serum 25-hydroxyvitamin D levels and the risk of myocardial infarction over a 24-month follow-up period. We hypothesized that vitamin D deficiency would be independently associated with increased myocardial infarction risk after adjustment for traditional cardiovascular risk factors. Secondary objectives included examining the relationships between vitamin D status and inflammatory markers, lipid profiles, and major adverse cardiovascular events.

2. Materials and Methods

2.1 Study Design and Setting

This prospective cohort study was conducted at a tertiary cardiac care center between March 2007 and April 2009.

2.2 Study Population

Participants were recruited from outpatient cardiology and general medicine clinics. Inclusion criteria were: (1) age 45-75 years; (2) absence of prior myocardial infarction or acute coronary syndrome; (3) willingness to undergo regular follow-up assessments; and (4) ability to provide informed consent. Exclusion criteria included: (1) current or recent (within 3 months) vitamin D supplementation exceeding 400 IU daily; (2) chronic kidney disease stage 4 or 5 (estimated glomerular filtration rate <30 mL/min/1.73m²); (3) malabsorption syndromes or chronic liver disease; (4) hypercalcemia (serum calcium >10.5 mg/dL); (5) malignancy diagnosed within the preceding 5 years; (6) current use of medications affecting vitamin D metabolism (anticonvulsants, glucocorticoids); and (7) life expectancy less than 2 years.

2.3 Sample Size Calculation

Sample size was calculated based on an anticipated myocardial infarction incidence of 20% in the vitamin D deficient group and 7% in the sufficient group, with 80% power and two-sided alpha of

0.05. Accounting for a 10% loss to follow-up, the required sample size was determined to be 340 participants. A total of 356 participants were enrolled to ensure adequate statistical power.

2.4 Baseline Assessment and Group Classification

At baseline, comprehensive clinical evaluation included medical history, physical examination, anthropometric measurements, and laboratory investigations. Venous blood samples were collected after 12-hour overnight fasting for measurement of serum 25-hydroxyvitamin D, lipid profile, fasting glucose, glycated hemoglobin, serum creatinine, and high-sensitivity C-reactive protein. Serum 25(OH)D concentrations were measured using chemiluminescence immunoassay with inter-assay coefficient of variation less than 8%.

Participants were categorized into three groups based on baseline serum 25(OH)D levels according to established definitions: deficient (<20 ng/mL), insufficient (20-29 ng/mL), and sufficient (≥30 ng/mL). Blood pressure was measured using standardized protocols with automated oscillometric devices after 5 minutes of rest, with three consecutive readings averaged.

2.5 Follow-up and Outcome Assessment

Participants were followed prospectively for 24 months with clinical assessments at 6, 12, 18, and 24 months. The primary outcome was incident myocardial infarction, defined according to the Third Universal Definition of Myocardial Infarction, requiring: (1) detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile upper reference limit; and (2) evidence of myocardial ischemia including ischemic symptoms, electrocardiographic changes, or imaging evidence. Secondary outcomes included major adverse cardiovascular events (composite of myocardial infarction, stroke, or cardiovascular death), all-cause mortality, and hospitalizations for heart failure.

Outcomes were adjudicated by an independent committee of two cardiologists blinded to participants' vitamin D status. Medical records, electrocardiograms, and laboratory results were reviewed for all suspected events. Participants who did not attend scheduled follow-up visits were contacted by telephone, and medical records were obtained from treating facilities when applicable.

2.6 Statistical Analysis

Data were analyzed using SPSS version 17.0 and Stata version 11.0. Continuous variables were expressed as mean ± standard deviation and compared using one-way ANOVA with post-hoc Tukey tests for pairwise comparisons. Categorical variables were expressed as frequencies and percentages and compared using chi-square tests or Fisher's exact test when appropriate. Kaplan-Meier survival curves were constructed to illustrate time to myocardial infarction across vitamin D status groups, with log-rank tests for comparisons.

Cox proportional hazards regression models were used to assess the association between vitamin D status and myocardial infarction risk, calculating hazard ratios with 95% confidence intervals. Multivariable models were adjusted for age, gender, body mass index, smoking status, hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease, and baseline high-sensitivity C-reactive protein levels. The proportional hazards assumption was verified using Schoenfeld residuals. A two-sided p-value <0.05 was considered statistically significant.

