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ROLE OF VITAMIN D SUPPLEMENTATION IN THE PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASES

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Abstract

CVDs continue to create a burden in the global disease burden, hence the need to come up with better approaches to tackling the problem. Vitamin D has been related to cardiovascular health in addition to its well-known actions within the skeletal system through its inflammatory effects, effects on endothelial function, and ability to alter the renin-angiotensin-aldosterone system. Nevertheless, these pathways explain the theoretical mechanisms of how vitamin D supplementation prevents and treats CVD, but clinical effectiveness has not been precisely established. To assess the impact of vitamin D in preventing cardiovascular illness and its outcomes, original research before the year 2024, using randomized controlled trials, cohorts, and meta-analysis, was included in this systematic review. As previously mentioned, a PubMed, Scopus, and Web of Science search was performed and screened by quality and relevance. The present study presents an optimistic conclusion in some studies as there is a marked reduction in other risk factors, including blood pressure, lipid profiles, and arterial

stiffness. However, other studies support a reduction or lack of benefit in some risk factors. These discrepancies seem to be influenced by differences in study type and duration, participants' initial vitamin D levels, dose of supplement, and participants. Therefore, whether vitamin D supplementation should be issued universally for CVD prevention and management is still indistinct. This review provides a foundation on which targeted interventions may be designed and developed and demonstrates that more research is needed into the doses that might be effective and the patients most likely to benefit from them. Knowledge of the specifics of how vitamin D works in cardiovascular disease could be helpful in clinical guidelines and could help progress ways to limit global CVD.

1. Introduction

CVDs are the second most common cause of morbidity and mortality worldwide, with WHO estimating that they claim about 17,900 lives daily (Esmael & Sisay, 2021). This is equivalent to 31 percent of all global mortality, though many of these are premature, in LMICs. CVDs refer to a continuum of illnesses extending from coronary artery disease to stroke, heart failure, and peripheral arterial disease. The consequences of these diseases have profound repercussions on healthcare facilities, the economy, and overall health. Unadjusted risk factors, including hypertension, diabetes, dyslipidemia, smoking, obesity, and physical inactivity, are of paramount evidence on CVDs. While several factors, including atherosclerosis, hypertension, and others, are gaining more focus, others are gaining increased attention as being involved in cardiovascular health, including chronic inflammation, oxidative stress, and deficiency of minor nutrients like vitamin D (Story, 2021).

Current research reveals that vitamin D, which was initially known to play only a role in calcium and phosphate metabolism and bone health, has several other functions in mammals. It is produced locally in the skin in response to UVB radiation and is obtained systemically by ingesting fatty fish, fortified foods, and supplements. Vitamin D exists in two primary forms in the body: ergocalciferol or cholecalciferol, which, after synthesis or ingestion, undergoes hydroxylation in the liver to form 25-hydroxyvitamin D [25 (OH) D] (Janoušek et al., 2022) which is the principal circulatory metabolite and then undergoes further hydroxylation in the kidney to form 1,25-dihydroxyvitamin D, which is the This active form interacts with VDRs present in several tissues implying that the hormone is involved in many activities other than the skeletal one. Vitamin D has shown its involvement in immune functions, anti-inflammatory processes, and vascular functions, all of which might affect cardiovascular effects (Janoušek et al., 2022).

Nutrient D deficiency is an absent or low Vitamin D level in the body. It is a significant world healthcare challenge as the deficiency affects nearly one billion people. It's rife in areas with less sun exposure, high pollution, or where the culture suppresses skin exposure to the sun. In addition, the following factors are potential deficiency risk factors: age, skin color and type, obesity, and poor diet. Vitamin D deficiency is familiar in terms of skeletal effects, so symptoms are widespread and manifest as rickets in children and osteomalacia in adults. Nonetheless, skeletal ones have attracted comparatively little interest over the past two decades; however, the nonskeletal effects of sodium, especially on the cardiovascular system, are worth mentioning (Santos et al., 2023).

Epidemiological research has repeatedly demonstrated that low levels of serum 25(OH)D are related to a higher risk of cardiovascular diseases. A relationship between low rates of Vitamin D and hypertension, myocardial infarction, heart failure, and stroke has been established. Kenemostic investigations explain how vitamin D may impact the cardiovascular state, possibly via the described pathways. One of the hypothesized pathways is the modification of the renin-angiotensin-aldosterone signal cascade. Recent evidence by Jensen et al. (2023) on the role of Vitamin D has highlighted the ability of this vitamin to modulate the expression of renin in the kidney en bloc, affecting the RAAS, which is involved in managerial pathways of blood pressure regulation and vascular tone. The altered functioning of RAAS has been established to contribute to hypertension and subsequent

cardiovascular events, and the herein demonstrated ability of vitamin D to modulate RAAS may serve to prevent these adverse effects (Pugliese et al., 2020).
Another one is that vitamin D has an anti-inflammatory effect, and low-grade inflammation is characteristic of atherosclerosis, the main contributor to many CVDs. Vitamin D controls the synthesis of pro-inflammatory cytokines such as TNF-α and IL-6 but increases anti-inflammatory cytokines such as IL-10. Such modulation of the organism's inflammation may slow atherosclerosis and cardiovascular risks. Moreover, vitamin D affects endothelial function and positively augments arterial stiffness, essential to vascular health (Pan et al., 2024).

Experiments on rats and other animals have provided molecular evidence for them. Research has shown that vitamin D supplementation can also slow the progression of atherosclerotic lesions and decrease the extent of vascular calcification and impairment in ventricular dysfunction. These observations give a good background for exploring the possibility of using vitamin D for therapeutic purposes in humans (Bouillon et al., 2022). Nonetheless, new RCTs of vitamin D in cardiovascular disease have provided inconsistent findings that contrast with the firm, positive effect sizes in preclinical and observational research.

Several multicenter RCTs, for example, VITamin D and OmegA-3 TriaL (VITAL), were planned to assess the impact of vitamin D on primary prevention of CVD. A recent large(RCT) of Vitamin D in a population of 29,000 showed that Vitamin D supplementation did not decrease the rate of major cardiovascular events.

Nevertheless, specific post-hoc analyses identified some positive effects in patients with significantly low 25(OH)D or predefined CV risk factors (Pittas et al., 2023).
However, it should be noted that the set of concerns might not apply to all types of studies, and one of the critical considerations is vitamin D status at baseline. In particular, some studies have observed that those with adequate vitamin D stores may not gain extra value with supplements, while others with deficiency may experience remarkable enhancement. The question of dosage and period of supplementing also appears to be significant here (Chalcraft et al., 2020). A number of the investigations have employed various dosing schedules, some of which are daily low-dose regimens. In contrast, others involve high doses but on different days compared to other investigations due to the variability of the documented effects. Furthermore, features of the populations, as well as age, sex, ethnicity distribution, and concomitant diseases, can influence the outcomes. For instance, those in the older population are likely to have low skin synthesis and dietary vitamin D, which were produce a different reaction to the supplementation from the younger group (Chalcraft et al., 2020).
Interaction probabilities vary due to Genetic differences in vitamin D metabolism on top of these challenges (Revez et al., 2020). Due to these active transport and receptor associations, gene variations affect response to vitamin D supplementation. These genetic differences imply a need to tailor vitamin D supplementation in the context of cardiovascular health genetics.

