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REVIEW ARTICLE

Hypovitaminosis D Influences Chronic Ailments; Implication for Health

V. Rajalakshimi[1], Vijey Aanandhi M[2]*

[1]Research Scholar, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies (VISTAS), Chennai, India

[2]Professor and Head, Department of Pharmaceutical Chemistry and Analysis, School of Pharmaceutical Sciences, Vels Institute of Science Technology and Advanced Studies (VISTAS), Chennai , India

*Corresponding Author E-mail: **hodpchemistry@velsuniv.ac.in**

ABSTRACT:

In the past two decades,Vitamin D has developed a major space for research and that has transformed from the simple concept that vitamin D is important for the prevention of rickets to more physiological relevance on adults. Hypovitaminosis D being acknowledged as a pandemic, affects almost 50% of the population worldwide. The literature review recommends that the vitamin D insufficiency and its occurrence increases along with latitude, obesity, sedentary lifestyle, limited sunlight exposure and aging. A huge body of evidence revealed that subjects with vitamin D insufficiency have augmented cardiovascular disorder, abdominal obesity, insulin resistance, type 2 diabetes, hypertension and malignancies. The aim of the current review is to make an enhanced understanding of the processes by which deficits in vitamin D cause specific changes in cell and organ functions and thus augment the risk for chronic diseases of different etiology.This article also observed the frequency of vitamin D insufficiency and to assess the prospective inference for skeletal and extraskeletal health. The broad variety of disorders connected with the scarcity of vitamin D in combination with the high occurrence of these conditions signifies a unique challenge for preventive medicine.

KEYWORDS: Chronic diseases, Vitamin D, Deficiency, Health.

INTRODUCTION:

Vitamin D, the sunshine vitamin, as the major source it is obtained from Sunlight. Though it can also be acquired orally all the way through food and supplements. Vitamin D requires hepatic metabolism to produce 25-hydroxyvitamin D (25 (OH)D) which is the recognized dietary biomarker for vitamin D status [1,2]. Almost in the past two decades, significant progress has been made in the study of vitamin D. Primarily, the essential role of vitamin D is in the development of skeletal integrity, but current factsare escalating that vitamin D generates favorable effects on extra-skeletal tissues and that the amounts needed for optimal well-being are possibly advanced than formerly thought [3].

In combination with parathyroid hormone (PTH), vitamin D is accountable for the control of calcium and phosphate homeostasis.

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Vitamin D deficiency leads to calcium deficit, myopathy, and osteomalacia in adults and rickets in children. Increasing evidence also indicates that vitamin D controls the secretion of parathyroid hormone, plays a role in the Renin Angiotensin Aldosterone System (RAAS), regulates the immune system, and may directly affect cardiac muscle [4]. Consequently, vitamin D has an immense effect on forming and preserving sturdy bones. Moreover, recently it has been found that vitamin D receptors be present at various range of cells and as a result, it has a biological outcome on more than only mineral metabolism. The aim of this information is to assess key feature relating to vitamin D deficiency, its causes, and its influences on major conditions/diseases. Thus, following a general literature review on deficiency and its causes, an overview of persistent alarming on ailments due to vitamin D deficit. This methodical approach encloses of reviews listed in Pubmed during the precedent 2 decades.

VITAMIN D –BIOSYNTHESIS:

The two prime biologically inert precursors of fat-soluble vitamin D are vitamin D3 (cholecalciferol) and

vitamin D2 (ergocalciferol), the former is present in human form and the latter is present in plants and invertebrates. Primarily vitamin D is synthesized internally in the skin as vitamin D3 (cholecalciferol) when exposed to ultraviolet B (UVB-270-300nm) radiation in sunlight, but little amounts can also be acquired from animal foods such as oily fish, egg and meat (Table-1). Vitamin D3, that moves in the body attaches to vitamin D binding protein and is quickly transformed into its major circulating form, 25-hydroxyvitamin D (25 (OH)D), by the liver. This 25 (OH)D, along with the persuade of parathormone, mostly converted to the active form 1,25 DHCC by the help of an enzyme 1-alpha-hydroxylase in the kidney. A negligible amount of 25 (OH)D is also converted into 24,25 DHCC [5].Though several additional tissues in the body can convert 25(OH)D to 1,25 DHCC, only the renal conversion appreciably contributes to the circulating 1,25 DHCC levels [6]. The synthesis and regulation of vitamin D is clearly described in the Figure:1