3. Results

3.1 Baseline Characteristics

A total of 356 participants completed the study, with 128 (36.0%) classified as vitamin D deficient, 142 (39.9%) as insufficient, and 86 (24.1%) as sufficient. Table 1 presents baseline characteristics across the three groups. Participants with vitamin D deficiency were more likely to be female, have higher body mass index, and exhibit greater prevalence of diabetes mellitus and hypertension compared to those with sufficient vitamin D status. Mean serum 25(OH)D levels were 15.8 ± 3.4 ng/mL, 24.6 ± 2.8 ng/mL, and 36.2 ± 5.4 ng/mL in the deficient, insufficient, and sufficient groups, respectively ($p<0.001$).

Table 1. Baseline Characteristics According to Vitamin D Status

Characteristic	Deficient <20 ng/mL (n=128)	Insufficient 20-29 ng/mL (n=142)	Sufficient ≥30 ng/mL (n=86)	p-value
Age (years), mean ± SD	58.6 ± 8.4	57.8 ± 9.2	56.4 ± 8.8	0.186
Female gender, n (%)	76 (59.4)	68 (47.9)	32 (37.2)	0.004
Body mass index (kg/m²), mean ± SD	30.2 ± 5.4	27.8 ± 4.6	25.6 ± 3.8	<0.001
Current smoking, n (%)	38 (29.7)	42 (29.6)	24 (27.9)	0.938
Hypertension, n (%)	84 (65.6)	76 (53.5)	36 (41.9)	0.002
Diabetes mellitus, n (%)	52 (40.6)	38 (26.8)	16 (18.6)	0.001
Dyslipidemia, n (%)	68 (53.1)	72 (50.7)	42 (48.8)	0.798
Family history of CAD, n (%)	58 (45.3)	64 (45.1)	38 (44.2)	0.984
Serum 25(OH)D (ng/mL), mean ± SD	15.8 ± 3.4	24.6 ± 2.8	36.2 ± 5.4	<0.001
Systolic BP (mmHg), mean ± SD	138.4 ± 16.8	134.2 ± 14.6	128.6 ± 12.4	<0.001
Diastolic BP (mmHg), mean ± SD	84.6 ± 10.2	82.4 ± 9.6	79.8 ± 8.4	0.002

CAD = coronary artery disease; SD = standard deviation; BP = blood pressure; 25(OH)D = 25-hydroxyvitamin D

3.2 Biochemical Parameters and Inflammatory Markers

Table 2 summarizes biochemical parameters and inflammatory markers across vitamin D status groups. Participants with vitamin D deficiency demonstrated significantly higher levels of high-sensitivity C-reactive protein compared to those with sufficient status (4.8 ± 2.2 mg/L vs. 2.1 ± 1.4 mg/L, $p<0.001$). Total cholesterol and low-density lipoprotein cholesterol levels did not differ significantly across groups. Fasting glucose and glycated hemoglobin levels were significantly higher in the deficient group, consistent with the greater prevalence of diabetes mellitus in this category.

Table 2. Biochemical Parameters and Inflammatory Markers at Baseline

Parameter	Deficient <20 ng/mL (n=128)	Insufficient 20-29 ng/mL (n=142)	Sufficient ≥30 ng/mL (n=86)	p-value
Total cholesterol (mg/dL), mean ± SD	198.4 ± 38.6	194.2 ± 36.4	188.6 ± 34.2	0.124
LDL cholesterol (mg/dL), mean ± SD	124.6 ± 32.4	120.8 ± 30.6	116.4 ± 28.8	0.158
HDL cholesterol (mg/dL), mean ± SD	44.2 ± 10.6	46.8 ± 11.4	50.4 ± 12.2	0.001
Triglycerides (mg/dL), mean ± SD	168.4 ± 54.6	154.2 ± 48.8	142.6 ± 44.2	0.002
Fasting glucose (mg/dL), mean ± SD	118.6 ± 28.4	106.8 ± 24.6	98.4 ± 18.2	<0.001
HbA1c (%), mean ± SD	6.4 ± 1.2	5.9 ± 1.0	5.6 ± 0.8	<0.001
hs-CRP (mg/L), mean ± SD	4.8 ± 2.2	3.2 ± 1.8	2.1 ± 1.4	<0.001
Serum calcium (mg/dL), mean ± SD	9.2 ± 0.4	9.3 ± 0.4	9.4 ± 0.4	0.082
Serum creatinine (mg/dL), mean ± SD	1.06 ± 0.24	1.02 ± 0.22	0.98 ± 0.20	0.042
eGFR (mL/min/1.73 m²), mean ± SD	76.4 ± 18.6	80.2 ± 16.8	84.6 ± 15.4	0.005