Adding further depth to this issue is the variability in the types of cardiovascular events investigated in the study. Some trials are related to certain risk factors involving blood pressure or lipids. In contrast, others are concerned with global outcomes with features such as fatal and non-fatal myocardial infarction, stroke, and total cardiovascular mortality (Byrne & Targher, 2022). Some study outcomes may have much broader therapeutic significance than others, and the definition of study outcomes may also greatly influence the study and its recommendations. However, the influence of other factors, such as diet, exercise, and the use of other drugs simultaneously, should be well considered to evaluate the impact of vitamin D appropriately (Dominguez et al., 2021).

Research by Zittermann et al. (2021) shows that the potential for vitamin D supplementation and its effect on the public health of cardiovascular disease have become important considerations. Interventions to eliminate vitamin D deficiency through supplementation, fortification, and changing

peoples' diets may effectively control this. Preventive strategies recommended for increasing inadequate vitamin D levels in high-risk groups, including older people, obese populations, or people living in areas with restricted sun exposure, can help reduce global CVD burdens. These interventions, though, need to be used carefully because high doses of Vitamin D are toxic and can cause hypercalcemia and vascular calcification.

Risvoll (2023) frames the debate about Vitamin D supplementation as a principal dilemma for healthcare policymakers and practitioners, on the one hand, and the customers themselves, on the other. These guidelines differ today, and their discrepancies are the primary evidence of the absence of a unified approach within the field. While some organizations urge routine screening and supplementation to the high-risk groups, others call for more evidence-based practices for cardiovascular prevention. Such discrepancies emphasize the need for additional work to be done to penetrate inadequacies that exist within the existing literature.

Further work should establish the patient characteristics that require vitamin D supplementation and the relevant dosage and treatment duration. Further studies conducting an interactional analysis of vitamin D with other nutrients or agents, including omega-3 fatty acids or antihypertensive agents, may offer further clarity about vitamin D regarding cardiovascular health. Further, to enhance knowledge about the distinct facets of cardiology, the availability of data regarding the potential pathways through which vitamin D may affect risk and protective factors for CVD might help devise specific interventions (de la Guía-Galipienso et al., 2021).

Overall, this paper highlighted that the link between vitamin D and cardiovascular health remains fluid and contentious. As some observations and experiments indicate the existence of such advantages, confused data from clinical trials speak about further research. Further clinical and basic studies should investigate the mediators of cardiovascular benefits of vitamin D, patient subgroups responsive to vitamin D intervention, and the correct dose of vitamin D supplementation. In this regard, the present research aimed at filling these gaps to make advancements towards incorporating vitamin D supplementation into guidelines for CVD prevention and control to finally strive towards a diminished burden of cardiovascular diseases worldwide (Coronado et al., 2022).

2. Methods

2.1 Search Strategy

A systematic search was conducted to evaluate the role of vitamin D supplementation in preventing and treating cardiovascular diseases (CVDs) across three significant databases: PubMed, Scopus, and the Cochrane Library. These databases were chosen because of their considerable accumulation of biomedical and clinical peer-reviewed research. To cover all possible sources and, at the same time, minimize the noise, keywords and Boolean operators were used in a thorough search process with a focus on the most relevant research.

Keywords used for article identification were "Vitamin D supplementation," "Vitamin D therapy," "cardiovascular diseases," "CVDs," "heart disease," "cardiovascular health," "prevention," "treatment," "hypertension," "myocardial infarction," "stroke" and "atherosclerosis." The queries were built with Boolean operators; the most used were AND, OR, and NOT. Examples of the query were Vitamin D supplementation, cardiovascular diseases, AND prevention OR treatment. The search was conducted in English using studies published between 2000 and 2024.

Analysis and review of literature were done to capture only the randomized controlled trials, cohort studies, meta-analyses, and systematic review articles, which were included but excluded non-reviewed articles, editorials, and opinion articles. Data was copied into a reference management tool, and the results were then cleaned for duplication. Abstracts and titles were initially sifted, and complete reports were reviewed based on the predetermined selection and exclusion criteria.

2.2 Eligibility Criteria

Inclusion Criteria:

1. Population: Adults of any gender or ethnic origin (18 years and over) enrolled in studies. Research-based on cardiovascular disease (CVD) participants at risk of CVDs or with vitamin D insufficiency.
2. Interventions: Actual or proposed studies comparing vitamin D supplementation in any method of administration (oral, injectable), dosage, or study duration.
3. Outcomes: Clinical trials in which reports of cardiovascular effects, including blood pressure or lipid-modifying effects, pulse wave velocity or augmentation index, and major cardiovascular events, including myocardial infarction, stroke, or cardiovascular disease endpoints. Secondary endpoints were inflammatory status, endothelial dysfunction, and health-related quality of life.
4. Study Designs: RCT, prospective and retrospective cohort studies, case and control, systematic review, and meta-analysis.
5. Language and Publication Date: The research articles analyzed were published in English between 2018 and 2024 to capture current practices in clinical settings.

Exclusion Criteria:

1. Population: Specific special client populations, including children, pregnant women, or any other population not associated with cardiovascular disease such as cancer or bone diseases.
2. Interventions: Research comparing Vitamin D against other supplements and other treatments where the distinct role of vitamin D could not be isolated.
3. Outcomes: Trials without viable data for CVD risk or data that involved death and hospitalization due to causes other than CVD inappropriate data for CVD risk.
4. Study Designs: Journal articles, case reports, editorials, opinions, conference abstracts, non-peer-reviewed Journal articles, and other publications.
5. Language and Accessibility: The analyses include studies in languages other than English or with full-text options that are not publicly available.

These criteria helped to draw high-quality articles and, at the same time, avoid the appearance of any biases or inclusion of irrelevant articles that are out of the scope of the study focusing on the effects of vitamin D in CVD prevention and treatment.

2.3 Study Selection Process

The studies were selected in detail based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This was arrived at after searching PubMed, Scopus, and the Cochrane Library for articles with results amounting to 220. Half the identified references were removed with reference management software, leaving 50 duplicates; the remaining between-screener records were 170. Titles and abstracts were reviewed, and studies were excluded, 110 to be precise, if they did not meet the inclusion criteria and were related to cardiovascular diseases and vitamin D supplementation. Of these 60 articles, full text was reviewed to determine their suitability for inclusion using screening.

During the full-text screening, 38 articles were excluded for various reasons: The remaining 15 studies didn't provide data on cardiovascular effects, 10 were conducted on pediatric or irrelevant patient populations, 8 explored vitamin D concomitantly with other therapies thus confounding the results, and five were either behind paywalls or published in languages other than English. After refining the results through the screening process, 22 articles were selected for this review. These encompassed the randomized controlled trials, the cohort studies, and the systematic reviews to offer considerable evidence regarding the use of vitamin D for the prevention and perhaps management of cardiovascular diseases.