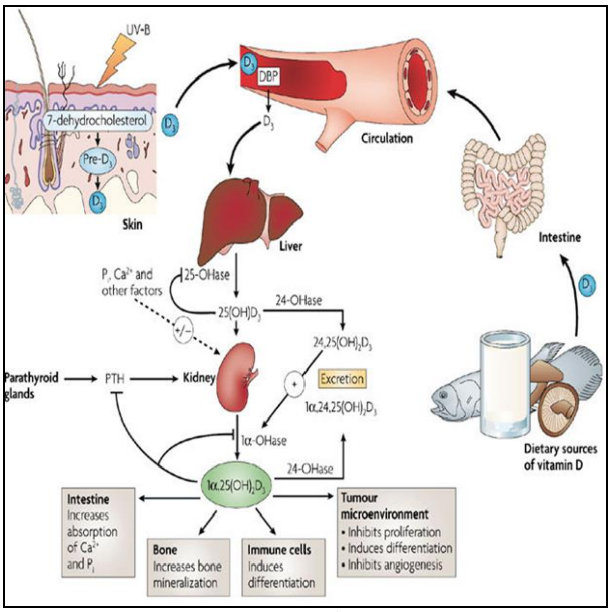

Figure 1: Synthesis and regulation of Vitamin D

The active form i.e., 1,25 DHCC is responsible for many of its biologic role in multiple tissues, including effects on hormone secretion, regulation of immune responses, and modulation of cellular proliferation and differentiation, by controlling gene transcription through the vitamin D receptor (VDR). Serum calcium, phosphorus, and parathyroid hormone (PTH) regulate the circulating levels of 1,25 $(OH)_2D$ by which makes the hormone an inadequate indicator of vitamin D status. Instead, the status is best reflected by the serum 25 (OH)D concentration, which represents the combined amounts of synthesized and dietary vitamin D [7,8].

Table 1: [10]

NATURAL SOURCES	VITAMIN D CONTENT
Exposure to sunlight UVB (5 to 10 minutes of exposure)	3000 IU of vitamin D3
Salmon, fresh, wild (3.5 oz)	600-1000 IU of vitamin D3
Salmon, fresh, farmed (3.5 oz)	100-250 IU of vitamin D3 or D2
Salmon, canned (3.5 oz)	300-600 IU of vitamin D3
Tuna, canned (3.6 oz)	230 IU of vitamin D3
Cod liver oil (1 tsp)	400-1000 IU of vitamin D3
Mushrooms, fresh (3.5 oz)	100 IU of vitamin D2
Egg yolk	20 IU of vitamin D3 or D2

*IU- International unit (1 IU OF VITAMIN D =25 ng)

HYPOVITAMINOSIS D:

The status of Vitamin D has been evaluated by determining the serum DHCC (1,25 dihydroxychole calciferol) levels; While there is no agreement in the finest levels of serum DHCC as it varies with countries, but it is defined by Current International Osteoporosis Foundation guidelines (Table: 1) as vitamin D insufficiency as 1,25 DHCC levels less than 50 nmol/L (20 ng/mL) and deficiency as levels less than 25 nmol/L (10 ng/mL)[9].

Global Status of Vitamin D	Serum 1,25 (DHCC Levels)		Clinical Manifestations
	ng/mL	nmol/L	
Deficiency	≤ 10	≤ 25	Hyperparathyroidism, Rickets, Osteomalacia
Insufficiency	10-20	25-50	high PTH levels, decreased bone mineral density
Hypovitaminosis D	20-28	≥ 50 -70	Less stores of vitamin D, slightly elevated PTH levels
Sufficiency	28-40	70-100	No clinical symptoms

*To convert values for 25-hydroxyvitamin D to ng/ml, divide by 2.50.

