Review Article

Vitamin D: A New Therapy for Prevention of Cardiovascular Disease

Manjunatha H. R.
Department of Community Health Nursing, Kempegowda College of Nursing, Bengaluru, Karnataka, India

Abstract

Vitamin D is a fat-soluble vitamin that is naturally present in some foods and available as a dietary supplement. It is also produced endogenously from sunlight. The liver converts Vitamin D to 25-hydroxyvitamin D [25(OH)D], known as calcidiol, and the kidney forms the physiologically active 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol. The Vitamin D receptors in the body convert 25(OH)D to 1,25$(OH)_2$D. Serum concentration of 25(OH)D is the best indicator of Vitamin D status. Vitamin D helps in calcium absorption from the gut and maintains adequate serum calcium and phosphate levels. Vitamin D deficiency causes rickets in children and osteomalacia in adults.

Keywords: Vitamin D, calcidiol, calcitriol, 25-hydroxyvitamin D, rickets, osteomalacia

Introduction

Vitamin D is an important prohormone; there has been interested in evaluating other potential functions of Vitamin D, particularly in cardiovascular diseases (CVDs). Vitamin D deficiency is a condition that affects a high percentage of individuals of all ages. Considerable attention has been paid recently to the possible role of deficiency of this vitamin in the development of several chronic diseases including cardiovascular and metabolic diseases. There is also a significant correlation with mortality for major cardiovascular events such as heart failure, myocardial infarction, sudden cardiac death, stroke, atrial fibrillation, and peripheral vascular disease. It has also been shown that children with rickets who suffered from severe heart failure could be successfully treated with supplementation of Vitamin D + calcium. In adults, almost all patients with heart failure exhibit reduced 25-hydroxyvitamin D levels, which are used to classify the Vitamin D status. The pathophysiological mechanisms of these correlations are yet to be determined, but hyperactivity of the renin-angiotensin-aldosterone system (RAAS) seems to play a leading role. The role of therapy with Vitamin D supplements in improving cardiovascular outcome in patients with low levels of Vitamin D remains to be determined.

Access this article online
Website: http://innovationalpublishers.com/Journal/ijnmi
ISSN No: 2656-4656
DOI: 10.31690/ijnmi/34

Vitamin D - the "Sunshine Vitamin"

Vitamin D is a fat-soluble vitamin and an essential nutrient for healthy bones and teeth.[1] Vitamin D is not just a vitamin but it is a prohormone, a substance that the body converts to a hormone. Vitamin D binds to Vitamin D receptors present in the cells of the human body and has a key role in many body processes.[2] The two forms of Vitamin D are Vitamin D2 ("Ergocalciferol" or pre-Vitamin D) and Vitamin D3 ("Cholecalciferol"). Vitamin D2 mainly comes from fortified foods such as breakfast cereals, milk, and other dairy items. Vitamin D3 is made by our own body when we are exposed to sunlight. It is also found in some foods, including eggs and fatty fish, such as salmon and tuna.[1]

The deficiency of Vitamin D is not commonly seen in people who neither expose much to sunlight nor do they get enough of it through their diets. The Vitamin D level in the body can be measured by vitamin assay (blood test). This test is for people at risk of Vitamin D shortage.[2] In the human body as a part of metabolic process, the Vitamin D2 and Vitamin D3 are

Address for Correspondence:
H. R. Manjunatha, Department of Community Health Nursing, Kempegowda College of Nursing, Bengaluru - 560 004, Karnataka, India.
Phone: +91-9916134286. E-mail: manjunathhr2005@yahoo.co.in

changed into a form of Vitamin D called 25-hydroxyvitamin D also known as 25(OH)D.[1] The kidneys convert the 25(OH) D to 1.25(OH)2D.

The human body also produces its own Vitamin D from cholesterol, through the action of sunlight on skin, so it is called "The Sunshine Vitamin." but the elderly persons, people with obesity and those who avoid sunlight exposure may not make enough vitamin D from sun [Figure 1].[3]

What Is The New Thinking About The Vitamin D?

The research studies show that low blood levels of Vitamin D may increase the risk of chronic health problems and that adequate levels of Vitamin D may decrease those disease risks. Health problems that may be attributed deficiency of Vitamin D are as follows:

- Cancer
- Heart disease
- Diabetes mellitus
- Obesity
- Muscle weakness.