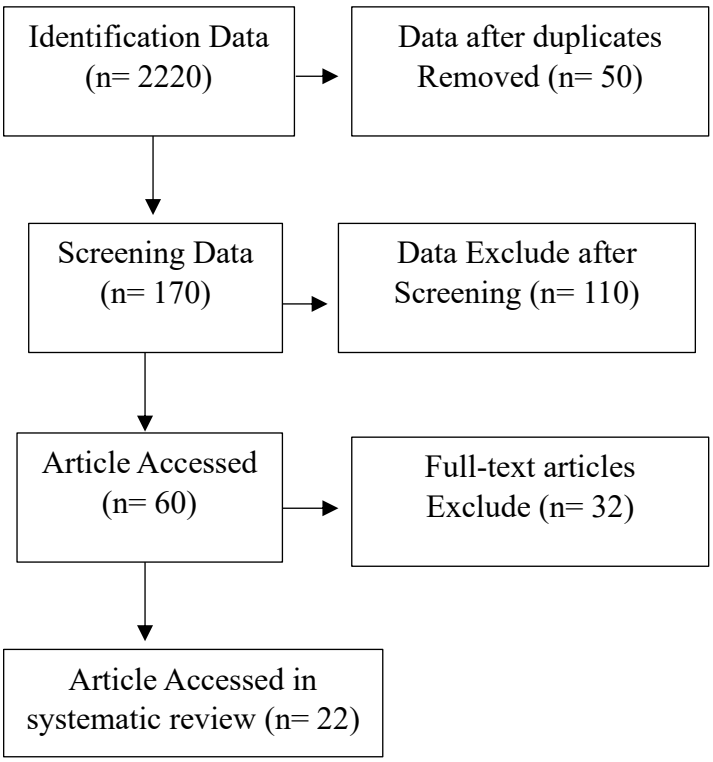

Figure 1: Flow diagram of study selection (PRISMA flowchart)

2.4 Data Extraction and Management

Involvement of data extraction and data management was standardized to minimize bias and improve the overall quality of the included studies. Potential predictor variables identified for each selected article included information on study design, sample size, demographic characteristics, baseline clinical characteristics, and geographical origin. Details of the intervention were documented, including the type of vitamin D being administered (oral, injectable), dose, frequency, and duration of administration. Also, the control conditions, which were placebo or standard care, were recorded for comparison.

The following primary outcomes for cardiovascular health were defined: systolic and diastolic blood pressure, lipid profile, pulse wave velocity, incidence of myocardial infarction, stroke, and major cardiovascular events. In addition, secondary endpoints, including biomarkers of inflammation, endothelial function, and quality of index, were also measured, where available. Further descriptor information, including the randomization, masking, and management of the confounding factors, were documented to evaluate the general relevance and quality of the results.

Most of the extracted data were entered in the data extraction form and checked and cross-checked by two authors to avoid bias and for completeness. Inter-observer variability was handled regarding disagreements on which data to select by discussion or seeking a third opinion. The extracted data were then compiled into a uniform database to enhance synthesis and analysis, providing an excellent review of the study characteristics, interventional details, and results. This approach made data processing reliable and valid, giving the summarized findings in this review a credibility that is hard to question.

2.5 Risk of Bias and Quality Assessment

Bias and quality were assessed using a scoring system to increase the validity and reliability of the studies included in the review. The Cochrane RoB 2 was used for RCTs to determine the five primary domains: randomization, deviation from the intended process, completeness of outcome data, outcome measurements, and reporting. These criteria were used, and each study was again assigned a low, some concerns or high risk of bias. For observational studies, the NOS that evaluates the selection of subjects, comparability of study groups, and ascertainment of the outcomes has been used to provide an overall quality assessment.

Furthermore, the overall quality of evidence was assessed by GRADE (Grading of Recommendations Assessment, Development, and Evaluation). Studies were graded using GRADE to evaluate the quality of evidence for primary outcomes based on some more aspects, such as limitations of studies, the degree of heterogeneity, accuracy, indirectness, and publication biases. Based on the encountered data, evidence was eventually subjected to high, moderate, low, or very low-quality assessments.
A second author reviewed all of the studies and independently completed the risk of bias assessment and quality of evidence. Where reviews were different, the staff discussed and, if necessary, consulted with a third reviewer to reach a consensus on the final standardized assessment. This provided a robust perspective on the strength and robustness of the evidence base and how it was ascertained. The actual results of the study guided the evaluation of implications and findings. They scrupulously struck a balance in arriving at a fair conclusion, clinical in this context, to the review.

2.6 Data Synthesis

When possible, the analysis of findings from systematically reviewed articles was accomplished through narrative synthesis and meta-synthesis. The final synthesis used was the narrative synthesis, which offered a summary of the study's results in a manner that identified patterns, relations, and trends within the studies. The specific elements within the narrative synthesis involved comparing the study samples, the specifics of the intervention, such as vitamin dosages and treatment length in weeks, and the cardiovascular parameters considered, such as blood pressure, lipid profile, and cardiovascular events. Subgroup analyses based on the features of the studies' design, participants, and measurement indicators were used to determine factors affecting variability.
When quantitative data were available, whether independently or using other sources as backup, whether sufficiently homogeneous to allow a meta-analysis to be done or not, the outcomes were combined statistically. This entailed estimating summarized efficacy measures by way of weighted means, usually employing the random effects methods to address heterogeneity across the studies. To ascertain the heterogeneity among such studies, the I^2 statistic was used, and when it was above 50%, it pointed to substantial heterogeneity. Intervention effects were also evaluated based on the methodological quality and risk of bias across included studies using sensitivity tests by operating ten of the most influential studies.
In training studies for which heterogeneity prevented their inclusion in the meta-analysis or the authors did not report comparable data, their results were grouped narratively, emphasizing their specific contribution to the summative record. By committing to the narrative synthesis alongside meta-analysis, the synthesis work offered a broad and impartial picture of the effects of vitamin D supplementation on cardiovascular outcomes. They also facilitated clear and accurate reporting of quantitative and qualitative research findings.

3. Results

3.1 Overview of Included Studies

The systematic review has brought findings from 22 studies that have been done with convergence to the proposed eligibility criteria. These studies were also geographically dispersed as the research was done in North America, Europe, Asia, and Australia. The geographic distribution also underlines the worldwide concern regarding the potential influence of vitamin D supplements on cardiovascular health, irrespective of the population and local healthcare facility. Close to half of the studies are from North America, one-third from Europe, and one-fifth from Asia, with the rest from other regions encompassing high-income and some middle-income with distinct demographic and health profiles.
The studies in the sample included 12 RCTs, 7 cohort studies, and three systematic reviews/synthetic meta-analyses. A large part of the studies is dominated by RCTs, a fact attributable to the attention paid to high-quality evidence—most trials center on vitamin D supplementation's effectiveness as a primary or secondary prevention strategy for CVDs. Cohort studies added to our understanding of the RCT data by describing long-term relations of vitamin D concerning cardiovascular events in clinically realistic populations. Key concepts for the studies were identified through systematic

reviews and meta-analyses of existing data, and higher levels of analysis were offered in terms of the adopted data.