The different causes of vitamin D deficiency can be categorized into two wide groups [10]. The primary group comprises of people due to deficient exposure to ultraviolet radiation, there occurs a scarce conversion of inactive vitamin D to DHCC. This is usually seen in the darker skin public, aged persons, less mobilized groups, those working in the organization and extreme consumer of sunscreen [11-13]. The Risk Factors for vitamin D Deficiency are mentioned in the table:2 [14]. The subsequent group embraces the various therapeutic and physical conditions that can direct to vitamin D deficiency [15-19].

Risk Factors for Vitamin D Deficiency
Aged population
Institutionalized or home-bound
Sunscreen usage
Dark pigmentation
Air Pollution
Higher Latitudes
Smoking
Adiposity
Malabsorption syndromes such as celiac disease, Crohn's disease, lactose intolerance, and intestinal damage
Hepatic or Kidney Failure
Anti-Seiziures or Anti-Viral medications

Several studies have reported opposite interaction among serum 25- (OH) D levels and the risk for a broad variety of conditions, including vascular disease [20], autoimmune disorder [21], type 2 diabetes mellitus [22], obesity [23], and cognitive impairment [24]. Numerous promising circumstances, including the persuade of confounders, may explain these associations. For example, vitamin D insufficiency may only act as a replacement indicator for an ill-health status as it reveals an inability to get outdoors for ultraviolet B exposure due to amplified body mass index, manifold co-morbid surroundings, or reduced exercise tolerance. [25]

LINKED TO CARDIOMETABOLIC: CONSEQUENCES:

Vitamin D Deficiency is associated with the advancement of many cardio-metabolic disorders such as hypertension, coronary artery disease (CAD) and diabetes. A rat model of vitamin D deficiency was initially accomplished to prove the association between cardiovascular homeostasis and vitamin D status. This study also established that any deficiency in vitamin D3 can cause intense variation in cardiovascular function, as well as producing the discriminating contractile effect of both cardiac and vascular smooth muscle, indicating that the normal cardiovascular function is well maintained by this vitamin [26]. Though numerous small studies perhaps didnot recognize an efficient role for vitamin D insufficiency in the pathophysiology of hypertension [27, 28], big studies such as the cross-sectional and the cohort and Health Study established a reverse association between serum levels of 25 (OH)D levels and blood pressure [29,30]. The General mechanism for Vitamin D Deficiency provoked cardiac damage has been reviewed in Figure 2

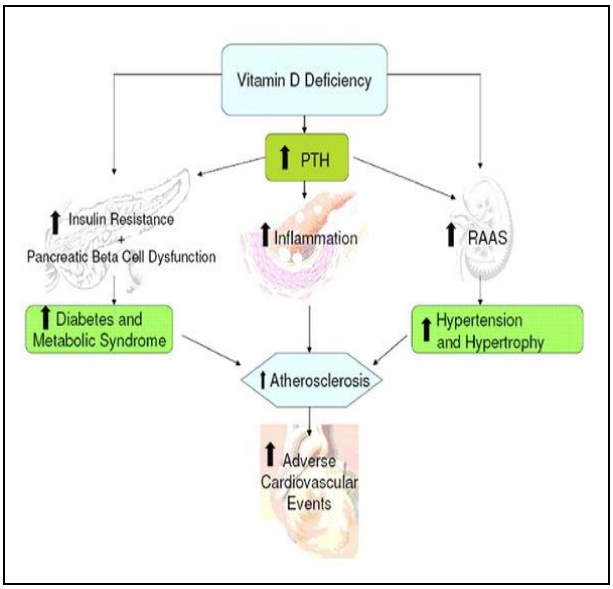

Fig 2: Hypovitaminosis D and CVD Risk

People residing at higher latitudes are at increased risk of hypertension and cardiovascular disease. Moreover, hypertension is also less frequent or less rigorous at elevated altitudes [31]. Frequency rates of vitamin D deficiency and cardiovascular disease amplify with distance from the equator, with elevated rates of ischemic heart disease prominent in nations with lower levels of ultraviolet B exposure [32]. Epidemiologic reviews [33,34] have described an inclination towards the higher occurrence of ischemic heart disease and hypertension with rising distance from the equator, and these higher rates are ascribed to the elevated rates of vitamin D insufficiency in places with less exposure to sunlight. Prior studies [35,36] have established relation exist between low vitamin D levels and augmented plasma renin activity, coronary artery calcification, blood pressure, and cardiovascular disease.