Few research studies suggest a link between low blood levels of Vitamin D and increased risk of cardiovascular problems such as high blood pressure, heart attack, and stroke. Although it is possible that Vitamin D supplements will decrease the risk of heart disease and stroke over time, there is not enough scientific proof. Too much Vitamin D may even raise the risk of heart disease. Until there is proof, experts do not advise taking Vitamin D supplements to try to lower your cardiovascular risk.[2]

Magnitude Of Vitamin D Deficiency

World

It is estimated that over 1 billion people worldwide have a deficiency of Vitamin D, also known as hypovitaminosis D, which the World Health Organization has defined as a public health problem.[4] In advanced countries, the strategies to fortify the food with Vitamin D were partially effective and have failed to provide adequate Vitamin D.[5]

The worsening worldwide trend toward nutritional insufficiency and the emerging knowledge of the non-hormonal functions of Vitamin D and its metabolites have increased interest in the synthesis, metabolism, and action of Vitamin D. Vitamin D deficiency has been linked with hypertension, myocardial infarction, and stroke, as well as other cardiovascular-related diseases such as diabetes, congestive heart failure, peripheral vascular disease, atherosclerosis, and endothelial dysfunction.[6]

India

In India, the prevalence of Vitamin D deficiency has been estimated to be 70–100% in the general population. This may be attributed to lack of legislation to fortify the food items such as dairy products with Vitamin D and Indian socioreligious and cultural practices which do not facilitate adequate sun exposure, thereby negating potential benefits of plentiful sunlight. Consequently, subclinical Vitamin D deficiency is highly prevalent in both urban and rural areas, and across all socioeconomic groups. More importantly, it is estimated that 79% of adult medical and paramedical personnel have Vitamin D deficiency.[5]

Risk Factors For Vitamin D Deficiency Include The Following [Figure 2]

- Inadequate sunlight exposure
- Dark skin tone
- Advanced age
- Being institutionalized
- Decreased dietary intake of Vitamin D
- Living in northern latitudes
- Malabsorption syndrome
- Drugs that accelerate metabolism of 1,25(OH)2D (e.g., phenytoin, phenobarbital, and corticosteroids)
- Chronic kidney disease
- Liver dysfunction
- Obesity.

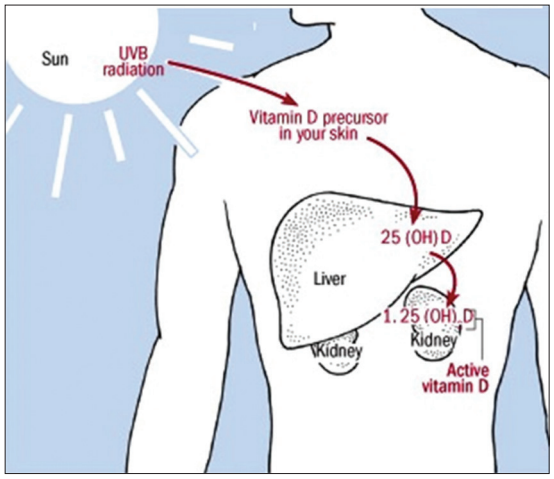

Figure 1: Effects of sunlight on Vitamin D metabolism

Figure 2: Risk factors of Vitamin D deficiency

Pathophysiology Of Vitamin D And Its Effects On Cardiac Health

Vitamin D is critical in mineral homeostasis and skeletal health and plays a regulatory role in non-skeletal tissues.[7]

The heart muscle being a skeletal muscle has receptors for Vitamin D.[8] Hence, perhaps, it's no surprise that studies are finding Vitamin D deficiency may be linked to heart disease. The health professional follow-up study checked the Vitamin D blood levels in nearly 50,000 men who were healthy and then followed them for 10 years. They found that men who were deficient in Vitamin D were twice as likely to have a heart attack as men who had adequate levels of Vitamin D.[9]

Other studies have found that low Vitamin D levels were associated with higher risk of heart failure, sudden cardiac death, stroke, overall CVD, and cardiovascular death.[10-13] There is evidence that Vitamin D plays a key role in controlling blood pressure and preventing artery damage, and this may explain these findings.[14] Still, more research is needed before we can be confident of these benefits.

The first evidence that Vitamin D deficiency could lead to CVD was derived from patients with end-stage renal disease (ESRD). The damaged kidney fails to convert 25(OH) D to 1, 25(OH) 2D, resulting in a severe deficiency. Thyroidism develops resulting in elevated levels of circulating parathyroid hormone.[6]

Experimental data suggest that 1, 25(OH) (2)D affects cardiac muscle directly, controls parathyroid hormone secretion, regulates the RAAS, and modulates the immune system. Because of these biologic effects, Vitamin D deficiency has been associated with hypertension, several types of vascular diseases, and heart failure.[15]

