Journal of Nutrition & Food Sciences
ISSN: 2155-9600
Rojekar and Rojekar, J Nutr Food Sci 2016, 6:3
DOI: 10.4172/2155-9600.1000509

Commentary Open Access

Vitamin D and Spectrum of Its Roles

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Received date: Feb 15, 2016; **Accepted date:** May 27, 2016; **Published date:** May 31, 2016

Introduction

Since last few years vitamin D, i.e., calcitriol is gaining popularity for its various nonconventional roles. Vitamin D and its metabolites have their receptors present in various body tissues. Its use in the body is not limited as mere vitamin but now has been extended through many other actions too. Hormones and vitamin D have many similarities. These similarities are based on mainly the mechanism of action. Like hormones vitamin D is subjected to 'feedback inhibition' and also have definite 'target hormone'.

Nature presents us with the two types of vitamin D. One is ergosterol which is pro-vitamin D2 produced by ultraviolet radiations in a variety of plant materials and yeast. Other one is 7-dehydrocholesterol pro-vitamin D3 found in the skin.

Differences exist in their binding to the major transport protein in blood, vitamin D binding protein, and in their metabolism due to structural variation. This results in less increase in circulating 25-OH vitamin D than single doses of D3 [1,2] although daily administration of D2 and D3 maintains comparable levels of 25OH vitamin D [3].

Vitamin D3 is produced in the skin from 7-dehydrocholesterol through a two-step process in which the B ring is broken in UV rays and the pre-D3 so formed isomerizes to D3 in a thermo-sensitive but non-catalytic process. The vitamin D binding protein transports the vitamin D3 to the liver where it undergoes hydroxylation to 25(OH)D (the inactive form of vitamin D) and then to the kidneys where it is hydroxylated by the enzyme 1 α-hydroxylase to 1,25 (OH)2D3, its active form [4].

Once formed through various chemical reactions, vitamin D is now ready for action. Mechanism of action is similar to steroid hormone. The action is mediated by its binding with vitamin D receptor (VDR).

VDR is a member of nuclear hormone receptor superfamily including receptors for steroid and thyroid hormones and retinoic acid. VDR functions as a heterodimer generally with the retinoid X receptor for regulation of vitamin D target genes. These heterodimeric complexes interact with specific DNA sequences [vitamin D response elements (VDREs)], generally within the promoter of target genes, resulting in either activation or repression of transcription [5 -8]

Vitamin D effect over bone is well known. This is through calcium and phosphate homeostasis regulation by action of vitamin over intestine, kidney. It is believed that synthesis of Ca^{++} binding proteins like osteocalcin and alkaline phosphatase is promoted which increases calcium and phosphate ions in the bone. These ions enhance the mineral deposition in the bone. But this may be proved to be only the tip of the iceberg in near future. The research suggests that the 'arena' of vitamin D is much wider than thought previously.

Regulation of vitamin D is a bit complicated. Various cascades are involved in it. Plasma concentrations of biologically active vitamin D (1,25-(OH)2D) are tightly controlled via feedback regulation of renal 1α-hydroxylase (CYP27B1; positive) and 24-hydroxylase (CYP24A1; catabolic) enzymes. However, the CYP24A1 gene is methylated in human placenta, purified cytotrophoblasts, and primary and cultured chorionic villus sampling tissue. No methylation was detected in any somatic human tissue tested. Methylation was also evident in marmoset and mouse placental tissue [9]. Epigenetics also plays important role. Since JMJD3 histone demethylase is induced by vitamin D [10] and G9a/GLP complex could maintain imprinted DNA methylation independent of their catalytic activity [11], the DNA methylation at CYP24A1 gene in mammalian placenta might directly controlled by G9a/GLP/DNMT histone/DNA methyltransferases complex. Therefore, the levels of vitamin D might be controlled by epigenetic regulation mechanisms.

Diabetes and Vitamin D

Receptors of vitamin D3 have strong immune-modulatory effect. Data from various epidemiological studies have suggested that there is link between vitamin D3 and development of type 1 diabetes [12,13]. Literature also reports the vitamin D receptor gene polymorphism in relation with type 1 diabetes [14,15]. Studies reveal the association between vitamin D and β cell function, insulin secretion and its action. But the reports await long term clinical trials. Various roles of vitamin D with respect to insulin include presence of specific vitamin D receptors (VDRs) on pancreatic β-cells [16] expression of 1-α-hydroxylase enzyme in pancreatic β-cells catalyzing activation of vitamin D [17] presence of a vitamin D response element in human insulin gene promoter [18] and presence of VDR in skeletal muscle (Figure 1) [19].

Autoimmunity and Vitamin D

Interaction between vitamin D and immune system was evidenced by finding on mononuclear cells of VDRs [20]. Later it was also found that active vitamin D3 regulates immune responses to a great extent that some experiments have shown increased susceptibility to inflammation in vitamin D deficiency [21]. Vitamin D3 also regulates the T cell development and proliferation. In T cells it is shown to down-regulate Th1 response by decreasing proliferation and cytokine secretion [22]. *In vitro* studies have shown this vitamin as differentiating factor for monocytes and tumor cells [23].

Cancer and Vitamin D

Animal as well as human studies have shown that vitamin D has role in cancer prevention. This might be related to its effect over regulation of cell growth and differentiation [24]. Majority of the studies conducted in cancer patients including postmenopausal women regarding incidence and survival have shown beneficial effect of vitamin D3 [25,26]. It is suggested that living at higher latitudes and

Citation: Rojekar AA, Rojekar MV (2016) Vitamin D and Spectrum of Its Roles. J Nutr Food Sci 6: 509. doi: 10.4172/2155-9600.1000509

an increased risk of common diseases are associated with a decrease in the synthesis of vitamin D3 in the skin. Increased exposure to sunlight at lower latitudes would increase blood concentrations of vitamin D3. Because 1,25(OH)2D3 is extremely potent in inhibiting cancer cell growth, this all seemed to make sense [27].