HYPOVITAMINOSIS D AND: ATHEROSCLEROSIS:

An inverse relationship exists between 25- (OH)D levels and subclinical atherosclerosis has been revealed, as calculated by the carotid thickness and computed tomography [37-39]. A survey from National Health and Nutrition Examination Survey (NHANES) [40] observed the relationship between vitamin D and atherosclerosis and described that Hypovitaminosis D was related to higher levels of peripheral arterial disorder. Low serum 25-(OH)D levels are also associated with reduced levels of HDL [41].

HYPOVITAMINOSIS D AND HYPERTENSION:

Numerous research studies [42, 43] have recommended that relationship exists between low 25-(OH)D levels and an advanced risk for hypertension. The proposed mechanism for the link between vitamin D and high blood pressure involves in the inhibition of the Renin AngiotensinAldosterone System by vitamin D. These data are mainly derived from in vitro and animal studies [44, 45]. Earlier studies have revealed an involvement of parathyroid hormone and hypertension. The pathogenesis for such link cannot be clearly emphasized, but current reports [46] propose that parathyroid hormone may augment arterial stiffness and stimulate atherosclerotic transformation by performing in the endothelial smooth-muscle cells.

HYPOVITAMINOSIS D AND HEART FAILURE:

The certainty that the deficiency of vitamin D stimulates the activation of the Renin Angiotensin Aldosterone System (RAAS) and the immune system led to the comprehension that this deficit can cause harmful effects in patients with heart failure. Research executed on patients with decompensated and compensated heart failure and the performance of systolic heart failure patients on the walk test about 6 minutes showed a

constructive correlation between vitamin D deficiency and heart failure [47, 48]. To sum up, from the various studies the fact suggests that subjects with heart failure have reduced serum vitamin D levels.

HYPOVITAMINOSIS D AND CVD RISK:

Consequently, vitamin D deficiency was caught up in numerous types of vascular disease with myocardial infarction (MI), coronary heart disease (CHD), and Ischemic stroke. In an investigational study, about 454 men with cardiovascular disease were reported to have significantly lower levels of 25 (OH)D when compared with 900 matched controls without cardiovascular disease; even after the modification of other risk factors including family history, diabetes, hypertension, race/ethnicity, body mass index, and others, this deficit remained significant [49]. In yet another cross-sectional study it was found that patients with levels below 20 ng/mL had a higher prevalence of cardiovascular disease by measuring serum 25 (OH)D concentrations at a single outpatient visit of more than 400 diabetic patients [50]. A similar study, with 1739 subjects were assessed prospectively and established that vitamin D concentration below 15 ng/mL was found to be constantly linked with an augmented risk of cardiovascular events [51]. Thus, it can be securely mentioned that vitamin D deficiency acts as an independent risk factor for several cardiovascular diseases including MI and CHD.

HYPOVITAMINOSIS D AND DIABETES:

A study by Bayani et.al., [52] where about 120 DM patients selected as a study group and 120 healthy individuals as control group, wherein the results of the study showed that vitamin D concentration was significantly lower in diabetic patients than the healthy individuals. Therefore it was found that vitamin D deficiency has been found to have an inverse relationship with the occurrence of type-2 diabetes mellitus (DM).

In a study in Saudi Arabia, in a total of 340 patients, vitamin D deficiency has been concerned in reduced insulin secretion and augmented insulin resistance, and further currently with development of type 2 diabetes mellitus [53].

