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Vitamin D in Rheumatic Diseases: Interpretation and Significance

Binit Vaidya and Shweta Nakarmi

Abstract

The pleiotropic effects of vitamin D on the various metabolic, anticancer, and immunomodulatory functions of the body based on the presence of vitamin D receptors (VDR) on various cell types has been recognized worldwide now. Of few understood mechanisms of immunomodulatory actions of vitamin D are the suppressive action on the maturation of antigen-presenting cells and decrease in the levels of pro-inflammatory cytokines. Vitamin D deficiency has been implicated in the immune diseases like rheumatic diseases, asthma, psoriasis, and multiple sclerosis. Vitamin D deficiency has been associated with increased frequency and severity of disease flares in rheumatic diseases like lupus and rheumatoid arthritis. Other studies have shown higher prevalence of persistence and evolution in to more definite rheumatic disorder in undifferentiated arthritis and undifferentiated connective tissue disorder patients with vitamin D deficiency. Multiple factors like avoidance of sunlight, the use of corticosteroids and hydroxychloroquine, skin pigmentation, etc. should be considered when evaluating vitamin D levels in these patients, needless to say the consideration of higher-dose supplement for these patients. It is thus prudent that all patients with established or undifferentiated rheumatic diseases are evaluated for vitamin D status and an adequate supplementation is recommended to prevent the associated consequences.

Keywords: vitamin D, vitamin D deficiency, immunomodulation, rheumatic diseases, inflammation

1. Introduction

Vitamin D has two bioequivalent forms, D2 (ergocalciferol) and D3 (cholecalciferol). It is synthesized mainly from 7-dehydrocholesterol in keratinocytes of the skin stimulated by UVB of sunlight and metabolized in the liver to 25(OH)D and subsequently converted to its active form 1,25(OH)₂D in the kidney [1, 2]. It maintains calcium and phosphorus homeostasis, optimizes bone health and muscle function and immunomodulation, has antiproliferative effect on keratinocytes, and suppresses cytokine production [3, 4]. Serum 25(OH)D3 level of at least 50 nmol/l is considered to be optimal for bone health and extra skeletal effects [5]. The term hypovitaminosis D includes vitamin D insufficiency and deficiency. Vitamin D insufficiency is defined as a serum 25(OH)D concentration of 21–29 ng/ml (50–75 nmol/L), whereas deficiency means serum 25(OH)D level of <20 ng/ml (<50 nmol/L) [6].

Vitamin D is also known as the sunshine vitamin. The importance of sunlight for human health came into light with the industrial revolution in Northern Europe [7]. Sniadecki first published an article in 1822 about high prevalence of rickets in children who lived in the inner city in comparison to those who lived in the rural areas [8]. Many observations regarding the sun exposure and rickets have been published in the course of time. Studies have also revealed the high prevalence of vitamin D deficiency in general population, mostly owing to lack of sun exposure.

2. Vitamin D structure, synthesis, and metabolism

Vitamin D is a fat-soluble seco-steroid made from four cholesterol rings IOM (Institute of Medicine) [9]. It has two bioequivalent forms, D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D2 is derived from the plant sterol ergosterol [1, 9]. Vitamin D from the diet or dermal synthesis is biologically inactive [10]. Vitamin D3 is synthesized mainly from 7-dehydrocholesterol in keratinocytes of the skin stimulated by UVB of sunlight [3]. Under the influence of sunlight (ultraviolet radiation, action spectrum 280–320 nM, or UVB), 7-dehydrocholesterol in the epidermis is converted to vitamin D (**Figure 1**). Keratinocytes express the vitamin D receptor (VDR) due to which they are capable of responding to the 1,25(OH)₂D produced [11]. Both UVB intensity and skin pigmentation level contribute to the rate of D3 formation [12]. D3 is converted to 25(OH)D (calcidiol) in the liver by a number of enzymes. 25-Hydroxyvitamins D2 and D3 produced by the liver enter the circulation and the kidney bound to vitamin D-binding protein. The kidney metabolizes 25(OH)D to the active metabolite 1,25(OH)₂D3.

