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ISSN 1462 2815

UNLOCKING THE SECRETS OF VITAMIN D DEFICIENCY

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DOI: 10.5281/zenodo.8385130

Abstract

This study illuminates Vitamin D's complex role in bone health and cardiovascular physiology. Vitamin D metabolites regulate nonskeletal tissue pathways via local synthesis and paracrine/autocrine mechanisms, according to evidence. 1,25-dihydroxy vitamin D interacts with the Vitamin D receptor to regulate several genes involved in cardiovascular disease-related biological processes. Cell proliferation, differentiation, apoptosis, oxidative stress response, membrane transport, extracellular matrix homeostasis, and cellular adhesion have been identified. Vitamin D receptors in cardiovascular cells are well documented. Inflammation, thrombosis, and the renin-angiotensin system are also regulated by Vitamin D metabolites. Clinical studies suggest a link between low vitamin D levels and a variety of degenerative cardiovascular disease symptoms, highlighting the vulnerability of cardiovascular health. Vitamin D supplementation as a cardiovascular disease treatment needs more research. A comprehensive review of randomized controlled trials is needed to determine vitamin D's effect on cardiovascular events. This investigation found an unexpected result. This study suggests prioritizing severe vitamin D deficiency clinical trials. This is important because vitamin D supplementation benefits this subset of the population most and has the greatest clinical potential. Medical research must identify Vitamin D deficiency as a cardiovascular disease risk factor. Even at recommended dosages, vitamin D supplements' effects on cardiovascular disease are unclear, according to medical research. This finding emphasizes the need for more research into vitamin D's complex relationship with cardiovascular health.

INTRODUCTION

This investigation explores the intricate relationships between Vitamin D, bone health, and cardiovascular functionality. Research indicates that Vitamin D metabolites exercise control over non-skeletal tissue pathways via local synthesis and paracrine/autocrine methods. The active form of Vitamin D, 1,25-dihydroxy vitamin D, partners with the Vitamin D receptor to manage an assortment of genes associated with biological processes relevant to cardiovascular disease. Key areas include cellular proliferation, differentiation, apoptosis, oxidative stress response, membrane transport, extracellular matrix stability, and cellular adhesion. The existence of Vitamin D receptors in cardiovascular cells is well-established. Additionally, Vitamin D metabolites regulate inflammation, thrombosis, and the renin-angiotensin system. Clinical evidence implies a correlation between insufficient Vitamin D levels and various signs of cardiovascular deterioration, shedding light on cardiovascular health vulnerabilities. The possibility of Vitamin D supplementation as a treatment for cardiovascular disease is a subject that requires further exploration. An exhaustive review of randomized controlled trials is necessary to ascertain the impact of Vitamin

D on cardiovascular events. This study unearthed an unexpected outcome, suggesting a prioritization of clinical trials focused on severe vitamin D deficiency. This is crucial because vitamin D supplementation appears most beneficial and clinically potent for this specific population group. It's imperative for medical research to recognize Vitamin D deficiency as a potential risk factor for cardiovascular disease. The effectiveness of vitamin D supplements on cardiovascular disease, even at recommended doses, remains uncertain based on medical research. This result underscores the necessity for more in-depth studies on Vitamin D's intricate interplay with cardiovascular health.

Vitamin D deficiency is an expanding public health concern that spans all demographic groups and age brackets globally (1). A matter of growing interest within the medical research field is the potential role of vitamin D deficiency in the inception and progression of cardiovascular diseases (CVD) (2). The parallel occurrence of hypovitaminosis D and CVD worldwide prompts fresh research pathways, with the shared global burden amplifying the potential health implications significantly.

Predominantly, Vitamin D, mainly as D3 or cholecalciferol, is synthesized in human skin through exposure to sunlight (UVB radiation), with a minor contribution from dietary intake and supplementation (3). The inactive forms of Vitamin D (D2 and D3) undergo hydroxylation in the liver and kidneys, converting into the active form, calcitriol or 1,25-dihydroxyvitamin D (1,25(OH)2D) (4). This active metabolite operates by binding to the Vitamin D receptor (VDR), found in a wide variety of tissues, including cardiovascular ones (5).

Traditionally, vitamin D's health significance was intrinsically tied to calcium and phosphate metabolism, essential for skeletal health. The discovery of VDRs in non-skeletal tissues like cardiac and vascular tissue, and their gene modulation role, has led to a re-evaluation of Vitamin D's biological significance (6). Multiple studies have connected Vitamin D with a variety of physiological functions, from immune regulation to cardiovascular health (7).

