International Journal of Advances in Medicine
Patil DV et al. Int J Adv Med. 2020 Sep;7(9):1441-1445
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: http://dx.doi.org/10.18203/2349-3933.ijam20203612

Review Article

Association between serum vitamin D3 status and essential hypertension: a review

Divya V. Patil*, Tarun Kumar Dutta

Department of Medicine, Mahatma Gandhi Medical College and Research Institute, Puducherry, India

Received: 08 July 2020
Accepted: 04 August 2020

***Correspondence:**
Dr. Divya V. Patil,
E-mail: ashwinrao2404@gmail.com

ABSTRACT

The fat-soluble vitamin D is synthesized when the ultraviolet rays strike the surface of skin. The relationship between cardiovascular disease mainly arterial hypertension with low vitamin D levels is supported by literature. It has been observed that arterial hypertension has been associated with low levels of vitamin D. Obesity and reduced sunlight exposure are factors associated with lower serum vitamin D levels. Isolated systolic hypertension has been associated with vitamin D deficiency and insufficiency. Protective mechanism implicated in lowering the blood pressure is the suppression of renin angiotensin aldosterone pathway with optimal vitamin D levels. But randomised controlled trials are necessary to clarify whether vitamin D supplementation is beneficial in the control of blood pressure; as the results of many studies do not consistently favor the association of low vitamin D levels with hypertension.

Keywords: Hypertension, Renin angiotensin aldosterone system, Sunlight exposure, Vitamin D

INTRODUCTION

Hypertension (HTN) is the most prevalent non-communicable disease accounts for about 30%-40% of the hospital visits for the population aged between 45-65 years.[1] About 50% of the population through the world is affected by deficiency of vitamin D.[2] Vitamin D is produced endogenously and is fat soluble .When ultraviolet rays from the sunlight strike the skin and trigger vitamin D synthesis. Vitamin D is biologically inert and it undergoes to two hydroxylation in the body to undergo activation. Vitamin D is a precursor for several biochemical reactions in the body and mainly involved in calcium-phosphorus metabolism and mineralization of the bones. The renin-angiotension system acting unopposed with angiotensin induces stiffening of arteries and causes endothelial dysfunction.[2] This leads to hypertension and predicts the risk of cardiovascular disorders. Additionally, from landmark studies suggest that vitamin D is involved in the pathogenesis of various cardiovascular diseases including hypertension.[3,4]

This narrative review insights into vitamin D its mechanism of absorption, risk groups for deficiency, effects of hypertension on the body and mechanism of vitamin D causing hypertension and finally regarding the supplementation of vitamin D in subjects with essential hypertension.

OVERVIEW OF VITAMIN D

Vitamin D is a fat-soluble vitamin produced endogenously. Vitamin D unlike other vitamins does not require daily supplementation; sunlight exposure replenishes the body stores. Vitamin D deficiency can lead to skeletal deformities like soft and brittle bones in children and adults which can lead to lethargy and frequent fractures.

Vitamin D deficiency is commonly observed when people are subjected to inadequate sunlight exposure, poor dietary habits, bedridden individuals and extremes of age.

MECHANISM OF ABSORPTION OF VITAMIN D

Vitamin D is synthesized in the skin by the ultraviolet B rays induced conversion of 7-dehydrocholesterol to vitamin D. 7-dehydrocholesterol undergoes two hydroxylations for activation to form the active component of Vitamin D. In the kidneys, calcidiol is converted by renal or extrarenal 1α-hydroxylase into 1,25-dihydroxyvitamin D (calcitriol). Calcitriol circulates at lower concentrations when compared to calcidiol, its affinity to the vitamin D receptors is more.

Vitamin D levels depends on various factors but mainly the synthesis from sunlight and its action on the vitamin D receptors by the various signaling pathways. Various tissues in our body express the receptors for the vitamin D which are heart, brain and blood vessels. Many factors influence the absorption of the vitamin D in the gastrointestinal system. There are various proteins synthesized by the hepatocytes in the liver which help in the transport vitamin d to its target of requirement.

The role of the parathyroid hormone in the activation of vitamin D is via the increase in the 1- alpha hydroxylase enzyme which converts vitamin D into its active form.

