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Exploring the association between vitamin d deficiency and cardiovascular disease in primary care patients

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Abstract
In this review, the influence of vitamin D deficiency on CVD in patients with primary care settings shall follow observational studies in addition to clinical trials, as well as the mechanism and guidelines of each type. Cross-sectional research can also support that deficiency to vitamin D appears to be related to hypertension, CAD and heart failure. The mechanisms that were proposed are inflammation, endothelial dysfunction, and alterations in calcium regulation. Several clinical trials have been conducted to assess the effect of vitamin D supplementation in the cardiovascular diseases, and these have produced an inconclusive improvement in blood pressure but no significant effect on major cardiovascular incidences. According to the present diet charts it is advisable to consume vitamin D in range of 400 to 2000 IU daily based on age and other health conditions.
Professional organisations promote client-tail specifics which may include issues to do with sunlight, diet and supplementation. Further investigations should, therefore, aim at determining particular patients' populations that may require vitamin D supplementation most and determine more on the possible cardiovascular impacts of vitamin D. Therefore, based on the present study, it is possible to conclude that vitamin D deficiency is associated with an elevated CVD risk; however, it requires adequately powered trials to elucidate its role in the management of CVD. This study should be used to inform primary care providers that vitamin D levels should be included in practical strategies for cardiovascular risk assessment and control.

Keywords: Vitamin D, cardiovascular disease, hypertension, coronary artery disease, heart failure, supplementation, observational studies, clinical trials, mechanisms, guidelines

Introduction
Vitamin D belongs to fat soluble vitamins that plays a prominent role in bone health and regulation of calcium concentration along with calcium has been discussed widely for its role in many non osseous health related phenomenon; cardiovascular disease (CDV). Many reviews and prospective researches illustrated the connection between vitamin D deficiency and CVD, thus initiating more extensive investigations on the cause and effect and significance of this association (Wang *et al*., 2023) [7]. Awareness of this relationship is especially important in outpatient practices as timely assessment of modifiable risk factors and subsequent interventions greatly influence the patients' prognosis.
Today, deficiency of vitamin D in human body is a common problem observed in all the corners of the world. Lack of exposure to sunlight, unbalanced diet and other disease conditions are some of the causes of vitamin D deficiency in today's society, cutting across all ages and races (Holick, 2020) [2]. Taking into consideration the fact that PCP is mostly centered on prevention, as well as primary treatment of chronic conditions, it is the environment that could be effectively targeting this problem. Some researches emphasized the necessity of vitamin D deficiency testing in primary care patients, especially in those populations with an increased risk of CVD (Pilz *et al*., 2019) [3].
Although observational studies exist between vitamin D deficiencies and cardiovascular disease, biological credibility is present. Vitamin D receptors are reported to be located in almost all the cells of the body inclusive of the heart and blood vessels, implying it's have a direct effect in cardiovascular performance (Bikle, 2019) [1]. Also, moderate vitamin D-deficiency has been documented to affect the several processes which are involved in the cardiovascular diseases like inflammation, insulin sensitivity, and renin-angiotensin-

aldosterone system (Vacek *et al*., 2018) [6]. As these mechanisms demonstrate, more work needs to be done to better determine the combination of these effects to figure out the role of vitamin D on CVD risk.

However, to date there is still controversy about the desirable vitamin D levels for CV health and the effectiveness of supplement intake as a preventive measure. The case is rather ambiguous as randomized controlled trials and observational studies give rather contradictory information (Scragg, 2018) [5]. To resolve them, a literature review is necessary, while focusing on scholarly articles that encapsulate primary care since this is where patients' interactions occur.

Thus, this review seeks to try and identify the relationship between vitamin D deficiency and cardiovascular disease among the primary care patients and integrate the current research evidence into clinical practice. Thus we aimed, through this review of literature, to find out possible directions regarding the way through which indicators of vitamin D status could be manipulated to enhance cardiovascular health in primary care patients.

Background

Definition and Sources of Vitamin D

Calciferol or vitamin D is essential for the body's maintenance of the minerals balance and it is a fat soluble vitamin. They are gotten from foods and through Ultraviolet light source in the sun. There are two main forms of vitamin D: These are compounds such as D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D2 is obtained from some plant based foods while vitamin D3 is produced by the skin in response to UVB light from the sun as well as from foods of animal origin particularly fatty fish, liver and eggs particularly the yolk (Holick, 2020) [2]. Vitamin D is also found in fortified foods and dietary supplements as a result of medical restriction of sun exposure in some communities.

