

Low levels of Vitamin D an emerging risk for cardiovascular diseases: A review

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ISSN: 1658-3639

PUBLISHER: Qassim University

ABSTRACT

Sunlight is regarded among greatest gifts that are presented in abundance to the human beings from the God. Sunlight is also a rich source of Vitamin D (Vit D) that prevents us from numerous ailments such as autoimmune disorders, various types of cancer, and the above all cardiovascular diseases (CVD). Evident from recent research that Vit D deficiency may be the cause for hypertension, cardiac autonomic imbalance, vascular endothelial dysfunction, metabolic syndrome, and even diabetes. Concurrently, many studies present research outcomes that are contradictory to earlier results and also raised a concern not for general public but also among their treating physicians. The sole focus of this review is to systematically present the available research data and critically evaluate the link between Vit D deficiency and development of risk factors for CVD.

Keywords: Cardiovascular disease, hypertension, Vitamin D

Introduction

Modern research revealed new horizon and function of vitamin D (Vit D) beyond its proven role in the treatment of rickets. Vit D deficiency is believed to be associated with multiple sclerosis, respiratory disorders, many types of cancers, and cardiovascular diseases (CVD).¹⁻³ Worldwide CVDs are regarded as number one cause of death. Modern researchers are keenly investigating to reveal the possible relevance of Vit D deficiency with CVDs.⁴

Vit D (a fat-soluble substance) can be obtained either by direct exposure to sunlight (ultraviolet B, 290-320 nm) or through dietary sources and supplements that is absorbed through the intestine.⁵ Under normal conditions, levels of Vit D remains within target range 20-60 ng/mL a person is in the state of Vit D deficiency if blood level is ≤ 20 ng/mL.⁶ The world is in the state of hypovitaminosis D primarily due to less exposure to sunlight. Other factors that also influence Vit D level are age, gender, ethnicity, skin color, season, clothing, and housing.^{7,8} It is estimated that 1 billion people worldwide suffer from Vit D deficiency,⁹ more than 40% of U.S. and European,¹⁰ 82% Italian,¹¹ 70% Korean,¹² and around 70% Malaysian population is experiencing hypovitaminosis D.¹³ Regardless of abundant sunshine Saudi Arabia has one of the lowest Vit D levels in the region particularly in females as proven by literature.¹⁴ Normal levels of Vit D in different regions of Saudi Arabia comprised, 47% in Riyadh,¹⁵ 32.2% in Qasim,¹⁶ and around 60 to 70% in a population of the Eastern region.¹⁷

Low Vit D levels found to be associated with various CVDs including congestive heart failure, coronary heart disease, and

stroke.^{18,19} Although exact mechanism and linkage have not been established but the association between the two has been proven by many studies some are in favor while other deny any such link. According to National Health and Examination survey report, the prevalence of CVDs is considerably higher in Vit D deficient subjects.²⁰ Among 1432 adults enrolled in the ORISCAV-LUX study found higher incidence of CVDs in Vit D deficient subjects.²¹

Few clinical trials have also been documented to determine the association of Vit D supplementation with CVDs. Schrotten *et al.* observe improvement in 101 stable heart failure patients after 6 weeks 2000 IU supplementation of Vit D.²² VINDICATE study group observed significant improvement in cardiac function in 229 patients of chronic heart failure after consumption of 4000 IU of Vit D in 1 year.²³ The PRIMO trial and OPERA trial also found improvement in cardiac functions after consumption of Vit D supplementation.^{24,25} Contradictory to above trials APCAPS study group did not find any clear evidence for an association between serum Vit D levels and CVDs.²⁶ They propose that the link between serum Vit D and CVD merely connected with lifestyle factors such as obesity and physical inactivity.

The present review is designed to examine the clinical evidence for low Vit D level in the pathogenesis of CVDs and to explore possible underline mechanism.

Methods

The electronic databases Pub Med and Google Scholar were searched using the terms “cardiovascular system,”

“cardiovascular risks,” “hypertension,” “coronary artery disease,” “atrial fibrillation,” “heart failure,” and “cardiac autonomic disturbance” paired with Vit D deficiency.