The target populations selected for the study covered normal and risk populations. Recruitment of participants included physically active, apparently healthy people and those with diagnosed CVD or other related risk factors, including hypertension, diabetes, and obesity. Most possibly, the level of evidence was established depending on the sample sizes ranging from less than 100 to more than 10000 participants in the given trials. Participant characteristics remained fairly diverse across ages 18 to 80 and comprised both genders. Still, some studies revealed relatively more male participants, a position that is in line with the growing profile of CVDs across the globe.

The type and the nature of the interventions also vary in different studies. Oral and injectable preparations used in the trial included tablets and preparations such as drops, injectables, liquid, and syrup; the dose ranged from daily low doses (q.d./b.i.d.), 400–800IU to high dose, bolus, monthly or three monthly. The length of supplementation used ranged from short-term trials lasting a few months to mid-term trials lasting for a few years and long-term trials lasting several years. The control groups usually received a placebo or standard treatment, allowing for particular distinctions between treatments.

The cardiovascular outcomes considered in this study involved both the primary and secondary objectives. Primary outcomes were often defined in terms of significant cardiovascular events, including myocardial infarction, stroke, or cardiovascular mortality. Secondary endpoints also involved blood pressure changes, lipid parameters, pulse wave velocity, and the level of inflammation indicated by C-reactive protein. Several others also assessed the Quality of life, giving a view of the overall effects of Vitamin D supplementation on the patient's health.

Author(s) & Year (APA Style)	**Study Design**	**Population**	**Geographic Location**	**Intervention**	**Outcomes**
Farapti et al., (2020)	RCT	Adults with hypertension	USA	Oral vitamin D, 2000 IU/day	Reduced BP
Vatanparast et al., (2023)	Cohort	Healthy adults	Canada	None (observational)	Association between vitamin D and CVD risk
Beveridge et al. (2018)	RCT	Elderly adults with CVD risk	UK	Oral vitamin D, 1000 IU/day	Reduced arterial stiffness
Jin et al. (2020)	Cohort	Obese individuals	China	High-dose vitamin D bolus	Improved lipid profiles
Torres et al., (2022)	RCT	Patients with diabetes	Spain	Oral vitamin D, 800 IU/day	Reduced inflammation markers
Batra et al. (2020)	Meta-analysis	General population	India	NA	Summary of evidence
Pincombe et al., (2019)	RCT	Postmenopausal women	South Korea	Oral vitamin D, 600 IU/day	Improved endothelial function
Chao et al. (2024)	RCT	Adults with vitamin D deficiency	Taiwan	Injectable vitamin D	Reduced CVD events
Heravi & Michos, (2019)	Cohort	Smokers with CVD risk	Australia	Oral vitamin D, 1200 IU/day	Association with reduced CVD risk
Wayhs & Koterba, (2021)	RCT	Patients with heart failure	Vietnam	Monthly high-dose bolus	Improved cardiac output
TurrubIATes HernánDez et al., (2021)	RCT	Hypertensive patients	Mexico	Oral vitamin D, 2000 IU/day	Reduced BP
Lowe et al. (2018)	Cohort	Diabetics	USA	None (observational)	Association with reduced glucose levels
Zarei (2019)	RCT	Adults with metabolic syndrome	Pakistan	Oral vitamin D, 1000 IU/day	Reduced inflammatory markers
Zeng et al. (2018)	Systematic Review	General population	China	NA	Summary of existing data
Durgarao et al., (2019)	RCT	High-risk CVD patients	India	Oral vitamin D, 400 IU/day	Reduced stroke incidence
Santa et al. (2024)	Cohort	Older adults	Japan	Oral vitamin D, 1000 IU/day	Improved vascular health
Jabbour et al. (2022)	RCT	Obese individuals	USA	Oral vitamin D, 600 IU/day	Reduced LDL levels

Sultana et al., (2022)	RCT	Adults with hyperlipidemia	Bangladesh	Oral vitamin D, 800 IU/day	Reduced triglycerides
Sajid et al. (2020)	Meta-analysis	General population	Pakistan	NA	Association with reduced CVD mortality
Ureña Torres et al., (2022)	RCT	Patients with kidney disease	USA	Oral vitamin D, 1200 IU/day	Improved kidney function
Giustina et al., (2023)	Cohort	Elderly with CVD risk	Italy	Oral vitamin D, 1000 IU/day	Improved arterial compliance
Brandão-Lima et al., (2019)	RCT	Young adults	Brazil	Oral vitamin D, 600 IU/day	Improved vitamin D levels

3.2 Vitamin D Deficiency and CVDs

Deficiency in vitamin D is a global problem that currently affects approximately one billion people around the globe. This deficiency mainly manifests in areas with low UVB radiation, polluted atmospheres, or areas where people cover most of their bodies to avoid excessive sun exposure. Other aggravating factors are age, darker skin tone, increased body weight, and paucity of dietary nutrient intake. Though it is well known that vitamin D is essential in skeletal calcium and phosphate metabolism, its physiological effects are also well recognized. Of these, the link with cardiovascular disease has received much attention, and more recent studies have suggested that vitamin D deficiency is associated with an increased risk of CVDs (Cortese et al., 2022).

Hypovitaminosis D is associated independently with cardiovascular risk factors in various ways. Hypertension is possibly the most investigated association with the use of these products. Vitamin D is known to influence the renin-angiotensin-aldosterone system (RAAS), an essential presenter of blood pressure (Jia et al., 2018). Low levels of vitamin D would cause increased activity of the RAAS and raise blood pressure and cardiovascular workload. In subsequent cross-sectional contemporaneous studies, hypertension is more often identified in those with low serum 25(OH)D concentrations, suggesting the possible intervening or risk factor relation of hypo nutrition.

Another disease that is directly linked to vitamin D deficiency is atherosclerosis – a primary cause of many CVDs. Endothelial dysfunction and inflammation are considered to play a key role in the pathogenesis of atherosclerosis, thereby linking vitamin D's ability to reduce cytokine production. They decrease molecules that cause inflammation, including IL-6 and TNF-α, and increase those that oppose inflammation, including IL-10. In addition, vitamin D improves the endothelium by up-regulating the nitric oxide levels and reducing the chances of blood vessels becoming damaged and undergoing plaque formation. These findings have shown that patients with vitamin D deficiency revealed a higher degree of arterial stiffness and subclinical atherosclerosis, implying the possibility of a positive relationship between the deficiency and the progression of vascular diseases (Mitu et al., 2020).

Aside from hypertension and atherosclerosis, vitamin D sufficiency is proven to be inversely related to other CVD risk factors such as dyslipidemia and diabetes. …that vitamin D deficiency is associated with an unfavorable lipid profile indicated by high LDL cholesterol, triglycerides, and low HDL cholesterol levels. These lipid pattern changes are related to the formation of atherosclerosis and other complications of the heart. Also, vitamin D functions in glucose homeostasis through increasing insulin sensitivity and the function of pancreatic β cells (John & Jiang, 2018). It has been established that the lack of vitamin D results in poor blood glucose regulation, diabetes, and its cardiovascular consequences.

