REVIEW ARTICLE

Coronary artery disease and its association with Vitamin D deficiency

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ABSTRACT

Coronary artery disease (CAD) has become the latest scourge of humankind and referred to in this article as CAD, is the end result of the accumulation of atheromatous plaques within the walls of coronary arteries that supply the myocardium, a process also known as atherosclerosis and manifests mostly in the form of chronic stable angina or acute coronary syndrome. Vitamin D has attracted considerable interest recently due to its role in a number of extraskeletal disease processes including multiple sclerosis, malignancies, diabetes mellitus, and CAD. It is also known as sunshine vitamin due to its production in the body following exposure to ultraviolet rays, and it is a unique vitamin as it acts like a hormone with its receptor present in a wide range of tissues including endothelium, which is the important mediator of atherosclerosis and subsequent CAD. A large number of studies conducted in the past have provided the basic scientific framework and this article attempts to explore the role of Vitamin D deficiency in the pathogenesis of CAD and stresses the need for further research to fill up gap in our knowledge.

Key Words: Atherosclerosis, coronary artery disease, Vitamin D deficiency

INTRODUCTION

Coronary artery disease (CAD) is one of the major life-threatening diseases and has emerged as a major cause of death worldwide. Like many high-income countries during the last century, low- and middle-income countries are witnessing an alarming increase in the rates of CAD and this change is accelerating. CAD affects people at younger ages in low- and middle-income countries like India compared to high-income countries, thereby having a greater economic impact on low- and middle-income countries except Sub-Saharan African countries where it leads causes of death in those older than 45 years. The situation in India is especially gruesome with limited resources for setting up an effective screening program and evaluation or management for that matter and statistics projecting India to be the leader in the world for CAD-associated mortality in the next 15–20 years.[1] CAD manifests clinically in a predictable manner in the form of stable angina characterized by the mismatch in myocardium oxygen requirement and supply; however, the dramatic and unpredictable manifestation in the form of acute coronary syndrome is responsible for most of the mortalities caused by the disease. Besides, there are traditional risk factors for CAD such as tobacco, diet, physical inactivity, dyslipidemia, obesity, hypertension, and diabetes mellitus. There has been increasing evidence from animal and human studies to suggest that Vitamin D deficiency may be an important risk factor in the

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pathogenesis of CAD.[2,3] Given the gravity of the problem posed by CAD, it is imperative to conduct an extensive research to determine the novel risk factors which can be potential therapeutic targets for the treatment and prevention of the disease.

VITAMIN D

Vitamin D is one of the fat-soluble vitamins also known as sunshine vitamin due to its synthesis in the body following exposure to ultraviolet (UV) B rays, however it is unique in a way that it acts as a prohormone and mediates its functions by binding to a member of nuclear receptor superfamily, the Vitamin D receptor. Vitamin D can also be obtained through the diet which is referred to as Vitamin D_2 (ergocalciferol) whereas the form of vitamin that is endogenously synthesized by UV-B rays and also occurs in small quantity in the food of animal origin, which is referred to as Vitamin D_3 (cholecalciferol). Both of these forms are activated equally efficiently by the hydroxylases in humans, of which the first step of 25 hydroxylation is mediated by cytochrome P-450 like enzyme present in mitochondria and microsomes of hepatocytes. The level of 25(OH)D is not tightly regulated, therefore it represents the most accurate measure of Vitamin D level in the circulation, also its long half-life of 3 weeks[4] makes it the preferred form to be measured to determine the Vitamin D level of an individual.[5] The second hydroxylation reaction is mediated by 25-hydroxyvitamin D-1-hydroxylase which is a tightly regulated cytochrome P-450 like mixed function oxidase expressed in the proximal convoluted tubule cells of the kidney and leads to the formation of active hormone. Major inducers of this enzyme are parathyroid hormone (PTH) and hypophosphatemia, and major inhibitors of this enzyme are calcium, fibroblast growth factor 23, and the enzyme's product $1,25(OH)_2D$. Small amount of 1 hydroxylase was also found in keratinocyte, trophoblast of placenta, and macrophages associated with granulomata and lymphomas.[6] Since the level of $1,25(OH)_2D$ is under considerable influence of various regulatory factors and also due to its short half-life of 24 h,[7] it is not the true representative of Vitamin D level of the body. For supplementation, Vitamin D_3 should be preferred[8] as it is the most natural form, less toxic than Vitamin D_2 as its high receptor binding prevents excessive rise in blood level, more potent, stable, and mostly utilized form in clinical trials. Vitamin D_3 is also more effective at raising and maintaining the Vitamin D level. The major dietary sources of Vitamin D are fortified dairy products. Other dietary sources include egg yolks, fish oils, and fortified cereal products.