The endocrine phenomena

The sustained stress on myocardial tissue leads to cardiac hypertrophy, myocardial fibrosis, and heart failure [Figure 2]. Administration of activated forms of Vitamin D (1,25 [OH]2D or analogs) to patients with ESRD and secondary hyperparathyroidism has resulted in decreased the left ventricular hypertrophy, along with a decrease in cardiovascular mortality. Since elevations in parathyroid hormone levels are thought to be a primary cause of cardiac dysfunction, therapies aimed at decreasing circulating parathyroid hormone concentrations are often used in these patients. It indicates that Vitamin D metabolites not only regulate parathyroid hormone secretion but also may have direct effects on cardiac function.[15]

Neurohormonal phenomena

The direct physiologic consequences of the absence of the Vitamin D receptor on cardiac function have been evaluated in several animal studies. In these studies, Vitamin D receptor knockout mice were compared with their wild-type littermates at 12 months of life. Histologic staining of cardiac tissue showed highly significant cellular hypertrophy in the Vitamin D receptor knockout mice, and the heart-body weight ratio was significantly larger in Vitamin D receptor knockout mice compared with that in wild-type mice. In addition to cardiac hypertrophy, cardiac fibrosis and collagen deposition were observed exclusively in the Vitamin D receptor knockout mice. Overall, these findings suggest an important role for the Vitamin D receptor in cardiac physiology [Figure 3].

There is evidence that Vitamin D indirectly affects cardiac functioning because of its role as a negative regulator of the RAAS [Figure 3]. One group of authors found that Vitamin D receptor knockout mice had more than a 3-fold increase in renin messenger RNA (mRNA) expression and more than a 2.5-fold increase in plasma angiotensin II levels. Since 1, 25(OH) 2D regulates parathyroid hormone secretion and maintains calcium homeostasis, the homeostasis of calcium is a vital component for healthy cardiac system.[15]

The immune regulatory phenomena

Immune system activation has been associated with atherosclerotic and valvular calcification and plays a role in plaque instability and rupture. Overproduction of inflammatory cytokines contributes to the development and progression of heart failure. Experimental studies have suggested that Vitamin D plays a role in the regulation of several important inflammatory and anti-inflammatory cytokines. In one study, a reduction of inflammatory cytokine (interleukin [IL]-6 and tumor necrosis factor [TNF]) production was observed when activated monocytes were exposed to 1, 25(OH) 2D. Conversely, in another study, the production of the anti-inflammatory cytokine IL-10 significantly increased when dendritic cells were exposed to 1, 25(OH) 2D compared with control cells not so exposed. The aggregate data from these investigational studies suggest that the hormonal form of Vitamin D plays an active and direct role in the regulation of several immune modulatory cytokines, resulting in an overall downregulation of inflammation.[15]

Treatment Of CVDs With Vitamin D

A rat model was used to demonstrate a relationship between cardiovascular homeostasis and Vitamin D status more than 20 years ago. These animal studies established a connection

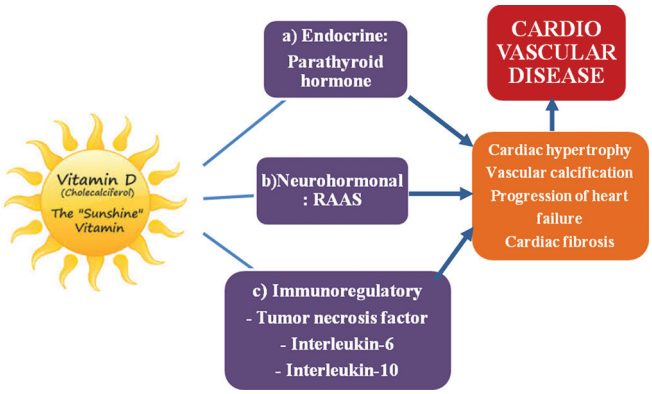

Figure 3: Cardiovascular pathophysiology of vitamin deficiency. RAAS: Renin-angiotensin-aldosterone system

Table 1: Relationship between Vitamin D and health

25-hydroxyvitamin D concentration (ng/ml)	Status	Health consequence
<15	Severe deficiency	Can lead to rickets and severe bone disease
<20	Deficient	Inadequate bone health and osteoporosis
20–30	Relative insufficiency	Recently considered inadequate for optimal health status
> 30	Adequate stores	Optimal health status
> 150	Toxicity	Hypercalcemia, hyperphosphatemia, and renal impairment

between Vitamin D deficiency and cardiovascular dysfunction, including cardiac hypertrophy, fibrosis, hypertension, as well as alterations of serum calcium, parathyroid hormone, and renin levels. The studies supported a role for Vitamin D in maintaining cardiovascular homeostasis through both a direct action of 1, 25(OH) 2D on cardiomyocytes Vitamin D receptor and indirect actions on circulating hormones and calcium [Table 1].[6]

