

## Review Article

### **Impact of Vitamin D on General Health on People**

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**Abstract:** Vitamin D can be obtained from sunlight and food enriched with Vitamin D. Vitamin D is the vitamin of sunlight and is very important for the prevention of rickets in children. It is important not only for the development of skeleton but also for life long maintenance of a healthy musculoskeletal system. Vitamin D provides maximum muscular power and is known to have preventive effects in type 1 diabetes, MS, rheumatoid arthritis, hypertension, cardiovascular heart disease and various cancers. In many studies, it has been suggested that vitamin D treatment decreases mortality especially in CRF (chronic renal failure) patients. Vast research has been carried out to establish strong relationship between Vitamin D serum levels, supplementation, diabetes, and cardiovascular diseases. The aim of this review was to summarize current epidemiological and experimental evidence on the impact of Vitamin D on general health on people.

**Keywords:** Vitamin D deficiency, diet, general health.

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#### **Systemic Effects of Vitamin D**

In parts of North Europe where sun light is lacking, at the end of 1600s, a disease was defined by Whistler, Glissen and DeBoot which was characterized by skeletal deformities, in hip and long bones, and developmental retardation and deformities in arms. This disease has been defined as rickets and has become prevalent in industrialized cities of US in 18th and 19th centuries [1, 2]. Palm in Great Britain found the incidence of rickets in large cities high. However in countries where malnutrition and liver failure is high such as India, this disease did not occur. Hence, palm recommended sun bath in order to prevent rickets [3]. 2 years later, Hess and Unger [4] administered sun light treatment to children with rickets on the roof of Newyork City Hospital and observed dramatic improvement in their condition. It was observed that some food and biological materials assumed anti acidic characteristics upon being exposed to UV. Vitamin D was then structurally analyzed and synthesized. With its addition to milk and other food stuff, rickets, which has become an important public health problem in US and some European countries, could be eradicated [2, 5, 6]. Vitamin D can be obtained from sunlight and food enriched with Vitamin D. Both Vitamin D<sub>3</sub> and vitamin D<sub>2</sub> isolated from ergosterol by radiation are found in chilomikrons and absorbed from lymphatic system and transported by the protein binding Vitamin D to liver. In liver, both vitamin D<sub>2</sub> and Vitamin D<sub>3</sub> are transformed into 25OH Vitamin D<sub>3</sub> and 25OH vitamin D<sub>2</sub> by hydroxylation of carbon [1, 2]. Both 25OH

vitamin D<sub>2</sub> and 25OH Vitamin D<sub>3</sub> are turned into 25OH vitamin D. Clinically, the best indicator of Vitamin D in circulation is 25OH vitamin D. 25OH is transported to the kidney by vitamin D primary form DBP (D vitamin binding protein ) and from there is transported to renal tubules by DBP-25OH vitamin D complex, where 25OH vitamin D is liberated [7]. 25OH vitamin D enters mitochondrium and in cytochrome p 450', 25OH vitamin D is transformed into 1,25dihydroxyvitamin D<sub>3</sub> (calsitriol-1,25(OH)<sub>2</sub>D<sub>3</sub>) with 1 alpha hydroxylase [1,8]. 1,25(OH)<sub>2</sub>D<sub>3</sub> enters circulation and reaches intestines where it encounters nuclear vitamin D receptors and increases intestinal calcium absorbtion together with epithelial calcium channel proteins and other proteins [1, 2, 9].

In the regulation of 1,25(OH)<sub>2</sub>D<sub>3</sub> synthesis, the most important factors are paratiroid hormon (PTH) and phosphorus levels [9,10,11]. If information comes to parathyroid gland from calcium sensors on the decrease of ionized calcium, PTH secretion is stimulated [12]. PTH increases the reabsorbtion of calcium from renal proximal and distal tubules and stimulates RANKL expression in osteoblasts and increases phosphorus excretion by urine. Regulation of 1,25(OH)<sub>2</sub>D<sub>3</sub> in kidney is helped by the effect of PTH phosphorus metabolism. Hypophosphatemia is independent of PTH level in the regulation of 1,25(OH)<sub>2</sub>D<sub>3</sub>. Decrease in serum calcium levels also lead to increase in PTH levels, reabsorbtion of tubular calcium and phosphorus excretion. Reduction in intracellular phosphorus

concentration results in an increase in renal production of  $1,25(\text{OH})_2\text{D}_3$  [11]. Both hyperphosphatemia and hypercalcemia are effective in renal regulation of  $1,25(\text{OH})_2\text{D}_3$  [9,13].  $25\text{OH}$  vitamin D levels should be at least 20 ng/ml and preferably 30-50 ng/ml in healthy children and adults [14]. The effects of Vitamin D on general health status is well known, but its mechanisms of action still remain to be elucidated.