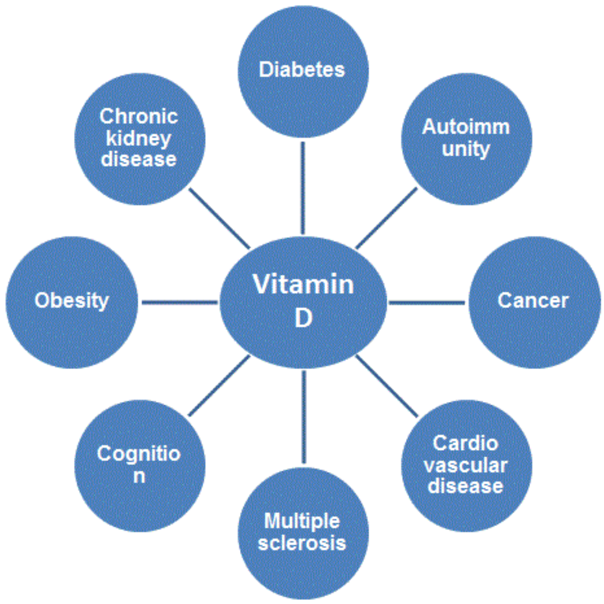

Figure 1: Diapason of vitamin D.

Cardiovascular Diseases and Vitamin D

VDRs are found to be present on endothelium, smooth muscles, cardiomyocytes Part of famous Framingham study-'Framingham offspring study' observed the occurrence of cardiovascular events with respect to vitamin D. The study reveals the inverse correlation between vitamin D levels and cardiovascular events [28]. Vitamin D metabolites have been associated with the regulation of blood pressure and hormonal mechanisms regulating blood pressure. The most notable mechanism implicating vitamin D with hypertension is its role as a negative regulator of the RAS. Other notable hypotheses have suggested that vitamin D influences vascular endothelial function or vascular smooth muscle intra-cellular calcium concentrations [29]. There are reports of low vitamin D levels in coronary occlusion and lack of collateral development [30]. Since activated vitamin D is negative inhibitor of renin-angiotensin-aldosterone system [31] and low vitamin D is associated with incident hypertension [32], hypertension has been noted as a possible mediator in causal pathway between low vitamin D and incident cardiovascular disorders.

Multiple Sclerosis and Vitamin D

Multiple sclerosis (MS) is neurodegenerative, T-lymphocyte-mediated, autoimmune disease of uncertain etiology. Exposure to sun in early childhood has reduced risk of developing multiple sclerosis [33]. Seasonal variations in the incidences of the MS are noticed in countries in Arctic Circle in a manner that statistically significantly fewer patients with MS born in November and more born in May compared with controls [34].

Cognition and Vitamin D

An observational study reports that levels of vitamin D in cases of Alzheimer's disease are found to be less than controls [35]. A cross-sectional study of 225 outpatients diagnosed with Alzheimer disease found a correlation between vitamin D levels and their score on a Mini Mental Status Examination [36].

Obesity and Vitamin D

Reduced concentrations of vitamin D are frequently observed in obese individuals. It is speculated that vitamin D deficiency is not only due to lower sun exposure in obese, but also one of the factors triggering accumulation of body fat [37,38]. Evidence suggests that one cause of disability of 25 (OH) D in obese subjects with T2DM and may be linked to the deposit of vitamin D in adipocytes, decreasing their bioavailability and triggering the hypothalamus to develop a cascade of reactions that results in increased feeling of hunger and decreased energy expenditure [39].

Chronic Kidney Disease and Vitamin D

Some studies indicate that 1,25(OH)2D3 levels decrease in patients suffering from chronic kidney disease (CKD) [40]. There are the several theories about the pathogenesis of vitamin D deficiency in CKD. Megalin, which is present in endocytic receptors in proximal tubule cells, is involved in the reabsorption of DBP from glomerular ultra-filtrate [41]. In addition, megalin also mediates the subsequent intracellular conversion of 25(OH)D to its active form. As kidney function declines, megalin expression in the proximal tubule decreases [42].

Low 25(OH)D levels are associated with all-cause mortality and cardiovascular disease in patients with CKD as well as in patients undergoing dialysis [43]. Another study showed that among these patient groups, those with low levels of 25(OH)D and high levels of fibroblast growth factor-23 (FGF-23) have worse outcomes [44]. However, there is not sufficient evidence regarding vitamin D supplementation for patients with CKD and those undergoing dialysis [45]. Although studies have reported that cholecalciferol decreases albuminuria [46] and improves the parathormone levels [47] in patients with CKD, there is no study with set clinical outcomes such as all-cause mortality or cardiovascular disease.

Conclusion

From above evidences it is clear that vitamin D is having action not only over bone, kidney and intestine but also related to many other disorders as causative agent when deficient. However prospective and intervention studies in humans that prove the effectiveness of the adequacy of the status of vitamin D in the prevention and treatment of these diseases are still scarce. Still the exact mechanism through which vitamin D related to the disorders it is linked with is lacking. These gaps in the knowledge will certainly be fulfilled in near future. So the vitamin D could be used for the prevention as well as treatment of above mentioned diapason of vitamin D.

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