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CALCIDIOL (25-HYDROXY VITAMIN D_3) -A HEALER OF CARDIOVASCULAR DISEASE

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ABSTRACT

Calcidiol also known as 25-hydroxy vitamin D_3 is a steroid prohormone synthesised in the liver. 25-hydroxy vitamin D_3 is major form of vitamin D in the circulation and the major storage form in the liver. In the renal tubules and in variety of tissues such as endothelial cells, vascular smooth muscle cells, and bone, the 25-hydroxy vitamin D_3 is further hydroxylated by 1-alpha-hydroxylase. The product is 1-alpha, 25 -dihydroxy vitamin D_3 or calcitriol, the most potent vitamin D metabolite. Several epidemiologic and clinical studies have suggested that low levels of vitamin D affect the cardiovascular system. Lower plasma vitamin D levels are correlated with a higher risk of incident hypertension. Prolonged vitamin D deficiency causes secondary hyperparathyroidism. An increased PTH is associated with myocardial contractility which leads to cardiac hypertrophy and calcification of heart valves. This article reviews the role of vitamin D in cardiovascular health; however, the cardioprotective hypothesis of vitamin D to date is inconclusive. This should be explored further whether cardiovascular disease is treatable with supplemental vitamin D.

KEYWORDS: *Calcidiol, calcitriol, cardiovascular disease, PTH, hyperparathyroidism,*

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INTRODUCTION

A growing body of evidence suggests that vitamin D deficiency is a global health problem that impacts varied acute and chronic diseases.[1] Vitamin D deficiency is widespread in individuals irrespective of their age, gender, race and geography.[2] Cardiovascular diseases (CVDs), including heart failure and coronary artery disease are a major cause of morbidity and mortality worldwide. There is accumulating epidemiological evidence from observational studies suggesting that CVDs are associated with vitamin D deficiency.[3-4] The primary circulating form of vitamin D is 25-hydroxy vitamin D_3 and that individuals with reduced 25-hydroxy vitamin D_3 levels will exhibit an excess of CVD risk factors.[5] Vitamin D receptors have a broad tissue distribution that includes vascular smooth muscles, endothelium, and cardiomyocytes have the ability to convert circulating 25-hydroxy vitamin D_3 to 1, 25-dihydroxy vitamin D_3 which supresses renin gene expression and control blood pressure.[3] Vitamin D is essential for utilization of dietary calcium. In a vitamin D–deficient state, the amount of calcium absorbed is inadequate to satisfy the body's calcium requirement resulting in an increase in the production and secretion of PTH.[6] PTH is a biomarker of 1, 25-dihydroxy vitamin D_3 is an independent cardiovascular risk factor that contributes to the progression of CVD.[7] Secondary hyperparathyroidism causes vascular calcification and recent studies indicate that high PTH is an important novel cardiovascular risk factor with strong predictive value for cardiovascular disease and mortality.[8-9]

RELATIONSHIP BETWEEN VITAMIN D AND RENIN-ANGIOTENSIN SYSTEM AND HYPERTENSION

The Renin-Angiotensin System is involved in the regulation of blood pressure. The primary hormone in these process is Angiotensin II an octapeptide made from angiotensinogen is a substrate for renin an enzyme produced in juxta-glomerular cells of the renal afferent arteriole. Angiotensin II increases blood pressure by causing vasoconstriction of the arterioles and is a very potent vasoactive substance.[10] Impairment in regulation of the Renin angiotensin system is involved in the pathogenesis of several hypertensive disorders. Approximately 15% of patients with essential hypertension have mild to moderate increases in plasma renin activity.[11] 1,25-dihydroxy vitamin D_3 inhibits renin expression in the juxtaglomerular apparatus which could influence systemic blood pressure.[12-13] The renin inhibitory activity of 1, 25-dihydroxy vitamin D_3 is mediated by the vitamin D receptor (VDR), a member of the nuclear receptor superfamily.[14] Vitamin D receptors have a broad tissue distribution that include smooth muscles, endothelium and cardiomyocytes.[3] Mice lacking the VDR or deficient in vitamin D developed hyperreninemia and high blood pressure. Vitamin D suppresses renin gene expression by targeting the cAMP signalling pathway, a major regulatory pathway involved in renin biosynthesis[14]. Forman *et al.,*[15] suggested that lower plasma 25-hydroxy vitamin D_3 levels are associated with a higher risk of incident hypertension that was independent of age, physical activity, race and other covariates. Forman *et al.,* also observed an independent inverse association between predicted 25-dihydroxyvitamin D levels and risk of incident hypertension.

