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Review Article

Vitamin D deficiency and its association with non communicable diseases

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Abstract

Vitamin D Deficiency (VDD) has become a worldwide public health problem. Globally about one billion people suffer from VDD. It is well known that vitamin D has an established role in skeletal growth, development and its maintenance. Adequate vitamin D status is also important for optimal function of many organs and tissues throughout the body. Vitamin D receptors are present on a large variety of cell types, including myocytes, cardiomyocytes, pancreatic beta-cells, vascular endothelial cells, neurons, immune cells and osteoblasts. Deficiency of vitamin D leads to skeletal disorders like rickets in children and osteomalacia in adults. Recent evidence suggest that in addition to skeletal disorders VDD is also responsible for exacerbating various non-communicable diseases such as obesity, hypertension, cardio vascular disease, diabetes mellitus, metabolic syndrome, cancer, neurological disorders etc. Due to paucity of scientific evidence on the role of vitamin D in the manifestation of these non-communicable diseases, it becomes necessary to carry out further research and establish the association of VDD with these diseases.

Keywords: Rickets, Osteomalacia, Neurological Disorders, Cancer

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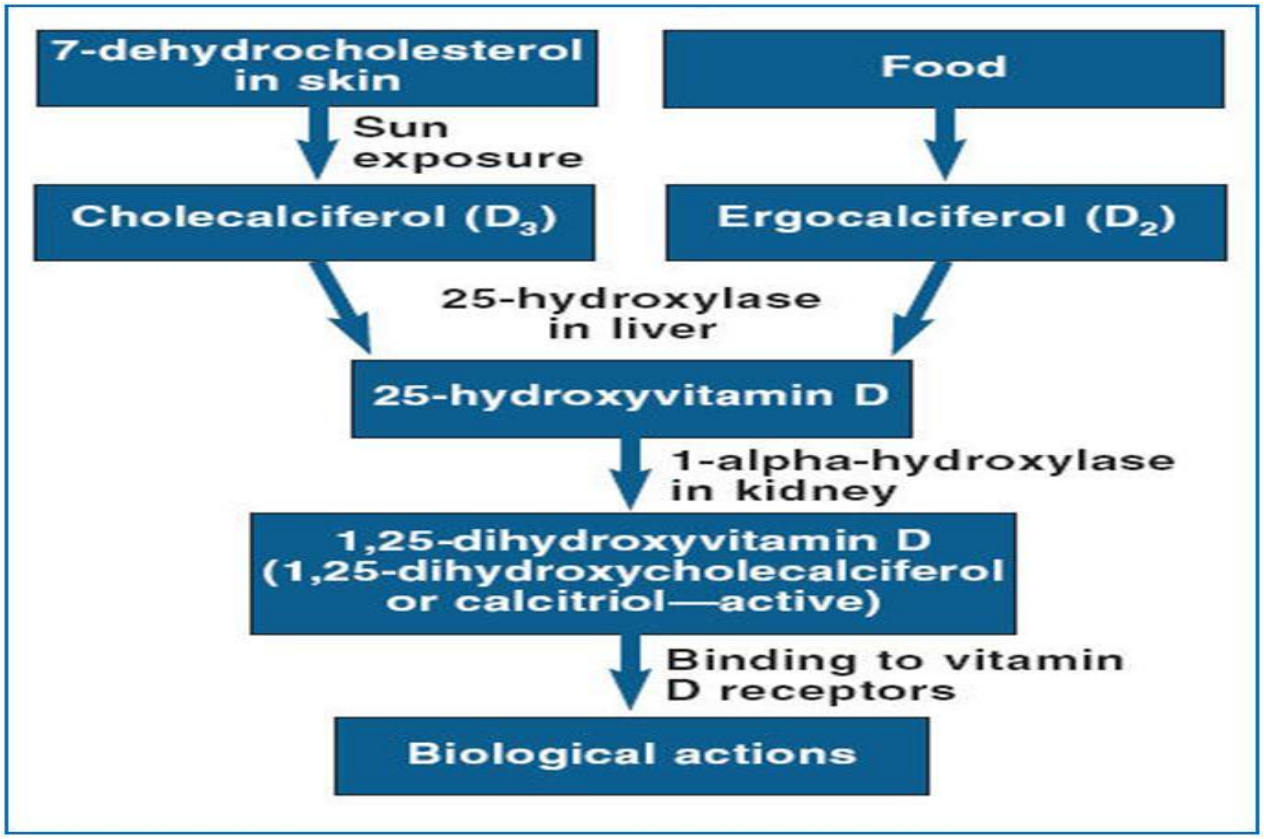
1. Introduction