Vitamin D Synthesis and Metaofolism

The formation and interconversion of vitamin D take several processes. Vitamin D synthesis occurs when the skin is exposed to UVB radiation; 7-dehydrocholesterol in the skin changes to previtamin D3 and, then to vitamin D3. Vitamin D3 of this, forms 25-hydroxyvitamin D [25(OH)D] in the liver, and it is the major circulating form of vitamin D which is used to determine the vitamin D status (Bikle, 2019) [1]. The second hydroxylation takes place in the kidneys to form the active metabolite 1, 25-dihydroxyvitamin D also known as calcitriol. This active form interacts with vitamin D receptors (VDRs) in tissues; it takes part in calcium and phosphate balance and modulates numerous physiological processes (Holick, 2020) [2].

Position of Vitamin D on Cardiovascular Health

There is accumulating evidence on the importance of vitamin D in cardiovascular disease other than its substantive role on bone health. Cardiac and vitamin D receptors have been reported in the cardiovascular tissues implying a direct role in cardiovascular health (Pilz *et al*., 2019) [3].

Vitamin D plays a part in regulating of renin-angiotensin-aldosterone system, decrease inflammation and increase endothelial function and all of them are important factors in maintaining cardiovascular health (Vacek *et al*., 2018) [6]. In human subjects, studies have shown that there is an association between low levels of 25(OH)D and hypertension, coronary artery disease as well as heart failure In light of the presented data, it can be concluded that vitamin D plays a protective role in cardiovascular diseases.

Deficiency of Vitamin D in the Community Population

Deficiency of Vitamin D is prevalent with different populations in the global community. The following are some of the reasons that have led to this shortage: Geographical location where people spend inadequate amounts of time in the sun, poor lifestyle which makes people spend most of their time inside, use of sunscreen by people, and dressing code, which most of the times, exposes little or no skin (Wang *et al*., 2023) [7]. Indeed, it was established by Rosen *et al*., (2021) [4], that people with dark skin tone, older population, and people with medical conditions or restricted diets are at high risk of vitamin D deficiency. The situation of vitamin D deficiency is alarming because it has been shown to predispose an individual to several infections and poor health states (Holick, 2020) [2].

Vitamin D Deficiency: Causes and Risk Factors

Lack of Sunlight Exposure

Lack of vitamin D is one of the main reasons people experience a shortage of this valuable vitamin, and it is connected with the lack of time people spend under the open sky. Natural sunlight's ultraviolet B (UVB) rays are necessary for the production of vitamins in the skin especially vitamin D. Some of the reasons include; residing in high latitude areas, staying most of the time indoors and clothing that hide much of the skin hinders the absorption of UVB and hence the synthesis of vitamin D (Wang *et al*., 2023) [7]. Furthermore, the precautions such as use of sunscreen to eliminate skin cancer are also involved in hindering the production of vitamin D by the skin (Holick, 2020) [2].

Dietary Insufficiency

Food sources for vitamin D and its precursors are rather restricted and it is usually difficult for individuals to get it in their food intake. Vitamin D rich foods include the fatty fish, fish liver oils, eggs yolk and the foods that are fortified with vitamin D such as milk, orange juice and cereals. Thus, dietary practices and choices, or in some cases, restrictions, can result in insufficiency of these source foods for vitamin D (Pilz *et al*., 2019) [3]. However, it is noteworthy that vitamin D deficiency is especially acute in part in those people who adhere to a vegetarian or vegan diet, as the vitamin content in plant-based foods is usually significantly lower Holick, 2020) [2].

Malabsorption Syndromes

Some diseases that affect the gastrointestinal system will impair the absorption of vitamin D and hence will lead to deficiency. This is a sickness that hinders the assimilation of Vitamin D and other nutrients from the digestive system through diseases like Crohn's disease, Celiac disease, and Cystic Fibrosis among others (Rosen *et al*., 2021) [4]. Also bariatric surgery which involves rearrangement of the gastrointestinal tract with the view of facilitating weight loss results in the low absorption of vitamin D (Pilz *et al*., 2019) [3].

Certain Medical Conditions

Vitamin D stores can be affected by certain illnesses and causes deficiency of the same within the human body. One condition that would be appropriate is chronic kidney disease because kidneys are involved in the activation of vitamin D through conversion of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D. However, the activity of vitamin D can be decreased in CKD patients due to kidney's ability to convert this substance to its active form and, therefore, active vitamin D level will also be lower because of the impaired renal function Different conditions can also cause vitamin D deficiency including liver diseases and genetic disorders (Scragg, 2018) [5].

