REVIEW ARTICLE

Association of Vitamin D and Cardiovascular Disease: A Review

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ABSTRACT

Acute and chronic cardiovascular issues are on the rise globally. A range of essential treatments is opted to counter the situations. Accurate diagnosis with proper medication can improve the outcomes along with much more survival chances. Vitamin D is a lipid-soluble vitamin that was known to be essential for calcium and phosphorus metabolism and bone health in general. Alongside, ever-growing cardiac complications, the increment of Vitamin D deficiency in several populations are also on the rise globally. Changing lifestyles and food habits are mostly responsible for such outcomes. However, the impact of Vitamin D deficiency is far-reaching and not limited to only mineral metabolism and bone health. Literature evidence suggests that Vitamin D deficiency can directly or indirectly induce cardiovascular risk factors and can elevate cardiovascular diseases. Hence, vitamin D deficiency should be considered seriously and treated with the utmost care. Molecular investigations suggested several benefits of Vitamin D in relation to Atherosclerosis, hypertension and cardiovascular issues. However, clinical trial outcomes are not satisfactory. In this review, we would like to present certain facts that provide the molecular level research outcomes and their important outcomes and the results related to the clinical study as well. The present situation and dilemma pertaining to the use of Vitamin D in cardiovascular complications suggest further specific extensive research on this subject encompassing assessment of vitamin D level to the clinical outcomes.

Keywords: cardiovascular diseases; Vitamin D; Atherosclerosis

INTRODUCTION

Cardiovascular disease (CVD) has become a global threat to human health. Irrespective of continent or country the number of cardiovascular patients is on the rise. Previously, it was assumed that CVD is a major health risk for the elderly population, but with time and with an increased number of cases reports it is evident now that CVD is a concern to almost all the age groups and population.Probably, changing sedentary lifestyles, polluted environment, and modern unhealthy food habits are the major reasons for the growing CVD cases. The global assessment by the global disease burden estimation group (GBD) from 2007 to 2017 suggests that the mortality rate due to CVD is more than 220 deaths per 100,000 populations.[1] The condition is associated with multiple factors related to CVD such as heart failure, ischemic heart disease, congenital heart problems, stroke, peripheral arterial and vascular diseases, and valve associated issues. Each disease type is having its own prognosis, progress, and treatment. Therefore, early diagnosis and treatment are mandatory to save more lives. Globally, the estimation of death due to CVD was 17.8 million.[2] The global prevalence of CVD is presented in Figure 1.

There are several earlier epidemiological reports on the growing concern of CVD from the USA, the European region, Australia, and Asia.[3] Barquera et al. reported that the higher-income group population is having higher mortality due to ischemic heart disease (IHD) and atherosclerosis compared to their lower-income group counterparts. Further investigation suggested that demographic, societal, and hematological factors such as Body Mass Index (BMI), blood pressure, stress, lipid profile, and blood sugar play an important role in the disease onset and progress in the higher-income group population.[4] Therefore, assessment of social, biochemical, molecular, and hematological risk factors is important to understand the onset and progress of the disease conditions.

Figure 1: The global burden of disease (GBD) related to CVD[Courtesy: Institute for Health M etrics and Evaluation (IHME). Estimated presentation of GBD for 2019 in 21 regions.Source:

Institute for Health Metrics and Evaluation (IHME).Global Burden of Disease Study.Seattle, WA, University of Washington, 2019.

Associated Risk Factors: The involvement of multiple and varied risk factors with the CVD conditions requires constant analysis and assessment with the altering pattern of the disease in a population.[5] Due to the lack of exercise, improper food habits, and lifestyle issues in several countries the disease is on the rise in the young population.[6] Several prominent risk factors are associated with CVD such as obesity, diet, hypertension, individual genetic makeup, sedentary lifestyle, age issues, and mostly the cholesterol level in the blood, especially the proportion of high density (HDL) and low density (LDL) lipoproteins.[7]

Vitamin D: Vitamin D is also referred to as the sunshine vitamin due to its unique nature of production in the presence of sunlight.[7] Vitamin D is present in two forms, i.e., D2 and D3 where the latter one is considered as the predominant natural form. The biologically active form of natural vitamin D is formed after hydroxylation in the liver

and in the kidney.[8] The physiological functioning of this vitamin is associated with calcium and phosphorous absorption in the intestine. Vitamin D plays an active role in the acceleration of calcium and phosphorous absorption.Vitamin D functions via Vitamin D receptors that are omnipresent in almost all the cell types in the human body.