The following inclusion criteria were used: The study should have evaluated the relationship between Vit D and cardiovascular risk, should be in English language and published between 2007 and 2017. Studies with the animal model were only incorporated to elucidate the pathogenesis of Vit D deficiency in CVD.

Studies were excluded if they have incomplete data, review articles and letter to editor.

Out of 2526 articles published in English, 110 were identified as meeting our criteria and were reviewed. Of those 110, 81 were employed in the final version of this article.

Discussion

Although the precise mechanism that describes the influence of Vit D on the development of CVD is still in debate. It is believed that cardiocytes, vascular endothelial cells, inflammatory cytokines, and the renin angiotensin aldosterone system receive some positive effects of Vit D.³⁵⁻³⁷ It might be possible that alteration in Vit D level leads to CVD risk factors such as hypertension, obesity, diabetes mellitus, and metabolic syndrome probably due to the lack positive feedbacks from this vitamin (Table 1).

Vit D and cardiac autonomic effects

Data suggest that Vit D deficiency directly influences CVD and related mortality risk by arbitrating autonomic nervous system (ANS) activity.³⁸⁻⁴⁰ It is believed that ANS nuclei of mid-brain and brainstem have abundant Vit D receptors and plays noncalcium related role in regulating the ANS functions.⁴⁰

Vit D supplementation has found to normalize the relaxant and hyperpolarizing effects of acetylcholine in spontaneously hypertensive rat arteries, suggesting a mechanism by which Vit D supplementation in humans might help to maintain cardiac autonomic tone.⁴¹ In another study from Vit D receptor knockout mice showed fast contraction and relaxation postulate that Vit D directly affected contractility of cardiac myocyte.³⁸ Employing National Health and Nutrition Examination Survey (NHANES) data of 27,153 individuals, Scragg *et al.* reported that subjects with Vit D levels less than 10 ng/mL show significantly higher mean heart rate, systolic blood pressure, and rate-pressure product (cardiac autonomic work), compared to those with Vit D levels 25 to 35 ng/mL or more.³⁸ Hansen *et al.* also found decline in cardiac autonomic response in their Diabetic patients with low Vit D levels.²⁷

Vit D and hypertension

The effect of low levels of Vit D on blood pressure has been observed in numerous clinical trials among various study populations and at different doses.^{28,36,42,43} A recent meta-analysis by Beveridge *et al.* on the blood pressure lowering effects of Vit D supplementation found no effect of treatment across various patient subgroups, and therefore advised against using Vit D for the treatment of hypertension.³⁶ Another analysis with same results revealed that higher blood pressures were associated with high parathyroid hormone levels, but not with low Vit D levels.³⁸

On the other hand, a study evaluating four large prospective cohorts found that serum Vit D levels were indeed inversely associated with the risk of hypertension.⁴³ Cross-sectional analyses of data from NHANES-III also shows that low Vit D levels are associated with higher blood pressures.⁴⁴ Underlying mechanism might be negative association between Vit D concentrations and plasma renin activity in hypertensive patients as short course of Vit D supplementation resulted in a significant decrease in plasma renin activity and maintain blood pressure in such patients.⁴⁰ It was also found that the active hormone of Vit D, 1,25D, has been shown to decrease the expression of the renin gene through a Vit D receptor-dependent mechanism, thus decreasing both renin and angiotensin II concentrations.^{45,46}

Vit D and vascular endothelial dysfunction

Numerous laboratory studies have demonstrated that Vit D deficiency impaired vascular endothelial functions by influencing vascular stiffness, oxidative stress, proinflammatory responses, platelet aggregation, and nitric oxide syntheses.⁴⁷⁻⁴⁹ All of these factors might lead to atherosclerosis and CVD. There is strong evidence to support the role of inflammation in the pathogenesis of endothelial dysfunction. Literature survey established that Vit D suppresses inflammation through several pathways, including the inhibition of prostaglandin and cyclooxygenase 2 pathways, and up-regulation of the anti-inflammatory cytokines.⁵⁰⁻⁵² Chen *et al.* found, among 348 patients referred for elective coronary angiography showed low Vit D levels and high inflammatory markers.⁵³ Sogomonion *et al.* also observed higher coronary artery calcium scores and impaired endothelial functions in their newly diagnosed coronary artery disease patients.²⁹

