REVIEW ARTICLE

HYPOVITAMINOSIS D: AN EMERGING NEW RISK FACTOR OF CORONARY ARTERY DISEASE

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ABSTRACT

Coronary artery disease (CAD) is one of the most important medical and public health problem and leading cause of death throughout the world. It is often premature in onset, rapidly progressive and angiographically more severe. The underlying pathophysiology is poorly understood. Genetic predisposition high prevalence of metabolic syndrome and other conventional risk factors play important role. Some new risk factors inclauding hypovitaminosis D, chronic arsenicosis, air pollution may play unique role. Among the new predictors of coronary artery disease, the focus has been shifted to vitamin D. Because hypovitaminosis D may play unique role in the pathogenesis of coronary artery disease, promoting accelerated atherosclerosis and subsequent cardiovascular events. Recent researches have highlighted vitamin D deficiency as an emerging risk factor for coronary artery disease, in addition to conventional and genetic risk factors. In this review, we will provide an overview on the currently available evidence supporting the relationship between hypovitaminosis D and coronary artery disease and its possible underlying mechanisms.

Key words: Hypovitaminosis D, Coronary artery disease, Atherosclerosis

Introduction

Coronary artery disease is one of the wost commonest public health problems throughout the world. Now it is considered as the leading cause of mortality and morbidity worldwide[1]. About 110 million people were affected by CAD in 2015 and resulted in 8.9 million deaths[2]. In the last few years the prevalence of vitamin D deficiency has been increased, among all ethnicities and populations[3]. Almost one billion people in the world suffer from vitamin D deficiency or insufficiency[4]. According to the National Health and Nutrition Examination survey 2005 to 2006, the prevalence of vitamin D levels <20 ng/mL was 41.6% in US adults. Suboptimal vitamin D level is very common among the women of many Southeast Asian countries like India and Pakistan despite adequate sunshine[5]. In Bangladesh serum 25(OH) D<37.7 nmol/L was seen in 50% of those in low income groups compared to 38% of high income groups median. Lactating women have higher prevalence of hypovitaminosis D in Bangladesh. Majority of Bangladeshi women wear covered style of dress (like Burkha and Sari) which may negatively affect the Vitamin D status of many women in this part of the world[6].

Bangladeshi population are unduly prone to develop CAD, which is often premature in onset, rapidly progressive and angiographically more

is poorly understood. The 'classic' risk factors like diabetes mellitus, hypertension, dyslipidemia, obesity, smoking and excessive alcohol consumption undoubtedly play vital role. Poor dietary habits, excess intake of saturated and trans fat, high salt intake, and lack of physical activity also play important role. Beside conventional risk factors and genetic predisposition, some emerging new risk factors like hypovitaminosis D, arsenic contamination, particulate matter air pollution may play unique role[8].

There is a parhcular role of vitamin D on calcium homeostasis and it has beneficial anti-inflammatory and anti-atherosclerotic effects. Pathogenesis of metabolic syndrome and insulin resistance also associated with hypovitaminosis D. Recent researches have highlighted vitamin D deficiency as an arising risk factor for coronary artery disease. Pathogenesis of coronary artery disease (CAD), accelerated atherosclerosis and subsequent cardiovascular events occur due to hypovitaminosis D[9].

While the exact relationship between hypovitaminosis D and increased cardiovascular risk has not yet been established, multiple hypotheses have been postulated. Vitamin D receptors (VDRs) have been distributed widely throughout the cardiovascular system[10]. Vitamin D acts via this receptors and reduces cardiac ischemia-reperfusion injury and reactive oxygen species[11]. It also shows favourable effects on inflammation and thrombosis. Atherosclerosis, chronic inflammation, endothelial dysfunction and arterial calcification occur due to hypovitaminosis D. Moreover, vitamin D insufficiency may activate the renin angiotensin system and increase insulin resistance, endothelial dysfunction, inflammation, platelet function, and blood pressure (BP) regulation[12]. An experimental trial revealed that vitamin D supplementation suppressed vascular inflammation by inhibiting the Nuclear Factor-κB (NF-κB) pathways and decreasing the process of atherosclerosis and hence subsequent coronary artery disease (CAD)[13].

