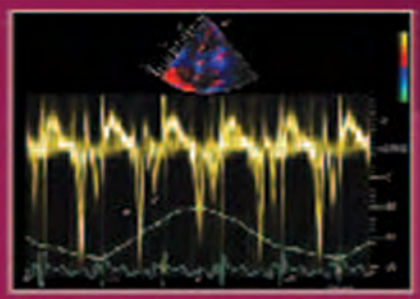
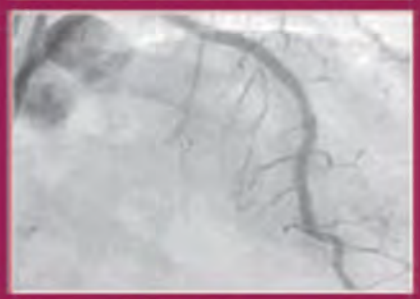
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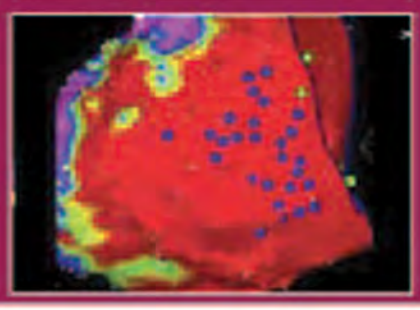
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CHAPTER 3

Vitamin D and Cardiovascular Disease: Indian Perspective

Ramu Adela, Rajesh Khadgawat

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INTRODUCTION

Vitamin D

Vitamin D, a secosteroid (steroid with open or broken ring), is fat-soluble vitamin involved in maintenance of calcium metabolism as well as musculoskeletal health. It exists in two forms, ergocalciferol (D2, from plant origin) and cholecalciferol (D_3, from animal origin). With limited sources in diet except for seafood, main source of vitamin D in humans is synthesis from cholesterol in epidermis by exposure to the UV radiation (sunlight). Exposure to sunlight for sufficient duration bring out chemical change in structure by opening a double bond which further initiates series of structural changes resulting in formation of cholecalciferol (also known as "Calciol"). Once formed, cholecalciferol, an inactive form, undergoes hydroxylation in liver and converted to 25-hydroxycholecalciferol [(25(OH)D) also known as "Calcidiol" or "Calcifediol"] which is further, hydroxylated in kidney to form active form of vitamin D, 1,25-dihydroxycholecalciferol [$(1,25(OH)_2D$ also known as "Calcidiol"]. Vitamin D receptors (VDRs) are intracellular receptors and found in all tissues of the body, including vascular smooth muscle, endothelium, and myocardium. The active metabolite $1,25(OH)_2D$ binds with the vitamin D receptor in cytoplasm in the targeted cell and form a heterodimeric complex (VDR-RXR) with retinoid receptor (RXR). Further VDR-RXR complex translocate to the nucleus where it binds with vitamin D responsive element (VDRE) in the DNA and exert its biological function through transcriptional regulation of targeted genes in targeted cells (Fig. 1).[1]

ASSESSMENT OF VITAMIN D NUTRITIONAL STATUS

Nutritional status of vitamin D is assessed by measuring serum levels of 25-hydroxyvitamin D. Although measurement of $1,25(OH)_2D$, active form is also possible but measurement is cumbersome and at the same, not useful in providing nutritional status of vitamin D. One of the most debatable issues about vitamin D is cutoff used for defining vitamin D deficiency (VDD). Many societies suggest serum vitamin D levels between 12 and 20 ng/mL to define VDD; however, most widely used cutoff, all over the world is less than 20 ng/mL while levels between 20 and 30 ng/mL are considered as insufficient and levels more than 30 ng/mL is used to define vitamin D sufficiency. Further, levels of VDD (<20 ng/mL) are divided into severe (<5 ng/mL), moderate (5 ≤10), and mild VDD (10 ≤20 ng/mL).[2] These cutoffs are based on the physiological fact of occurrence of secondary hyperparathyroidism with decrease in vitamin D levels.