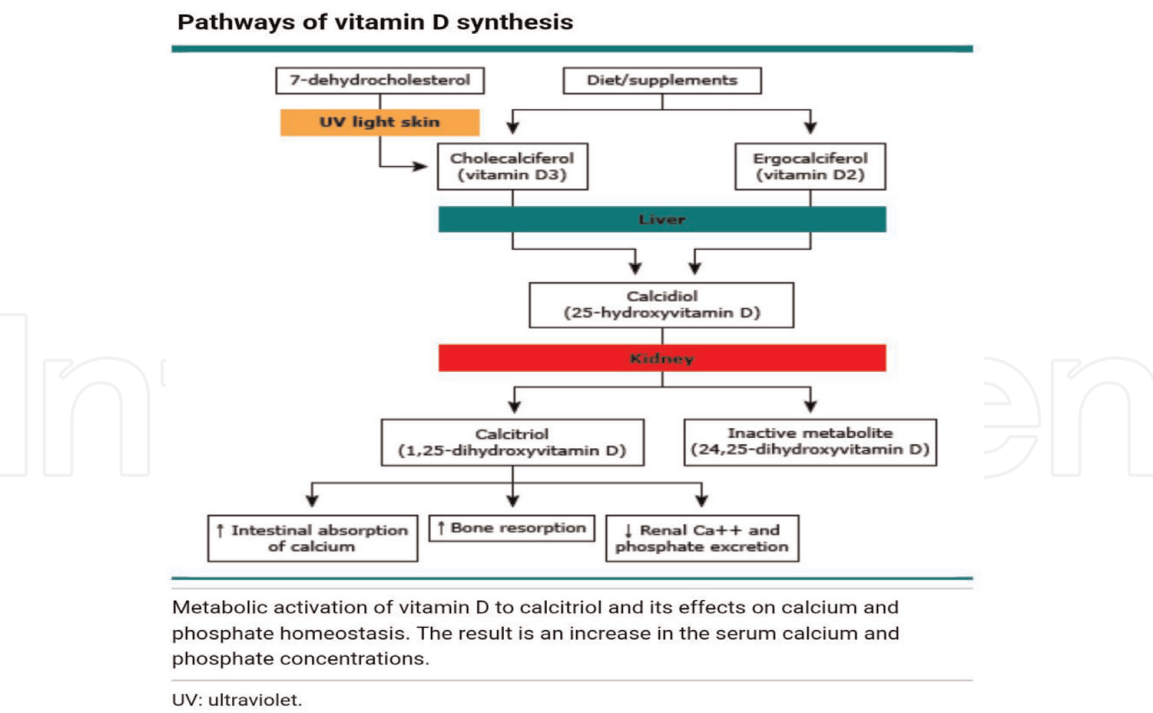


Figure 1.
Overview of vitamin D, UpToDate 2019.

3. Sources of vitamin D

More than 90% of vitamin D requirement comes from sunlight. According to Holick, exposure of ≥20% of the body’s surface to either direct sunlight or tanning

bed radiation is effective in increasing blood concentrations of vitamin D₃ and 25-hydroxyvitamin D₃ [25(OH)D₃]. One minimal erythral dose (MED) is equivalent to 10–50 times the recommended intakes [3]. Oily fishlike salmon, mackerel, sardines, and cod liver oil are also considered good sources of vitamin D [13].

4. Causes of vitamin D deficiency

There are numerous causes of vitamin D deficiency. Decreased synthesis from the skin is one of the main causes. Less exposure to sunlight, lifestyle, skin pigmentation, abundant use of sunscreen lotion, and geographical variation owe to less dermal synthesis. Decreased bioavailability due to malabsorption, decreased synthesis of active form of vitamin D due to liver or renal failure, or increased catabolism with the use of various medications like glucocorticoids and anticonvulsants also cause deficiency. VDD is also seen in diseases like rickets, osteomalacia, hyperparathyroidism, and granulomatous disorders [14].

5. Daily recommended dose of vitamin D

The daily recommended allowance of vitamin D is 400–600 IU in children and adults and 800 IU in adults >70 years [9].