DEFINING VITAMIN D DEFICIENCY

There is considerable controversy and no consensus has been reached yet on the level of Vitamin D, which reflects the optimum state of health. Vitamin D status has been categorized into various types[9] by most of the experts [Table 1].

Current International Osteoporosis Foundation guidelines[10] define Vitamin D insufficiency as a level of 25(OH)D <50 nmol/L and deficiency as a level <25 nmol/L. A recent position statement from International Osteoporosis Foundation recommends that target level of Vitamin D should be 75 nmol/L as this level has been found to achieve maximal suppression of PTH hormone.

VITAMIN D DEFICIENCY: A GLOBAL PROBLEM

Vitamin D deficiency is widely prevalent across the globe and the problem is more severe in elderly patients[11] and nursing home residents.[12] Apart from the countries of Northern Hemisphere where Vitamin D deficiency is quite prevalent due to decreased sunshine[13,14] and contrary to the popular belief, Asian countries such as India are not immune to Vitamin D deficiency despite abundance of sunshine,[15] where factors such as cultural avoidance of skin exposure, increased skin pigmentation, crowded houses with limited sunlight exposure, and frequent pregnancies coupled with calcium deficiency may be responsible.

ROLE OF VITAMIN D DEFICIENCY IN THE PATHOGENESIS OF CORONARY ARTERY DISEASE

Vitamin D deficiency is involved in the pathogenesis of CAD at several steps due the fact that its receptor is present in various tissues and may be involved in the regulation of blood pressure (BP) (through renin–angiotensin system) and modulation of cell growth and proliferation including vascular smooth muscle cells and cardiomyocytes.

Cardiac function

There is accumulating evidence that low Vitamin D status adversely affects cardiac function. A receptor to the active metabolite 1,25-dihyroxyvitamin D_3 has been identified in the rat heart.[16] Vitamin D deficiency results in increased cardiac contractility, hypertrophy, and fibrosis in rats.[17,18] Matrix metalloproteinases (MMPs) may be involved in the pathophysiology arising from Vitamin D deficiency.[19,20] Framingham study proved that men with elevated plasma

Table 1: Vitamin D status of population based on serum levels

Serum 25-hydroxyvitamin D (ng/ml)	Vitamin D status
<10	Severe deficiency
10-20	Deficiency
21-29	Insufficiency
>30	Sufficiency
>150	Toxicity

levels of MMP-9 had increased left ventricular end-diastolic dimensions and wall thickness[21] with consequent increased risk of mortality and morbidity from cardiovascular (CV) diseases.[22] Vitamin D supplementation lowers blood levels of MMP-9 and MMP-2. Similarly, reversal of cardiomegaly by calcium and Vitamin D supplementation has been described in children with rickets[23] and in an adult with congestive heart failure.[24]

Hypertension

A receptor to 1,25-dihydroxyvitamin D has been described in smooth muscle tissue, supporting a potential role for Vitamin D in the regulation of smooth muscle contraction and BP.[25] Observational studies of dietary Vitamin D showed that both measured 25(OH)D and estimated 25(OH)D were inversely associated with risk of incident hypertension in both men and women.[26] This finding is supported by a recent publication from NHANES III which found that serum 25(OH)D was inversely associated with both systolic BP and pulse pressure.[27] Several mechanisms can explain the preventive effects of Vitamin D against hypertension:

