Review Article

Role of Vitamin D in Cardiovascular Disease

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Abstract

Background: According to many studies, vitamin D deficiency has been linked to cardiovascular diseases (CV). Other than maintaining skeletal health, vitamin D has been shown to decrease the risk of developing CV disease such as hypertension, coronary artery disease (CAD) and thromboembolism.

Materials and Methods: To perform a comprehensive review of the current literature on vitamin D and CV disease, we searched the online database, including PUBMED, Scopus, and Google Scholar until data inception January 2016. The search term included "vitamin D", "blood pressure", "hypertension", "coronary artery disease "and "thrombosis". We only included human studies that were published in English.

Results: A majority of data indicate that there is no relationship between vitamin D and hypertension, but the association of vitamin D with thrombosis is yet to be determined. Vitamin D is a fair predictor of adverse outcomes in coronary artery disease (CAD), which highlights it for future studies.

Conclusion: According to research, there is a high prevalence of vitamin D deficiency among patients with CV diseases, which needs to be diagnosed and treated.

Keywords: Cardiovascular disease, coronary heart disease, hypertension, thromboembolism, vitamin D

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Introduction

Cardiovascular disease is one of the leading causes of death around the world.[1] Vitamin D deficiency has been reported among patients with myocardial infarction,[2] stroke[3] and peripheral arterial disease.[4] Essential key elements for vitamin D function and metabolism e.g. vitamin D receptor and the enzymes 1-alpha-hydroxylase, and 24-hydroxylase are present in the heart.[5] Vitamin D could be involved in the pathogenesis of cardiovascular disease by exerting regulatory roles in vascular inflammation,-[6]calcification,[7] and renin-angiotensin aldosterone system.[8]

Method

To perform a systematic review of the current literature on vitamin D and CV disease, we searched the online database, including PUBMED, Scopus, and Google Scholar until data inception January 2016. The search term included "vitamin D", "blood pressure", "hypertension", "coronary artery disease "and "thrombosis". We only included human studies that were published in English.

Vitamin D and Blood Pressure

The first category of clinical trials on this subject is conducted on healthy individuals. In a clinical trial by Scragg, et al. 200,000 IU of vitamin D or placebo for two months and then 100,000 IU per month was given to 161 healthy individuals without vitamin D deficiency. According to results, no beneficial antihypertensive effect was observed between intervention and control group after 18 months of follow up.[9] In the second clinical trial among healthy South Asian women with vitamin D deficiency, administration of a single dose of 100,000 IU of oral vitamin D_3 or placebo didn't improve blood pressure after 8 weeks.[10] Interestingly, an experiment carried out by Liu, et al. demonstrated that exposing skin to UV radiation among 24 healthy volunteers resulted in a lowered blood pressure by rising nitrate concentrations.[11]

The DAYLIGHT trial, which was one of the largest sampled trials on vitamin D, included 534 patients with vitamin D deficiency and systolic pressure of 120 – 159. Patients were 18 – 50 years old and were randomly assigned to receive either 4000 IU/d or 400 IU/d of oral vitamin D3. After 6 months of follow up, there was no significant reduction in blood pressure.[12] On the other hand, a similar study among hypertensive individuals (blood pressure ≥ 140/90) who received 100,000 IU of oral vitamin D_3 or placebo every two months for 6 months yielded the same results.[13] The VitDISH trial also included patients with vitamin D deficiency and systolic hypertension. All patients were 70 years and older. Supplementation with 100,000 IU of oral cholecalciferol or matching placebo was carried out every 3 months. The follow up time was 1 year. As a result, this supplementation was unable to improve vascular health.[14] Additionally, according to Styrian Vitamin D Hypertension Trial, supplementation of 200 individuals with hypertension and vitamin D deficiency with 2800 IU vitamin D/day or placebo had no effect on blood pressure and cardiovascular risk factors.[15]

Vitamin D and coronary artery disease

Endothelial dysfunction is one of the primary markers of arterial

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stiffness[16] and atherosclerosis.[17] On the other hand, there is a high prevalence of vitamin D deficiency among patients with CAD[18,19] and low vitamin D level is potentially a predictor of adverse outcomes in CAD.[20–22] Even though, low concentration of vitamin D receptor in coronary arteries is associated with a larger atherosclerotic plaque size.[23]

According to a recent study, among 1811 female patients undergoing angiography, vitamin D deficiency has more significant effects on severity of CAD.[24] Another population based study among elderly Chinese population reported that serum levels of 25(OH)D were associated with CAD.[25] Additionally, a similar study indicated the association between vitamin D level and severity of CAD.[26] An interesting experiment by Dozio, et al. demonstrated that among patients with CAD, the level of serum vitamin D was inversely associated with expression of pro-inflammatory cytokines such as TNF-α and IL-6. However, there was no link between vitamin D and epicardial adipose tissue thickness.[27]

To find out if vitamin D supplementation has any beneficial effect on improving CAD, a randomized placebo-controlled trial was conducted among 90 patients with CAD. A daily amount of 0.5 μg vitamin D_3 was supplemented to these patients and severity of CAD was evaluated using the SYNTAX score. Results indicated that compared to the control group, the vitamin D receiving group had a significant fall in SYNTAX score, lower concentrations of high sensitivity C-reactive protein, and decreased activity of the rennin angiotensin system.[28]According to the DIABHYCAR trial, genetic variations in vitamin D receptor genes can be associated with an increased risk of CAD among diabetic patients.[29]

Furthermore, level of vitamin D could be a predictor of coronary collateral circulation, which is a protection against ischemia in chronic coronary total occlusion.[30]

Vitamin D and thrombosis

The possible relationship between vitamin D and thrombosis emerged when a seasonal variation was observed in the risk of venous thromboembolism. Several studies have been conducted regarding this subject, but data from human studies are less conclusive than in vitro or animal studies.

