**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 ricket 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 New York 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 other European countries, could be eradicated [2, 5, 6]. Vitamin D can be obtained from sunlight and food enriched with Vitamin D. Both Vitamin D$_3$ and vitamin D$_2$ 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$_2$ and Vitamin D$_2$25 are transformed into 25OH Vitamin D$_3$ and 25OH vitamin D$_2$ by hydroxylation of carbon [1, 2]. Both 25OH vitamin D$_2$ and 25OH Vitamin D$_3$ are turned into 25OH vitamin D$_3$. 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$_3$ (castsintiol-1,25(0H)$_2$D$_3$) with 1 alpha hydroxylase [1,8]. 1,25(OH)$_2$D$_3$ enters circulation and reaches intestines where it encounters nuclear vitamin D receptors and increases intestinal calcium absorption together with epithelial calcium channel proteins and other proteins [1, 2, 9].

In the regulation of 1,25(OH)$_2$D$_3$ synthesis, the most important factors are parathyroid 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 reabsorbion 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)$_2$D$_3$ in kidney is helped by the effect of PTH phosphorus metabolism. Hypophosphatemia is independent of PTH level in the regulation of 1,25(OH)$_2$D$_3$. Decrease in serum calcium levels also lead to increase in PTH levels, reabsorbion of tubular calcium and phosphorus excretion. Reduction in intracellular phosphorus...
Vitamin D and cardiovascular heart diseases

Atherosclerosis is characterized by dilatation, hyperthrophy 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.

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 prevention of cancer

It has been demonstrated that, in some patients whose 25(OH)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.

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(OH)2D3 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(OH)2D3 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(OH)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.
In many clinical studies, hyperphosphatemia PTH abnormalities and increase in vascular calcification abnormalities 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 - and tumor necrotizing factor (TNF- ) 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 –KB activity, increasing IL-10 regulation, and decreasing IL-6, IL-12, IFN- 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 and 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 calcitriol decreased. Negative correlation has been found between Vitamin D levels and CHF incidence. Following 6 weeks of i.v. 1,25(OH)D3 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)2D3 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
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, is activated with 1, 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)2D3 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 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)2D3 receptors are present in rat aorta vascular smooth muscles and cardiac muscle cells. Serum 1,25(OH)2D3 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 supression in hypertension was probably related to supression 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].

**References**

3. Palm TA; The geographical distribution and aetiology of rickets. Practitioner, 1890; XLV(4) :270-342.
6. Hess AF, Weinstock M; Antirachitic properties imparted to inert fluids and to green vegetables
32. Levin A, Chun Li Y; Vitamin D and its analogues: Do they protect against cardiovascular disease in patients with kidney