Another study suggested an inverse connection amid vitamin D status and A1C levels in the U.S. adult residents about 35–74 years of age and subjects who do not report a history of diabetes. This suggests a mechanistic connection between serum vitamin D concentrations and glucose homeostasis. [54].

Numerous reports suggest that there showed a reduced risk of a type of Diabetes-I on vitamin D supplementation. Even on increasing vitamin D intake during pregnancy lowers the expansion of islet autoantibodies in the progeny [55].

A study by Hypponen et.al. [56], children in Finland were given 2000 IU of vitamin D3 per day during their first year of life and were subsequently given for 31 years, however, it reduced the risk of type 1 diabetes by roughly about 80%. This proved the fact that the adequate vitamin D supplementation for neonates could help to oppose the rising trend in the occurrence of type 1 diabetes.

HYPOVITAMINOSIS D AND METABOLIC SYNDROME:

Current epidemiologic findings suggest that an increased risk of metabolic syndrome is observed in low serum 25-hydroxyvitamin D, an estimate of vitamin D status. A study by Ford, et.al. [57], suggested that the metabolic syndrome was found around 1 in 5 adults. Those patients with metabolic syndrome carried an average of 67.1 nmol/L of 25-hydroxyvitamin D levels which was considerably lower than that in subjects without metabolic syndrome, who had a mean concentration of 75.9 nmol/L.

An article [58] mentioning a study which included a group of healthy (n=126), glucose-tolerant subjects was the first to demonstrate the positive correlation between 25(OH) D concentration with insulin sensitivity index using a hyperglycemic clamp technique. The unpretentious result of vitamin D on insulin sensitivity in individual persons may interpret into a striking effect because of the towering frequency of hypovitaminosis D, which, in a large population, brings a characteristic risk for type 2 diabetes and the metabolic syndrome.

In yet another study by StefaniaMakario et.al [59], patients with metabolic syndrome have lesser 25(OH)Vit D levels compared with non-metabolic syndrome patients. Significantly, it was reported an inverse relationship between 25 (OH) Vit D serum levels and sdLDL-C (small dense), that could be possible through increased triglyceride levels.

In recent times, the importance of vitamin D status as a risk factor in the advancement of metabolic syndrome has been the focal point of numerous studies [60].

HYPOVITAMINOSIS D AND CANCER:

People living at higher latitudes is at increased risk for different types of cancer. A prospective study of vitamin D ingestion and the threat of colorectal cancer in 1954 men showed a direct relationship [1]. A study by Suda et.al [61] showed that leukemic mouse survived longer with the treatment of vitamin D analogues. However, in

the human trials, the results are still disappointing. Some in-vitro studies have shown that the anti-proliferative effect of the vitamin D in the form of 1,25 $(OH)_2$ D exhibited a better response on breast, prostate, and colon cancer cells, osteosarcomas, and melanomas. Numerous epidemiological reports have shown that elevated 25 (OH)D levels are connected with decreased cancer occurrence and reduced cancer-related mortality. (62-67) Addition to this information, there are numerous retrospective and prospective research showed that when serum 25 (OH) D levels are greater than 20 ng/mL (50 nmol/L) have reported decreasing 50% or greater in risk of large bowel cancer and prostate cancer.[63,66,68-72]. Related results have been analyzed for breast cancer. In a study, where women with elevated concentration of 1,25 $(OH)_2$ D had only one-fifth risk of acquiring breast cancer than those subjects without it [73]. Tuohimaa et al. [74]carried out longitudinal case-control study occurrence of prostate cancer in Scandinavian countries along with vitamin D status.

VITAMIN D AND MULTIPLE SCLEROSIS:

As with preceding epidemiological fact reporting a latitudinal risk inclined for cancer and cardiovascular disease a similar risk exists for developing multiple sclerosis. Patients who stayed below 35°N latitude during their first decade had reduced overall lifetime risks of developing multiple sclerosis [1,75,76]. A double-blinded randomized control trials illustrated that subjects who were given vitamin D supplementation had improved serum transforming growth factor β1 levels than those subjects who did not receive supplementation [77]. Similar two observational studies observed from Nurses' Health Study (I and II) stated that increased intake of vitamin D was associated with a lower risk of developing multiple sclerosis [78].