Vitamin D is a prohormone that is essential for normal absorption of calcium from the gut and for growth, development and maintenance of skeletal system. Vitamin D Deficiency (VDD) is associated with rickets in growing children and osteomalacia in adults [1]. Vitamin D is primarily synthesized in the skin after exposure to ultraviolet radiation (UVR), and <10% of vitamin D is derived from dietary sources [2]. Various factors such as traditional dressing, lifestyle and low sunlight exposure may prevent a large proportion of the population from synthesizing healthy amounts of vitamin D in the body [1]. It has been estimated that worldwide about 1 billion people suffer from VDD [3]. According to various scientific evidence published earlier there is a widespread prevalence of varying degrees (50- 90%) of VDD with low dietary calcium intake amongst Indian population [4]. Apart from its conventionally

understood role in bone health and calcium homeostasis, vitamin D is believed to have an effect on body's endocrine system, immune system, cardiovascular system, neuropsychological functioning, neuromuscular performance and is also believed to act as a potent antioxidant protecting against free radical damage, as well as being an inducer of cellular differentiation, protecting against carcinogenesis [5, 6]. In recent years, significant relationships have been documented between VDD and development of non-communicable diseases, notably cardiovascular diseases and diabetes, as well as their predisposing factors, such as obesity and insulin resistance. Vitamin D also has an important role in glucose and insulin metabolism [7].

Therefore, in this article, the association of VDD with non communicable diseases both in terms of skeletal and non-skeletal diseases would be discussed with the help of studies documented in the past.

Figure: Vitamin D Synthesis [8]



Vitamin D Deficiency and Skeletal Disorders

The primary function of Vitamin D is calcium homeostasis [9]. VDD leads to calcium malabsorption and consequent hyperparathyroidism resulting in increased bone turnover. In addition to this, it also causes increased fragility of bones and reduced acquisition of peak bone mass which results in development of rickets in children and osteomalacia in adults [10,11]. VDD among children also prevents them from reaching their genetically programmed height and peak bone mass. For adults, VDD has more subtle effects on the skeleton [5]. VDD also causes muscle weakness amongst children and adults with osteomalacia [12-16]. VDD had also been associated with poor Bone Mass Density (BMD) in subjects with osteoarthritis of the

knee and hip joint. Several investigators have assessed the possible relation between presence and progression of osteoarthritis of the knee joint and VDD [17,18]. A meta-analysis of 7 RCTs concluded that vitamin D in the range of 700–800 IU/d reduced the risk of hip/non-vertebral fractures by 25% [19]. In India, on an average 25-30 case of patients with VDD related osteomalacia in adolescent and adults are managed in indoor endocrine services every year [20]. Prevalence of knee osteoarthritis in elderly subjects with a mean age of 75 years was assessed and a comparable prevalence of osteoarthritis in vitamin D sufficient and deficient subjects (43.6 versus 50.4%) was reported [19]. The time to get up from a sitting to standing position and to walk eight feet decreased with increasing serum 25(OH) D levels above 14 ng/ml [21]. Nursing home residents receiving 20 µg (800 IU) of vitamin D for five months resulted in a reduced risk of fall by 72% among them [22].

Vitamin D Deficiency and Non Skeletal Disorders

Vitamin D and Obesity:

Obesity is closely associated with VDD and it has been hypothesized that vitamin D deposition in the adipose tissue could be an explanation for this association [23]. It has been shown that changes in body weight are accompanied by changes in 25(OH)D levels [24]. It has also been shown that prevalence of VDD increases with the increase in body mass index (BMI) [25]. Numerous studies and surveys have shown that obesity is associated with lower serum 25(OH)D concentration in multivariate analysis that considered dietary intake, sun exposure, and other potentially influencing factors [25,26]. A study conducted amongst overweight/obese women to prospectively examine the effect of weight loss on serum 25(OH)D concentration in a two year clinical trial documented that the subjects who did not lose weight at 24 months had an increase in serum 25(OH)D of 1.9 (9.7) ng/ml (mean (SD)); subjects who lost 5–10% of baseline weight had an increase in serum 25(OH)D by 2.7 (9.1) ng/ml and subjects who lost >10% of baseline weight had maximum increase in serum 25(OH)D level 5.0 (9.2) ng/ml) [24].