VITAMIN D AND ITS EFFECTS ON THE ORGAN SYSTEMS

Vitamin D plays a crucial role in the gastrointestinal system causing increased production of calbindin which helps in phosphorus and calcium absorption from the intestine. Within the Skeletal system, it causes bone resorption by increasing the number of osteoclasts and synthesis of osteocalcin which is a potent inhibitor of mineralization of the bones. Adequate amount of vitamin D in the muscles, causes increased uptake of the amino acids and hence deficiency can cause myopathy.

Vitamin D receptors and enzyme activators are located in the brain which helps in the development new brain cells. It also plays a significant role in maintaining the immune system as vitamin D receptors are located on all immune cells, macrophages, T cells and B cells.

CLASSIFICATION OF SERUM VITAMIN D3 LEVELS

Serum vitamin D3 levels is classified into 3 categories; vitamin d deficiency when the serum levels are <20 ng/ml (<50 nmol/l), vitamin d insufficiency if serum levels are 20-29.9 ng/ml (50-74 nmol/l) and vitamin D sufficiency if serum levels are ≥30 ng/ml (≥75 nmol/l).[5]

VITAMIN D DEFICIENCY RISK GROUPS

Certain groups lack the innate ability to maintain sufficient levels of vitamin D.

Extremes of age: hypovitaminosis D in the mother is associated with hypovitaminosis D in the infant. Old people who spend a longer duration of the day indoors and are less exposed to sunlight. Inadequate exposure to sunlight fails to replenishes the calciferol stocks in the body. In chronic kidney disease, there is a deficiency of this enzyme and hence there is a shortage of calcitriol. Vitamin D synthesis by sunlight exposure is sequestered by the subcutaneous adipose tissue as vitamin D is a fat-soluble vitamin and decreased gut absorption in condition like inflammatory bowel diseases, celiac sprue, irritable bowel disease and certain liver diseases decreases absorption of fats and vitamin D.[6]

DEFINITION OF HYPERTENSION

According to the Joint National Committee seventh report classified essential hypertension.[7]

1. Normal: systolic BP <120 and diastolic BP <80.
2. Prehypertension: SBP 120-139 or DBP 80-89.
3. Stage 1 hypertension: SBP 140-159 or DBP 90-99.
4. Stage 2 hypertension: SBP ≥160 or DBP ≥100.

(All values are expressed in mm of Hg)

EFFECTS OF HYPERTENSION ON THE BODY

Cardiovascular system under hypertension may depict as High blood pressure, myocardial infarction, heart failure and sudden cardiac death associated with hypertension. High blood pressure is associated intracerebral haemorrhage and abdominal aortic aneurysm. Renal dysfunction and hypertension which are a vicious cycle and one may lead to exacerbation of the other. Benign and malignant nephrosclerosis are the patterns histopathological patterns. Essential hypertension is associated with non-alcoholic fatty liver disease, resistance to insulin and metabolic syndrome on the hepatic front. Essential hypertension in the brain is associated with cognitive decline, cerebral amyloid angiopathy, hypertensive encephalopathy. Many visual changes can also be attributed to essential hypertension such as hypertensive retinopathy, optic neuropathy and choroidopathy. Capillaries in the choroid show necrosis in chorioretinopathy.

Vascular diseases such as dissection of the aorta is a hypertensive emergency. The mainstay of management is beta blocker and calcium channel blocker. Other peripheral vascular diseases causing. Intermittent claudication is also seen in essential hypertensives. Pulse pressure correlates with peripheral vascular disease. Patients with peripheral vascular disease and hypertension are at risk of myocardial infarction and stroke.

VITAMIN D DEFICIENCY AND ESSENTIAL HYPERTENSION-MECHANISM AND VITAMIN D AND RENIN ANGIOTENSIN ALDOSTERONE ACTIVITY

Studies by totally different teams in each animals and humans have provided robust proof that vitamin D decreases renin angiotensin aldosterone activity. It is postulated that lower vitamin D levels were associated with higher blood pressure. Vitamin D receptor-null mice were found to have ventricular hypertrophy and high blood pressure which was implicated to the elevated renin and plasma angiotensin II levels. Furthermore, in animal models it was found that administration of vitamin D caused decrease in the plasma renin activity. Hence it is interesting to note that RAAS was suppressed by vitamin D3. Additionally, the vascular tone is affected by the presence of the vitamin d receptors on the endothelium.8