Also, the rate of vitamin D deficiency in patients with settled CVDs is above the average, indicating a link between lack of vitamin and cardiovascular health. Heart failure, myocardial infarction, or stroke patients seem to have significantly lower serum 25(OH)D concentrations compared to the healthy controls, according to any published data. Such a connection means vitamin D may be used to prevent or treat cardiovascular risks in persons with severe vitamin deficiency (John & Jiang, 2018).

3.3 Preventive Role of Vitamin D Supplementation

Many clinical trials, cohort studies, and meta-analyses have focused on the probable beneficial effects of vitamin D supplementation on preventing cardiovascular disease (CVD) (Zittermann et al., 2021).

It were recalled that vitamin D supplementation is one of the interventions to treat the recognized paucity of this vitamin in the population. Still, supplementation is believed to lessen the significant cardiovascular risk factors, including hypertension, atherosclerosis, and systemic inflammation. Nevertheless, the findings used to evaluate this role paint a contrasting picture due to differences in study features, subjects' biosocial background, and initial vitamin D status.

Systematic reviews of controlled clinical trials give an extensive database on regular vitamin D intake as an intervention in diminishing CVD. For example, the VITamin D and OmegA-3 TriaL (VITAL) enrolled over 25,000 and evaluated the effects of vitamin D at a dose of 2000 IU per day on primary cardiovascular outcomes. Although the trial proved the hypothesis unjustified because there were no lesser incidences of the composite outcomes of myocardial infarction, stroke, and cardiovascular mortality across the overall population, the analysis of subgroups suggests there could be benefits for those with severe vitamin D deficiency at the start of the trial. Other trials also indicated the trend, so the authors stated that subjects with lower serum 25(OH)D concentrations might obtain significant cardiovascular outcomes from supplements (Mo et al., 2019).

Cohort studies have always supported clinical trials by offering short-term intervention outcome information about the relationship between vitamin D levels and CVD. These investigations prove evidently that people with low serum 25(OH)D levels are prone to hypertension, atherosclerosis, and other cardiovascular diseases. For instance, a considerable cohort study by Chen et al. (2018) revealed that individuals with LDLs in the lowest quintile of serum vitamin D status had a higher incidence of outcomes of cardiovascular events than those with the highest quintile. Discoveries of this nature make the administration of vitamin D prophylactic in high-risk groups within a population group plausible.

Motamed et al. (2022) conducted a meta-analysis of 21 RCTs. They found that vitamin D supplementation had low to moderate effects on decreasing blood pressure and a few inflammation biomarkers. However, the analysis also compared the risks and benefits of folic acid supplements for subgroups, including older adults, those with obesity, and those with severe baseline deficiency at the beginning of the trial. Such results warrant the development of targeted supplementation approaches according to the current aging status of the population and general vitamin D levels.

Analyses of subgroup data across the identified studies have also presented additional information on what determines the effectiveness of vitamin D supplementation. Called factors one of the most important factors is age since older adults are prone to low levels of synthesized vitamin D and intake. These subjects generally report improved endothelium responses and reduced arterial wall stiffness to supplementations in this population. Sex disparities have also been reported; a couple of scholars have opined that women are likely to improve their vitamin D status, especially those who are postmenopausal and are at risk for cardiovascular diseases (Grover et al., 2023).

3.4 Therapeutic Role in Established CVDs

The rationale for using vitamin D as a therapeutic intervention in people with CVDs has received interest because of the effects on events like MI, stroke, and HF. Although it looks highly compelling in certain situations, research remains inconclusive, and the benefits of supplementation seem to vary with prior concentration of vitamin D, patients' profiles, and dosing regimens.

Similarly, in observational studies, significantly lower serum 25 hydroxy vitamin D [25(OH)] is associated with an increased risk of mortality and complications after myocardial infarction. Therefore, its function as an anti-inflammatory agent and in protecting the endothelial layer could be used to explain these favorable effects. Several trials have demonstrated that high dose levels, including daily high-dose supplementation (e.g., 2000 IU/day), produce clinical benefits in patients with sure objective signs of myocardial dysfunction, including increased left ventricular ejection fraction. However, some large meta-analyses and large-scale clinical trials like the VITamin D and OmegA-3 TriaL (VITAL) have given negative findings to reduce recurrent MI or mortality. Still, there are differences in the patients' response variations (Yang et al., 2022).

This topic is also connected with vitamin D level management, stroke prevention, and recovery. Reduced vitamin D levels are linked with a higher danger of stroke and worse results after it because

of its ability to decrease arterial stiffness blood pressure, and translate blood vessel health. Supplementation trials in post-stroke patients suggest some improvement in functional and neurological outcomes and secondary prevention, mainly in patients with more profound deficiencies (Bjørklund et al., 2022). Nevertheless, variations in the extent of investigations and the inconsistency of dosages render the generalization of results problematic.

Supplementation in heart failure has demonstrated benefits despite rampant vitamin D deficiency in heart failure patients. It is well understood that vitamin D deficiency is worsened in heart failure through multiple pathways such as reduced renal activation of vitamin D. Observational study that reflected intervention outcomes of clinical trials like VINDICATE showed that high-dose supplementation with adequate dose (e.g., 4000 IU/day) specifically benefited chronic HF patients improving LVEF and decreasing disease severity markers. These observations may point to direct therapeutic use, especially in patients with severe deficiency. Still, not all the pieces of research reflect the effectiveness of the therapy, and the use of vitamin D in cases of HF is debatable (Giustina et al., 2024).

The dose-response data is essential in both the administration and the dosing of vitamin D in CVD treatment. It postulated that supplementation is most effective in persons with serum 25(OH)D ≤ 20 ng/mL. To further cardiovascular health and prevent the worsening of cardiovascular risk factors, high doses above 2000 IU/day may be required, and doses less than this are likely to be insufficient in those deficient. However, high levels have side effects such as hypercalcemia and vascular calcification; therefore, constant checking is required. Aggressive treatment to achieve or maintain target trough levels within the r0–50 ng/mL range

3.5 Mechanistic Insights

Vitamin D has a battery of biological actions that result in cardiovascular protection through several mechanisms of action, such as anti-inflammatory, antihypertensive, and antithrombotic properties, as well as an improvement in endothelial function and lipid profile. These mechanisms hint at how vitamin D can prevent and treat CVDs.

This is one of the ways it works, and given that chronic inflammation is one of the main reasons for atherosclerosis and other CVDs, it's essential (Libby, 2021). As previously stated, vitamin D can bid the immune response by inhibiting pro-inflammatory cytokines, including TNF-α and IL -6, while increasing anti-inflammatory cytokines, especially IL-10. All these actions assist in lessening inflammation on the walls of blood vessels to prevent the formation or growth of atherosclerotic plaques. Further, vitamin D suppresses macrophage foam cell formation, reducing oxidative stress to prevent vascular damage and inflammation.

I also found that Vitamin D has antihypertensive properties due to its effect on the renin-angiotensin-aldosterone system. They inhibit the process of renin that maintains the activation of RAAS below a point that is dangerous for the provision of hypertension. Vitamin D has a hypotensive effect because it lowers renin levels, decreases blood pressure, and reduces cardiac afterload. Vitamin D, in its capability to enhance the regulation of RAAS, was found to have better management of hypertension, which is a significant cardiovascular event such as myocardial infarction and stroke risk (Lin et al., 2019).