Vitamin D and Hypertension:

Several mechanisms have been proposed on the role of vitamin D in blood pressure regulation and the pathophysiology of arterial hypertension, which is a major risk factor for stroke. Vitamin D has been implicated in the proximal regulation of the rennin-angiotensin system (RAS) and in interacting with the RAS to determine the intracellular calcium surroundings in vascular smooth muscle [27]. The third National Health and Nutrition Examination Survey (NHANES-III), [28] a representative of the non-institutionalized US civilian population, showed that systolic blood pressure and pulse pressure were inversely and significantly correlated with 25(OH)D levels. These results were confirmed by a subgroup analyses, in which the age-associated increase in systolic blood pressure were significantly lower in individuals with vitamin D sufficiency [29,30]. In the Health Professionals' Follow-Up Study (HPFS) and the Nurses' Health Study (NHS), the risk of hypertension incident was greater for individuals with 25(OH)D levels below 15 ng/ml compared with those whose 25(OH)D levels were 30 ng/ml or higher [31-34]. A meta-analysis of 18 studies on blood calcidol concentration and hypertension reported the pooled odds ratio of hypertension as 0.73 [95% confidence interval (CI) 0.63–0.84] for the highest versus the lowest category of blood

calcidol level. In a dose response meta-analysis, the odds ratio for a 40 nmol/L increment in blood calcidol level was 0.84 (95% CI 0.78–0.9). Thus, it was concluded from this meta-analysis that calcidol level is inversely associated with hypertension [35]. An association of VDD with increased RAS activity was studied among patients with hypertension in India. All the three blood pressure parameters [Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP)] were significantly higher among individuals with lower 25(OH)D levels. Mean SBP was 162.4 ± 20.2 mm/Hg and mean DBP was 100.2 ± 11.2 mm/Hg [36]. Data from cross-sectional studies reported that low 25-hydroxy vitamin D levels are associated with higher systolic blood pressure and higher incidence of hypertension [37].

Vitamin D and Diabetes Mellitus:

Several studies have noted an association between vitamin D and the physiological function of the pancreatic β cell. Vitamin D affects pancreatic islet cells through its receptors and may increase insulin secretion. Insulin secretion is calcium dependent and it is reported that vitamin D deficiency may predispose to glucose intolerance, altered insulin secretion and type 2 diabetes mellitus. Vitamin D replenishment improves glycaemia and insulin secretion in patients with type 2 diabetes with established hypovitaminosis D, thereby suggesting a role of vitamin D in the pathogenesis of type 2 diabetes mellitus [38]. Several cohort studies have noted an association between vitamin D depletion and risk of Type 2 Diabetes Mellitus (T2DM). An association was found between low UVB irradiance, indicating a low level of vitamin D, and high incidence of type 1 diabetes, whereas the incidence rate approached zero in regions with high UVB irradiance [39-42]. A trial conducted amongst obese men to determine the short-term effect of vitamin D3 supplementation on insulin sensitivity reported that vitamin D3 supplementation improves oral glucose insulin sensitivity (OGIS) in apparently healthy men likely to have insulin resistance (centrally obese but non-diabetic) [43]. Another study reported that VDD was associated with highly significant increase in the prevalence of diabetes and subjects without risk factors but with severe VDD had an increased likelihood of developing diabetes [44]. A study conducted amongst adult females to establish an association between 25-hydroxyvitamin D (25-OHD) concentration and risk of type 2 diabetes incident reported that higher levels of plasma 25-OHD were associated with a lower risk for type 2 diabetes [45]. Vitamin D status in newly detected youth-onset diabetes (age < 25 years) was estimated in a case control study in India. It was found that vitamin D deficiency was seen in 91.1% of the subjects with diabetes, and 58.5% of the healthy controls. Mean 25(OH)D was significantly low i.e.7.88 ng/mL in subjects with diabetes against 16.64 ± 7.83 ng/mL in controls. Sixty percent of cases had severe Vitamin D deficiency compared with 8.3% in controls [46]. A trial was conducted to study the levels of 25(OH)D3 and the relationship between 25(OH)D3 levels and glycemic control in patients with type 2 diabetes mellitus. Glycosylated hemoglobin (HbA1c) and 25(OH)D3 levels were measured in diabetes mellitus type 2 patients and in control group (non-diabetic patients). It was documented that 25(OH)D3 levels were lower in the diabetes mellitus type 2 patients than in the control group, being 19.26 ± 0.95 ng/ml and 25.49 ± 1.02 ng/ml, in the patient and control groups, respectively and 25(OH)D3 levels were found to be inversely associated with HbA1c levels in the diabetic patients [47]. A study conducted amongst adult men and

women with T2DM showed a significant improvements in serum fasting plasma glucose levels and insulin in a period of 2 months after treatment with vitamin D thus suggesting that vitamin D supplementation could reduce insulin resistance in T2DM [48].