VITAMIN D NUTRITIONAL STATUS IN THE WORLD AND IN INDIA

High prevalence of VDD has been recognized very early at the start in 19th century (1920s) especially in causing rickets, which led to initiation of food fortification programs in most of the developed countries.[3] Over the years, vitamin D food fortification has resulted in improvement in vitamin D status of general population. However, errors in fortification (fortification of large amount of vitamin D by mistake) had raised concerns about these fortifications, which resulted in many countries converting universal fortification to optional fortification with vitamin D. Vitamin D food fortification program could not be started with wider success in our country.

In spite of food fortification, high prevalence of VDD has been reported all over the world, across all age groups and both sexes.[4,5] VDD is considered to be pandemic with report of widespread deficiency coming from every part of the world with maximum prevalence reported from Middle East and South Asian countries in spite of availability of sunlight throughout the year. Prevalence of VDD has been estimated to be approximately 30–60% in the general population.[6]

In spite of geographical location of India (located at 28° 36.8' N and 77° 12.5' E in the northern hemisphere of the

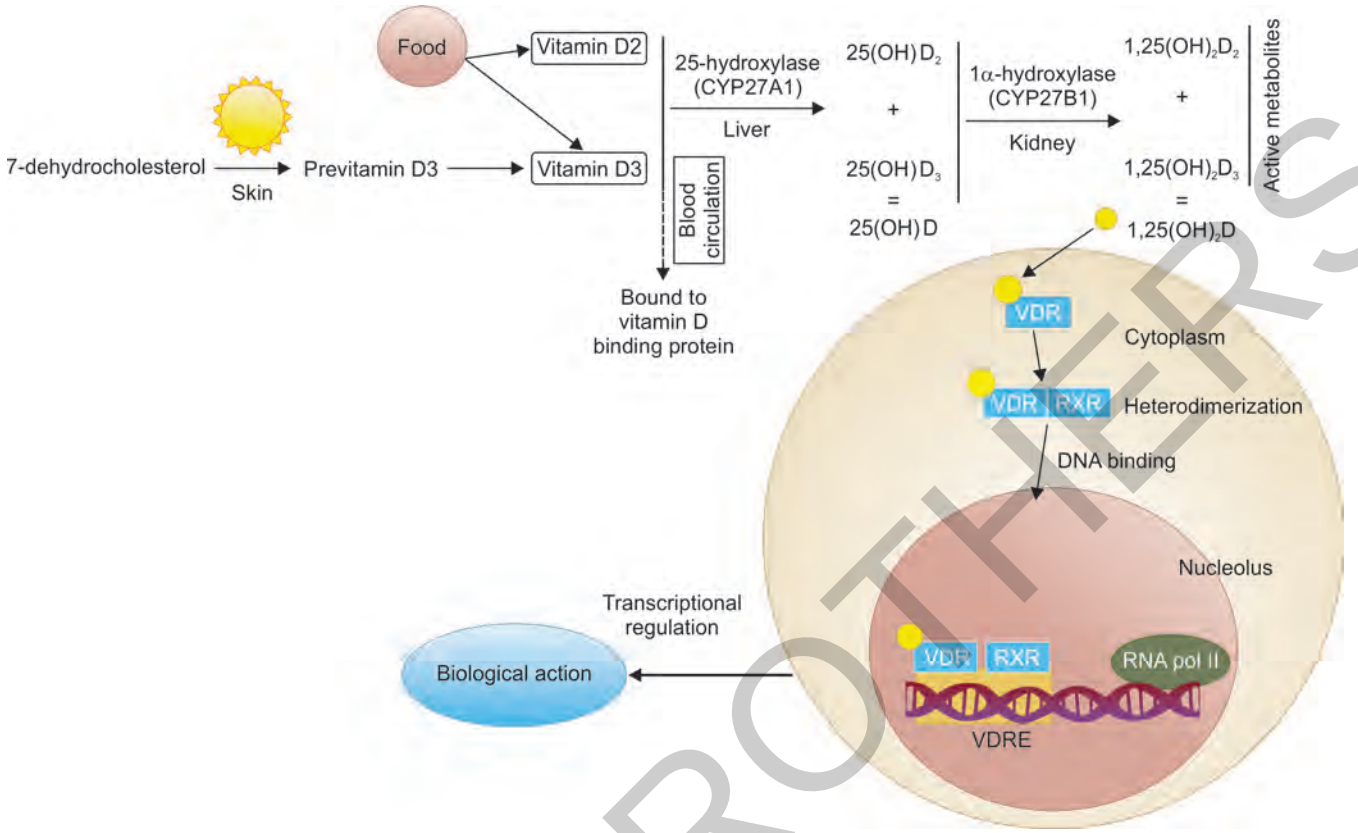


FIG. 1: Vitamin D synthesis, metabolism, and cellular action.