Clinical diagnostic and Assessment of Vitamin D: Vitamin D assessment is crucial to estimate and understand the level of the Vitamin in the serum of a possible deficient person. Generally, the present measurement process of the vitamin is predominantly concentrated on the level of 25(OH) D in the blood serum and further treatment is prescribed once there is any deficiency estimated. However, there are differences in opinion among different authorities regarding the standard amount and estimation of the vitamin in the serum. Furthermore, the assessment of the serum level of 25(OH) D is quite difficult and expensive as well. A significant variation was observed in the results of Vitamin D estimations through various biochemical assays performed. A comparison of the outcomes suggests that even results can vary by more than 30% also. A number of studies have been conducted to standardize the assays to estimate the serum Vitamin D levels. In this regard, different methods have opted including immunoassays, HPLC based estimations, and LC/MS/MS-based analysis.[8] All these methods are having their individual pros and cons in estimating the serum Vitamin D levels. For instance, immunoassays are fast and sensitive towards better results and can estimate a range of 3.4-156 ng/mL. However, this method is not efficient in determining the Vitamin D form. On the other hand, the HPLC based method lacks sensitivity but cost-effective. However, the LC/MS/MS-based method is highly sensitive but lacks proper throughput during sample analysis, hence, it does not have practical applicability so far. Moreover, the clinical determination of serum Vitamin D also depends on the availability, form of Vitamin and other factors. Recently it has been reported that genetic polymorphism is also having an impact on the serum Vitamin D availability. Therefore, the estimation of Vitamin D requires much more detailed information to improve the accuracy of the estimation and proper diagnosis.[9]

Dosage and adequate level: An adequate level of Vitamin D in a healthy person is within the range of 20ng/mL to 50 ng/mL.Vitamin D deficiency is biochemically determined by the reduction of Vitamin D level below 12 ng/mLwhereas the toxicity is considered for Vitamin D level of >150ng/mL.However, the value pertaining to the determination of the standard Vitamin D range is ambiguous and there is disagreement among the authorities regarding Vitamin D value for deficiency or toxicity.[10]

Vitamin D Deficiency:A Global Concern: Vitamin D deficiency or VDD has become a health concern for all age groups in several countries including India, Australia, Africa, and South America.[11] Investigations revealed that the primary cause of such deficiency is the lack of exposure in sunlight. Another important reason is the usage of cosmetic product that hinders sunlight exposure through the skin. Patients having a problem with fat absorption also have a Vitamin D absorption problem as this vitamin is lipid-soluble in biochemical nature. Therefore, lack of Vitamin D promotes several health issues such as an imbalance in calcium and phosphorus absorption, poor bone health, elevated parathyroid (PTH) hormone level. Such an imbalance in bone mineral absorption and deposition may further cause bone weakness, skeletal muscle weakness, and similar health issues.

Vitamin D and CVD: Apart from the calcium and phosphorous absorption, Vitamin D performs multiple important physiological functions including angiogenesis prevention, elevating insulin production, regulating the bone mineral density, regulating renin production, and different cellular proliferation.[12] The role of vitamin D is also well documented for supporting disease prevention such as cancer, diabetes, and CVDs.[13]

Impact on the renin-angiotensin system: Several studies have reported the relation between vitamin D and cardiovascular issues.[14] Vitamin D deficiency plays a pivotal role in altering the reactive oxygen species (ROS)andalteredrenin and angiotensin II production that impacts the inflammation and augments insulin resistance and hindering the metabolic homeostasis.[15] The renin-angiotensin-aldosterone (RAAS) pathway is associated with cardiac issues such as hypertension, hypertrophy, atherosclerosis, arrhythmia, and heart failure.[16] Experimental evidence suggests that Vitamin D impairs the RAAS activity through downregulating the renin gene expression, thus modulating the blood pressure directly.[17] Further, renin gene expression modulation through a cis DNA element affects the angiotensin II, a vasoconstrictor, production. Hence, influencing hypertension and promoting the hypertrophy in the left ventricle.[18] An equivalent outcome of high blood pressure and left ventricular hypertrophy was also reported forVitamin D deficiency mice.[19] In humans, the role of calcitriol in downregulating angiotensin-I receptor gene expression was established that in turn aids in reducing the production of ROS.[20]

Calcification in smooth muscles: At a molecular level, it was also observed that Vitamin D deficiency causes proliferation of the smooth muscles along with calcium deposition, this may impact the cardiovascular homeostasis directly.[21] The classical Framingham Heart Study has established that patients with lower Vitamin D levels (< 15ng/mL) displayed an association with the increased heart disease compared to the patients who had an appropriate level of VitaminD. Another report suggests that an adequate level of Vitamin D to diminish the cardiovascular risk or improve the CVD condition is around ~30ng/mL.[22] The calcification of the vascular smooth muscles may occur due to hypervitaminosis that may lead to stimulating the RAAS pathway. Therefore, such modulations may accelerate the impairment of the myocardial function byimpacting the muscles, blood pressure, and altered cardiovascular regulations.