1. Direct suppression of the renin–angiotensin system as $1,25(OH)_2D$ functions as a negative endocrine regulator of renin gene expression *in vivo*[28]
2. Decreases intimal thickening of blood vessels by inhibiting the accumulation of extracellular matrix within the inner vessel wall through its inhibitory effect on MMP[20]
3. Decreases arterial stiffness by causing upregulation of nitric oxide synthesis which is synthesized by endothelium.[29,30]

A recently conducted double-blinded randomized controlled trial also proved that Vitamin D supplementation decreases arterial stiffness by reducing mean pulse wave velocity from 5.41 m/s (standard deviation [SD], 0.73) at baseline to 5.33 m/s (SD: 0.79) ($P = 0.031$).[31]

Atherosclerosis

Vitamin D inhibits the uptake of cholesterol by macrophages and in case of Vitamin D deficiency, cholesterol uptake by macrophages is promoted and these cholesterol-laden macrophages, also known as foam cells, deposit in the endothelium forming atheromatous plaque and promote atherosclerosis.[32] Vitamin D deficiency has also been associated with decreased levels of high-density lipoprotein and apolipoprotein A-1, which promotes atherosclerosis.[33]

Inflammatory factors

It is now well established that inflammatory factors are centrally involved in the process of atherosclerosis and plaque rupture.[34] Blood levels of inflammatory markers, such as C-reactive protein and the cytokine interleukin-6 (IL-6), predict a subsequent risk of CV disease.[35] Positive associations have been reported between IL-6 and insulin resistance.[36] The latter is a risk factor for type 2 diabetes, which is itself inversely related to Vitamin D status[37] and predisposes to CAD.

Hyperparathyroidism

Chronic Vitamin D deficiency causes secondary hyperparathyroidism, which in turn may mediate many of the detrimental CV effects of inadequate Vitamin D levels. The threshold for the elevation of PTH is a 25(OH)D level of 30 ng/ml. Further decreases in serum 25(OH)D levels will result in proportionally higher PTH levels to maintain serum and total body calcium. An increased PTH level is associated with an increase in both BP[38] and myocardial contractility, which eventually lead to hypertrophy, apoptosis, and fibrosis of both the left ventricle and vascular medial smooth muscle.[39]

Diabetes and metabolic syndrome

Vitamin D deficiency has been associated with diabetes mellitus[40] and metabolic syndrome due to its receptor-mediated effects leading to increased insulin resistance and pancreatic beta cell dysfunction. These are the independent risk factors for CAD.

AREA OF UNCERTAINTY

Despite abundant evidence of the involvement of Vitamin D deficiency in the pathogenesis of CAD, very few well-conducted randomized controlled trials address this issue and also several randomized controlled trials where Vitamin D supplementation was evaluated in high-risk population in relation to improvement in CV outcome have failed to provide any conclusive results.[41,42] A systematic review conducted by Pittas *et al*.[43] of longitudinal studies examining the relationship of Vitamin D supplementation on cardiometabolic outcomes (type 2 diabetes, hypertension, and CV disease) concluded that association of Vitamin D status and cardiometabolic outcome is uncertain. Out of the 13 trials, they examined four trials which showed that Vitamin D supplementation does not influence the cardiometabolic outcomes. Similarly, a recent randomized controlled trial examining the effect of Vitamin D supplementation on 24 h systolic ambulatory BP monitoring values and CV risk factors in hypertensive patients concluded that there is no significant effect of Vitamin D supplementation on BP and other CV risk factors; rather it increases triglyceride levels in the experimental group.[44]

CONCLUSION

Vitamin D, a fat-soluble vitamin, has well-established endocrine system and by virtue of its receptor which

is present in myriad of tissues, it modulates cellular processes. Vitamin D deficiency is widely prevalent across the globe and appears to be involved in the pathogenesis of CAD at several steps. However, on a background of conflicting studies, the authors conclude that large-scale well-randomized controlled trials are needed to prove that Vitamin D supplementation improves the CV outcome before guidelines for Vitamin D measurement and its supplementation for risk stratification and prevention of CAD can be recommended.

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Conflicts of interest

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