Metabolic Syndrome

A large number of observational studies suggest a relationship between low levels of 25(OH)D and the metabolic syndrome or its individual clinical features [49]. The relationship between 25-hydroxyvitamin D levels and the prevalence and incidence of metabolic syndrome was assessed in a population-based cohort study in Spain. The results showed that mean levels of 25-hydroxyvitamin D were lower in subjects with metabolic syndrome i.e.21.7 (6.21) vs 23.35 (6.29) ng/ml. The prevalence of VDD (25-hydroxyvitamin D<20ng/ml) was 34.7%, with significant differences between subjects with and without metabolic syndrome (34.6 vs 26.5%, P<.01) [50]. Vitamin D status and its association with components of the metabolic syndrome in adolescent girls aged 14-17 years were investigated in Iran. Mean serum 25(OH)D was 7.26 ng/ml and 96 % of the participants had VDD. According to age-modified definitions of the National Cholesterol Education Program Adult Treatment Panel III, Metabolic Syndrome was diagnosed in 10.6 % of the participants [51]. Vitamin D status, the prevalence of vitamin D deficiency and its association with metabolic syndrome risk was investigated among adults aged 20 years or older in Korea. Vitamin D status (25-hydroxyvitamin D [25(OH)D]) was categorized as < 20, 21-29, and ≥ 30 ng/mL, indicatingdeficiency, insufficiency and normal limits. VDD was found in 53.9% of men and 70.5% of women. Mean BMI, systolic BP, HbA1c and low density lipoprotein cholesterol (LDL-C) were highest in the VDD group in both genders. Metabolic syndrome was most prevalent in the VDD group in both genders (12.3% in men and 9.2% in women) [52]. The association of serum 25(OH)D with Metabolic Syndrome was studied in China among subjects aged 20-83 years. The prevalence of VDD (<50 nmol/l) was 39.9 %, with 34.5 % in men and 47.8 % in women. Participants with vitamin D sufficiency had a 35 % lower risk of metabolic syndrome than those with VDD (OR = 0.65, 95 % CI 0.51-0.84, P = 0.0009) [53].

Vitamin D and Cardiovascular diseases:

VDD is associated with increased risk of cardiovascular disease (CVD) and this may be due to the relationship between low vitamin D levels and obesity, diabetes mellitus, dyslipidaemia, endothelial dysfunction and hypertension [54]. Various studies reporting association between CVD and VDD in context of increased prevalence of coronary artery disease (CAD), vascular calcification and essential hypertension have been conducted. [55]. Low levels of 25(OH)D are also associated with increased risk of CVD and mortality. A meta-analysis of seven studies showed that when adjusting for cardiovascular risk factors, the risk of cerebrovascular disease was significantly reduced in individuals with high 25(OH)D levels [56]. Data from randomized controlled trials (RCTs) are sparse and have partially, but not consistently, shown some beneficial effects of vitamin D supplementation on cardiovascular risk factors (e.g. arterial hypertension) [57]. Data from several observational studies indicated that vitamin D deficiency is also an independent risk factor for stroke [56,58]. It has also been found that stroke patients are at high risk of musculoskeletal complications,

including fractures and falls that are related to VDD [59]. The results of a study conducted in India showed that deficiency of 25-hydroxyvitamin D was significantly associated with dyslipidemia. Multivariate analysis also showed that 25-hydroxyvitamin D deficiency was independently associated with dyslipidemia (odds ratio: 1.9; 95%CI:1.1–3.5) [60].

Vitamin D and Cancer:

In addition to bone mineralization and maintainance of calcium balance, vitamin D exerts physiological functions including regulation of growth and differentiation in a broad variety of normal and malignant cells [61-64]. A study conducted in the USA found that Colorectal Cancer (CRC) mortality was inversely related to serum 25(OH)D level [65]. Another study was conducted in the USA with post-menopausal women (mean age 67 years) treated with 1100 IU/day vitamin D3 plus 1.4–1.5 g/day calcium vs calcium alone for 4 years. Treatment with vitamin D3 plus calcium reduced total cancer incidence, including CRC [66]. A study conducted in Germany including postmenopausal women with breast cancer and controls matched on year of birth and month of blood sampling found a strong inverse correlation between serum 25-hydroxyvitamin D level and breast cancer risk for levels below12 ng/mL compared to levels equal to or greater than 30 ng/mL [67]. A study evaluated the circulating levels of 25-hydroxyvitamin D in relation to early-stage non-small cell lung cancer survival patients. After 72 months, 25% reduction in risk of death for the highest versus lowest quartile of the serum vitamin levels was reported [68]. A similar association was obtained in a case–control study that included an ethnically diverse population of Japanese, Latino, African-American, Caucasian and Native Hawaiian participants [69]. A meta-analysis of 35 independent studies confirmed a consistent inverse relationship between serum 25(OH)D levels and CRC risk [70]. The serum vitamin D level in cases of ovarian cancer was studied in India. The median of serum vitamin D levels in cases were 20.1 ng/ml which was significantly lower than that in controls (24.6 ng/ml). Women with low vitamin D levels (bottom 33%) were at a higher risk for epithelial ovarian cancer than those with high levels (top 33%) [71].