Atherogenesis and Vitamin D: Atherosclerosis is signified by plaque formation in the arteries and subsequently narrowing down the regular blood flow followed by cardiac arterial disease (CAD). The process of plaque formation or atherogenesis was known to be a mechanical process due to the deposition of monocyte and T cell-derived fatty

streak at the subendothelial layer. At the progressive stage, the plaque contains cholesterol esters, macrophages, mast cells, and T-cells. In the more advanced level, deposition of calcium hydroxyapatite is also observed.[23] Recent researches unveiled that atherogenesis is a continuous and dynamic process induced by inflammation. Role of inflammatory cells and specific adhesion molecules such as P selectin, and intercellular adhesion molecule 1 (ICAM 1) are essential in plaque formation and disease progression.

Modulating endothelial cell function: Vitamin D deficiency is having a direct and indirect relation with atherogenesis. The endothelial activation and deactivation are directly associated with the function of Vitamin D where the vitamin facilitates the endothelial nitric oxide synthase (eNOS) coupling through suppressing the NADPH oxidase subunit and promotes nitric oxide production. In parallel, Vitamin D also reduces the reactive oxygen species (ROS) production which reduces the local inflammation and prevents the aggregation of the inflammatory cells that form atherosclerotic plaques. Vitamin D promotes a cascade of the molecular chain through NF-ĸB that allows inhibition of a number of molecules that are involved in inflammation and plaque formation such as platelet endothelialcell adhesion molecule-1 (PECAM-1),interleukin-6, interleukin-8, receptor of advanced glycation end products (RAGE), ICAM1, vascular cell adhesion molecule-1 (VCAM-1),etc.[24]

Modulating vascular smooth musclecells (VSMCs) function

Effect on VSMC proliferation: Vascular smooth muscle cells (VSMCs) are predominant in the medial arterial wall throughout the arteries. The VSMCs remain active in propagating the atherosclerotic conditions from the middle layer to the intima layer by altering the morphological appearances and also by secreting specific inflammatory molecules.[25] The Vitamin D receptors or VDRs are an integrated part of the VSMCs and actively take part in anti-proliferative and inflammation suppression activity through 1a,25(OH)2D and maintains the stable state.[26] This is done through the suppression of the epidermal growth factor (EGF) and via inhibiting the function of the endothelin that are present in the VSMCs.[27] Endothelins are inhibited through the cyclin-dependent kinase 2(CDK2) regulation at the cellular level.[28]

Effect on VSMC migration: Apart from the anti-proliferative activity on VSMCs, Vitamin D exerts opposite outcomes on the migration of the VSMCs. Within the normal dosage, the calcitriol diminishes the activity of the Vitamin D binding proteins by kinase ½ phosphorylation. This activity ultimately reduces VSMC migration or proliferation.[29] On the contrary, the same vitamin shows an opposite effect of inducing the VSMC migration at a higher dosage than the physiological dosage through a cascading activation of the PI3K pathway or by downregulating the β1 integrin receptors.[30]

Effect on VSMC morphology: Interestingly, research evidence suggests that Vitamin D directly modifies the morphology of the VSMCs through impacting the elastogenesis of the VSMCs. The vitamin regulates the production of the important proteins that are crucial for the VSMC wall formation. Elastin, myosin, metalloprotein, and Type 1 collagenare some such proteins, the production of which is regulated by Vitamin D.[31] The vitamin also reduces the formation of aggravation caused due to the atherogenesis through increasing the prostacyclin formation using the cycloxygenase pathway.[32]

Other effects of Vitamin D on atherogenesis: Apart from the mentioned direct impact on the reduction of the atherogenesis or atherosclerosis at the molecular level, Vitamin D also modulates the inhibition of plaque formation indirectly. Such impact functions through acting on the important immune cells such as T-cells, various interleukins, and others. An antagonistic effect occurs in the function of the T-Helper cell 1(Th1), and T-Helper cell type 2 (Th2), where the former one promotes the atherogenic activity and the latter one reduces such effect. Vitamin D is evidently known to support Th2 activity instead of Th1 to reduce the atherogenic impact of the Th1, hence, exerting an antagonistic effect on the atherosclerotic plaque formation.[33] Furthermore, Vitamin D shows a direct effect on diabetes where the insulin gene contains a Vitamin D responsive element in the gene. Deficiency of Vitamin D can induce diabetes that in turn affects the blood sugar level followed by the blood pressure which can lead to cardiovascular complications.[34]