globe) which provides plenty of sunlight throughout the year, VDD was never a concern among Indians. Contrary to this assumption, high prevalence of VDD has been reported throughout the country for all age groups including neonates, infants, school going children, adolescents, adults, pregnancy, lactating women, and senior citizens. This is probably a result of poor sun exposure, dark skin complexion, atmospheric pollution, vegetarian foods habits, absence of food fortification with vitamin D, and poor intake of vitamin D supplements.[7] The most of the published studies on vitamin D status of general population report that very high prevalence to the extent of 70–95% using a cutoff of less than 20 ng/mL.

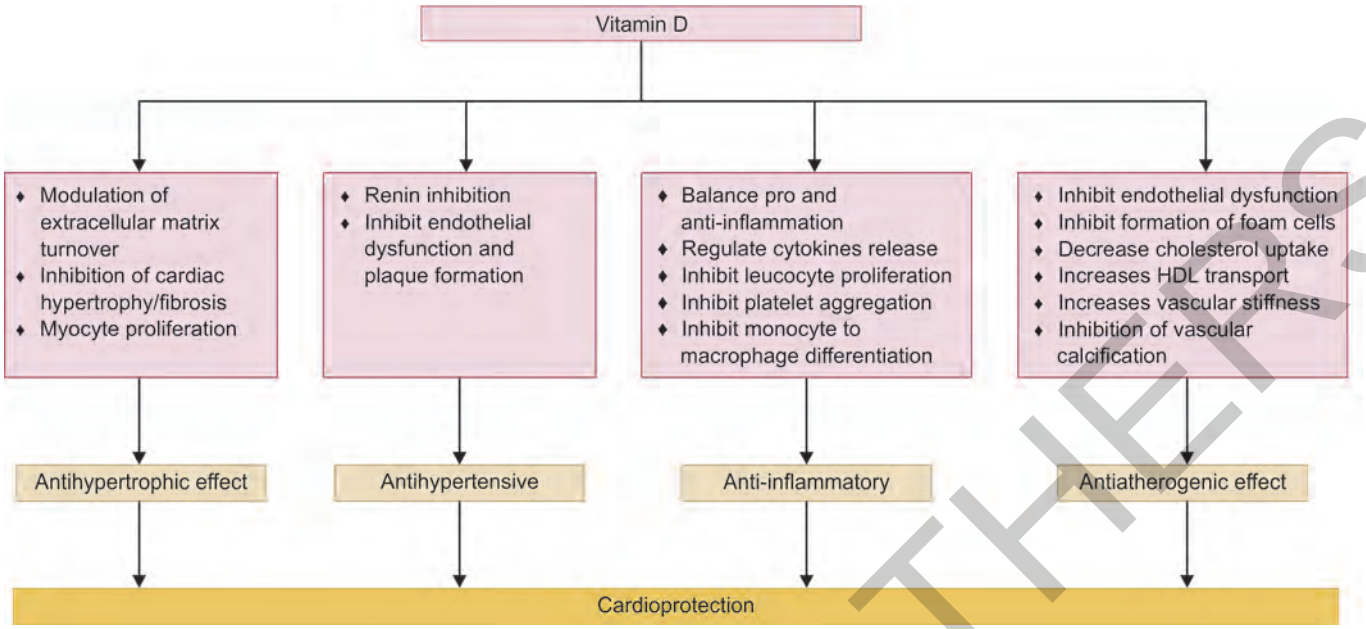
VITAMIN D AND NONSKELETAL EFFECTS

One of the major functions of vitamin D is maintenance of musculoskeletal health. However, over the years, association studies of levels of serum vitamin D with many chronic diseases has given a newer concept of role of vitamin D in nonskeletal diseases especially, noncommunicable diseases. Vitamin D has been reported to influence not only insulin sensitivity or resistance but also insulin secretion.[8] There are several studies, including data from the Framingham Heart Study,[9] demonstrating an inverse association between insulin resistance and serum 25-hydroxyvitamin D levels.