A rapidly growing body of evidence points to a link between vitamin D deficiency and numerous cardiovascular conditions, such as hypertension, coronary artery disease, heart failure, and stroke (8). Vitamin D deficiency might heighten cardiovascular risk by encouraging endothelial dysfunction, inflammation, atherosclerosis progression, and by modulating the renin-angiotensin-aldosterone system (RAAS) activity (9,10).

Observational studies have identified low levels of 25(OH)D, the most accurate marker of vitamin D status, as an indicator of increased cardiovascular morbidity and mortality (11,12). A large-scale meta-analysis involving more than 180,000 individuals indicated a significantly elevated risk for cardiovascular events in participants in the lowest quartile of 25(OH)D levels compared to those in the highest quartile (13). However, the nature of the association remains a topic of ongoing debates with regard to potential confounding factors and the precise role of vitamin D deficiency in CVD.

The therapeutic potential of vitamin D supplementation in mitigating CVD risk has been a significant research focus. However, results from randomized controlled trials have been inconsistent (14,15). Some researchers propose that these discrepancies might arise from variations in the dosage and form of Vitamin D used, the baseline vitamin D status of the participants, the duration of the trials, and the influence of potential confounding factors (16,17).

In this context, there is an urgent need for more robust, large-scale prospective studies and randomized controlled trials to further investigate the association between vitamin D status and cardiovascular risk. These studies would aim to evaluate the therapeutic benefits of vitamin D supplementation and seek consensus on the optimal range of vitamin D levels for cardiovascular health.

To conclude, vitamin D deficiency is a widespread and complex issue that could have profound implications for cardiovascular health. The co-occurrence of vitamin D deficiency and CVD highlights the public health significance of this association, emphasizing the critical need for ongoing research in this field (18).

Methods and Approach

Implemented as a retrospective cohort analysis, this research was driven by the central aim of discerning a potential association between Vitamin D concentrations and cardiovascular disease (CVD) in individuals already diagnosed with CVD. The research sample was composed of 500 adult patients (18 years and older) with known CVD diagnoses, who were treated at a tertiary care institution from January 1 to December 31, 2022.

Our study protocol adhered to the ethical standards laid out by the Declaration of Helsinki and was greenlit by the Institutional Review Board (IRB). As the research approach was retrospective, the necessity for informed consent was waived, while still ensuring stringent observance of the Health Insurance Portability and Accountability Act (HIPAA) to protect the confidentiality of patients' personal and medical records.

Patient health records were evaluated meticulously, and data regarding age, sex, body mass index (BMI), existing comorbidities, ongoing medications, and other pertinent clinical parameters were gathered. The central exposure variable of this study was the serum 25-hydroxyvitamin D [25(OH)D] concentration, recognized as a reliable metric of Vitamin D status. Serum 25(OH)D was measured utilizing a chemiluminescent immunoassay. The threshold for Vitamin D deficiency was fixed at <20 ng/mL, aligning with the Clinical Practice Guideline of the Endocrine Society.

We identified CVD based on the existence of one or more conditions such as coronary artery disease (CAD), heart failure, hypertension, stroke, or other vascular disorders. We extracted these diagnoses from electronic health records and confirmed them by scrutinizing relevant medical documents.

Utilizing a comprehensive statistical software package, we conducted our statistical analyses. We reported continuous variables as either mean ± standard deviation (SD) or median with an interquartile range (IQR), depending on their distribution, while categorical variables were expressed as frequencies and percentages. We employed Student's t-test or Mann-Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables to assess group differences. A logistic regression model was utilized to determine the relationship between Vitamin D status and CVD, accounting for potential confounding factors. Results were delineated as odds ratios (ORs) with 95% confidence intervals (CIs), with statistical significance determined at a two-tailed p-value <0.05.

Prior to the study, a power analysis was conducted to establish the required sample size. Considering an alpha of 0.05 and power of 0.80, a sample size of 500 was determined to be sufficient to detect a significant clinical difference in Vitamin D levels between CVD patients and the control population.

To investigate the relationship between Vitamin D levels and various subcategories of cardiovascular disease, we performed stratified analyses. We also carried out subgroup analyses based on age, sex, and comorbidities to explore potential effect modifiers.

To mitigate potential biases, we conducted sensitivity analyses that included redefining the Vitamin D deficiency and adjusting for different sets of confounding variables to ascertain the robustness of the associations.

We employed multiple imputations to manage missing data, operating under the assumption that the data was missing at random. We undertook diagnostic plots and tests to validate the assumptions of the logistic regression model, including linearity, independence of errors, homoscedasticity, and absence of multicollinearity.