Vitamin D deficiency is an emerging risk factor for coronary artery disease now a days. Although the prevalence of coronary artery diseases among South Asian people is rising, studies with angiographically documented coronary artery diseases and its association with Vitamin D level are very limited. These studies revealed conflicting results also. In this review, we will provide an overview on the currently available evidence supporting the relationship between hypovitaminosis D and coronary artery disease, its prognostic relevance, and the possible underlying mechanisms.

Vitamin D metabolism

Vitamin D is a fat soluble vitamin, known as sunshine vitamin because it is synthesized in the body following exposure to ultraviolet (UV) B rays. It acts as a prohormone by binding to the vitamin D receptor which is a member of nuclear receptor super family[14].

There are two major forms of vitamin D: vitamin D2 and vitamin D3. Vitamin D2 is found in plants and fortified foods. Vitamin D3 is obtained from aliments or through the conversion of dehydrocholesterol in the skin[15]. Cutaneous synthesis of vitamin D3 from sunlight exposure is the main source of vitamin D in humans. Vitamin D undergoes hydroxylation in the liver to 25-hydroxyvitamin D which is the main circulating form in the blood. This 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. It has long

half life of 3 weeks that makes it the preferred form to be measured to determine the Vitamin D level of an individual. The 25-hydroxyvitamin D is again hydroxylated into 1,25-dihydroxyvitamin D in the kidney. This second hydroxylation reaction is mediated by 25 hydroxyvitamin D1 hydroxylase which is a tightly regulated cytochrome P-450 like mixed function oxidase-expressed in the proximal convoluted tubule cells of the kidney. Parathyroid hormone (PTH) and hypophosphatemia are the major inducers of this enzyme. The final activated form, 1,25(OH) vitamin D3 reaches the nucleus where it binds to vitamin D receptor (VDR) and regulates the transcription and function of more than 200 genes[16]. Vitamin D receptors (VDR) are usually expressed in enterocytes, osteoblasts, parathyroid glands, distal renal tubule cells and regulate calcium homeostasis. Recent investigations have also demonstrated their presence on endothelial cells, lymphocytes, macrophages, smooth vascular muscle cells, beta-pancreatic cells and cardiomyocytes, through which vitamin D3 mediates cardiovascular effects[17].

Vitamin D is involved in glycemic control, lipid metabolism, regulate insulin secretion and sensitivity, explaining the association between vitamin D deficiency and metabolic syndrome. The antihypertensive properties of vitamin D include suppression of the renin-angiotensin-aldosterone system. It has reno-protective effects, having direct effects on endothelial cells, inhibit the growth of vascular smooth muscle cells, prevent secondary hyperparathyroidism and it has also beneficial effects on cardiovascular risk factors. Vitamin D deficiency was associated in some studies with the number of affected coronary arteries, post infarction complications, inflammatory cytokines and cardiac remodeling in patients with myocardial infarction[18].

The main causes of vitamin D deficiency are listed in Table I[19]

Table I: Most relevant factors for Vitamin D deficiency

Age
Increased distance from the equator
Winter season
Darkly pigmented skin
Institutionalized/housebound
Sunscreens and cover-up clothing
Air pollution
Smoking
Obesity
Physical inactivity
Malabsorption
Chronic kidney disease
Liver disease
Drugs (glucocorticoids, antirejection medications, human immunodeficiency virus medications, antiepileptic drugs etc.)

Definition of Vitamin D Deficiency

Most experts define vitamin D deficiency as a calcidiol level of <20 ng/ml and insufficiency as 21-29 ng/mL. Vitamin D is sufficient if >30 ng/mL and vitamin D intoxication is considered if >150 ng/mL (Table II)[20].

Table II: Status of Vitamin D based on serum levels

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

Vitamin D and cardiovascular diseases

Several cardiovascular risk factors are associated with vitamin D deficiency. Vitamin D deficiency can increase the production of reactive oxygen species and G protein RhoA, resulting in inhibition of the pathways necessary for intracellular glucose transporter. As a result insulin resistance and metabolic syndrome occurred.[21] In addition, vitamin D could contribute to their beneficial effects on cardiovascular health by its direct effects upon smooth muscle calcification and proliferation. In the Inter 99 study of 6784 individuals, high vitamin D level was associated with a favorable lipid profile and lower incidence of metabolic syndrome[22].