VITAMIN D AND CARDIOVASCULAR DISEASES

Vitamin D status has also been linked to cardiovascular (CV) risk factors, morbidity, and mortality.[10] VDD state has been shown to be associated with cardiovascular diseases (CVD) risk factors such as obesity, hypertension, hyperlipidemia, and diabetes mellitus. In a random sample of 6,784 subjects in the age group of 30–60 years, high serum levels of vitamin D was reported to be associated with lower incidence of metabolic syndrome and lipid profile favorable to CV health; however, no association between vitamin D level and blood pressure was found.[11] In one of the largest study, population-based sample of 16,603 men and women aged 18 years or older (Third National Health and Nutrition Examination Survey, 1988–1994). Subjects with CVD had a greater frequency of 25(OH)D deficiency (<20 ng/mL) than those without VDD. Even after adjustment of all CV risk factors, subjects with VDD had an increased risk of prevalent CVD with odds ratio 1.20.[12] Another large study of 18,225 US men (Health Professionals Follow-Up Study), low vitamin D status was found to be associated with increased risk of myocardial infarction (MI) as compared to subjects with vitamin D sufficiency.[13] Another data base study of 41,504 subjects, VDD was associated with highly significant ($p < 0.0001$) increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral

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FLOWCHART 1: Proposed mechanisms for cardioprotection with vitamin D.

vascular disease. Serum vitamin D levels were also found to be significantly associated with coronary artery disease (CAD), MI, heart failure (HF), and stroke. Even in subjects without risk factors but with severe deficiency, also had increased likelihood of developing diabetes, hypertension, and hyperlipidemia.[14] In a recently published meta-analysis of 19 prospective studies with 66,000 participants, a linear and inverse association was found between circulating vitamin D level and risk of CVD.[15] Similarly, VDD has also been reported to be associated with subclinical markers of atherosclerosis like intima-media thickness (IMT), arterial stiffness, and coronary calcification.

MECHANISM OF VITAMIN D AND PROPOSED CARDIOPROTECTION

The exact mechanism of role of vitamin D in proposed cardioprotection has not been elucidated well. The most of the information is coming from individual studies assessing effect of vitamin D on cellular, molecular, and biochemical parameters associated with CVD. Vitamin D has shown to inhibit proliferation of vascular smooth muscle cells and increases calcification of smooth muscle cells.[16] It has also been shown to regulate the growth and proliferation of smooth muscle cells and cardiomyocytes. It has been reported to inhibit renin–angiotensin–aldosterone system (RAAS) and inhibit the endothelial dysfunction, the initiation step of plaque formation.[17] Similarly, vitamin D has also been found to be affecting the immune balance by suppressing proinflammatory and increasing anti-inflammatory cytokines and chemokines and inhibits endothelial dysfunction, leukocyte proliferation, cytokine release, and platelet aggregation the process involved in the atherosclerosis development.[18-21] It also shows antiatherogenic function by inhibiting the formation of foam cells, cholesterol uptake by the macrophages, and enabling high-density lipoprotein (HDL) transport.[22]