LOW VITAMIN D TRIGGERS PTH-THE CULPRIT OF CARDIOVASCULAR DISEASE

Parathyroid hormone is an 84-aminoacid peptide is a principle regulator of calcium balance in physiological and pathological conditions associated with CVDs and plays a major physiological role in bone homeostasis[16]. Secondary hyperparathyroidism characterized by hypersecretion of PTH, is due to the decreased conversion of 25-hydroxy vitamin D_3 to 1, 25-dihydroxy vitamin D_3 in the diseased renal parenchyma which results in low calcium and the secondary release of PTH in a compensatory attempt to maintain normal extracellular fluid calcium levels.[10] High levels of calcium due to high parathyroid hormone levels have been found to induce arrhythmia.[17] The presence of PTH receptors within the cardiovascular system including vasculature and heart, suggests that secreted PTH may play a role in the pathophysiology of cardiovascular diseases beyond its role in mineral and bone metabolism[18]. Low vitamin D and increased PTH is associated with calcification of heart valves[19]. Flechtenmacher *et al.,*[20] suggested that vitamin D deficiency is involved in secondary hyperparathyroidism and parathyroid hormone has been proved to have unfavourable cardiovascular effects, promoting arterial hypertension, left ventricular hypertrophy and cardiac fibrosis. PTH is a main uremic toxin, and may be responsible for long-term outcomes that include severe vascular calcifications, alterations in heart structure and function and anaemia.[17] PTH excess increases intracellular calcium and increases protein synthesis and total cell mass within cardiac myocytes eventually lead to cardiac hypertrophy.[21] Furthermore, low vitamin D and increased PTH has a proinflammatory effect, stimulating the release of cytokines by vascular smooth muscle cells[22]. Agarwal *et al.,*[23] demonstrated that treatment of vitamin D deficiency could prevent secondary activation of the PTH gland, which in turn could aid in preventing pathologic cardiac remodelling. Mancuso *et al.,*[24] revealed that treatment with calcitriol results in reduction in plasma renin activity and myocardial hypertrophy.

LABORATORY MEASUREMENT OF VITAMIN D AND EPIDEMIOLOGICAL EVIDENCE

Biological active form of vitamin D is 1,25-dihydroxy vitamin D_3, however, the plasma concentration of 25-hydroxy vitamin D_3 is usually considered to be the best indicator of vitamin D status in individuals without kidney disease, because its concentration is closely associated with the amount of ingested or endogenously synthesized vitamin D.[3-25] Moreover, the plasm half-life

of 25-hydroxy vitamin D_3 is 2 to 3 weeks whereas the 1, 25- dihydroxy vitamin D_3 is 4 to 6 hours.[26] Two main analytical techniques usually employed in the laboratories to measure serum and plasma 25-hydroxy vitamin D_3 concentrations are chemical methods and competitive immunoassays. The chemical methods are based on chromatographic separation, followed by non-immunological direct detection. The competitive immunoassay methods are based on competitive protein binding and the examples are RIA, CLIA, enzyme immunoassay, electrochemiluminescence immunoassay, chemiluminescent microparticle immunoassay (CMIA). In a clinical laboratory, Abbott Architect 25-hydroxy vitamin D_3 immunoassay based on CMIA principle are a useful, rapid and accurate method for measuring total 25-hydroxy vitamin D_3 (as per ISO 15189, 5.6.2 requirements). The assay is standardized against NIST SRM 2972 (National Institute of Standards and Technology Standard Reference material 2972).[27]A general agreement regarding the optimal level of 25-hydroxyvitamin D has not yet been established. Most experts define 25-hydroxy vitamin D_3 deficiency as <20 ng/mL, insufficiency as 21-29 ng/mL, and the optimal level as ≥ 30 ng/mL.[28]A data from the Third National Health and Nutrition Examination Survey (NHANES III) revealed the prevalence of serum levels of 25-hydroxy vitamin D_3 less than 30 ng/mL was higher in women, elderly persons who have exhibited CVD risk factors. [29] Recently, Wang *et al.,*[3] observed that individuals with low 25-hydroxy vitamin D_3 levels, <30 ng/mL, are prone to cardiovascular disease such as myocardial infraction, coronary insufficiency, and heart failure compared with those with 25-hydroxy vitamin D_3 levels of at least 30 ng/mL. Giovannucci *et al.,*[30] revealed men with 25-hydroxy vitamin D_3 deficiency (≤15 ng/mL) were at significantly increased risk of developing myocardial infarction, compared with those with sufficient levels of 25-hydroxy vitamin D_3 (≥30 ng/mL).