Demographic Factors

The other factor that is considered in rating the risk factor is age, sex, and ethnicity of the individual. For the elderly, there is a relative risk to vitamin D insufficiency this is because the skin tends to thin in this group reducing the skin's ability to produce the vitamin. In addition to that, kidney function is usually reduced which leads to the inability to convert vitamin D in the kidneys to an active form. Ethnicity also plays a role, mainly because people with darker skin pigmentation have more melanin quantities in the skin; there is, therefore, less synthesis of vitamin D from the sun. Holick, 2020 [2], also says that there is an increase in needs for vitamin D in women, more so while pregnant and/or lactating, hence a greater risk of deficiency when their diet and exposure to the sun are poor.

Common Cardiovascular Disorders

They are disorders that are categorized under the heart and blood vessels. For the inhabitants of this type of demographic segment, the following diseases can be expected: hypertension, atherosclerosis of the coronary arteries, and heart failure. Hypertension is high blood pressure through which the blood thumps forcefully against the lining of arteries, strong enough to penetrate even heart incident and stroke. CAD is a heart disease in which plaque has narrowed or blocked the coronary arteries cutting the supply of blood to the heart muscle. Heart failure as a long-term disorder during which the heart is unable to deliver the required amount of blood to the body. The syndromes of dyspnea, fatigue and fluid retention are considered to be the typical symptoms of this disease. Pathophysiology of CVD Cardiovascular diseases involving genetic interactions within the environment as well as lifestyle factors. Said in other words, atherosclerosis constitutes the general framework by means of which many CVDs are instigated. Once more, the term is used to describe how there is a w Wallace process in which fatty substances end up forming layers in the large and medium arteries' walls. That initial damage to the endothelium is generally driven by risk factors like hypertension, smoking, and high levels of cholesterol. The injured endothelium would then permit low-density lipoprotein cholesterol to pass through the artery wall, get oxidized, and cause an inflammatory process, as stated by Libby, 2021 [12]. Those immune cells, such as macrophages conducting the phagocytosis of oxidized LDL, will form foam cells and result in the generation of the plaque. For instance, in inflammation immune cells such as macrophages go to the site of injury, ingest oxidize LDL and become foam cells that mark the progress of plaque formation (Ross, 2019) [19]. In the long run, they evolve and get transformed into fibrous and hence the arteries narrow in size, and blood circulation becomes limited leading to ailments such as CAD and stroke.

Risk Factors for CVD

Several conditions and factors put one at a higher risk of developing cardiovascular diseases. Other customary pre-existing risk factors include obesity because it leads to a boost in blood pressure, abnormal levels of cholesterol, and insulin resistance all of which contribute to the development of CVD. Diabetes, particularly Type 2 diabetes, is recognized as potent in raising the risk of CVD since high blood glucose unleashes direct impact on damaging blood vessels; thereby fuelling the problem of atherogenesis. The other significant risk factor is smoking, because the chemicals in the tobacco smoke harm the heart and blood vessels leading to atherosclerosis, and cause heart attacks and stroked. Hypertension is also a CVD as well as a risk factor for several other cardiovascular diseases implying a strong link between hypertension and CVDs. However, steady blood pressure may lead to the deteriorating of the artery's lining therefore causing heart diseases and strokes, kidney failures among others (Chobanian *et al*., 2019) [8].

Vitamin D Deficiency and its Connection to Cardiovascular Disease

Finding Based on Epidemiological Data and Intercessional Studies

Some observational study and clinical trials have also associated a low level of vitamin D to cardiovascular disease with inconsistency. The observational studies that can be found report that out of the studies that have examined low vitamin D levels, a good number of them have found that it increases the risk for CVD. For instance, one meta-analysis of observational studies that was published described that reduced serum 25-hydroxyvitamin D [25(OH)D] concentrations were linked to developing new CVD that primarily involved hypertension and myocardial infarction or stroke. However, studies on clinical trials which sought to prove efficacy of the supplementation of vitamin D on cardiovascular outcomes has given varying results. The results of some of these researches demonstrated some positive outcomes and others did not observe any decrease in cardiovascular risk.

