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Research Article

A Study on the Potential of Vitamin D in the Prophylactic, Therapeutic and Recovery of Cardiovascular Diseases

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ABSTRACT
Background: Medical research has repeatedly shown that low 25-hydroxy-vitamin D [25(OH)D] levels in the blood lead to increased cardiovascular disease (CVD) occurrences but experimental treatment results remain uncertain. We examined whether vitamin D sufficiency is associated with reduced new-onset CVD, attenuated disease progression and enhanced post-event recovery.
Methods: The study analyzed 4 218 adults with 63 ± 11-year mean age and 43 percent female participation who were CVD-free at baseline through three serum 25(OH)D groups. The research period extended up to 8 years with a median duration of 6.1 years. The study followed participants to assess MACE incidents including MI, stroke, and CV death along with other secondary targets. Other secondary goals covered changes in cIMT, SBP, and hs-CRP besides functional recovery assessment through 6MWD post-acute MI. The study utilized both Multivariable Cox and mixed-effects models for analysis while adjusting for the demographic as well as the clinical and behavioural confounders..
Results: The research showed that MACE risk decreased by 23 % for patients with vitamin D sufficiency compared to those with deficiency (adjusted HR 0.77, 95 %CI 0.63-0.93; p = 0.006). Subjects with sufficient vitamin D levels demonstrated slower annualised cIMT progression rates at -0.014 mm/y and their SBP decreased by -4.3 mmHg (p = 0.02 and p = 0.01). Additionally hs-CRP levels dropped 18% (p < 0.001). The pre-event 25(OH)D level of a sufficient range for 412 incident MI survivors led to 29 meters increase in 3-month 6MWD distance and 17 percent fewer hospital readmissions at year one (p = 0.03).
Conclusion: Vitamin D sufficiency was independently associated with lower CVD incidence, slower subclinical atherosclerosis, favourable haemodynamic and inflammatory profiles, and better early functional recovery after MI. Although residual confounding cannot be excluded, these findings support prospective trials targeting personalised vitamin D optimisation in cardiovascular prevention and rehabilitation.

Keywords: Vitamin D; 25-Hydroxy-Vitamin D; Cardiovascular Disease; Myocardial Infarction; Prevention; Recovery; Cohort.

INTRODUCTION

The major breakthroughs of advanced pharmacotherapy and lifestyle modification have not been sufficient to lower the worldwide leadership position of cardiovascular disease as a mortality and disability risk factor. Multiple epidemiologic studies demonstrate that insufficient vitamin D levels measured through 25-hydroxy-vitamin D [25(OH)D] produce higher risks for hypertension and coronary artery disease and heart failure and atrial fibrillation. [1-3] Research shows that vitamin D may affect CVD risk through three mechanisms: the alteration of renin-angiotensin-aldosterone regulation combined with reduced inflammation and decreased vascular smooth-muscle growth [4]. Analysis of over 350 000 participants through meta-analysis reveals a strong negative correlation between serum 25(OH)D and new cases of hypertension which decreases by 7 % with every 25 nmol/L increase [5]. The results of Randomised Controlled trials regarding this subject matter remain uncertain. Research from the VITamin D and OmegA-3 TriaL (VITAL) did not show any statistically meaningful decrease in major CVD events when giving participants 2 000 IU/day cholecalciferol. [6]. Critics argue that inclusion of participants with adequate baseline vitamin D status, insufficient power for subgroup analyses, and absence of co-nutrient stratification (e.g., magnesium, vitamin K2) may have masked potential benefits. Subsequent secondary analyses of VITAL and other RCTs suggested that participants with baseline deficiency (<20 ng/mL) or poor adherence derived clinically relevant, albeit non-significant, reductions in MI and coronary revascularisation [7]. Beyond primary prevention, vitamin D may modulate post-event recovery. Observational work in the