VITAMIN D AND CARDIOVASCULAR DISEASE: EVIDENCES FROM OBSERVATIONAL STUDIES

High prevalence of VDD has been reported from all ages in Indian population all across the country. Details of the Indian observational studies mentioned in table 1. Most of the studies reporting association between vitamin D and CAD had recruited patients admitted in hospital setting for management of CAD. Priya et al. reported high prevalence of VDD (80.4% using cutoff of <20 ng/mL) in North Indian hypertensive subjects in comparison to controls with 67.7%.[23] Another study reported VDD (<30 ng/mL) in 53.3% hypertensive pregnant women while only 3.3% healthy pregnant women without hypertension had VDD. In the same study, lower vitamin D levels were also found to be associated with hypertension disorders in pregnancy and circulatory cytokine and chemokine levels.[24] Cross-sectional studies have also reported higher prevalence of VDD in subjects with CAD patients and found to be independent predictor of CAD.[25-27] Multiple studies have also reported high prevalence VDD in patients admitted with MI patients.[28-30] Similarly, higher prevalence of VDD has also been reported in patients with ischemic stroke and is independent predictor of ischemic stroke.[31] Higher prevalence of VDD in patients with dilated cardiomyopathy has been reported and found to be correlated with cardiac function.[32]

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TABLE 1: Indian studies exploring vitamin D status of subjects with coronary artery disease

Cardiovascular disease; reference	Study type and place	Study population and size	Outcome parameter assessed	Serum 25-hydroxyvitamin D level	Conclusion
Acute myocardial infarction (AMI)[28]	Observational study, Delhi	Healthy controls: 120 AMI cases: 120	Compared vitamin D status of AMI cases with healthy controls	Controls: 11.1 ng/mL Cases: 6.0 ng/mL	High prevalence of vitamin D deficiency among cases of acute MI as well as controls
AMI[29]	Observational study, Delhi	Control cases: 50 AMI cases: 50	Compared vitamin D status of AMI cases with healthy controls and correlation between FMD and vitamin D	Controls: 25.4 ng/mL AMI cases: 14.5 ng/mL	Majority of AMI cases were vitamin D deficient FMD was positively correlated with vitamin D
AMI[30]	Observational study, Bangalore	AMI: 314	Compared vitamin D deficiency among AMI patients	67.5% patients were vitamin D deficient and 16% were insufficient, 83.5% patient had abnormally low vitamin D	Vitamin D deficiency is common in patients with AMI
CAD[26]	Observational study, Uttar Pradesh	Control: 101 CAD: 140	Compared vitamin D status in CAD cases with controls	Controls: 28.8 ng/mL CAD: 18.2 ng/mL	Significantly low vitamin D levels observed in CAD Vitamin D deficiency was found to be an independent predictor of CAD
CAD[25]	Observational study, Andhra Pradesh	Healthy controls: 50 T2DM: 71 CAD: 28 T2DM + CAD: 38	Compared vitamin D status among study groups	Controls: 38.0 ng/mL T2DM: 32.0 ng/mL CAD: 30.8 ng/mL T2DM + CAD: 20.1 ng/mL	Low vitamin D levels observed in the T2DM, CAD and T2DM + CAD groups, compared to healthy controls
CAD[27]	Observational study, Chandigarh	Patients who underwent coronary angiography: 315	Compared vitamin D status of CAD patients with normal coronary artery	Normal coronary artery 11.3 ng/mL CAD: 14.1 ng/mL	Prevalence of vitamin D deficiency is very high in CAD, but it does not correlate with the angiographic severity of CAD
Hypertensive disorders in pregnancy[24]	Observational study, Hyderabad	Healthy pregnant: 30 Hypertension disorders in pregnancy: 30	Compared vitamin D status between the two groups	Healthy pregnant: 50.2 ng/mL Hypertension disorders in pregnancy: 28.64 ng/mL	Vitamin D levels decreased in severity of hypertensive disorders in pregnancy
Hypertension[23]	Observational study, Lucknow	Controls: 99 Hypertension cases: 102	Compared vitamin D status between the two groups	Controls: 33.5 ng/mL Hypertension cases: 15.1 ng/mL	Vitamin D deficiency is more prevalent with hypertension
Elderly subjects visiting cardiac checkup camp[47]	Observational study, Rajasthan	Control: 47 CAD: 53	Correlation between serum vitamin D level and cardiovascular morbidity	Vitamin D deficiency CAD: 28.30%; Controls: 25.53% Vitamin D insufficiency Cases: 49.05%; Controls: 23.40% Vitamin D sufficiency Cases: 22.64%; Controls: 51.04%	Vitamin D deficiency is common in elderly persons
Ischemic stroke[31]	Observational study, Hyderabad	Controls: 250 Ischemic stroke: 250	Compared vitamin D status between the two groups	Vitamin D deficiency Stroke cases: 48.8%; Controls: 31.6%	Vitamin D deficiency is an independently associated with ischemic stroke
Dilated cardiomyopathy (DCMP)[32]	Observational study, Lucknow	Controls: 60 DCMP: 56	Compared vitamin D status between the two groups	Controls: 28.2 ng/mL DCMP: 14.5 ng/mL	DCMP subjects had lower vitamin D levels than controls

