



## Health and the Vitamin D

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### ABSTRACT

Vitamin D is a steroid hormone that has long been known for its role in regulating body levels of calcium and phosphorus, and in mineralization of bone. Research also suggests Vitamin D regulates numerous physiologic processes in addition to maintaining calcium homeostasis. Its importance has been proven for muscle strength and performance, stimulation of the immune system and helping to treat infection and preventive role against autoimmune diseases and certain type of cancers like prostate, breast and colon cancer.

Despite the close link of vitamin D with human health, its inadequacy is not widely recognized as a problem by physicians and patients and much awareness is needed.

**Key words:** Chronic Disease, Diabetes, Health, Vitamin D, Obesity.

### INTRODUCTION

Vitamin D, also known as the sunshine vitamin, since its discovery more than 100 years ago by McCollum and Davis in the year 1913, has been a constant topic and molecule of research. The role of vitamin D is very well documented in the regulation of musculoskeletal health and health-related homeostatic process. [1] Recently in the last decade role of vitamin D has attracted the mind of many researchers giving its role in pathogenesis of several chronic diseases, including diabetes, hypertension, infections, autoimmune diseases, cancer, and obesity. This vitamin has emerged ahead from the traditional concept of its role only in calcium and bone

mineral metabolism, to a hormone having various functions.

Vitamin D deficiency has become a major public health problem across the world in every country to pandemic proportions. [2] Despite being a tropical country full of sunshine, vitamin D deficiency is found to be highly prevalent in India and includes all age groups: school going children, [3] pregnant and postmenopausal women [4] and also the apparently healthy middle-aged healthcare professionals. [5]

#### Vitamin D Metabolism:

Vitamin D is a lipid soluble steroid prohormone which is synthesized in the skin under the exposure to ultra-violet (UV) light. 7-dehydrocholesterol present in the

skin absorbs UV light over wavelengths of 290-300 nm [UVB] to synthesize vitamin D (cholecalciferol) which is then transported to the liver. In the liver it gets converted to 25-hydroxyvitamin D [25(OH)D] and then is released into the blood and reaches the kidney where it is converted to the vitamin D hormone, 1, 25-dihydroxyvitamin D (calcitriol) by the activity of the enzyme 1 $\alpha$ -hydroxylase, which is strictly regulated and induced by parathyroid hormone, which in turn is regulated by serum concentration of calcium and phosphorus. [6,7]

The biological potency of 1, 25-dihydroxycholecalciferol is several times higher than that for 25-hydroxycholecalciferol. [6,7]

#### **Deficiency:**

Definition: [8]

-25(OH)D concentration <50 nmol/L (20 ng/mL) indicates vitamin D deficiency,

- 25(OH)D concentration of 51–74 nmol/L (21–29 ng/mL) indicates insufficiency,

- 25(OH)D concentrations >75 nmol/L (30 ng/mL) are considered to be sufficient

*Causes of vitamin D deficiency:* [8]

- Decreased intake of vitamin D in the diet, usually together with inadequate sun exposure
- Inability to absorb vitamin D from the intestines
- Inability to process vitamin D due to kidney or liver disease

*Decreased/ inadequate intake -*

Infants, children, and elderly persons are at high risk. Human breast milk contains low levels of vitamin D and most infant formulas do not contain adequate vitamin D. Elderly adults often do not consume enough vitamin D rich foods, and even when they do, absorption may be limited. [9,10] Foods rich in vitamin D are fatty fish (salmon,

mackerel, and sardines), cod-liver oil, cow's milk, egg and vitamin D fortified foods.

*Inadequate sun exposure* [11,12] -

Usually seen in people who have mainly indoor activity, elderly patients or infants who have limited exposure to sunlight and also in people who are dark skinned or use sun screen creams. Reduced amounts of vitamin D are made in the skin and stored in the body as we age. In urban areas the pollution causes filtering of sun's ultraviolet B rays.

*Diseases or surgery that affects fat absorption* [13] -

Certain diseases affect the body's ability to absorb adequate amounts of vitamin D through the intestinal tract. Examples include celiac disease, Crohn's disease, and cystic fibrosis. Surgery that remove or bypasses portions of the stomach or intestines can also lead to low vitamin D levels, example gastric bypass or bariatric surgery.

#### **Drugs:**

Induction of the catabolism of 1,25-dihydroxyvitamin D by few drugs (long-term use of some antiepileptic drugs [14] like phenobarbital, phenytoin, and carbamazepine and the antimicrobial agent rifampicin [15] can result in osteomalacia.