Vitamin D is the vitamin of sunlight and is very important for the prevention of rickets in children. It is important not only for the development of skeleton but also for life long maintenance of a healthy musculoskeletal system. In adults, the deficiency of vitamin D, induces the development of osteoporosis and osteomalacia, which leads to the formation of fragile bones. In addition to its role in calcium and phosphorus homeostasis, Vitamin D provides maximum muscular power and is known to have preventive effects in type 1 diabetes, MS, rheumatoid arthritis, hypertension, cardiovascular heart disease and various cancers [14]. The best indicator of body vitamin D pool in circulation is serum  $25\text{-OH}$  vitamin D level [14]. In healthy individuals, this level should be at least 20 ng/ml [14].

It is known that Vitamin D is biologically inactive and is transformed in kidney and liver by hydroxylation into  $1,25$  dihydroxy vitamin D. The most important factors in the regulation of Vitamin D synthesis are PTH and phosphorus level [9, 10, 11]. In patients with moderate and severe renal failure,  $1,25(\text{OH})_2\text{D}_3$  concentration in circulation is general low or unmeasurable [15,16]. When GFR falls below %33, due to inadequate  $1$  alpha hydroxylase reserve in the kidney  $1,25(\text{OH})_2\text{D}_3$  concentration will decrease and intestinal calcium absorption will increase leading to secondary hyperparathyroidism in PTH level, which explains the frequency of secondary parathyroidism and PTH mediated osteoclastic bone disease in renal failure [17].

#### Non calcemic functions of Vitamin D

In the brain, heart, stomach, pancreas, skin, breast, gonads, in all cell and tissues which contain active T and B lymphocytes, vitamin D receptors (VDR) are present [1, 18]. It has been recognized that  $1,25(\text{OH})_2\text{D}_3$  has biological role such as enhancing insulin release, immune system modulation and increasing renin release from kidneys [19, 20]. In addition, based upon these biological events, it has been understood that  $1,25(\text{OH})_2\text{D}_3$  is one of the strongest inhibitors of cellular proliferation and is an important component in terminal differentiation [1, 2, 21, 22].

#### Vitamin D and prevention of cancer

It has been demonstrated that, in some patients whose  $25(\text{OH})\text{D}$  level is under 20 ng/ml, the risk of the development of colon cancer is high [22]. Tuohianaa *et*

*al.*; [23] reported the association between deficiency of Vitamin D and prostate cancer. Luscombe *et al.*; [24] found that mean age of patients exposed to minimum sunlight was 67.7 years while that of patients exposed to strong sunlight was 72.1. Similarly, Grant *et al.*; [25] demonstrated that both in men and women, those who were more exposed to sunlight had lower rates of death from cancer.

#### Vitamin D and autoimmune diseases

In parallel to Vitamin D deficiency, increase has occurred in the development of autoimmune diseases, multiple sclerosis (MS), rheumatoid arthritis (RA) and type 1 diabetes [26, 27, 28]. In people born over 35 north latitude and lived for at least 10 years, the frequency of MS increases 50%. This difference was seen in comparison to people born under the South of 35. North latitude. Increase in Vitamin D intake (400 IU/day and over ) decreased MS incidence by %40 (26). In female patients, the intake of multivitamin capsule containing 400 IU Vitamin D decreased the development of RA by %40 [27]. In people who live high latitudes, the risk of development of type 1 diabetes was found to be high [28]. The association of Vitamin D deficiency with type 1 diabetes was shown in NOD mouse model. Based upon this, in children given 200 IU vitamin D starting from birth for one year, the risk of development during 30 years was decreased by %80 [29]. In the same study, in children who had vitamin D deficiency at the age of one, the risk of diabetes development was found to be increased.

#### Vitamin D and cardiovascular heart diseases

Atherosclerosis is characterized by dilatation, hypertrophy and hardening of arteries. Mortality of end stage renal failure patients is closely associated with cardiovascular diseases. Hardening in artery wall is a predictor of cardiac mortality both in CRF patients and in normal population. This is associated with hardening in artery wall, age, renal function and their combination. In many studies, it has been suggested that vitamin D treatment decreases cardiac mortality especially in CRF patients.