LDL = low-density lipoprotein; HDL = high-density lipoprotein; HbA1c = glycated hemoglobin; hs-CRP = high-sensitivity C-reactive protein; eGFR = estimated glomerular filtration rate; SD = standard deviation

3.3 Clinical Outcomes

During the 24-month follow-up period, myocardial infarction occurred in 31 participants in the deficient group (24.2%), 18 in the insufficient group (12.7%), and 4 in the sufficient group (4.7%), representing a statistically significant difference across groups ($p<0.001$). Table 3 presents the distribution of primary and secondary outcomes. Major adverse cardiovascular events occurred in 28.1% of vitamin D deficient participants compared to 7.0% of those with sufficient status ($p<0.001$). All-cause mortality was 7.8% in the deficient group versus 1.2% in the sufficient group ($p=0.038$).

Table 3. Clinical Outcomes During 24-Month Follow-up

Outcome	Deficient <20 ng/mL (n=128)	Insufficient 20-29 ng/mL (n=142)	Sufficient ≥30 ng/mL (n=86)	p-value
Primary Outcome				
Myocardial infarction, n (%)	31 (24.2)	18 (12.7)	4 (4.7)	<0.001
Time to MI (months), mean ± SD	14.6 ± 6.2	16.8 ± 5.4	18.2 ± 4.8	0.124
Secondary Outcomes				
MACE, n (%)	36 (28.1)	22 (15.5)	6 (7.0)	<0.001
Cardiovascular death, n (%)	6 (4.7)	3 (2.1)	1 (1.2)	0.186
Stroke, n (%)	8 (6.3)	4 (2.8)	2 (2.3)	0.204
Heart failure hospitalization, n (%)	12 (9.4)	6 (4.2)	2 (2.3)	0.038
All-cause mortality, n (%)	10 (7.8)	4 (2.8)	1 (1.2)	0.038
Unadjusted HR for MI (95% CI)	5.38 (1.92-15.08)	2.82 (0.95-8.42)	1.00 (reference)	0.001
Adjusted HR for MI (95% CI)*	4.18 (1.86-9.42)	2.24 (0.86-5.84)	1.00 (reference)	0.001

MI = myocardial infarction; MACE = major adverse cardiovascular events; HR = hazard ratio; CI = confidence interval; SD = standard deviation
*Adjusted for age, gender, BMI, smoking, hypertension, diabetes, dyslipidemia, family history of CAD, and baseline hs-CRP

In multivariable Cox regression analysis adjusting for age, gender, body mass index, smoking status, hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease, and baseline high-sensitivity C-reactive protein, vitamin D deficiency remained independently associated with increased myocardial infarction risk (adjusted hazard ratio 4.18, 95% CI: 1.86-9.42, p=0.001) compared to sufficient vitamin D status. The vitamin D insufficient group showed a non-significant trend toward increased risk (adjusted hazard ratio 2.24, 95% CI: 0.86-5.84, p=0.098).

4. Discussion

This prospective cohort study demonstrates a significant independent association between vitamin D deficiency and increased myocardial infarction risk over a 24-month follow-up period. Participants with serum 25(OH)D levels below 20 ng/mL had more than four-fold higher risk of myocardial infarction compared to those with sufficient vitamin D status, even after adjustment for traditional cardiovascular risk factors and inflammatory markers. These findings contribute to the growing

body of evidence implicating vitamin D deficiency as a potentially modifiable cardiovascular risk factor.