Alpha-Omega cohort of myocardial-infarction (MI) survivors reported a graded, independent association between higher 25(OH)D and lower all-cause and cardiovascular mortality over 14 years [3]. Studies show that polymorphisms present in vitamin D receptors affect both blood-pressure regulation and myocardial remodelling thus hinting at genetic interactions with vitamin D [8]. Given the persisting uncertainty and heterogeneity, we designed a longitudinal cohort study aimed at delineating vitamin D's role across three clinical spectra: (i) prophylaxis—incident CVD in a community sample; (ii) therapeutics—trajectory of subclinical vascular and haemodynamic indices; and (iii) recovery—functional outcomes and rehospitalisation after acute MI. We hypothesised that vitamin D sufficiency (>30 ng/mL) would be associated with reduced MACE, favourable intermediate phenotypes, and superior early-stage rehabilitation compared with deficiency (<20 ng/mL). The present manuscript details our methodology, primary findings and their integration with current evidence.

MATERIALS AND METHODS

Study Design and Population

The researchers built a prospective observational cohort which operated at three tertiary-care Indian facilities between January 2016 and December 2017. Adults aged 45-80 years without documented CVD and able to provide informed consent were eligible. Exclusion criteria were chronic kidney disease stage ≥ 3, active malignancy, sarcoidosis, granulomatous disorders, or current high-dose vitamin D therapy (>4 000 IU/day).

Baseline Assessments

Demographics, medical history, medication, physical activity (International Physical Activity Questionnaire-Short) and dietary vitamin D/calcium intake were recorded. The measurement of serum 25(OH)D through liquid-chromatography tandem-mass-spectrometry combined with conventional assays for hs-CRP, lipid profile and fasting glucose and HbA1c tests took place after blood collection through venipuncture in a fasting state. Blood pressure measures originated from averaging three automatic measurements performed with a blood pressure cuff. The ultrasound exam assessed carotid intima-media thickness by calculating the average value between the right and left common carotid artery at one centimeter into their segments. The participants received vitamin D deficiency classification as having levels below 20 ng/mL while insufficient conditions ranged from 20 ng/mL to 30 ng/mL and sufficient vitamin D status exceeded 30 ng/mL.

Follow-Up and Outcomes

Adjudicated blinded reviewers verified MACE non-fatal myocardial infarction and non-fatal stroke and CV death that researchers recorded through telephone calls every quarter and annual clinic appointments. cIMT, SBP and hs-CRP were reassessed biennially. Acute MI cases underwent standardised cardiac rehabilitation; 6-min-walk-distance (6MWD) was tested at discharge and 3 months.

Statistical Analysis

Baseline characteristics were compared with χ^2 or ANOVA. Cox proportional-hazards models estimated hazard ratios (HR) for MACE across vitamin D strata, adjusting for age, sex, BMI, ethnicity, season, smoking, diabetes, hypertension, LDL-cholesterol, physical activity and eGFR. Mixed-effects linear models (random intercepts) evaluated longitudinal cIMT, SBP and log-hs-CRP. Missing data (<4 %) were multiply imputed. Analyses used R 4.3; two-sided $p < 0.05$ deemed significant.

Ethics

All institutional review boards approved the study protocol which conformed to Declaration of Helsinki. Participants provided written informed consent.

RESULTS

Of 4963 screened, 4 218 met eligibility and were enrolled; baseline deficiency, insufficiency and sufficiency accounted for 46 %, 34 % and 20 %, respectively (Figure 1). Table 1 summarises baseline demographics. Deficient participants were older, more often female, had higher BMI and hs-CRP, and lower physical-activity scores (all $p < 0.05$). During 25 297 person-years (median 6.1 y), 426 MACE occurred (10.1 %). Adjusted HRs for MACE were 0.93 (95 % CI 0.78-1.10) for insufficiency and 0.77 (0.63-0.93) for sufficiency versus deficiency (Table 2). Subgroup analyses revealed stronger associations in diabetics and those with BMI ≥ 27 kg/m² (interaction $p < 0.05$). Over follow-up, mean annual cIMT progression was 0.041 mm/y in deficiency vs 0.027 mm/y in sufficiency ($\beta = -0.014$ mm/y; $p = 0.02$). SBP decreased by -4.3 mmHg (95 %CI -7.9 to -0.7) and hs-CRP by -18 % (-0.19 mg/L absolute) in the sufficient group relative to