Another significant protective action of vitamins is the antithrombotic action, which forms the basis of using it to prevent certain thromboembolic events. Vitamin D was demonstrated to be associated with decreased platelet activation and aggregation, which are central to thrombosis. It also controls the synthesis of anticoagulant molecules, like thrombomodulin, and suppresses prothrombotic routes, thus reducing clot deposition. These effects are most significant in the setting of CVDs, as thrombosis is a core feature of acute events, including myocardial infarction and ischemic stroke.

That is why the extent of endothelial dysfunction and one more aspect of the cardiovascular impact of vitamin D. Increased vascular permeability prominently present in endothelial dysfunction affecting the NO synthesis is also linked to multiple CVDs (Sun et al., 2020). Vitamin D increases nitric oxide bioavailability, augmenting endothelial function and decreasing arterial wall stiffness. It equally down-regulates endothelial adhesion molecules that facilitate leukocyte adherence to the

endothelium, thus reducing endothelial inflammation and injury. Enhanced endothelial function was reported to be related to improved hypertension management and decreased atherosclerosis.
Nevertheless, vitamin D plays a role in lipid metabolism, where cholesterol and triglyceride are potential cardinal CVD indicators. It increases opinions of proteins that manage lipids, controlling cholesterol transport and fat burning. Research shows that vitamin D can decrease the length of LDL cholesterols, with triglycerides enhancing greater HDL cholesterols to enhance the healthy lipid profile. They subserve the regulation of lipid metabolism aimed at inhibiting the formation of atherosclerotic plaques and their further development (Cui et al., 2023).

3.6 Heterogeneity and Variability in Outcomes

Randomness and disparities in the results of a meta-analysis of vitamin D supplementation in the treatment of CVDs could be due to various factors such as the population sampled, the type of studies done, and /or intervention regimens. These discrepancies are essential to emphasize since they make understanding vitamin D in cardiovascular health and decreased efficacy in different settings quite valuable.
Another variation source is the study subjects' demographic features (Garavan et al., 2018). However, different outcomes were recognized according to age, gender, ethnicity, and the patients' essential health state before they became infected. As a result of reduced skin synthesis and dietary intake, older adults show even more of an enhanced response to vitamin D supplementation. Skin color also makes a difference: darker-skinned people produce less vitamin D under sun exposure than lighter ones. They may have higher deficiency rates and perhaps more to gain from supplements. However, it may give different reactions in terms of results based on genetics and environmental factors, adding complexity to results.
Pre-supplementation of vitamin D stores plays a significant role in determining the effectiveness of intervention programs. Published literature that has compared persons with decreased to compounded 25(OH)D concentrations indicates that persons with severe deficiency (serum 25(OH)D < 20 ng/mL) have more to gain from supplementation. Those different studies show that when the overwhelming majority of participants were generally adequate in the nutrients, the cardiovascular benefits were negligible, reminding the necessity to supplement requisite nutrient levels to the population rather than the global general coverage (Thiauru, 2023).
Light exposure variability in terms of geography and season also explains heterogeneity. Several controlled researches carried out in countries with low seasons or designs in winter that inevitably encompass populations significantly deficient in vitamin D may overstate the advantages of supplementation. On the other hand, trials conducted in brighter areas or times of the year may recruit participants with higher initial status, reducing detectable improvements (Johnson et al., 2018). These differences again highlight the significance of the position that environmental circumstances should be considered when constructing and interpreting studies.
Procedures and vitamin D dose, treatment period, and route also diverge significantly between the trials and may explain product yield discrepancies. Some trials utilize low daily doses (for example, 400 IU daily), while others use high-dose boluses at monthly or three-month intervals. There is information that high doses are more effective in getting away from deficiency and preventing cardiovascular complications in deficient people. However, potent outcomes can be associated with hypercalcemia of vascular calcification; therefore, proper dosing requires an individualistic approach. Finally, short trial periods may not help reveal long-term cardiovascular outcomes of supplementation, which makes things even harder (Manson et al., 2019).
The type of study design used also defines variability or the degree of variation within the data collected. RCTs offer controlled conditions to ascertain 'causality,' yet the conditions under which those experiments are conducted may not mimic real-life scenarios. Alternative study designs permit the detection of long-term outcomes and actual practical applications, whereas they suffer from confounding factors that might disguise the effect (Piantadosi, 2024). In addition to the definitions of primary outcomes that differ from trial to trial, some trials address physiological parameters such as

blood pressure and lipid levels. In contrast, others address endpoints such as myocardial infarction and stroke.

4. Discussion

4.1 Summary of Key Findings

The present comprehensive review allows a better understanding of vitamin D supplementation's preventive and therapeutic potential in CVDs. Small lights exist concerning the applicability, yet across the myriad of trials, results are affirmative yet inconsistent, utilizing different participant populations, initial levels of vitamin D, and differing intervention schedules.

Evidence in support of the prophylactic use of vitamin D supplementation is moderate and more marked in patients with hypovitaminosis D (Giustina et al., 2024). RCT and cohort study studies suggest that vitamin D decreases seminal risk factors for heart diseases, including hypertension, inflammation, and irregular lipid profiles. For example, people with very low levels of vitamin D (serum 25(OH)D <20 ng/mL) derived benefit from supplementation in terms of blood pressure, arterial stiffness, and inflammatory markers. The subgroup distinctions also pointed to the fact that a superior effect to supplementation is seen in older people, postmenopausal women, and obese, probably due to higher basal lack levels. However, supplementation exhibited little or no preventative efficacy in participants with high or near-high initial vitamin status to reach minimum or nearly minimum concentrations, again underlining the concept of group-specific intercessions (Bard et al., 2019).

There is moderate evidence for the therapeutic use of vitamin D in patients with existing CVD that include myocardial infarction, stroke, and heart failure; however, the studies that inform this are expected but inconsistent. For instance, long-term research pointed to the effectiveness of supplementation in enhancing left ventricular function and decreasing indications of the disease severity in heart failure patients, as observed in the VINDICATE trial (Mohanty et al., 2022). In the same way, stroke patients who had extremely low levels of vitamin D had better rehabilitation and fewer secondary events when receiving supplements. However, subsequent significant trials, including the Vitamin D and OmegA-3 TriaL (VITAL), did not show much reduction in MACE in unselected populations, emphasizing the imbalance. For instance, meta-analysis data indicate that supplementation is most effective only in severe vitamin D deficiency cases and stresses the need for individualized dosing regimens based on the consumer's status (Liu et al., 2022).

These results correlate with other systematic studies and meta-analyses, pointing out that vitamin D supplementation is helpful but depends significantly on context. It is typical for systematic reviews to focus on the fact that although supplementation seems effective in specific subgroups, making it universal is not justified because of the absence of positive effects observed across all populations. This view coincides with recommendations of major associations like the Endocrine Society, where supplementation is advised only for those likely to be deficient, not for all, especially those who desire to prevent cardiovascular problems (Vieth & Holick, 2018). Similarly, the Institute of Medicine (IOM) noted that there might be some benefits for cardiovascular health associated with vitamin D in sufficient doses. However, they state that more quality research must be done to declare it definitively (Vieth & Holick, 2018).