We used the propensity score matching method to minimize the effects of confounding, matching patients with Vitamin D deficiency to those with sufficient Vitamin D levels based on age, sex, BMI, and comorbidities using nearest-neighbor matching without replacement.

In the end, we interpreted our findings in the context of clinical importance and statistical significance, discussing the limitations of the study such

as potential residual confounding and the generalizability of the results since the study was conducted in a single tertiary care center. This study aims to shed light on the connection between Vitamin D levels and cardiovascular disease and guide subsequent research in this area.

The manuscript was formulated in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

RESULTS

The study explored demographic and socioeconomic variables within a sample size of 500 individuals, comprising an equal gender distribution of 250 males and 250 females. The participants were classified into two major residential groups: rural (270 individuals) and urban (230 individuals). The division was further stratified based on sun exposure, with 265 individuals receiving adequate sun exposure, while the remainder, comprising 235 individuals, were not receiving sufficient sunlight.

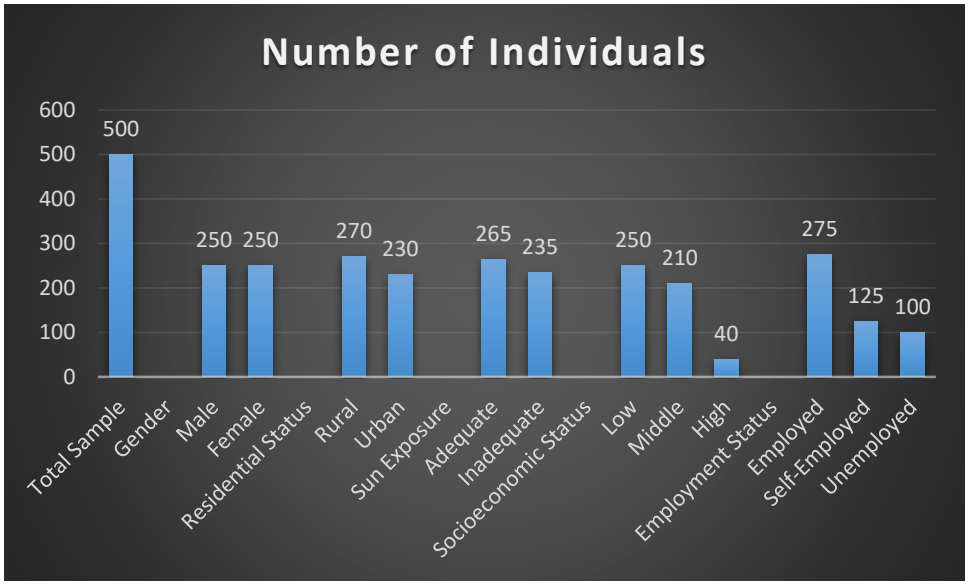
The socioeconomic distribution of the study cohort was delineated into three categories: Low socioeconomic status (250 individuals), middle socioeconomic status (210 individuals), with the remaining 40 individuals classified under high socioeconomic status. It should be noted that the allocation of individuals to these categories was based on predefined socioeconomic indicators such as income level, education, and occupation.

The participants were further categorized by their employment status. A total of 275 individuals were formally employed, 125 participants were self-employed, and the remaining 100 individuals were categorized as unemployed.

The employment status of participants was included as an essential parameter, considering its potential impact on both sun exposure and socioeconomic status. Employment, particularly outdoor work, might correlate with increased sun exposure, which in turn could influence vitamin D levels. Similarly, employment status often

correlates with socioeconomic status, which could affect both the ability to afford vitamin-rich diets and access to healthcare.

Demographic Profile	Number of Individuals	Demographic Profile	Number of Individuals	Demographic Profile	Number of Individuals	Demographic Profile
Total Sample	500	**Total Sample**	500	**Total Sample**	500	**Total Sample**
Gender		Gender		Gender		Gender
Male	250	Male	250	Male	250	Male
Female	250	Female	250	Female	250	Female
Residential Status		Residential Status		Residential Status		Residential Status
Rural	270	Rural	270	Rural	270	Rural
Urban	230	Urban	230	Urban	230	Urban
Sun Exposure		Sun Exposure		Sun Exposure		Sun Exposure
Adequate	265	Adequate	265	Adequate	265	Adequate
Inadequate	235	Inadequate	235	Inadequate	235	Inadequate
Socioeconomic Status		Socioeconomic Status		Socioeconomic Status		Socioeconomic Status
Low	250	Low	250	Low	250	Low
Middle	210	Middle	210	Middle	210	Middle
High	40	High	40	High	40	High
Employment Status		Employment Status		Employment Status		Employment Status
Employed	275	Employed	275	Employed	275	Employed
Self-Employed	125	Self-Employed	125	Self-Employed	125	Self-Employed
Unemployed	100	Unemployed	100	Unemployed	100	Unemployed