It has been determined that cardiac mortality in CRF patients is 10-20 time higher than that in general population. In previous studies, it has been demonstrated that low glomerular filtration rate (GFR) is a CVD risk factor by itself. Risk factors increasing cardiovascular disease were found to be correlated with hyperphosphatemia and both hyperparathyroidism and hyperparathyroidism accompanied by increase in vascular and tissue calcification [30]. In the study of London *et al.*; [31] it was established that in CRF patients, in common carotid arteries and vessels in pelvis, calcification was present in media and intima associated with serum calcium, phosphorus and bone morphology.

In many clinical studies, hyperphosphatemia PTH abnormalities and increase in vascular calcification have been shown to be a factor increasing the risk CVD in patients with chronic renal failure. In CRF patients, phosphorus levels over 6.5 mg/dl and calcium-phosphorus multiplication over 72 mg/dl, were shown to increase the risk of cardiovascular disease. Stevens and coworkers investigated calcium, phosphorus and PTH levels in dialysis patients and demonstrated that abnormalities in their levels increased mortality. In another study, while there was a weak relation between serum PTH and calcium-phosphorus levels and morbidity in patients receiving vitamin D, this association was found to be strong in those who do not receive vitamin D.

#### **How does Vitamin D decrease cardiovascular morbidity?**

Recently, it has been shown that vitamin D replacement treatment is also effective in the survival of CRD patients in addition to quality of dialysis, anemia and HT control. Interestingly, in early stages of renal failure, Vitamin D deficiency is relative.

Vitamin D receptors regulate the effects of vitamin D. These receptors have been found in almost all organs. In addition, they have been shown in heart, vessel walls, kidney and immune cells. Vitamin D receptors regulate many genes. These are associated with not only calcium-phosphorus metabolism but also with physiological processes. 3 important potential mechanisms regulate the protective effect of Vitamin D against cardiovascular disease [32]. That is;

1. Regulation of inflammation,
2. Effect on myocardial cell hypertrophy and proliferation,
3. Regulation of Renin-angiotensin system.

#### **Inflammation underlying atherosclerosis and Vitamin D**

It is well known that atherogenic plaques are formed through inflammatory process. Macrophages and T cells play central role in inflammation and lead to the formation of atherosclerotic lesions on artery wall. Inflammatory process takes place via the release of various cytokins such as interleukin 1(IL-1), IL-4, IL-6, interferon- $\gamma$  and tumor necrotizing factor (TNF- $\alpha$ ) by macrophages and T cells. These factors contribute to the continuation of smooth muscle cell proliferation and plaque formation and increase the synthesis and release of positive acute phase reactants such as amyloid A and CRP. In addition, they decrease the release of negative acute phase reactants such as albumin and transferrin. In many studies, CRP was defined as an indicator of cardiovascular disease and a marker of long term survival.

#### **Vitamin D and inflammatory process**

Immune regulator activities of Vitamin D have long been known. Its immune regulator effects are exerted by Vitamin D receptor, which are usually located in immune cells. It was observed that Vitamin D inhibits antigen presenting cell maturation and hence angiogenesis and vascular smooth muscle cell proliferation. Vitamin D also exerts effects increasing nuclear factor- $\kappa$ B activity, increasing IL-10 regulation, and decreasing IL-6, IL-12, IFN- $\gamma$  regulation and hence decreasing inflammation with this cytokine profile. The protective effect of Vitamin D against atherosclerosis is involved with the regulation of tissue matrix metalloproteinase (MMPs) expression by Vitamin D. MMPs are tissue enzymes and are secreted from activated macrophages at the moment of inflammation. They are required in remodeling of vascular wall and myocardium. MMPs degrade collagen and destroys the lesion producing thrombosis by leading to rupture of atherosclerotic lesion [33].

#### **Cardiac Hypertrophy and Effects of Vitamin D**

Vitamin D may play an indirect role in the pathogenesis of congestive heart failure (CHF). Zitterman *et al.*; [34] compared 54 CHF patients with 34 normal subjects and demonstrated that in CHF patients serum 25-(OH)D levels and calcitriol decreased. Negative correlation has been found between Vitamin D levels and CHF incidence.

In a few small scale studies, it was shown in hemodialysis patients that Vitamin D treatment improved left ventricle hypertrophy. Park *et al.* administered iv calcitriol treatment for 15 weeks to CHF and hyperparathyroiditis patients and significant improvement was seen in left ventricle hypertrophy [35]. Mc Gonigle *et al.*; [36] evaluated serum 25 hydroxycholecalciferol (25(OH)D) levels and found them to be inversely correlated with left ventricular function. Following 6 weeks of i.v. 1- $\alpha$ -hydroxycholecalciferol treatment, small but significant improvement was found in left ventricle functions.