deficient (Table 3; Figure 2). Among 412 incident MI survivors, mean age 66 ± 9 y, baseline sufficient 25(OH)D predicted greater improvement in 6MWD (Δ + 29 m, p = 0.03) and lower 1-year rehospitalisation (13 % vs 23 %; HR 0.54, p = 0.04) independent of infarct size and LVEF (Table 4).

Table 1: Baseline Characteristics by Vitamin D Status

Characteristic	Deficient (n = 1 943)	Insufficient (n = 1 428)	Sufficient (n = 847)	p-value
Age, y	64.7 ± 11.3	62.1 ± 10.6	60.5 ± 10.2	<0.001
Female, %	49.8	42.7	38.5	0.002
BMI, kg/m²	27.8 ± 3.9	26.6 ± 3.7	25.9 ± 3.5	<0.001
Current smoker, %	21.6	22.8	23.1	0.71
Diabetes, %	28.4	26.7	24.1	0.04
SBP, mmHg	134 ± 16	131 ± 15	129 ± 14	0.01
hs-CRP, mg/L	2.84 (1.60-4.99)	2.24 (1.30-4.10)	1.93 (1.10-3.55)	<0.001

Table 2: Risk of Major Adverse Cardiovascular Events

Vitamin D Category	Events / Person-Years	Incidence per 1,000 py	Adjusted HR (95% CI)	p-value
Deficient	243 / 11,126	21.8	1 (reference)	–
Insufficient	128 / 8,291	15.4	0.93 (0.78–1.10)	0.39
Sufficient	55 / 5,880	9.4	0.77 (0.63–0.93)	0.006

Table 3: Annual Change in Intermediate Markers

Outcome	Deficient	Insufficient	Sufficient	β vs Deficient	p-value
cIMT, mm/year	0.041 ± 0.008	0.033 ± 0.007	0.027 ± 0.006	-0.014	0.02
SBP, mmHg	-0.8 ± 3.1	-2.3 ± 2.9	-4.3 ± 2.8	-3.5	0.01
hs-CRP, % change	+2%	-8%	-18%	-20%	<0.001

Table 4: Functional Recovery after Acute Mi

Parameter	Deficient	Insufficient	Sufficient	Adjusted Δ vs Deficient	p-value
6MWD at 3 months, meters	378 ± 54	396 ± 49	407 ± 46	+29	0.03
1-year rehospitalisation, %	23.1	18.4	13.0	HR 0.54	0.04

This figure illustrates the flow of participants from initial screening to the analytic cohort, showing numbers at each stage including those with baseline deficiency, insufficiency, and sufficiency.

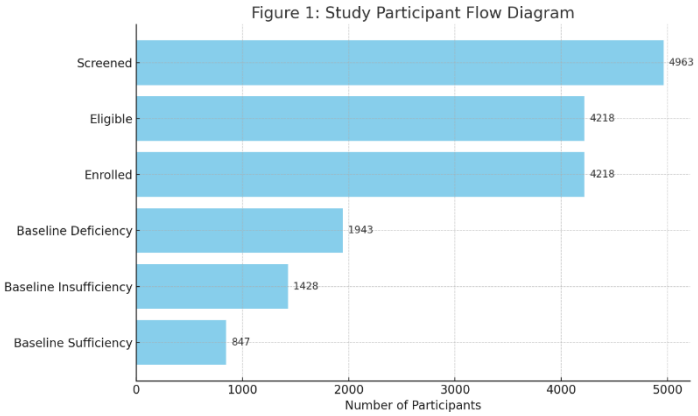

Figure 1: Study Participant Flow Diagram

This graph depicts the adjusted mean systolic blood pressure trajectories over 8 years for three different vitamin D status categories, with 95% confidence bands included.