Furthermore, numerous authors have studied the link between vitamin d3 levels and plasma rennin levels, in the population ranging from 100-3000 subjects. Additionally, the studies concluded that decrease in plasma vitamin D3 levels with proportional rise in plasma rennin concentration, lead to elevation of angiotensin II levels resulting in the subsequent, enhanced sympathetic activity, increased aldosterone activity causing sodium and water retention and arteriolar vasoconstriction which so result in elevation of blood pressure. In addition to the above mechanism, variation within the genetics Fok1polymorphism, increased the activity of renin.[9]

ENDOTHELIAL DYSFUNCTION

It has been observed from numerous studies that production of the endothelial nitric oxide synthase is raised by vitamin D, which causes increase in nitric oxide that modulates the vascular tone.[10,11] In vitro studies also have provided robust proof for the same.[12] Hence, the data suggest that the interplay between both or one of the above mechanisms that is activation of RAAS and endothelial dysfunction lead to hypertension in vitamin D deficient individuals. In a study carried out among healthcare workers with a sample base ranging from (7000 to 70,000) subjects over 20 years of age, it was concluded that serum vitamin D levels had an inverse correlation with blood pressure.[13-16] Meta-analysis performed by multiple authors found a causal relationship between serum vitamin D levels and hypertension events.[17-20]

VITAMIN D SUPPLEMENTATION IN ESSENTIAL HYPERTENSION

Randomized control trails were performed to test the hypothesis. These trails supplemented vitamin D in different formulations either orally or via intramuscular route, with doses ranging from 0.5 µg alpha-calcidiol daily to 100,000 IU orally 2 months apart in the former, significant reduction in both systolic and diastolic blood pressure but no reduction in blood pressure in the latter hence concluded that interval between the dosages should be less.[17,18] Moreover large RCT with daily supplementation 2000IU and 5 year follow-up concluded that there was a major reduction in the blood pressure.[19] In addition, several studies deduced that daily oral administration of vitamin D3 was much more effective than the same dose of vitamin D3 intramuscular.[20,21] However a contrasting proof was found in one study that concluded that intramuscular supplementation of vitamin D 100,000 IU showed no result in reduction of BP however considerably reduced the arterial stiffness, the pathogenesis of that is unidentified ,and hence there's a need for additional studies to substantiate this proof.[22] Contrasting evidence was found in trials with a duration of approximately 1 year off supplementation showed no effect on blood pressure, but incidentally noted that participants with vitamin D deficiency had lowered central blood pressure.[23,24] Another study in which the period of vitamin d supplementation was not effective even after 18 months.[25]

Various studies have investigated whether or not individuals who are supplemented with vitamin D show significant reduction in blood pressure, variety of studies have supported the hypothesis however alternative investigators haven't found such proof and therefore there a scope for analysis to prove the hypothesis.

VITAMIN D DEFICIENCY AND IMPLICATION OF DISEASE

Low levels of vitamin D associated with risk of developing multiple sclerosis. Vitamin D deficiency promotes the induction of regulatory T cells. Heart diseases can lead to essential hypertension and cardiomyopathy. Cardiomyopathy affects cardiomyocytes directly and vitamin D deficiency affects with Renin angiotensin aldosterone system. Vitamin D deficiency has also been associated with higher susceptibility mycobacterium tuberculosis. Vitamin D deficiency has also been associated with increased risk of type 2 diabetes. Higher maternal vitamin D is associated with decreased risk of asthma. Boosting regulatory T cell numbers inhibit pro-inflammatory cytokines.[26]

There might be some other factors that may impact the development of hypertension along with vitamin D deficiency, these factors needed to be excluded to prove a causal association between genesis of hypertension and vitamin D insufficiency and deficiency. This study highlights the prevalence of the isolated systolic hypertension amongst the vitamin D deficient population .and hence large randomized control trials with vitamin D supplementation are necessary to prove association between vitamin D deficiency and hypertension.[27]

CONCLUSION

The literature review on vitamin D and essential hypertension concluded that lower levels of serum vitamin D was correlated with higher blood pressure.

Further, more evidence is required to recommend extraneous supplementation of vitamin D3 in essential hypertension.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Patil DV, Dutta TK. Association between serum vitamin D3 status and essential hypertension: a review. Int J Adv Med 2020;7:1441-5.