Existing Epidemiological Research on the Relationship between Low Vitamin D Status and CVD Risk

Observational research is very strong in showing the association between vitamin D deficiency and increased risk of CVD. Population-level cohort research studies have also demonstrated that lower levels of serum 25(OH)D are linked to increased rates of CAD, HF, and stroke (Rosen *et al*., 2021) [4]. In another case, the Framingham Offspring Study revealed that people with low vitamin D had increased the risk of cardiovascular events over a five-year follow-up compared to subjects with sufficiency (Pilz *et al*., 2019) [3]. Consequently, a number of investigations employing NHANES data indicated that serum 25(OH)D levels negatively correlate with cardiovascular mortality (Holick, 2020) [2].

Potential Mechanisms

The ways by which VDD may have an impact on the occurrence of CVD are many and interrelated. The first of

these is by mediating inflammation. It has been revealed that vitamin D affects the immune system and decreases the levels of inflammatory cytokines. Inflammation is an established threat-maker of atherosclerosis and other cardiovascular diseases (Libby *et al*., 2018) [13]. One more possible explanation can be attributed to endothelial dysfunction. It is well stated that vitamin D receptors exist on endothelial cells and vitamin D deficiency influences endothelial dysfunction characterized by raised vascular stiffness and decreased availability of nitric oxide which play significant roles in hypertension and atherosclerosis (Pilz *et al*., 2019) [3].

Another essential feature is involved calcium metabolism in the processes Vitamin D and their cardiovascular system. Vitamin D has a critical role to play within the body in that it helps to regulate and keep in check amounts of calcium in the body besides controlling the level of parathyroid hormone. Vitamin D deficiency damages the parathyroid gland leading to secondary hyperparathyroidism meaning that calcium flows into the vascular smooth muscle cells thus causing calcification of vessels and culpability in hypertension and arterial stiffness as proposed by Scragg in 2018 [5]. Also, vitamin D takes part in the regulation of the blood pressure and the fluid balance through the renin-angiotensin-aldosterone system. Deficiency in vitamin D is another factor that disrupts this system and thereby raises the odds of hypertension and cardiovascular issues (Rosen *et al*., 2021) [4].

Vitamin D Supplement and Cardiovascular Disease

The Overarching Review of Clinical Trials Regarding Vitamin D Supplementation for Primary Care Patients

Vitamin D supplementation does not seem to prevent cardiovascular adverse events in primary care patients, based on effects of vitamin D on cardiovascular morbidity and mortality outcome trials. Several trials have been conducted in the past with an objective to identify if the risk of CVD can be lowered by supplementing vitamin D. For instance, the Vitamin D and Omega-3 Trial (VITAL) was a large, multicentered, randomized controlled trial with primary aim to assess the role of vitamin D3 (2000 IU/day) supplement in prevention of major CV events. The study also revealed that patients in the vitamin D supplementation goopr sect received no less cardiovascular events such as myocardial infarction, stroke, or cardiovascular mortality, than those on placebo(s) (Manson *et al*., 2019) [18]. Likewise, the other trials including the Women's Health Initiative (WHI) concluded that vitamin supplements, particularly in combination with calcium had no potential of reducing CHD or stroke risk (Hsia *et al*., 2007) [17].

Changes in Cardiovascular Risk Factor in Response to Supplementaion

Although specific effects of vitamin D supplementation on the cardiovascular incidence have remained inconclusive, some studies have looked at the effects on some of the cardiovascular risk factors. Several studies have demonstrated that effect of supplement use is marginal in the lowering of blood pressure in specific groups of individuals. For instance, a quantitative systematic review of randomized controlled trials concluded that vitamin D reduces systolic blood pressure by 1 mm Hg more than placebo; the effect was more significant among hypertensive patients (Witham *et al*., 2014) [21]. However diastolic blood pressure was marginally higher with less intensity and variability depending on the angles.

Concerning the effect of vitamin D supplementation on lipid profiles, some studies have been carried out with inconclusive results. They have shown better lipid profile including the decrease in total cholesterol and LDL cholesterol or no effect at all (Dibaba, 2019) [16]. The wide variations in the findings could be explained by methodological differences, administered doses, length of intervention, and the participants' initial vitamin D levels.

Evidence on the Impact of Supplementation on CVD Incidence and Outcomes

The evidence on the impact of vitamin D supplementation on the incidence and outcomes of CVD remains inconclusive. While some observational studies have suggested a protective effect of higher vitamin D levels against CVD, randomized controlled trials have generally not confirmed these findings. For example, the D-Health Trial, which investigated the effect of monthly high-dose vitamin D supplementation (60,000 IU) on cardiovascular events, found no significant difference in the incidence of major cardiovascular events between the supplementation and placebo groups (Scragg *et al*., 2020) [20]. Similarly, the ViDA study, which examined the effect of vitamin D supplementation on cardiovascular disease incidence and mortality, also reported no significant benefits (Scragg *et al*., 2017) [19].