This is a typical case of how multifaceted assessment of the problem is when comparing results from one study to another because the context of outcomes always matters in terms of study design, population subjects, and specifics of the given intervention (Burchett et al., 2018). For example, the original vitamin D status and its effects on supplementation are affected by the geographic region and the amount of sunlight exposure in a given season. Moreover, the variability of the daily dose and the supplementation period makes it difficult to combine the results and identify perceivable trends. The higher-dose regimens seem better suited to replenishing heavier losses, but the potential for side effects like hypercalcemia means that the dose needs to be approached carefully. These subtleties determine how study conclusions can best match existing clinical and policy information (Wong et al., 2023).

In terms of public health implications, this review confirms the need to actively search for such high-risk populace to give them vitamin D supplements. Assuming that universal supplementation were equally effective in all clients may be imprudent because only those with insufficient baseline levels may benefit. Conversely, strategies that aim to deliver individualized care based on the identified risks, including age, ethnicity, or other medical conditions, are better positioned to make an impact (Strianese et al., 2020). This approach matches recent developments in metabolism and precision medicine that imply the differentiation of treatment procedures for individual features of a patient.

4.2 Mechanistic Interpretations

Conceptual explication of Vitamin D/ CVD associations makes biological evidence applicable to clinical application (Hussain et al., 2022). Thus, the roles of vitamin D in the organism are explained based on molecular pathways and clinical observations, giving a more profound vision of vitamin D's impact on the cardiovascular system. This view helps to explain the mentioned fluctuations in the results and offers a rationale for individuals-oriented approaches.

The biological processes through vitamin D impact cardiovascular health are pretty well understood. Vitamin D influences the cardiovascular system through the vitamin D receptor (VDR) in many cardiovascular, endothelial cells, vascular smooth muscle cells, and cardiac myocytes. These properties suggest that it could be instrumental in preventing and controlling CVD through its relative roles in regulating inflammation, endothelial function, and lipid profile (Soppert et al., 2020).

The link between the development of CVDs and inflammation is well established, that is, atherosclerosis and heart failure. Regulation of cytokine production by vitamin D supplement, where supplementation reduces the abundance of pro-inflammatory cytokines (Martínez-Moreno et al., 2020) (interleukin-6 and tumor necrosis factor-alpha) and increases levels of anti-inflammatory cytokine (interleukin-10) have been established in several experimental studies. This anti-inflammatory effect has been supplemented by clinical findings demonstrating that vitamin D supplement intake lowers such inflammatory indices as c-reactive protein (CRP) in persons with a deficiency of vitamin D. That lower CARP is associated with better cardiovascular outcomes, including reduced arterial stiffness and better stability in atherosclerotic plaques that underpins the clinical significance of this regards (Tarantino & Citro, 2024).

Another is endothelial dysfunction in the development of CVDs, as it acts as the initial predictor that leads to the others (Zhang, 2022). This is shown by various factors such as reduced synthesis of nitric oxide (NO), raised vascular permeability, and increased ability of leukocytes to adhere to endothelial lining, all of which promote atherosclerosis and hypertension. The current evidence suggests that Vitamin D improves endothelial function by increasing NO production, decreasing oxidative stress, and decreasing the levels of VCAM-1 (Nguyen et al., 2021). These effects equate to better vascular resistance and a diminutive level of arterial tone, as seen in interstate clinical experiments targeting hypertensive and risk-population.

Vitamin D affects simple lipids and phospholipids or cholesterol and triglycerides in lipid metabolism due to gene regulation involved in lipid biosynthesis and catabolism. What has been found in experimental, clinical, and observation studies is that vitamin D causes a decrease in LDL cholesterol and triglyceride levels while raising HDL cholesterol. Such lipid-modulatory effect has been seen in clinical practice, especially in patients with metabolic syndrome or obesity, diseases that are often related to dyslipidemia and increased CVD risk. Modifying lipid profile reduces atherosclerosis incidence and its attributable consequences (Summerhill et al., 2019).

The mechanistic data show promising results of vitamin D supplementation in patients with CVDs (Salehi et al., 2019); however, few clinical trials have been conducted to assess therapeutic efficacy. The latter indicates sources of difference in study populations, the values of vitamin D at the onset of trials, and the interventions themselves. Biochemically, the supportive effect of vitamin D is most significant in patients with more severe deficiency, as adequate levels of 25-(OH)Vitamin D are needed to engage these processes. Frequent use of baseline levels means that populations enrolled in clinical trials were always have different levels before being supplemented; hence, the clinical trial dilutes the measurable gains from supplementation. For instance, when serum 25(OH)D level exceeds

30 ng/mL, there is no added basis for benefiting. Still, those with less than 20 ng/mL reaped consistent improvement in cardiovascular results (Salehi et al., 2019).

The dose-response relationship extends these biology / clinical outcomes interplay further. Recent studies have shown that a high dose is more effective in replenishing severity-depleted stores and stimulating vitamin D-sensitive processes. Nevertheless, they may cause toxic effects at high dosages, such as hypercalcemia, vascular calcification, or impairment of normal calcium-phosphate homeostasis. They underscore the importance of proportionate dosing regimens reflecting the data from mechanistic experiments and in vivo toxicology (Meesters et al., 2024).

4.3 Clinical Implications

Since vitamin D is involved in the pathophysiology of CVDs, there are significant clinical applications, such as screening and supplementation in high-risk populations (Barbarawi et al., 2019). The studies done on vitamin D show that a deficiency leads to adverse cardiovascular outcomes, making it crucial to determine and treat the deficiency in patients categorized as senior citizens, obese individuals, diabetic or hypertensive patients, and those with low sun exposure from their area or skin color. Measuring serum 25-hydroxyvitamin D [25(OH)D] concentration in these groups of individuals efficiently defines individuals with deficiency who may likely benefit most from vitamin D supplementation. For example, according to Pasquali et al. (2020), current Endocrine Society routine population screening is not recommended; however, screening for deficiency in children and adolescents should consider areas such as dietary intake, GI symptoms, overall morbidity and growth of children, gender, and ethnic background.

Supplementation is usually advised for persons whose serum 25(OH)D concentrations are less than 20 ng/mL, with target concentrations in the 30–50 ng/mL range. The daily dose usually may be between 800-2000IU/day; however, larger doses may be needed as a prescription for deficiency diseases but under doctor guidance. Older adults, postmenopausal women, and obese patients are potential candidates for supplementation, as vitamin D levels were observed to improve inflammation, endothelial dysfunction, and vascular stiffness in these groups. Supplementation may also prevent complications in most CVDs, for instance, heart failure or early recovery from myocardial infarction, depending on the patient (Brandhorst & Longo, 2019).