Control of lipid profile and Vitamin D: Other than the atherosclerotic conditions, Vitamin D has its impact on the lipid profile of the serum. It is a known fact that proper lipid profile maintains and controls the blood pressure. Altered lipid profile can induce blood pressure and can onset various cardiovascular issues. Reports suggest that Vitamin D is having a direct relation to the lipid content of the body. Generally, the high-density lipoprotein (HDL) aids in better mobilization of the lipid molecules from the heart and reduces the total cholesterol level in the serum whereas the low-density lipoprotein (LDL) on the other hand induces the cholesterol level as well as the triglyceride level in the serum. Vitamin D was found to have a significant causal effect of increasing the HDL and reducing the LDL and triglycerides with an increased dosage of Vitamin D.[35]

Chronic kidney disease, cardiovascular issues, and Vitamin D: Chronic kidney disease (CKD) is known to directly linked with the induction of cardiovascular complications.[36] CKD alters the patient's blood pressure and can induce hypertension followed by other acute symptoms and later on chronic cardiovascular complications. Efforts are reported to attempt to control obesity, hypertension and ultimately blood cholesterol levels in the CKD patients but the assessment did not reveal any direct or linear relation with the cardiovascular complications even though there was indirect evidence.[37] Vitamin D has acted as a better solution in this context and improved the dilation of the brachial arterial and the blood flow up to 6.1±3.7% using cholecalciferol (Dosage of 600,000 U) in non-diabetic patients.[38]

Understanding the effect of Vitamin D from clinical trials: A number of clinical trials conducted to understand the efficacy, safety, and specific effect of Vitamin D on cardiovascular issues and CKD. Cardiovascular disease and Vitamin D have been linked in clinical studies where peripheral vascular disease, carotid intima-media thickness, and other cardiovascular death was found to be

related to Vitamin D deficiency.[39] Trails on hospitalized patients with severe illness and Vitamin D deficiency were conducted by supplementing a higher dosage of Vitamin D but no significant difference in-hospital stay, mortality were noticed.[40] Another trial with cardiovascular patients was also supplied with Vitamin D and no significant improvement in the disease condition or mortality rate was observed. A similar null effect was observed while using cholecalciferol to improve the cardiovascular outcomes in another clinical trial conducted on more than 25000 participants. Therefore, these recent studies remained inconclusive in relation to the application of Vitamin D to improve the cardiovascular outcomes and in the presence of other complications such as CKD.

Relation of Vitamin D and CHD/CAD/Heart failure: Vitamin D is having a proven impact on heart function and imbalance, deficiency of normal vitamin D concentration can lead to severe heart function complications including ischemic heart problems, heart failure, and myocardial infarction. Vitamin D deficiency can directly promote atherogenesis through a proinflammation process. During the triggering atherogenic process, vitamin D directly impacts the endothelial cell functions as described later in this article. Atherosclerosis process onsets with mild chronic inflammatory impacts in the arterial wall region. Circulating 25(OH) components of vitamin D may have an inverse impact on this plaque formation process. A study reported that vitamin D can have a healing effect after myocardial infarction also. The vitamin enhances the cardioprotection post-myocardial infarction probably through impacting the cCFU-F cell cycle.

Clinical evidence of the probable role of vitamin D in coronary artery disease has been reported by Dziedzic et al. for the cardiac patients having type 2 diabetes. It was an important observation that patients with a higher degree of coronary artery disease were having a lower concentration of vitamin D. Apart from direct association with endothelial function coronary arterial flow and velocity were found related to vitamin D insufficiency. The relation was established with the slow coronary flow, subclinical atherosclerosis with vitamin D deficiency. In continuation of the reports on the association of vitamin D with CAD, some studies also remained either inconclusive or failed to establish any clinical correlation for vitamin D and coronary artery disease.

Future Perspective And Conclusions: Vitamin D is essential for our health especially bone health and calcium-phosphate metabolism regulation. Molecular studies provided in detail insight on the further functions of the use of Vitamin D. Our present understanding suggests that this specific vitamin is having a far-reaching impact on our mineral metabolism, immunity, cardiovascular health and several other aspects. However, our clinical understanding in this regard is inconclusive and not up to the mark. A greater number of clinical pieces of evidence are warranted to establish the direct impact of Vitamin D on cardiovascular health or cardiovascular outcome improvement. The present results did not establish the fact that Vitamin D deficient patients are having a different outcome in terms of recovery, mortality, and other clinical assessment factors. On the contrary, the cellular and molecular studies, and the studies conducted in mice models suggest the direct benefits of Vitamin D usage through regulating various essential cascading signaling pathways and through up-regulation, down-regulation and feedback mechanisms. Such information is intriguing and inspires us to investigate further at the clinical level to understand and harness the benefits of Vitamin D supplementation in patients with Vitamin D deficiency and cardiovascular complications. Specifically, patients with acute blood pressure issues, hypertension, and atherosclerosis are hoped to have benefits in outcomes. However, extensive clinical studies and further research and unveil the mysteries of the up-regulating and down-regulating impact of Vitamin D.

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