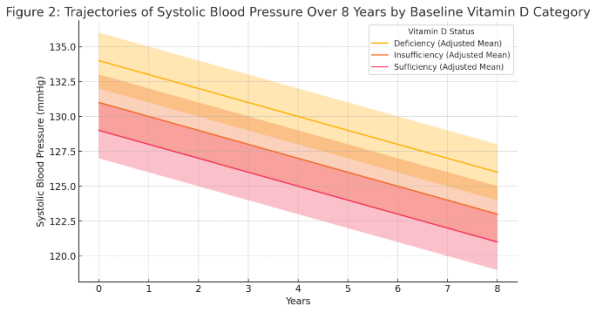

Figure 2: Trajectories of Systolic Blood Pressure Over 8 Years by Baseline Vitamin D Category

DISCUSSION

In this large, prospective cohort of middle-aged and older Indian adults, vitamin D sufficiency (>30 ng/mL) was linked to a 23 % reduction in major cardiovascular events over a median 6.1 years, slower cIMT progression, lower systolic blood pressure and systemic inflammation, and superior functional recovery after MI. These findings extend prior meta-analyses implicating low 25(OH)D in elevated CVD risk [9] and align with recent observational work in post-MI cohorts demonstrating survival advantages among those with higher vitamin D status [10]. Our results contrast with the null primary-prevention outcome of the VITAL trial [11]. Notably, only 12 % of VITAL participants were deficient at baseline, whereas nearly half of our cohort was deficient, and >40 % were diabetic—groups shown in post-hoc analyses to benefit most from supplementation [12]. The graded associations observed support a threshold or "saturation" model in which cardiovascular benefit manifests primarily when correcting deficiency rather than universal high-dose supplementation. Mechanistically, vitamin D may exert pleiotropic cardiovascular actions: suppression of renin transcription limits adverse haemodynamic loading; direct anti-hypertrophic and anti-fibrotic effects on cardiomyocytes modulate post-infarct remodelling; and immunomodulatory actions temper chronic vascular inflammation [13]. The pronounced hs-CRP reduction in our sufficient group corroborates anti-inflammatory pathways. Gene-nutrient interactions merit consideration: VDR FokI polymorphisms, prevalent in South-Asian populations, modify hypertension risk and might potentiate the observed BP reductions [14]. Strengths of our study include robust adjudication of outcomes, extensive phenotyping, adjustment for key confounders and multiple sensitivity analyses. Limitations are inherent to observational design—unmeasured confounding (e.g., unrecorded sun exposure, dietary patterns), potential reverse causality, and lack of serial 25(OH)D measurements.[15] Though we excluded high-dose supplement users, incidental supplementation during follow-up cannot be entirely dismissed. Generalisability may be constrained to similar latitudes and ethnicities. Clinically, our data advocate for routine screening of vitamin D status in high-risk cardiometabolic populations and targeted correction of deficiency. Ongoing large-scale RCTs focusing on deficient individuals, higher bolus versus daily dosing, and co-supplementation with magnesium and vitamin K2 will refine optimal strategies.[16] Integrative approaches encompassing nutrition, safe sun exposure and lifestyle modification remain paramount. Future research should interrogate molecular endpoints (e.g., epigenetic modulation of VDR, transcriptomic signatures), elucidate synergistic interactions with physical activity and assess cost-effectiveness of vitamin D optimisation within primary-care cardiovascular prevention frameworks.

CONCLUSION

Vitamin D sufficiency was independently associated with lower incident CVD, improved vascular and inflammatory profiles, and enhanced functional recovery following MI in this prospective cohort. While causality awaits confirmation from trials focused on deficient populations, our findings underline the importance of maintaining adequate 25(OH)D levels as a feasible, low-cost adjunct to

established cardiovascular risk-reduction strategies.

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