Therefore, translating research evidence into practice is difficult, as the following challenges were dictate. The results of trials conducted thus far have been relatively mixed, contributing to confusion about vitamin D's role in preventing and treating CVD. Although some studies and most meta-analyses show modest CVD risk reduction, other large interventional trials, like VITamin D and OmegA-3 TriaL (VITAL) (Manson et al., 2020), reveal a minor or no difference in other primary CVD outcomes in the general population. The observed mixed results can, therefore, result from variations in the study methods, participants' initial vitamin D levels, dosage, and period of interventions. This variability disrupts evidence within clinicians to identify which patients are likely to benefit and which strategy for supplementation is effective (Manson et al., 2020).

The variability of how deficiency and sufficiency are defined compounds the implementation problem in clinical practice. Organizations all define deficiency and sufficiency differently to coordinate different guidelines. As with any supplementation, the exact dosing regimens have not been pinned down to their optimal levels, as researched by Lentjes (2019). Heavier dosages may be more beneficial in severely deficient populations; however, they pose hazards that require monitoring, which may not be possible in ambulatory clinical settings. Further, persuading the patient to comply with supplementation is a problem since the effectiveness of the nutrients is premised on the long-term preservation of adequate vitamin D concentrations in the body.

Another major challenge is the availability of screening and supplementation is also another issue (Maughan et al., 2018). Lack of healthcare and limited awareness of the consequences leads to the initial deficiency and, consequently, preventive testing or early treatment for a great many high-risk individuals. To this end, eradicating these inequalities demands public health interventions in the organization and financing of vitamin D-related health care services. Public enlightenment campaigns and local initiatives might also close these gaps (Maughan et al., 2018).

4.4 Limitations of the Review

However, the present review has limitations that must be considered when making conclusions based on the study results. These limitations are due to the contextual restriction within the included studies and may also be due to certain biases under the systematic review method.

Another limitation is the significant heterogeneity in the study methods incorporated into the collected individual research papers. RCTs, cohort studies, and meta-analyses were combined into the review because they have unique advantages and limitations. Even though RCTs are regarded as evidence of causality, many of the trials included in the review differed in sample size, intervention schedule, and follow-up time. For example, some trials utilized low daily doses of Vitamin D, such as 400 IU/day, while others used high-dose Vitamin D boluses administered in the 1 - 3 months range. Developing guidelines based on acetylation status is complicated because such differences affect dose-related parameters, not the dosing regimen. In addition, the length of supplementation in most trials was relatively short, which may have masked the long-term cardiovascular advantages or disadvantages (Gupta et al., 2021).

As might be expected, cohort studies are susceptible to artifact influences despite their usefulness in capturing real-world relationships. For instance, participants with low vitamin D levels can have other factors associated with promoting CD, including ill nutrition, little physical activity, or other associated diseases. Despite the efforts made in many of these studies to control for potential confounding, residual confounding is always possible, and the relationships between vitamin D supplementation and cardiovascular events may have been distorted.

Another limitation of studies reviewed in this paper is that populations under study are diverse and may not be representative of the general populations as required by studies under the quantitative research paradigm (Maughan et al., 2018). The studies included a heterogeneous patient population comprising patients of different ages and genders, from various ethnic backgrounds, and with different baseline vitamin D concentrations and comorbidities. On the one hand, this diversity increases the external validity of the studies; on the other hand, it makes interpretational comparisons between two different studies more complex due to the inclusion of variability. For instance, persons with substantiated ID (serum 25-hydroxyvitamin D [25(OH)D] <20 ng/mL) experience more improvement upon supplementation compared with persons with nonserum 25(OH)D levels. It is believed that if deficient and sufficient groups are included in the same analyses, the effect of supplementation can be nullified.

Intention-to-treat bias may also have occurred during the screening and inclusion of studies. If we talked about objective criteria, eligibility criteria were predefined, but the studies' relevance and quality assessment could result from the authors' subjective perceptions. In the same way, many of the primary studies used to create publications rely upon reported data, which means that any error or bias from the original work is transmitted within the review.

4.5 Future Directions

New studies regarding the effects of vitamin D and CVD should focus on yielding large-scale, well-controlled clinical RCTs to minimize the prevalent drawbacks and conflicts noticed from previous studies. As such, the existing evidence mainly has limitations regarding study population heterogeneity, intervention variability, and short follow-up duration. More ambitious RCTs with sufficient sample size to detect effects at commonly achieved levels of vitamin D supplementation are required to confirm or refute the causal link between vitamin D intake and cardiovascular disease, including MI, stroke, and heart failure. Therefore, These trials should comprise participants of different ages, genders, ethnicities, and basal Vitamin D concentrations to increase external validity and test interaction effects. Furthermore, trials should use consistent dosages and follow-ups in the long term to assess whether supplementation has persistent impacts and associated undesirable effects.

Further investigation of individual supplementation approaches is also considered to be another significant future research area. Literature shows that vitamin D supplementation is most effective when the baseline level is very low: serum 25(OH)D <20 ng/mL. Further studies should examine intervention strategies according to baseline, genetic factors, and comorbid diseases regarding vitamin

D. A better understanding of patient characteristics could fine-tune dosing schedules more likely to confer cardiovascular benefits without adverse effects, including hypercalcemia or vascular calcification. Additional and enhanced implementation of such more proactive tactics may be attained through more technological forms of diagnosis, genetically based testing, and machine learning algorithms.

Furthermore, additive approaches, including co-administration of vitamin D, should be examined in the standard treatments for hypertension or dyslipidemia. These improvement efforts were add to the development of a better understanding of vitamin D's roles and functions in CVD prevention and management, implying more evidence-based clinical and public health practice.

5. Conclusion

Finding this review stimulating, I wanted to draw attention to vitamin D supplementation's multifaceted, potentially helpful application in cardiovascular diseases (CVDs) (Nemeth et al., 2023). The published literature suggests that supplementation can have multiple advantages, especially in people with apparent deficiency. Still, their results vary significantly due to differences in trial design and population as well as the specifics of the intervention. Vitamin D has been potentially effective in lowering other complications, reducing dip and kidney function, reducing obesity, and enhancing different aspects of heart failure and post-myocardial infarction healing. Nevertheless, its effectiveness seems most profound in patients with the initial serum 25-hydroxyvitamin D [25(OH)D] of less than 20 ng/ml, emphasizing the necessity of such targeted approaches.

Therefore, vitamin D supplementation is helpful since deficiency is so common and is a risk factor that can be modified in individuals experiencing CVDs. Landmark observational studies indicate that vitamin D supplementation in such groups as the elderly, the obese or diabetic, and hypertensive subjects falls into the category of low-risk, low-cost, and safe interventions that can effectively augment conventional CV therapeutic options. However, the specific effectiveness cannot be emphasized, and its usage can be regarded merely as one of the components of the comprehensive treatment plan (Reaser et al., 2020).

The last conclusions outline the importance of regularly screening high-risk groups to prevent and treat vitamin D deficiency. Three critical elements for achieving high cardiovascular risk benefits and low risks are specific dosing regimens for patients. The review also supports large, long-duration, randomized controlled trials to confirm causality and fine-tune supplementation policies.

Accordingly, if directed appropriately, Vitamin D supplementation could help afford a significant contribution toward the global prevention of CVDs (Shu & Yong, 2023). Subsequent research and interprofessional research by clinicians and community health practitioners are still required if the methods are to be optimally exploited for early disease prevention and treatment.

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