Generally, vitamin D can shift the hemostatic system towards fibrinolysis and decrease coagulation.[31] Vitamin D status is inversely related to tissue plasminogen activator (TPA) and tissue factor, which shift hemostasis system towards coagulation.[32–34] Vitamin D can decrease the vascular resistance and increase the expression of IL-10.[35] IL-10 is an important anti-inflammatory molecule and plays a key role in the regulation of thrombus-associated inflammation and thrombosis.[36]

In an attempt to find a relationship between vitamin D and venous thromboembolism (VTE), during a cohort study by Lindquist, et al. 29518 women were followed up for 11 years and the amount of sun exposure and risk of developing VTE were assessed. Risk of VTE was 30% lower in women who had an adequate sun exposure compared to those who did not. On the other hand, the risk for developing VTE was the highest in winter and the lowest in summer.[37]

Recent research demonstrates that there is a positive relationship between vitamin D serum level and amount of tissue factor pathway inhibitor.[31] In addition, vitamin D is able to decrease tissue factor expression, therefore ameliorate the inflammation, which contributes to a prothrombotic state.[38]

In a case control study among 82 patients with lower extremity DVT and matching control group, the level of 25(OH)D was significantly lower in patient with DVT.[39] Interestingly, in another research, adding calcitriol (active form of vitamin D) to angiotensin converting enzyme inhibitors and angiotensin receptor blockers, was successful in decreasing thrombosis to up to 65% among renal transplant recipients.[40] Entezari-Maleki, et al.[41] found no association between 25(OH)D levels and P-selectin as a marker of thrombosis and hs-CRP among patients with established venous thromboembolism.[42] A randomized clinical trial showed that 300,000 IU vitamin D_3 supplementation could not decrease P-selectin and hs-CRP levels in patients with thromboembolism.[43] Results from the Women's Health Initiative Randomized Controlled Trial, a major clinical trial on 36282 postmenopausal women was carried out during a mean follow up period of 7 years. Participants were supplemented with 1000 mg of calcium and 400 IU vitamin D. According to results, the risk of non-idiopathic DVT was similar between intervention and control group, but the risk of idiopathic DVT was lower in supplement receiving group.

Discussion

Clinical trials about the effect of vitamin D on blood pressure can be sorted into two categories. In the first category, subjects were healthy however, in the second group participants were hypertensive. Among reviewed articles, most of them used high dose vitamin D as supplementation, which could be a slight source of error because the digestive system might not be able to absorb all supplements comparing to daily low dose. In the DAYLIGHT trial, 6 months of follow up was not effective in reducing blood pressure.[12] The possible reason for this discrepancy could be the insufficiency of 6 months follow up or the lack of calcium supplementation together with vitamin D. Other clinical trials had a follow up period ≤1 year, and a small sample size. Therefore, further studies with a sufficient dose of vitamin D, and follow up period, among hypertensive participants are needed. Judgment among trials seems to be more rational, if baseline characteristics such as age and race were homogeneous. Results of Women's Health Initiative Randomized Controlled Trial also reported unfavorable results on vitamin D and hypertension. This large sampled clinical trial used only 400 IU of vitamin D supplementation every day while this amount is particularly not sufficient for 50 – 79 year old women, especially according to new guidelines.[44] On the other hand, office blood pressure measurement was mostly used instead of the more sophisticated assessment of blood pressure e.g. ambulatory blood pressure.

The present literature about vitamin D and coronary artery disease is almost promising as most of the data consider vitamin D deficiency as a marker of adverse outcome in CAD. Additionally, the prevalence of vitamin D deficiency is quite high among CAD patients and adding vitamin D as an adjuvant therapy can yield better clinical outcomes.

In the case of thrombosis, large studies such as those comprising 6538 British white subjects[45] and the observational study by Lindquist, et al. have reported a reverse relationship between vitamin D levels and thrombosis.[37] The relationship between vitamin D deficiency and thromboembolism needs to be further investigated among large populations with a dominant vitamin D deficiency such as women. It shouldn't be forgotten that the primary target would be resolving vitamin D deficiency and bringing its levels from 'low' to 'normal', and not to 'high' because bringing it from

low to high does not necessarily lower risk of thromboembolism.[46] Furthermore, serum level of 25(OH)D should be measured several times with more frequencies to ensure that the desired serum level is achieved.

In conclusion, the present data about the role of vitamin D in cardiovascular system seems to be promising; however the important prospect is the high prevalence of vitamin D deficiency all over the world. It is important to increase people's education regarding diagnosis, treatment, and prevention of vitamin D deficiency. On the other hand, food sources of this pivotal nutrient are not as abundant as other vitamins and a normal diet may not fulfill daily recommended amounts of vitamin D . Therefore, adequate exposure to sunlight and using vitamin D supplementations would be a good choice. Furthermore, fortifying food such as milk with vitamin D could be another option for countries. Perhaps the most pleasant advantage of using vitamin D in the treatment of cardiovascular disease would be its low cost and fewer side effects. For now, we cannot determine the main role of vitamin D deficiency as a risk factor of hypertension or thrombosis. However, vitamin D's role in improving coronary artery cannot be neglected and physicians should prevent and treat vitamin D deficiency among these patients. Therefore, it is highly recommended to health care professionals to measure vitamin D levels and treat vitamin D deficiency.

Conflict of interest: *None*

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