6. Clinical applications

1. Bone and vitamin D: Vitamin D maintains calcium and phosphorus homeostasis and optimizes bone health and muscle function [4]. Adequate vitamin D is necessary to prevent rickets and osteomalacia [3]. Though still controversial, it is reported that calcium and vitamin D supplementation prevents fall risk and also decreases the osteoporotic fracture in older adults [15]. Vitamin D supplementation of 700–800 IU per day reduces falls and fractures in older adults [16].
2. PTH and vitamin D: There is an inverse relationship between circulating 25 (OH)D levels and parathyroid hormone (PTH) [1].
3. Muscle function and vitamin D: There are several studies that suggest a relationship between vitamin D and muscle function. Though improvement of muscle strength with supplementation of vitamin D has been observed in few trials [17, 18], the causal relation has not been established yet.
4. Skin and vitamin D: 1,25(OH)₂D analogs calcipotriol and maxacalcitol can be used for the treatment of the hyperproliferative skin diseases like psoriasis [3, 19] and non-melanoma skin cancer [20].
5. Cancer and vitamin D: Vitamin D deficiency has been associated with cancers, especially colorectal [21, 22]. Calcium and 1,25(OH)₂D₃ participate in the regulation of keratinocyte proliferation and differentiation and may prevent the development of skin cancer [20]. Observational studies have shown the relationship between vitamin D deficiency and carcinoma of the breast, colon, and thyroid [3], but the results are not consistent.

6. Immune system and vitamin D: Vitamin D is a potent immunomodulator. 1,25(OH)₂D decreases the maturation of dendritic cells (DCs) decreasing their ability to present antigen and to activate T cells [23]. Furthermore, it suppresses production of IL-12 (important for Th1 development), IL-23, and IL-6 (important for Th17 development) [24]. But, there is no any approved vitamin D drug for immune modulation [1]. Studies have suggested an association of vitamin D with autoimmune diseases like multiple sclerosis [25] and asthma [26].
7. Cardiovascular disease and vitamin D: There is an inverse relationship between vitamin D deficiency and risk of heart disease, myocardial infarction, and early death. Low vitamin D causes increased parathyroid hormone release, inflammation, proliferation of vascular smooth muscle cells, insulin resistance, thrombogenicity, dyslipidemia, and progressive extracellular matrix remodeling. All of these are associated with increased risk of ischemic heart disease, myocardial infarction, and early death [27, 28].
8. Diabetes mellitus and vitamin D: Vitamin D deficiency is associated with insulin resistance. 1,25(OH)₂D promotes increased lipogenesis and decreased lipolysis. The pancreatic B cell expresses the VDR, and 1,25(OH)₂D promotes insulin secretion [29].
9. Neurological disorder and vitamin D: Vitamin D plays an important role in brain development as it has effects on neuronal proliferation, differentiation, migration, and apoptosis [30].

7. Vitamin D and immunomodulation

Vitamin D is involved in modulation of immune responses and has an important role in some autoimmune diseases like multiple sclerosis, diabetes mellitus, psoriasis, systemic lupus erythematosus (SLE), RA, etc. [31]. The biological effects or immunomodulation is mediated by the vitamin D receptor (VDR) which belongs to the nuclear hormone receptor family and is expressed in most cell types including macrophages, dendritic cells, B and T lymphocytes, and neutrophils [31, 32].

Along with the modulatory effects on T and B cell functions, VDR agonists inhibit the differentiation and maturation of DCs, thus influencing the function of DCs and promoting tolerogenic properties that favor the induction of regulatory T cells. VDR also downregulate expression of the costimulatory molecules CD40, CD80, and CD86, decrease production of IL-12, and increase production of IL-10. The inhibition of DC differentiation and maturation and production of pro-inflammatory mediators play an important role in the immunoregulatory activity of 1,25(OH)₂D₃ [33, 34].

1,25(OH)₂D₃ also plays an important role in the maintenance of B cell homeostasis. It has potent effects on functions of B cell, including induction of apoptosis and inhibition of proliferation, generation of memory B cells, plasma cell differentiation, and immunoglobulin production [35].

According to Grant, there is evidence in support of vitamin D reducing the risk of many autoimmune diseases including such as multiple sclerosis and type 1 diabetes mellitus. However, evidence for rheumatoid arthritis, osteoarthritis, type 2 diabetes mellitus, hypertension, and stroke is weak [36].