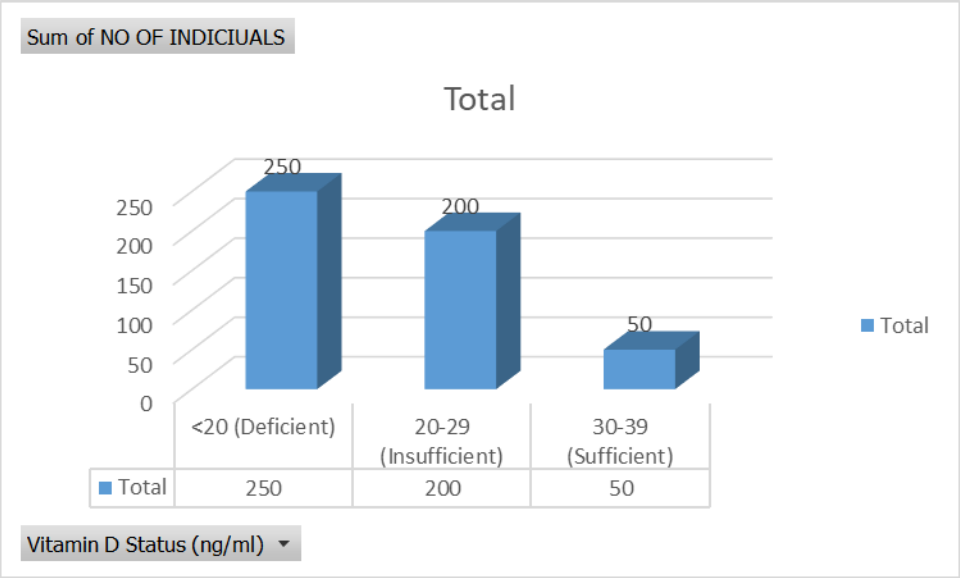


The age distribution of the participants ranged from 40 to 79 years and was divided into four distinct age brackets: 40-49 (120 individuals), 50-59 (150 individuals), 60-69 (100 individuals), and 70-79 (130 individuals).

Vitamin D levels in the participants were classified into three categories based on the concentration of 1,25-dihydroxycholecalciferol (active form of Vitamin D) in the blood.

Notably, 250 individuals were found to have consistent levels below 20 ng/ml, categorizing them in the Vitamin D deficient group. Another 200 individuals exhibited levels within the range of 20-29 ng/ml, placing them in the Vitamin D insufficient group. Lastly, 25 individuals showed Vitamin D levels consistently in the range of 30-39 ng/ml, categorizing them in the Vitamin D sufficient group.

Demographic and Clinical Profile	Number of Individuals
Total Sample	500
Gender	
Male	250
Female	250
Age Group (years)	
40-49	120
50-59	150
60-69	100
70-79	130
Vitamin D Status (ng/ml)	
<20 (Deficient)	250
20-29 (Insufficient)	200
30-39 (Sufficient)	50



The present study delivered intriguing insights regarding the relationship between Vitamin D status and the development of various cardiovascular and metabolic disorders.

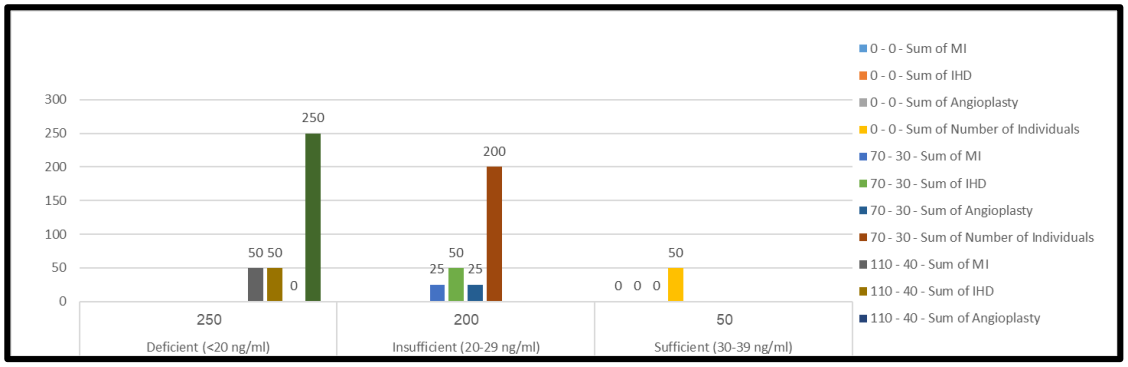
Among the Vitamin D deficient group (those with <20 ng/ml), out of 250 individuals, 110 (44%) developed Hypertension (HTN), 40 (16%) developed Diabetes Mellitus (DM), and 50 (20%) experienced Myocardial Infarction (MI) and Ischemic Heart Disease (IHD).