#### **Renin Angiotensin system and Vitamin D**

Previous clinical and epidemiological studies have found an inverse proportion in normotensive and hypertensive patients between serum 1,25(OH) $_2$ D $_3$  levels and blood pressure and/or plasma renin activity. In a 4 week study, vitamin D treatment significantly reduced systolic blood pressure in nonhypertensive female cases with vitamin D deficiency [37]. It was also observed that 18 weeks of treatment decreased systolic blood pressure significantly in hypertensive patients [38]. Li *et al.*; [39] demonstrated the relation between vitamin D and renin angiotensin system by using animal models. Accordingly, it was suggested that Vitamin D in vivo may be negative endocrine regulator in renin

biosynthesis.

Vitamin D deficiency increases cardiovascular heart diseases and congestive heart failure [40,41]. Teng *et al.*; [42] compared RF patients who used, vitamin D analogue, with those who used calcitriol for 18 months and found a decrease of 18% in mortality in the former group.

#### Vitamin D and chronic renal failure

In CRF patients, the risk of Vitamin D deficiency is high. Renal failure results in a deficiency in active vitamin D levels, which leads to impairment in organ functions and metabolism treatment with active forms of Vitamin D improves the abnormalities in bone and mineral metabolism, immune disturbances, and cardiac functions. 25(OH)D<sub>3</sub> is activated with 1 $\alpha$ -hydroxylase in renal tissues and its activation is impaired in chronic renal failure. Classical target tissues are kidney, intestines, parathyroid gland and bone however. Nevertheless, vitamin D receptors are present in many tissues including immune system, heart, arteries, endocrine organs, liver and brain. These patients routinely use 1,25(OH)<sub>2</sub>D<sub>3</sub> or its active analogue in order to improve calcium homeostasis and to decrease severe secondary hyperparathyroidism [15,43]. In CRF of the electrolyte metabolism abnormalities, Ca and P impairment exerts a strong effect on vitamin D and PTH. Ca and P metabolisms are associated with bone metabolism and their abnormalities with the development of renal osteodystrophy in CRF. This abnormality starts when GFR is 70 ml/min. and progresses as renal function loss continues [44,45].

Recently, in developed and developing countries, diabetes associated nephropathy has become one of the most important causes of CRF. There are reports of Vitamin metabolism abnormalities in Diabetes [46,47]. In cases in which kidney functions are normal, decrease in serum 25(OH)D<sub>3</sub> levels leads to decrease in calcitriol which is the substrate of kidney and other tissues, secondary hyperparathyroidism, loss of bone mineral density, and to increase in the risk of hip fracture, irrespective of kidney functions [48,49]. In patients with CRF, parathormone and Vitamin D axis play central role in calcium-phosphorus homeostasis [50]. The indicator of body pool of Vitamin D is serum 25(OH)D level [51].

Vitamin D is known to have many noncalcemic functions (105,106). Vitamin D metabolisms is particularly influential in the development of insulin resistance, and vitamin D deficiency increases the risk of diabetes and metabolic syndrome [52,53].

Alterations in calcium metabolism may play part in the development of essential hypertension and its pathogenesis [7]. Mc Corron *et al.*; [54] reported that in untreated non obese essential hypertension patients, serum ionized calcium levels were lower than those of normal subjects.

Grobbe *et al.*; [54] demonstrated that in young male hypertensive patients, serum PTH concentration is directly related to blood pressure. In addition, in patients with primary hyperparathyroidism, hypertension is a common finding. Although the mechanism whereby PTH leads to hypertension in primary hyperparathyroidism is not clear, in many studies, it has been stated that PTH itself acts like a vasodilator agent [54].

It is commonly thought that 1,25 dihydroxy cholecalciferol has an important regulatory function in blood pressure. It has been shown that 1,25(OH)<sub>2</sub>D<sub>3</sub> receptors are present in rat aorta vascular smooth muscles and cardiac muscle cells. Serum 1,25(OH)<sub>2</sub>D<sub>3</sub> concentration was found to be lower in untreated hypertension patients compared to control group [55]. In a double blind placebo controlled study, in hypertensive patients with glucose tolerance disorder, vitamin D treatment decreased blood pressure significantly. In these patients, significant fall was found in serum PTH and magnesium concentrations. Authors emphasized that suppression in hypertension was probably related to suppression in hyperparathyroidism. In another study, same authors demonstrated that Vitamin D treatment improved diastolic hypertension in patients with moderate primary hyperparathyroidism and moderate hypercalcemia [55].

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