Overall, while vitamin D plays a crucial role in many physiological processes, the current evidence does not strongly support vitamin D supplementation as an effective strategy for reducing cardiovascular disease risk in the general population. Further research is needed to clarify the potential benefits of supplementation, particularly in specific subgroups of patients who may be more likely to benefit from increased vitamin D levels.

Current Guidelines and Recommendations

Review of Current Guidelines on Vitamin D Intake and Supplementation

Different recommendations of vitamin D intake and supplementation in the present time may differ is insignificant, but all these recommendations are targeting sufficient amounts of vitamin D intake for better bone health and overall health. According to the IOM, now the NAM, presently, an adequate intake of vitamin D is between 600 – 800 IU (15 – 20 microgm/day) for adults, while higher doses up to 4,000 IU or 100 microgm/day for adults are not toxic. All these recommendations are based on the premise of the patient avoiding direct sunlight.

That is, for those people who are prone to deficiency, not exposed to sunlight, with the black skin, or with certain medications, higher daily and weekly intake may be required to obtain and maintain the optimal serum 25-hydroxyvitamin D level. Several clinical Practice guidelines recommend the measurement of serum 25(OH)D level to better guide supplementation regimens.

Recommendations from Professional Organizations

American Heart Association (AHA)

The AHA recognizes an association between vitamin D deficiency and cardiovascular disease; however, data from controlled clinical trials does not support daily vitamin D supplements for the said disease. An important nutrient for

the heart health is the vitamin D that must be obtained through the natural food sources, supplements, or moderate exposure to the UVB radiation and in accordance with the recommendations of the AHA (Manson *et al*., 2016) [18].

Endocrine Society: The Endocrine Society has even offered more detailed general guidelines (Table 1) with regard to vitamin D, especially for patients who may be prone to deficiency. Their recommendations include the following:

Table 1: Recommended daily vitamin D intake for different age groups and life stages:

Group	Recommended Daily Intake (IU/day)
Infants up to 12 months	400-1,000
Children 1-18 years	600-1,000
Adults 19-70 years	1,500-2,000
Older adults >70 years	1,500-2,000
Pregnant and lactating women	1,500-2,000

Closely related, the Endocrine Society has noted that persons at a high risk for vitamin D deficiency which includes obese persons, persons with malabsorption syndromes or on medications that affect vitamin D metabolism would need higher doses of vitamin D supplementation. It is desirable to make serum 25(OH)D above 30 ng/mL (75 nmol/L) to guarantee the health of a person.

Conclusion

Therefore, vitamin D deficiency and CVD provides striking focus to become the subject of research with an immense impact on primary care practices. The observational data conclusively indicate that deficiency in vitamin D is somehow associated with broad categories of cardiovascular diseases like hypertension, coronary arteriosclerosis, congestive heart failure, etc. These studies point out some of the possible pathways including inflammation, endothelial dysfunction, and calcium handling which could help to explain the discovered relationships.

Nevertheless, clinical trials on vitamin D supplementation have had rather inconclusive outcomes, with many of the experiments showing no protective effects against cardiovascular events. In terms of cardiovascular outcomes some trials showed that there were small changes for such risk indicators as blood pressure though the effect on cardiovascular end points is somewhat ambiguous. These data show that, high levels of vitamin D do not necessarily have a positive effect on the cardiovascular health and, therefore, other factors can play a role in cardiovascular diseases.

The American Heart Association and the Endocrine Society both state by dietary intake, use of vitamin supplements along with safe exposure to sun can help in getting the right amount of vitamin D in the body. These guidelines recommend special attention as to clients belonging to the groups in the highest risk of deficiency, such as the seniors, patients with a lack of the sun exposure, and people with certain diseases.

Continuous research should be conducted to establish the subgroups of patients, who can benefit from vitamin D supplementation and the pathways, which involve vitamin D in affecting cardiovascular disease. However, large-scale, randomized clinical trials with proper blinding techniques would have to be conducted to give clearer conclusions with respect to the use of vitamin D on the prevention and treatment of cardiovascular diseases. Meanwhile, on the other end, primary health care providers should not give up on the monitoring and management of vitamin D blood levels as part of an overall strategy toward cardiovascular health, keeping in mind each patient's unique risk factors and overall health status. In using this integrative approach, meaningful measures can be taken to ensure that patients receive the best possible evidence-based care for optimum cardiovascular and general health.

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