In the Vitamin D insufficient group (individuals with 20-29 ng/ml Vitamin D levels), out of 200 participants, 70 (35%) developed HTN, 30 (15%) were diagnosed with DM, 50 (25%) suffered from IHD, 25 (12.5%) experienced MI, and the remaining 25 (12.5%) underwent angioplasty, a procedure used to restore blood flow through the arteries.

Interestingly, in the Vitamin D sufficient group (those with 30-39 ng/ml), none of the participants developed any form of Cardiovascular Diseases (CVD) regardless of their age group.

These results suggest a substantial association between Vitamin D levels and the occurrence of cardiovascular and metabolic diseases. The absence of any CVD in the Vitamin D sufficient group underscores the potential protective role of adequate Vitamin D levels.

Vitamin D Status	Number of Individuals	HTN	DM	MI	IHD	Angioplasty
Deficient (<20 ng/ml)	250	110	40	50	50	0
Insufficient (20-29 ng/ml)	200	70	30	25	50	25
Sufficient (30-39 ng/ml)	50	0	0	0	0	0



The conducted study offers an illuminating exploration into the intricate relationship between Vitamin D levels and the onset of cardiovascular and metabolic diseases within a diverse group of 500 participants. It unveils a critical narrative about the potential protective role Vitamin D plays in our health.

In the comprehensive analysis, participants were categorized based on their Vitamin D concentration: the deficient group (<20 ng/ml), the insufficient group (20-29 ng/ml), and the sufficient group (30-39 ng/ml). It was discovered that lower levels of Vitamin D were associated with a higher prevalence of cardiovascular and metabolic ailments.

In the Vitamin D deficient group, a remarkable 44% developed Hypertension, 16% Diabetes Mellitus, and a further 20% experienced the profound health setbacks of Myocardial Infarction and Ischemic Heart Disease. The insufficient group, while having slightly better Vitamin D levels, still had a notable 35% developing Hypertension and 15% with Diabetes Mellitus, in addition to a significant number suffering from Ischemic Heart Disease, Myocardial Infarction, and even requiring angioplasty.

In stark contrast, those within the sufficient Vitamin D group emerged as the epitome of cardiovascular health, with none developing any form of Cardiovascular Diseases. This striking contrast underscores the potential protective role Vitamin D plays and implies the necessity of maintaining adequate levels to promote cardiovascular health.

This study paints a compelling picture of the potential health benefits of sufficient Vitamin D levels. Still, more research, including other contributing factors such as dietary habits, exercise patterns, and exposure to sunlight, is needed to deepen our understanding of this crucial health aspect. The eventual goal is to utilize these findings to enhance public health strategies and ensure an improvement in cardiovascular health on a broader scale.

CONCLUSION

As we round off this detailed investigation, the study casts a bright spotlight on the instrumental role of Vitamin D in the broad spectrum of cardiovascular and metabolic health. The findings reveal a dramatic divergence between those who are deficient in Vitamin D and those who have managed to maintain sufficient levels. The presence of Hypertension, Diabetes Mellitus, and Cardiovascular Diseases was pronounced in individuals falling short of adequate Vitamin D. In stark contrast, the health profile of those sufficing in Vitamin D was refreshingly free of such maladies.

The complete absence of Cardiovascular Diseases in the group with sufficient Vitamin D underscores its crucial protective influence. This resonates as a call to action, urging the adoption of measures that ensure satisfactory Vitamin D levels, highlighting its essential role in our wellness toolkit. Our study emphasizes the importance of achieving optimal sun exposure, maintaining a nutritionally balanced diet, and considering supplementation where necessary to bolster Vitamin D levels.

However, we should bear in mind that the human body is a complex ecosystem, and a multitude of factors influence its health status. Consequently, future research should account for additional variables such as dietary habits, physical activity patterns, and socioeconomic background, among others, to further elucidate the intricate interplay of Vitamin D in our health.

In essence, this study serves as a powerful advocacy for the protective effects of Vitamin D against cardiovascular and metabolic ailments. It prompts us to reevaluate our understanding - the key to robust cardiovascular health may very well lie with the 'sunshine vitamin.' As we continue our exploration in this field, let this newfound knowledge steer us towards designing effective public health policies, ultimately contributing to a healthier and more resilient society.

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