VITAMIN D AND PSORIASIS:

The huge achievement of vitamin D remedy for treating an extra-skeletal disease is in the management of psoriasis.The proliferation of Human keratinocytes is inhibited by 1,25 $(OH)_2D_3$ reported in a study by Smith et.al., [79]. Therefore, the recommended therapy for increased proliferative skin diseases such as psoriasis is proved to be 1,25 $(OH)_2$ D_3. Even the vitamin D topical treatments exhibited a great development in decreasing the lesions and wounds. Vitamin D analogues comprising calcipotriene, are the first-line therapy used for psoriasis. [80-83].

HYPOVITAMINOSIS D AND INFLAMMATORY BOWEL DISEASE:

The two clinically distinct forms of inflammatory bowel disease (IBD), includes Crohn's disease and ulcerative colitis (UC), wherein reports suggested that there is a number of environmental factors to the pathogenesis of IBD, mainly of UC [84]. Vitamin D deficiency might be one of those factors [85,86] and as a consequence of hypovitaminosis D, reduced local production of 1,25-$(OH)_2D_3$ causes inhibition of enhanced T helper cell reaction, which are characteristically connected with chronic enterocolitis [87]. The significance of the vitamin D for the continuance of normal immune responses in the gut is emphasized by the current observation that a deficit of expression of the vitamin D receptor intensifies the symptoms in colitis models [88]. A study by Cantorna et al. [89] exhibited that the active metabolite of vitamin D_3 inhibits the symptoms of IBD in an experimental mouse model.

HYPOVITAMINOSIS D AND RHEUMATOID ARTHRITIS:

A prospective cohort study by Linda A et.al. showed that an inverse association exists between vitamin D and RA risk. This report also stated that vitamin D deficit may be involved in the pathogenesis of rheumatoid arthritis. There are considerable facts from reports with animal models of rheumatoid arthritis that the advantageous consequence of vitamin D on the development of the disease results from its specific immunomodulatory effects. [90]

HYPOVITAMINOSIS D AND SKELETAL DISORDER:

Undoubtedly there is no requirement to highlight the significant role of vitamin D in the prevention of bone disorders such as rickets and osteomalacia. The stimulatory effect of 1,25-(OH) 2D3 has been recognized mostly for the effect of absorption of calcium and phosphate in the intestine. As realistically shown by Owen et al. [91], the fat hormone synchronizes the progression of osteoblast growth by specific VDR-mediated effects on the gene expression and helps in the production of several osteoblast proteins. The inadequacy of vitamin D status therefore not only causes rickets and osteomalacia but is also a significant risk factor for osteoporosis, which is usually caused by an inadequate rate of bone development. Furthermore, hypovitaminosis D could be connected with osteoporosis since, a decrease in serum 25-(OH) D levels augments secondary hyperparathyroidism and, accordingly, elevates osteoclastic bone resorption. [92,93]

CONCLUSION:

Hypovitaminosis D is a universal problem, as measured by 25-hydroxyvitamin D, which is referred as the biomarker for vitamin D status. Risk factors for hypovitaminosis D comprise of deficit exposure to adequate sunlight, inadequate nutritional intake and supplementation, and other causes, including adiposity, age, drug use, sunscreen use, clothing, and pigmentation

of the skin. As most of the cell express vitamin D receptors, the functions of different organs are affected by changes in the activity of 25-(OH)D-1α-hydroxylase. Henceforth we put forward that this kind of changes is likely to occur under the conditions of hypovitaminosis D. Thereby we provide an elucidation on a molecular level from many epidemiological reports that important relationship exists between hypovitaminosis D and the pathogenesis of frequent chronic diseases. We hope that this assumption will further stimulate the discussion on the importance of vitamin D replacement or still supplementation, for preventive and clinical medicine, as this review gives a more insight into the pathogenic consequences of the deficit vitamin D condition.

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