Vitamin D and Neurological Disorders:

VDD is associated with several neuropsychiatric disorders including dementia, Parkinson's disease, multiple sclerosis, epilepsy, and schizophrenia [72]. Scientific evidence suggests that subjects who live at higher latitudes are at an increased risk of VDD and are also more prone to develop schizophrenia [73]. An association between Vitamin D deficiency and neurological disorders was investigated among hospitalized patients to indicate its role in physiologic and pathological processes of the nervous system. The results indicated VDD (25OH(D) levels below 20 ng/ml) amongst 58.1% of the subjects. The mean serum 25OH(D) level was 11.6 ± 4.5 ng/mL. VDD was detected more frequently in patients suffering from ataxic syndromes (72.7%), Amyotrophic lateral sclerosis (66.7%), spine lesions (63.3%), polyneuropathies (63.0%), and stroke (62.6%) [74]. Neonatal vitamin D status and its association with risk of schizophrenia were examined in a case control study in Denmark. The quintiles for 25(OH)D3 in the control group were as follows: >19.7, 19.7 to 30.9, 31.0 to 40.4, 40.5 to 50.9, and <51 nmol/L. Compared with neonates in the fourth quintile those in each of the lower 3 quintiles had a significantly increased risk

of schizophrenia (2-fold elevated risk) [75]. An association between vitamin D status and dementia was examined among elders (aged 65–99 years) receiving home care in the United States. The results indicated that mean 25(OH)D concentrations were lower in subjects with dementia (16.8 vs 20.0 ng/mL) and there was a higher prevalence of dementia among participants with 25(OH)D insufficiency (≤20 ng/mL) (30.5% vs 14.5%) [76]. In a study of vitamin D3 supplementation (oral dose of 40,000–200,000 IU bolus in order to normalize VDD, and then a daily maintenance dose of 2000–2600 IU) resulted in improved seizure control in patients with pharmacoresistant epilepsy. Among all patients, the median seizure reduction was 40% [77]. An association of vitamin D with Multiple Sclerosis (MS) was determined in a case control study in India. Cases had significantly lower 25(OH)D levels than matched controls (p = 0.003) and VDD (< 50 nmol/l) was seen in a higher proportion of cases (71.8%) than controls (53.7%) (p = 0.01). The results of the study indicated that serum 25(OH)D showed an inverse relationship with MS [78]. Vitamin D status and its association with depression were investigated among older primary care patients aged ≥60 years in the United States. Lower vitamin D levels were associated with depression. Subjects with depression had a lower 25(OH)D than the non-depressed group subjects (32.7 vs 35.0, P = 0.002). Those with severe VDD were twice as likely to have depression [79]. Vitamin D levels in patients with Parkinson's disease (PD) and its relationship with severity of symptoms and signs were evaluated in Iran. The mean 25(OH)D3 concentration was lower in the PD population than in the normal group. Lower levels of 25(OH)D3 were associated with more severe postural instability and abnormal posture [80]. A meta-analysis of six studies on the 25(OH)D status in Alzheimer's disease (AD) patients showed that AD patients had lower levels of 25(OH)D than healthy controls [81].

Conclusion

Vitamin D is essential for good health. Poor vitamin D status or low circulating concentrations of vitamin D metabolites have been associated with increased risk for numerous diseases, including osteoporosis, several types of cancer, diabetes, hypertension, metabolic syndrome, cardiovascular disease and neurological disorders. Regulation of bone and mineral metabolism is a characteristic vitamin D effect, but the identification of the vitamin D receptor (VDR) in almost all human cells suggests a role of vitamin D also in extra-skeletal diseases. It can be concluded that increased weight loss amongst obese individuals was associated with increase in serum vitamin D levels. Low serum vitamin D levels serve an important risk factor in the development of cancer, type 2 diabetes, cardio vascular diseases and neurological disorders. Amongst hypertensive patients vitamin D sufficiency was associated with decrease in systolic blood pressure. Thus there is a need to further investigate and establish the role of vitamin D deficiency with the reviewed and possible other co-morbidities.

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