*Kidney and liver disease -* People with chronic kidney and liver disease are at increased risk of low active vitamin D levels because they lack these enzymes. Patients with chronic kidney disease (CKD) have decreased conversion of 25(OH)D to 1,25(OH)2D as a result of impaired renal 1- $\alpha$ -hydroxylase activity. Patients with liver disease or failure have decreased activity of the enzyme 25-hydroxylase activity.

Less common causes of vitamin D deficiency include familial diseases that impair the enzymes in the liver or kidney that create the biologically active form of the vitamin. This results in inadequate amounts of active vitamin D.

### **The role of vitamin D in health:**

Vitamin D is now considered to have a proven role in cell differentiation, proliferation, and immune function of the individual. It is considered an important factor in the prevention of some forms of cancer (prostate, colon), osteoporosis, rheumatoid arthritis, type 1 diabetes mellitus, multiple sclerosis, hypertension, cardiovascular disease, obesity, psoriasis, and psychiatric diseases and also in pregnancy. [16]

**Vitamin D and Pregnancy:** Vitamin D deficiency is commonly noted during pregnancy and throughout gestation. It may lead to a number of serious health problems like poor bone mineralization in infants, low birth weight baby and other adverse pregnancy outcomes. [17,18]

### **Immune system and autoimmune Diseases:** [19-21]

Vitamin D, through its receptors on the antigen presenting cells such as dendritic cells, macrophages, and T and B cells, play an important role in the vitamin D receptor-vitamin D endocrine system and can modulate most aspects of the innate and acquired immune system (and even mast cells) either in extreme deficiency or exposure to high 1,25-dihydroxyvitamin D (1,25[OH]2D).

The 1,25(OH)2D, functions as an inhibitor of dendritic cell maturation and thus acts as an immune modulator, reducing activation of the acquired immune system. Therefore, vitamin D deficiency could theoretically increase the risk of autoimmune diseases, which has been reported in animal models. Studies have association between vitamin D deficiency and type 1 diabetes, multiple sclerosis, bronchial asthma, psoriasis, inflammatory bowel disease and Crohn's disease. [22,23]

Various studies have shown that Vitamin D plays an important role in autoimmune and inflammatory diseases by

inhibiting the synthesis of mRNA of the leukocytes-derived cytokine's interleukin and tumor-necrosis factor and also decreasing the expression of MHC-II molecules on the cell surface.

The study done by McAllindon et al suggested that the risk of osteoarthritis was high when the serum 25(OH)D level was below 85 nmol/L with a decreased oral intake of vitamin D below 9.7 µg/d. [24]

### **Osteoporosis/Osteomalacia:**

Vitamin D deficiency is associated with a decrease in the intestinal calcium absorption and the impairment of calcium balance resulting in low bone mineral content and density leading to osteoporosis or osteomalacia. The association between vitamin D deficiency and osteoporosis is well established, especially in the elderly people. With the reduced bone mineral density (BMD) the risk of fractures increases in elderly and contributes significantly to morbidity and mortality in them. [25,26]

Hyperparathyroidism is a feature of vitamin D deficiency and contributes to bone loss. 1,25(OH)<sub>2</sub>D inhibits the synthesis and secretion of PTH and prevents proliferation of the parathyroid gland. [27]

### **Diabetes Mellitus:**

The association of vitamin D deficiency and diabetes mellitus was reported as early as the 1980's when the studies showed that severe vitamin D deficiency inhibits pancreatic secretion and turnover of insulin, resulting in low insulin levels thus causing impaired glucose tolerance. [28,29] Research and studies have also shown an association between low ultraviolet B (UVB) irradiance and high incidence of type 1 diabetes, therefore showing the association of low levels of vitamin D (due to low UVB radiation) with type 1 diabetes. [30-32]

**Muscle weakness/Myopathy:**

It has been shown that the skeletal muscle tissue contains vitamin D receptor and requires vitamin D to reach its maximum functional capacity. Thus making muscle weakness a prominent feature of vitamin D deficiency. Patients usually complain of non-specific weakness and myalgia. [33,34] This is also one of the main contributing cause of increased number of falls leading to fractures (especially hip).

**Multiple sclerosis:**

Studies have shown an association of vitamin D and Multiple sclerosis (MS), which is an autoimmune disease in which the body's immune system attacks myelin, which is a nerve insulator and helps in the transmission of nerve signals. It has been recognized for a long time that MS is more commonly seen in temperate climates than the tropics, giving a hypothesis that the increase of vitamin D resulting from sunlight exerts a protective effect. [35,36] Insufficient vitamin D levels have been found in individuals with MS.