8. SLE

Vitamin D deficiency is quite prevalent in SLE patients which may be attributable to various reasons. Avoidance of sunshine, photoprotection, renal insufficiency, and the use of medications which alter the metabolism of vitamin D or downregulate the functions of the vitamin D receptor like glucocorticoids, anticonvulsants, antimalarials, and the calcineurin inhibitors are some of the causes of VDD as shown in **Figure 2** [37]. In a study by Toloza, vitamin D insufficiency was found in 66.7% and deficiency in 17.9% of SLE patients [38]. The frequency varied in different studies: Saudi Arabia (89.7%) [39], Norway (82%) [40], Poland (71%) [41], Hong Kong (27%) [42], and the United States (20%) [43]. Low serum vitamin D levels were related to cumulative glucocorticoid dose [38]. Corticosteroids accelerate the catabolism of 25(OH)D and 1,25(OH)₂D and have a significant role in secondary osteoporosis [44]. Patients taking corticosteroids often require higher daily doses of vitamin D to maintain adequate levels [45]. Similarly, a commonly used antimalarial, hydroxychloroquine (HCQ), inhibits conversion of 25(OH)D to 1,25(OH)₂D leading to low levels of vitamin D [46].

A review by Sakthiswary demonstrated a substantial evidence in support of the association between vitamin D levels and SLE disease activity. However, vitamin D level is not associated with organ damage [47]. A study by Suzan showed a significant negative correlation that existed between 25(OH)D and anti-dsDNA and a positive correlation between 25(OH)D levels and C4 [48]. Another similar study showed a significant negative correlation between the serum concentration of vitamin D and the standardized values of disease activity scores as measured by the SLEDAI-2K and ECLAM scales [49]. An Australian study showed that low vitamin D