Researchers at the Intermountain Medical Centre Heart Institute in Salt Lake City have studied the effects of Vitamin D on the heart for several years; they evaluated the impact of Vitamin D levels on more than 230,000 patients. The patients were split up into four groups (<15 ng/ml, 15–29, 30–44, and ≥45) and were followed for the next 3 years for major adverse cardiac events including death, coronary artery disease, heart attacks, stroke, and incidents of heart or kidney failure. It was found that benefit to the heart will likely occur among patients whose Vitamin D level is <15 ng/ml. Later, they performed a randomized trial with patients whose levels are <15 and provided supplements for one but not the other to see what the long-term benefits for combatting heart problems. They found that patients are fine from a heart stand point and may need no further treatment, if their Vitamin D level is anywhere >15 ng/ml.[16]

The treatment with Vitamin D lowered blood pressure in patients with hypertension and modified the cytokine profile in patients with heart failure. Measurement of serum 25-hydroxyvitamin D concentration usually provides the best assessment of an individual's Vitamin D status. Serum levels <20 ng/ml represent Vitamin D deficiency, and levels >30 ng/ml are considered optimal. Although the observational data linking Vitamin D status to CVD appear robust, Vitamin D supplementation is not recommended as routine treatment for heart disease until definitive prospective, randomized trials can be carried out to assess its effects. However, such supplementation is often appropriate for other reasons and may be beneficial to cardiovascular health in certain patients.[15]

Conclusion

From the above discussion, we conclude that the Vitamin D has an important role in preventing cardiovascular diseases. Few randomized, controlled trials have evaluated the effect of Vitamin D replacement on cardiovascular outcomes, and the results have been inconclusive or contradictory. Carefully designed randomized, controlled trials are essential to evaluate the role of Vitamin D supplementation in reducing CVD.

It is important to conduct more studies to assess the real benefits induced by Vitamin D supplementation in cardiovascular patients and, in particular, in patients with heart failure and such a supplementation might represent a new low-cost therapeutic approach to improving quality of life.

References

1. MedlinePlus - Health Information from the National Library of Medicine. Medlineplus.gov; 2018. Available from: https://www.medlineplus.gov/. [Last cited on 2018 Jul 19].
2. Vitamin D and Disease Prevention. Hormone Health Network; 2018. Available from: https://www.hormone.org/~/media/Hormone/Files/Scientific%20Statements/SSVitaminD_2014. [Last cited on 2018 Jun 19].
3. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
4. Dattilo G, Casale M, Avventuroso E, Laganà P. Vitamin D dietary supplementation: Relationship with chronic heart failure. J AOAC Int 2018;101:939-41.
5. G R, Gupta A. Vitamin D deficiency in India: Prevalence, causalities and interventions. Nutrients 2014;6:729-75.
6. McGreevy C, Williams D. New insights about vitamin D and cardiovascular disease: A narrative review. Ann Intern Med 2011;155:820-6.
7. Nemerovski CW, Dorsch MP, Simpson RU, Bone HG, Aaronson KD, Bleske BE, *et al.* Vitamin D and cardiovascular disease. Pharmacotherapy 2009;29:691-708.
8. Rai V, Agrawal DK. Role of vitamin D in cardiovascular diseases. Endocrinol Metab Clin North Am 2017;46:1039-59.
9. Giovannucci E. Expanding roles of vitamin D. J Clin Endocrinol Metab 2009;94:418-20.
10. Giovannucci E, Liu Y, Hollis BW, Rimm EB 25-hydroxyvitamin D and risk of myocardial infarction in men: A prospective study. Arch Intern Med 2008;168:1174-80.
11. Pilz S, März W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, *et al.* Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab 2008;93:3927-35.
12. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, *et al.* Low vitamin D levels predict stroke in patients referred to coronary angiography. Stroke 2008;39:2611-3.
13. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, *et al.* Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503-11.
14. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, *et al.* Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med 2008;168:1340-9.
15. Holick MF. The vitamin D deficiency pandemic and consequences for nonskeletal health: Mechanisms of action. Mol Aspects Med 2008;29:361-8.
16. Intermountain Medical Center. Specific Vitamin D Levels Linked to Heart Problems. Science Daily; 2018. Retrieved from: http://www.sciencedaily.com/releases/2015/11/151109160556.htm. [Last accessed on 2015 Nov 9].

How to cite this article: Manjunatha HR. Vitamin D: A New Therapy for Prevention of Cardiovascular Disease. Int J Nurs Med Invest. 2018;03(3):99-102