**Cardiovascular Diseases:**

Vitamin D receptors are found to be expressed in a variety of tissues, including cardiomyocytes, vascular smooth muscle cells and endothelial cells. Vitamin D has been shown to affect inflammation and cell proliferation and differentiation as the activity of the intracellular adenylate cyclase in the sarcoplasmic reticulum has been found to be calcitriol dependent.

Vitamin D deficiency activates the renin-angiotensin-aldosterone system and can predispose to hypertension and left ventricular hypertrophy. Additionally, vitamin D deficiency causes an increase in parathyroid hormone, which increases insulin resistance and is associated with diabetes, hypertension, inflammation, and increased cardiovascular risk. [37,38]

Demir et al suggests that hyperparathyroidism secondary to vitamin D

deficiency may play a role in higher pulmonary arterial pressure and there might be an association between pulmonary hypertension (PHT) and vitamin D deficiency. [39] Vitamin D deficiency activates the renin-angiotensin-aldosterone system (RAAS) which affects the cardiovascular system. Activation of RAAS is associated with PHT.

**Obesity:**

It should be mentioned that cardiovascular diseases, hypertension, and diabetes mellitus is often associated with obesity. Obese subjects have relatively low circulating 25(OH)D levels due to the storage of vitamin D and 25(OH)D in adipose tissue so insufficient circulating levels. The alterations in vitamin D metabolism of obese subjects in comparison with lean subjects are also associated with functional alterations such as elevated PTH levels. [40,41]

**Cancer:**

Evidences have shown enhanced sunlight exposure or the sufficient levels of vitamin D are associated with lower prostate, breast and colon cancer incidence. Some studies showed inverse associations for vitamin D intake and colon or colorectal, breast, and prostate cancer. [42,43] Few studies reported that the incidence of breast and colorectal cancer can be reduced up to 50% if the concentration of 25-hydroxyvitamin D >32 ng/ml are achieved. [44,45]

**Rheumatoid Arthritis (RA):**

RA is a chronic inflammatory autoimmune disorder of unknown etiology in which both genetic and non-genetic factors play a role in disease susceptibility. [46] The immunomodulatory, in fact immunosuppressant, effect of Vitamin D has been proven in various studies. Vitamin D acts as a paracrine hormone to decrease T cell responsiveness through the inhibition of cellular proliferation and reduction in

lymphokine production. [46-48] Therefore, vitamin D has a beneficial effect in RA.

### **Tuberculosis (TB):**

Vitamin D has been used for the treatment of TB before the anti-tubercular antibiotics came into use. [49] Studies have shown that patients with TB have lower 25(OH)D levels in comparison with control subjects. [50,51] It was found that low vitamin D levels, resulting due a vegetarian diet acts as an independent risk factor for active TB in South Asians. [52]

### **Treatment of Vitamin D deficiency:**

Adequate sunlight exposure is the most cost effective means of obtaining vitamin D. Whole body exposure to UVB radiation, or sunlight to provide a mild reddening of the skin (minimal erythema unit) has been calculated to provide the equivalent of 10,000 IU vitamin D. [53]

*Vitamin D supplements* [54,55] -

There are many types of vitamin D preparations available for the treatment of vitamin D deficiency or insufficiency. The two commonly available forms of vitamin D supplements are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D3 is preferred as it is the naturally occurring form of the vitamin and raises vitamin D levels more effectively.

*Dosing* -

The recommended dose of vitamin D depends upon the nature and severity of the vitamin D deficiency.

- In people whose 25OHD is <20 ng/mL (50 nmol/L), treatment usually includes 60,000 international units of vitamin D3 by mouth once or more per week for six to eight weeks, and then 800 to 1000 (or more) international units of vitamin D3 daily thereafter.
- In people whose 25OHD is 20 to 30 ng/mL (50 to 75 nmol/L), treatment usually includes 800 to 1000 international units of vitamin D3 by

mouth daily, usually for a three month period. Once a normal level is achieved, continued therapy with 800 international units of vitamin D per day is usually recommended.

- In infants and children whose 25OHD is <20 ng/mL (50 nmol/L), treatment usually includes 1000 to 5000 international units of vitamin D3 by mouth per day (depending on the age of the child) for two to three months.

### **CONCLUSIONS**

Vitamin D inadequacy is a recognized global problem. In the past, vitamin D intake was associated with the treatment and prevention of bone related diseases, whereas its effect in other areas has received little attention. In recent years, vitamin D deficiency has been linked with the pathogenesis and/or progression of several disorders.

Despite the close link of vitamin D to human health, vitamin D inadequacy is not widely recognized as a problem by physicians and patients. Greater awareness of this problem is required among researchers, clinician, and patients of the high prevalence of vitamin D inadequacy.

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