FMD, flow-mediated dilatation; T2DM, type 2 diabetes mellitus; CAD, coronary artery disease; MI, myocardial infarction.

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VITAMIN D AND CARDIOVASCULAR DISEASE: EVIDENCES FROM INTERVENTIONAL STUDIES

International Studies

Results of cross-sectional studies of association of vitamin D with CAD have not been verified in interventional studies with vitamin D. In a randomized, double-blind, placebo-controlled clinical trial of 5,108 community-residents aged 50–84 years, oral vitamin D in an initial dose of 200,000 IU, followed a month later by monthly doses of 100,000 IU, or placebo for a median of 3.3 years did not prevent CVD compared with placebo.[33] Another randomized trial, also did not show a reduction of mortality in patients with advanced HF received a daily vitamin D of 4,000 IU compared with placebo.[34] Study of 112 patients receiving 3,000 IU cholecalciferol daily for 20 weeks did not result in a significant reduction in blood pressure.[35] However, study with female subjects aged over 69 years who received vitamin D3 (800 IU) and calcium (1,200 mg) daily for 8 weeks' supplementation resulted in borderline yet significant decrease in systolic blood pressure ($p = 0.04$).[36] Witte et al. conducted a study on 229 chronic heart failure (CHF) and VDD [cholecalciferol (<20 ng/mL)]. Participants were allocated to 1-year of vitamin D supplementation (4,000 IU/daily) or placebo. The study showed improvement in cardiac function like LV ejection fraction and reversal of LV remodeling like LV end-diastolic diameter and LV end-systolic diameter.[37] Dalbeni et al. conducted a randomized double–blind placebo-controlled study on CHF patients, high-dose 800,000 IU (4,000 IU/daily) of cholecalciferol for 6 months. The study revealed that 25(OH)D levels and ejection fraction were increased and systolic blood pressure decreased after 6 months treatment.[38] Similarly, another research group reported that vitamin D supplementation (100,000 IU) in subjects with baseline vitamin D insufficiency did not improve CVD risk factors profile.[39] Tomson et al. reported data of vitamin D supplementation in BEST-D (Biochemical Efficacy and Safety Trial of vitamin D) double-blind randomized placebo-controlled trial (4,000 IU/day for 12 months) did not show any improvement on blood pressure, arterial stiffness, and cardiac function.[40] Another recently conducted single-center, double-blind, randomized, placebo-controlled study with vitamin D dosage of 2,800 IU per day did not show any favorable effect on lipid metabolism.[41] Chowdhury et al. conducted a meta-analysis with observational and interventional studies and concluded that in observational studies, serum 25(OH)D level was negatively associated with death due to CVD, cancer, and other causes; however, supplementation studies did not support role of vitamin D supplementation in improving clinical outcomes.[42] Recently, published systematic review with meta-analysis by using placebo-controlled randomized trials of at least 4 weeks of vitamin D supplementation, did not show any significant effect of vitamin D supplementation on CV function, i.e., flow-mediated dilatation (FMD), carotid-femoral pulse wave velocity.[43] Although, it would be difficult to compare results of these studies because of many limitations like lack of randomization, placebo-controlled design, use of hospital admitted population, small sample size, shorter duration of intervention, and absence of VDD in study subjects at baseline, but still most of the studies have not reported any significant positive impact on outcome parameters. Multiple meta-analyses published assessing effects of vitamin D supplementation in various CADs, suggest no beneficial role of vitamin D supplementation in established CAD. However, pooling of results of all intervention studies would be not very logistic as design, duration, and dose of supplementation of vitamin D is highly heterogeneous.