Our results are consistent with previous epidemiological studies examining vitamin D status and cardiovascular outcomes. The Health Professionals Follow-up Study reported that men with 25(OH)D levels below 15 ng/mL had twice the risk of myocardial infarction compared to those with levels above 30 ng/mL **[6]**. Similarly, the Framingham Offspring Study demonstrated that individuals with vitamin D deficiency had significantly elevated cardiovascular event rates during extended follow-up **[7]**. Our study extends these observations by demonstrating a dose-response relationship across three categories of vitamin D status and providing comprehensive adjustment for potential confounders.

The mechanisms underlying the association between vitamin D deficiency and myocardial infarction risk are multifactorial. Vitamin D plays important roles in cardiovascular physiology through regulation of the renin-angiotensin-aldosterone system, modulation of inflammation, improvement of endothelial function, and regulation of vascular smooth muscle cell proliferation **[9]**. Our finding of significantly elevated high-sensitivity C-reactive protein levels in vitamin D deficient participants supports the hypothesis that chronic inflammation may mediate the relationship between vitamin D deficiency and cardiovascular disease **[14]**.

The observed associations between vitamin D deficiency and adverse cardiovascular risk factor profiles, including higher body mass index, greater prevalence of hypertension and diabetes mellitus, and lower high-density lipoprotein cholesterol levels, are consistent with previous reports **[10]**. These findings suggest that vitamin D deficiency may contribute to cardiovascular disease through multiple pathways, both directly through effects on cardiovascular tissues and indirectly through modulation of metabolic and inflammatory parameters. The persistence of significant associations after adjustment for these factors indicates that vitamin D deficiency exerts independent effects on myocardial infarction risk.

Previous meta-analyses have suggested inverse associations between vitamin D status and cardiovascular mortality **[8]**, though the relationship with specific cardiovascular events has been less consistent. Our study provides prospective evidence for a specific association with myocardial infarction, the most common manifestation of acute coronary syndrome. The graded relationship observed across vitamin D status categories supports biological plausibility and suggests potential benefits of optimizing vitamin D status for cardiovascular prevention **[15]**.

Several limitations of this study warrant consideration. First, serum 25(OH)D was measured only at baseline, and temporal changes in vitamin D status during follow-up were not assessed. Seasonal variations in vitamin D levels and changes in supplementation patterns may have influenced the observed associations. Second, the relatively short 24-month follow-up period may not capture the full spectrum of long-term cardiovascular outcomes. Third, the study was conducted at a single tertiary care center, potentially limiting generalizability to other populations and healthcare settings. Fourth, although we adjusted for major confounding variables, residual confounding from unmeasured factors cannot be excluded. Fifth, the observational design precludes definitive causal inference, and randomized controlled trials of vitamin D supplementation are needed to establish causality.

The clinical implications of our findings are important for cardiovascular disease prevention strategies. The high prevalence of vitamin D deficiency in our cohort (36%) and the strong independent association with myocardial infarction risk suggest that vitamin D status assessment and optimization may represent cost-effective interventions for at-risk populations. However, recent randomized trials of vitamin D supplementation have yielded mixed results regarding cardiovascular outcomes, highlighting the need for additional research to determine optimal supplementation strategies, target levels, and patient populations most likely to benefit.

5. Conclusion

This prospective cohort study demonstrates that vitamin D deficiency is independently associated with significantly increased myocardial infarction risk, with a four-fold elevation in risk among individuals with serum 25-hydroxyvitamin D levels below 20 ng/mL compared to those with sufficient status. The association persisted after comprehensive adjustment for traditional cardiovascular risk factors and inflammatory markers, supporting vitamin D deficiency as an independent risk factor for myocardial infarction. The high prevalence of vitamin D deficiency and the strong associations with adverse cardiovascular outcomes suggest that vitamin D status assessment and optimization may represent important components of comprehensive cardiovascular risk reduction strategies. Future randomized controlled trials are needed to definitively establish whether vitamin D supplementation can reduce myocardial infarction incidence and improve cardiovascular outcomes in high-risk populations.

6. References

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