According to an analysis of NHANES III 1988-1994, vitamin D deficiency was associated with cardiovascular disease (CVD) and CVD risk factors, such as diabetes mellitus (DM), obesity, and hypertriglyceridemia[23]. A prospective nested case-control study was conducted between 1993 and 1999 on 18,225 US men (Health Professionals Follow-Up Study) and this study revealed that vitamin D deficiency was associated with a higher risk of myocardial infarction in comparison with sufficient 25(OH)D after multivariate adjustment[24]. Kim and colleagues have found a high prevalence of hypovitaminosis D in individuals with cardiovascular diseases, like coronary heart disease and heart failure, after controlling for age, race and gender, using data from NHANES 2001-2004.

Additional prospective study of the Integrated Intermountain Healthcare system database of 41,504 patients has shown an association between vitamin D deficiency and an increase in the prevalence of DM, HTN, hyperlipidemia, and peripheral vascular disease (PVD) ($P < 0.0001$) as well as with incident death, heart failure, coronary artery disease/myocardial infarction, stroke and their composite[26]. Also, low serum 25(OH)D was identified as casually associated with increased risk for CVD on the basis of Hill's criteria for causality in a biological system. In a meta-analysis of 19 prospective studies in 65,994 participants, Wang et al. have demonstrated a linear and inverse association between circulating vitamin D level and risk of cardiovascular diseases[27].

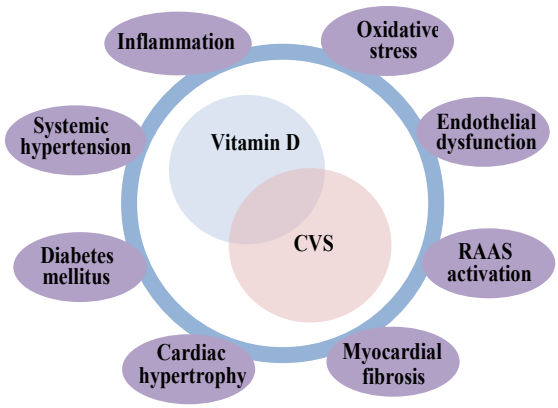

Fig 1. Major mechanisms underlying the association between vitamin D and cardio-vascular disease. RAAS= renin-angiotensin-aldosterone system, CVS= cardiovascular system

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 to its receptor present in various tissue. Vitamin D is involved in the regulation of blood pressure (BP) through renin-angiotensin system and modulates the cell growth and proliferation including vascular smooth muscle cells and cardiomyocytes[28].

Some studies revealed that hypovitaminosis D adversely affects cardiac function. A receptor to 1,25 dihyroxyvitamin D3 has been identified in the rat heart. Vitamin D deficiency results in increased cardiac contractility, hypertrophy, and

fibrosis in rats. Matrix metalloproteinases (MMPs) may be involved in the pathophysiology arising from Vitamin D deficiency[29]. Framingham study proved that men with elevated plasma levels of MMP 9 had increased left ventricular end diastolic dimensions and wall thickness, with consequent increased risk of mortality and morbidity from cardiovascular diseases[30]. 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, and in an adult with congestive heart failure[31].

A receptor to 1,25 dihydroxy vitamin D has been described in smooth muscle tissue, supporting a potential role for Vitamin D in the regulation of smooth muscle contraction and BP. 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[32]. 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[33]. Several mechanisms can explain the preventive effects of Vitamin D against hypertension:

1. Direct suppression of the renin–angiotensin system as 1,25(OH)2 D functions as a negative endocrine regulator of renin gene expression in vivo[34].
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[35].
3. Decreases arterial stiffness by causing upregulation of nitric oxide synthesis which is synthesized by endothelium[36]. 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)37.

Vitamin D inhibits the uptake of cholesterol by macrophages and cholesterol uptake by macrophages is promoted due to vitamin D deficiency. These cholesterol laden macrophages, also known as foam cells, deposit in the endothelium forming atheromatous plaque and promote atherosclerosis. Vitamin D deficiency has also been associated with decreased levels of high density lipoprotein and apolipoprotein Al, which promotes atherosclerosis[38].