Studies have shown that higher mean platelet volume is associated with both arterial and venous diseases such as coronary artery disease, venous thromboembolism, and stroke.^{54,55} While Vit D supplementation not only restores immune function but also works by decreasing the expression of the various adhesion molecules including those released by platelets for normal endothelial functions in such subjects.⁵⁶

Vit D and atrial fibrillation

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, affecting around 2% of the population with high

prevalence in the old age.⁵⁷ Mechanism of AF development involved structural and electrical remodeling of Atria including hypertrophy, fibrosis or even apoptosis.⁵⁸ In various case-control studies researchers found significantly lower serum Vit D level in the AF group than in the non-AF group, possible mechanism may be apparently raised levels of high-sensitivity C-reactive protein, and larger left atrial diameter along with activation of renin-angiotensin system in the AF subjects.^{32,59} Study from Chinese patients with low (<20 ng/mL) Vit D levels have two-fold higher incidence of AF than in control group.⁶⁰ While contradicting to above, Rotterdam Study rejects association of low Vit D level with AF.⁶¹

Vit D and metabolic syndrome

Increase incidence of Vit D deficiency in industrialized countries may be caused by sedentary lifestyle, consumption of junk food, less outdoor activities, and reduced sunlight exposure. All of these factors work by reducing endogenous Vit D manufacturing.⁶² As a consequence of this, researchers found decreased Vit D levels and increased body fat and weight in such populations make them prone to obesity-related diseases including CVD.

Serum concentration of 25-hydroxyvitamin D, an indicator of Vit D status, found to be low in many studies of obese adults and children.⁶³⁻⁶⁵ patients with Vit D deficiencies had higher body mass index (BMI) but also the percentage of body fat.⁶⁶ The explanation for this association has been the sequestration of Vit D in the subcutaneous fatty tissues of the body and as a consequence to this reduced bioavailability.

Vit D insufficiency associated with obesity is likely to be very significant, as compensatory hyperparathyroidism has been observed in such obese children and adolescents. It has been found that parathyroid hormone levels were positively, and Vit D concentration was negatively, related to weight status in prepubertal children.⁶⁷ Since this variation became normal after weight loss; the authors concluded that these changes were consequences rather than main causes of obesity.

Vit D and diabetes

It has become increasingly clear that Vit D deficiency is an important risk factor for the development of insulin resistance and that potentially leads to several adverse clinical and biochemical outcomes leading to type 2 diabetes and CVD, as proven by many studies.⁶⁸⁻⁷⁰ The research by Lee *et al.* showed that low serum Vit D in children and adolescents was strongly associated with increased risk for fasting hyperglycemia, hypertension, and metabolic syndrome in Korean population.³³ These researchers suggest that hypovitaminosis D subjects had decreased insulin sensitivity compared to Vit D-sufficient subjects. Moreover, serum Vit D levels were inversely correlated with HbA1c independently of body adiposity, implying a higher risk for developing impaired glucose

metabolism in subjects with Vit D deficiency. Another research trial among type 2 diabetic patients from Saudi setup revealed, 12-month Vit D supplementation of 2000 IU per day causing improvement of several cardiometabolic parameters including systolic blood pressure, plasma insulin, and insulin resistance.⁶⁸