INDIAN STUDIES

The most of the studies published from India are of observational design with only three interventional studies have been conducted so far. Details of these studies are given in table 2.

Abid et al.[44] randomized 72 subjects with HF (NYHA class II or more) with vitamin D level less than 30 ng/mL into two groups, group I, subjects received cholecalciferol 60,000 IU weekly for 12 weeks while in group II, subjects received optimized medical therapy but not vitamin D. Although, there was a significant improvement in echocardiographic parameters, but the extent of change from baseline did not differ significantly between the two groups.

Narasimhan et al.[45] in an open label randomized controlled design, supplemented a single dose of 600,000 IU of cholecalciferol intramuscular injection in patients with ischemic stroke, and compared with patients who did not receive vitamin D. Using Scandinavian Stroke Scale (SSS) as outcome parameter, it was found that vitamin D supplemented group had significantly higher SSS than patient who did not receive. Even in supplemented group, higher scores were seen in subjects who had VDD at the time of screening in comparison to subjects who did not have. The sample size was small (30 in each group) and not double blind design but requires further exploration of results in larger studies.

Another recently published randomized, double-blind, placebo-controlled study,[46] effect of cholecalciferol supplementation on vascular function was assessed in 120 patients aged 18–70 years, with nondiabetic chronic kidney disease (CKD) stage 3–4 and VDD (≤20 ng/mL).

Intervention group received two oral doses of cholecalciferol (300,000 IU) at baseline and 8 weeks, compared with matching placebo. In comparison to placebo group, cholecalciferol supplementation significantly increased endothelium-dependent brachial artery flow-mediated dilation at 16 weeks. Intervention also led to significant favorable changes in pulse wave velocity and circulating interleukin (IL)-6 levels.

However, another interventional study, i.e., Indian Polypill study [The International Polycap Study 3 (TIPS-3)] which was initiated to study vitamin D supplementation effect on reducing major adverse CV events (ClinicalTrials.gov Identifier NCT01646437), is still ongoing.

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TABLE 2: Indian studies assessing effect of vitamin D supplementation on cardiovascular outcomes

Cardiovascular disease, reference	Study type	Dose of vitamin D supplementation and frequency dosage	Duration of supplementation	Outcome parameters of intervention	Diseases groups and no. of subjects	Serum vitamin D levels before and after supplementation	Conclusion
Heart failure[44]	Nonrandomized	60,000 IU/week	3 months	Association between vitamin D levels and echocardiographic parameters	Group 1: n = 38, vitamin D supplemented Group 2: n = 36, no supplementation	Before: Group 1: 18.14 ± 6.07 ng/mL Group 2: 20.48 ± 5.86 ng/mL After: Group 1: 34.7 ng/mL Group 2: 20.5 ng/mL	No improvement in left ventricular function, serum vitamin D levels increased following supplementation
Ischemic stroke[45]	Nonblinded and randomized, placebo	Single dose 600,000 IU	3 months	Stroke outcome	Group 1: n = 30, supplemented with vitamin D Group 2: n = 30 patients received placebo	Baseline: Group A: 17.98 ± 3.81 ng/mL Group B: 18.44 ± 4.69 ng/mL vitamin D levels were not measured after intervention	Improvement in the stroke outcome and EF and decreased systolic blood pressure
Cardiovascular risk in CKD[46]	Randomized, double-blind, placebo-controlled trial	300,000 IU at baseline and 8th weeks	16 weeks	Cardiovascular risks	Group 1: Placebo: 59 Group 2: Vitamin D: 58	Before: Group 1: 13.21 ng mL Group 2: 13.4 ng/mL After: Group 1: No change Group 2: 23.4 ng/mL	Increased endothelium-dependent brachial artery flow-mediated dilation and favorable changes in pulse wave velocity and circulating IL-6 levels

CKD, chronic kidney disease; IL-6, interleukin-6; EF, ejection fraction.

CONCLUSION

Based on the observation studies, association between VDD and CVD has been well reported. However, studies of supplementation of vitamin D did not show improvement in any of the clinical outcomes studied so far.

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