VITAMIN D SUPPLEMENTATION AND CARDIOVASCULAR HEALTH

Vitamin D insufficiency/deficiency has been observed worldwide at all stages of life and in India approximately 70-90% of healthy population is vitamin D deficient.[31] Vitamin D deficiency is a major health concern in India, despite the brightly shining sun. Indians with darker skin has high melanin content acts as a natural sunscreen and produces significantly lesser amount of cholecalciferol which is the precursor for 25-hydroxy vitamin D_3. Commercially two forms of Vitamin D are available, Vitamin D_2 and Vitamin D_3. Vitamin D_2 is manufactured by ultraviolet irradiation of ergosterol from yeast. Vitamin D_3 is produced by the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Among the two commercially available forms, Vitamin D_3 is more effective than vitamin D_2 in achieving and maintaining higher serum 25-hydroxy vitamin D_3 levels [2]. In India, more than 99.9% of the preparations contain vitamin D_3 in the forms of cholecalciferol, 25-hydroxy cholecalciferol and 1,25 di hydroxycholecalciferol or calcitriol. Only 0.1% preparation contain vitamin D_2 ergocalciferol [31] and only few pharmacists are aware of vitamin D_2 supplements [2].

Table 1
Vitamin D Supplementation- Small clinical trials and cardiovascular outcome

Subject	Study period	Vitamin D supplementation	Dosage of supplementation	Cardiovascular outcome	References
87 patients with type 2 diabetes mellitus	8 weeks	Ergocalciferol	Single dose of 100,000 IU Ergocalciferol.	Improved endothelial function and decrease in systolic blood pressure	Sugden *et al*.,2007.[32]
123 congestive heart failure patients	9 months	Cholecalciferol and calcium	50 microgram of Cholecalciferol and 500 mg calcium.	Reduction in Tumour Necrosis Factor and proinflammatory cytokine	Schleithoff *et al.,* 2006. [33]
148 elderly women with Vitamin D deficiency	6 weeks	Cholecalciferol and calcium	1200 mg of calcium plus 800 IU of Cholecalciferol per day.	Decrease in systolic blood pressure by 9.3%	Pfeifer *et al.,* 2001.[34]
15 haemodialysis patients with secondary hyperparathyroidism	15 weeks	Calcitriol	2 microgram of Calcitriol twice weekly.	Significant Reduction in PTH, plasma renin, angiotensin II	Park *et al.,* 1999.[35]
10 haemodialysis patients	3-4.5 months	Calcitriol	1-2 microgram of Calcitriol 1-3 times a week.	Reduction in PTH	Lemmilä *et al.,* 1998.[36]

CONCLUSION

In summary, widespread prevalence of vitamin D deficiency in worldwide population is irrefutable. Moderate to severe vitamin D deficiency is associated with increased risk of cardiovascular disease. Lower plasma levels of 25-hydroxy vitamin D_3 are associated with higher risk of hypertension, coronary artery disease, and congestive heart failure. Although all the above-mentioned evidences in the current review suggest that Vitamin D has a protective role in cardiovascular system, the exact mechanism by which an adequate vitamin D status may protect against CVD are not fully understood. The cardioprotective hypothesis of vitamin D has not been without controversy and the results to date have been

inconclusive.No clear evidence indicates that vitamin D supplementation has a role to play in the prevention of cardiovascular disease. Further studies are required to clarify the association between Vitamin D and cardiovascular disease and the mechanism behind the association.

CONFLICT OF INTEREST

Conflict of interest declared none.

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