There are several possible mechanisms by which Vit D deficiency may affect insulin sensitivity. It is postulated that decreased Vit D concentrations cause elevation of parathyroid hormone levels, which in turn affects insulin sensitivity by regulating the intracellular free calcium concentrations in target cells.⁶⁹ Another hypothesis is that Vit D plays an important role in insulin action by stimulating the expression of insulin receptors, enhancing insulin responsiveness for the transport of glucose and also by directly acting on pancreatic b-cell secretion of insulin.³³ In a comparative study conducted in Turkey found, lower 25(OH)D levels, higher waist circumferences, fat masses, fasting insulin levels, and HbA1C, and PTH levels in obese group.⁷⁰ They suggested that subjects with Vit D deficiency not only displayed impaired b-cell function causing impaired glucose tolerance but also were at increased risk of developing insulin resistance and metabolic syndrome compared to Vit D-sufficient adults.

Could Vit D be a part of CVD treatment regime?

Vit D supplements easily available in market as “over the counter drugs” and commonly prescribed by orthopedics and pediatrician for their role in calcium homeostasis but few incidence of Vit D overdose and toxicity also been reported.⁷¹ As per literature survey it was found that Vit D has fundamental role in development of various CVDs by affecting potential mechanisms involved in development of disease. Vit D supplementations can be successfully used to reduce morbidity and mortality related with CVD. But one should be cautious about the harmful effects of this fat-soluble vitamin, for this purpose physician should be aware of signs and symptoms of its intoxication.⁷²

Another cost-effective and harmless supply of Vit D is heliotherapy; it was observed that the magnitude of increase in serum Vit D levels following heliotherapy was directly correlated to the magnitude of increased cardiac vagal activity.^{73,74} As people living at high altitudes have lower rate of CVD and incidence of CVD are generally higher in winter than in summer; this is true for countries with cold winters or even in countries with encroaching summer to avoid heat stroke as proven by many studies.⁷⁵⁻⁷⁷

Conclusions

Vit D deficiency is very common in Saudi Arabia and worldwide. Several studies have suggested that low levels of Vit D predispose individuals to increased risk of CVD. Although few researchers did not accept this thought and believed that other demographic, lifestyle, social, and metabolic factors as

Table 1: Cardiovascular manifestations of Vitamin D deficiency and possible mechanisms in various populations

Author	Year published	Number of participants	Cardiovascular manifestation	Possible mechanism
Hansen <i>et al.</i> ²⁷	2017	113	Cardiac autonomic disturbance	Cardio protective vagal tone decline
Kim <i>et al.</i> ²⁸	2015	20440	Hypertension	Activation of Renin angiotensin aldosterone system
Sogomonion <i>et al.</i> ²⁹	2016	9399	Coronary artery disease	Higher coronary artery calcium scores, impaired endothelial function#
Roy <i>et al.</i> ¹⁸	2015	240	Myocardial infarction	Obesity and high cholesterol, impaired endothelial function
Rapson <i>et al.</i> ³⁰	2017	11789	Peripheral artery disease	Atherosclerosis
Leung <i>et al.</i> ³¹	2017	3458	Stroke	High blood pressure
Ozcan <i>et al.</i> ³²	2015	227	Atrial fibrillation	Renin-angiotensin aldosterone system activation
Lee <i>et al.</i> ³³	2015	2880	Metabolic syndrome and diabetes	Insulin resistance
Lutsey <i>et al.</i> ³⁴	2015	12215	Heart failure	Presence of the rs7041 G allele in white race people

possible confounders, and their interrelationship may interfere to get a definite conclusion. Another possible explanation for this disparity is lack of follow-up in these trials, the difference in the normal level of Vit D creating dissimilarities regarding adequate intake levels suggested by related organizations. It was also found that there is currently no universal guideline available for screening and treatment of Vit D insufficiency. Furthermore, a detailed randomized clinical trial is suggested to optimize clinical recommendations and use of Vit D supplements in high-risk and healthy populations. It may be wise to consider low Vit D levels as a marker of an unhealthy lifestyle, requiring extra endeavor at modifying individuals' way of life, i.e., more sunlight exposure, weight control, physical activity, healthy diet, smoking cessation, and all factors absolutely influencing both Vit D status and cardiovascular risk.

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