It is now well established that inflammatory factors are centrally involved in the process of atherosclerosis and plaque rupture. Blood levels of inflammatory markers, such as C-reactive protein and the cytokine interleukin 6 (LL-6), predict a subsequent risk of cardiovascular diseases. Positive associations have been reported between IL 6 and insulin resistance[39]. Chronic vitamin D deficiency causes secondary hyperparathyroidism, which in turn may mediate many of the detrimental cardiovascular 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 and myocardial contractility, which eventually lead to hypertrophy, apoptosis, and fibrosis of both the left ventricle and vascular medial smooth muscle[40].

Vitamin D deficiency has been associated with diabetes mellitus 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[41].

Vitamin D deficiency and coronary artery disease

The association of vitamin D deficiency with coronary artery diseases (CADs) have been investigated in many studies. In 1978, a Danish study found that low vitamin D levels were significantly associated with angina and myocardial infarction[42]. In a multicenter US cohort study evaluating patients admitted with acute coronary syndrome (ACS), about 95% of patients were found to have low vitamin D levels[43]. In a study conducted by Dziedzic et al[44], low vitamin D levels were observed in patients with myocardial infarction history. In a case-control study (n=240), Roy et al. reported that severe vitamin D deficiency was associated with increased risk of acute myocardial infarction after adjusting for risk factors[45]. Similar findings were reported from Health Professionals Follow-up Study which included 18,225 participants. In this study, at 10-year follow-up, participants with normal vitamin D level had about half the risk of myocardial infarction[46]. In a large prospective study (n=10,170), low vitamin D levels were found to be associated with increased risk of ischemic heart disease, myocardial infarction, and early death during 9 years of follow-up. Additionally, in a meta-analysis of 18 studies, low vitamin D levels were found to have an increased risk of ischemic heart disease and early death[47].

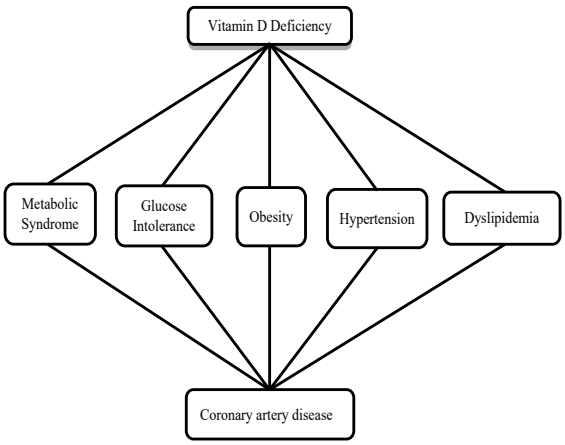

Fig 2. The relationship between vitamin D and risk factors of coronary artery disease

Conclusion

Several studies support the link between vitamin D status and cardiovascular diseases and highlighted that vitamin D deficiency as an emerging risk factor for coronary artery disease, in addition to conventional and genetic risk factors. Vitamin D exerts its cardiovascular effects by reducing the activity of the renin angiotensin-aldosterone system, lowering blood pressure values. It has anti-inflammatory, antiproliferative, antihypertrophic, antifibrotic, antidiabetic, and antithrombotic effects and beneficial modulation of classical cardiovascular risk factors.

Vitamin D deficiency is treatable and supplementation is inexpensive. Vitamin D could be combined with antihypertensive agents in order to control blood pressure as a simple, inexpensive, and important prophylactic method in order to prevent cardiovascular mortality and morbidity.

Large randomized controlled trials should be conducted to confirm the promising findings of observational studies, considering endothelial function, arterial stiffness, and patients undergoing percutaneous coronary interventions. Guidelines are needed in order to establish optimal vitamin D level and intake, to maintain a healthy vitamin D status in patients with cardiovascular diseases. Estimation of serum vitamin D level, genotyping for vitamin D receptor variants, serum calcium and phosphates level and bone mineral density are mandatory in evaluating patients with cardiovascular disease. The benefits of screening and treating vitamin D could reduced cardiovascular morbidity and mortality.

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