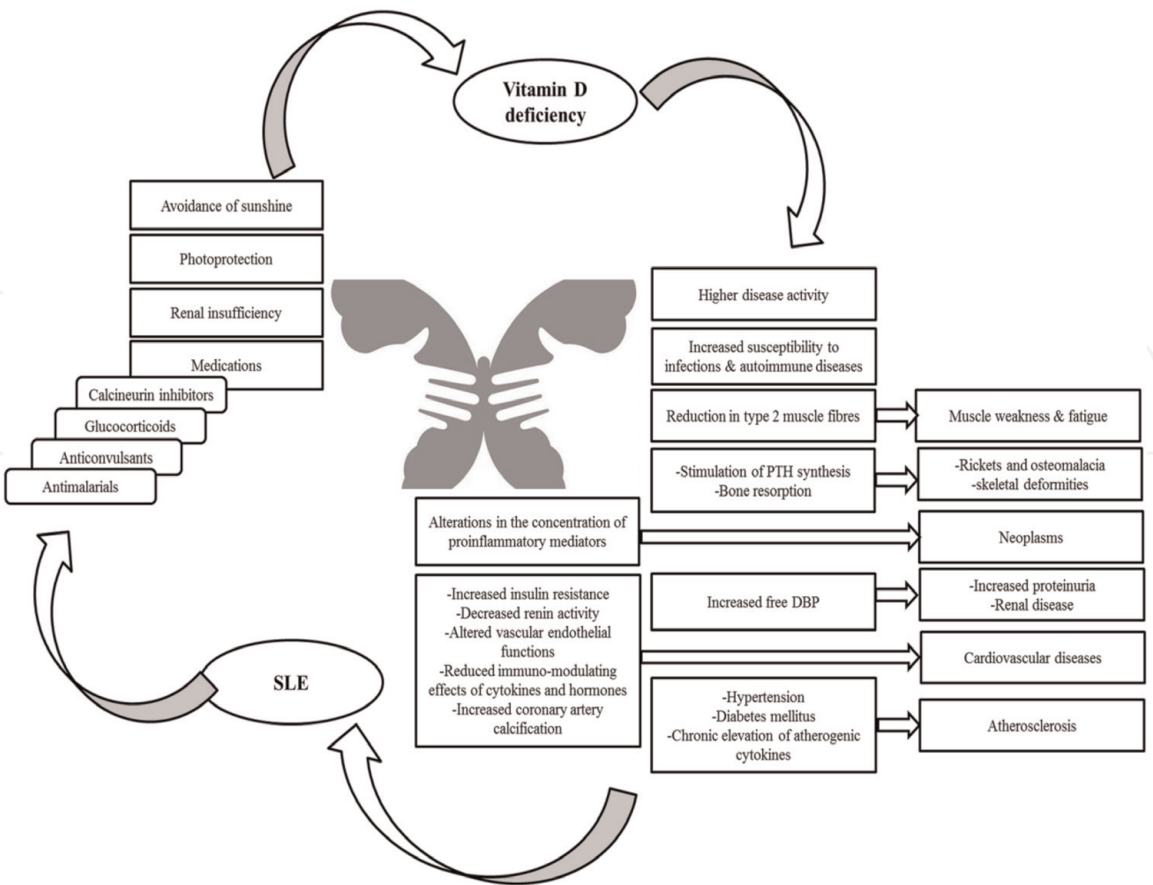


Figure 2.
The two-sided relation between vitamin D and SLE showing that low levels of vitamin D resulted from SLE and SLE complications that come from vitamin D deficiency [37].

was associated with a higher disease activity and an increase in serum vitamin D was associated with reduced disease activity over time [50]. Improving vitamin D status may improve other common manifestations as well, such as fatigue [51] and cognitive dysfunction [52].

9. RA

The role of hypovitaminosis D in the pathogenesis of rheumatoid arthritis has been the topic of interest in the recent past. Lower vitamin D levels possess increased risk for RA [53]. $1,25(\text{OH})_2\text{D}_3$ contributes to the regulation of matrix metalloproteinase and prostaglandin E₂ production by synovial fibroblasts and articular chondrocytes in RA [54].

High rates of vitamin D deficiency have been observed in patients with rheumatic diseases. A study demonstrated that in patients with RA, VDD was seen in 64% and insufficiency in 28%. Similarly, in spondyloarthritis (SpA) patients 48% had VDD and 35% had insufficiency [55]. The prevalence of VDD is quite in RA patients. The COMEDRA study showed that 55.8% of RA patients had vitamin D insufficiency and 3.6% had deficiency [56]. Eighty-four percent of RA patients were VDD in a recently published study by Meena. It also showed a significant inverse correlation between serum vitamin D levels and RA disease activity [57]. A meta-analysis by Lee and Bae supported this result suggesting that the vitamin D level is associated with susceptibility to RA and RA activity [58]. Similarly, a negative association between serum vitamin D and RA disease activity was demonstrated in few studies [59–62]. Levels of $25(\text{OH})\text{D}_3$ were also found to be negatively correlated to CRP and ESR [62]. However, relationship between $25(\text{OH})\text{D}$ and levels of rheumatoid factor or anti-cyclic citrullinated peptide antibodies has not been established yet [63].

The COMORA study showed that vitamin D was insufficient in 54.6% and deficient in 8.5% of the RA patients. Low levels of vitamin D were associated with disease activity of RA and corticosteroid dosage and comorbidities like lung disease and osteoporosis therapy [64].

10. CTD

In comparison to healthy adults, VDD is more prevalent in people with autoimmune diseases including connective tissue diseases (CTDs) [65]. It may also have a pivotal role in progression of undifferentiated CTDs to well-defined and more severe disease [65]. There are few evidences which showed the antifibrotic property of vitamin D [66]. Low vitamin D levels are also associated with more severe disease, low diffusing capacity for carbon monoxide (DLCO), and advanced-stage nailfold capillaroscopy changes in patients with scleroderma [67, 68]. However, a recent meta-analysis revealed that though VDD is quite common in scleroderma patients, it does not correlate to the disease activity [69].

Over the years, it has been proven that vitamin D is necessary for optimum muscle and bone health. In CTDs, vitamin D levels correlate with intensity of muscle weakness [68, 70]. It may also be considered as one of the risk factors in developing myositis [71]. However, the role of vitamin D in myositis or other CTDs has not been established yet. Studies have shown that in fibromyalgia, VDD is correlated with pain and disease activity [72] and correction of deficiency improves the symptoms [73].

11. Undifferentiated arthritis


Significant association has been reported between vitamin D deficiency and nonspecific musculoskeletal pain, arthralgias, or undifferentiated arthritis [74, 75]. A positive correlation of VDD with undifferentiated arthritis [76] and early inflammatory arthritis [77] has been observed. It has also shown VDD as one of the risk factors of disease progression to RA [76, 78].

Author details

Binit Vaidya* and Shweta Nakarmi
National Center for Rheumatic Diseases, Kathmandu, Nepal

*Address all correspondence to: drbinitvaidya@yahoo.com

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