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## Vitamin D and Autoimmune Disease

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### 1. Introduction

During the past decade, important advances in the study of vitamin D have been made as vitamin D insufficiency is emerging as a clinical problem at a global level. In addition to its important role in skeletal development and maintenance, evidence is mounting that vitamin D produce beneficial effect on extraskeletal tissues. Recent evidence shows that vitamin D deficiencies contribute autoimmune diseases susceptibility and severity. This chapter will provide a systematic review of the importance of vitamin D in preexisting autoimmune diseases and whether its deficiency predispose patients to such disorders.

### 2. Agenda

- Overview of vitamin D: structure, sources and metabolism
- Mechanism of vitamin D modulation of the immune responses, the difference between the bone and autoimmune tissues and the role of the vitamin D receptors.
- The optimum serum level of vitamin D for skeletal health
- Vitamin D and autoimmune disease: list of al the autoimmune diseases in which vitamin D is related to
  - Rheumatoogical
  - Non rheumatoogical
- Vitamin D level and vitamin D supplementation in
  - RA
  - SLE
  - Scleroderma
  - Ankylosing spondylitis
  - Undifferentiated connective tissue disease
- The immunological basis for the vitamin D role in preventing autoimmunity
- Summary
- Appendix: 1 Abbreviation

### 3. Vitamin D structure

Vitamin D is a secosteroid which carries a structure similar to steroid except that two of the B-ring carbon atoms (C9 and 10) of the typical four steroid rings are broken, in this case by ultraviolet B sunlight. It is considered as a prohormone. The main source of vitamin D is *denovosynthesis* in the skin through ultravioletirradiation of 7-dehydrocholesterol. It is biologically inert and mustbe metabolized to 25-hydroxyvitamin D<sub>3</sub>in the liver and then to 1 $\alpha$ , 25-dihydroxyvitamin D<sub>3</sub>in the kidney before it becomes functional **Figure 1.** (1, 2)

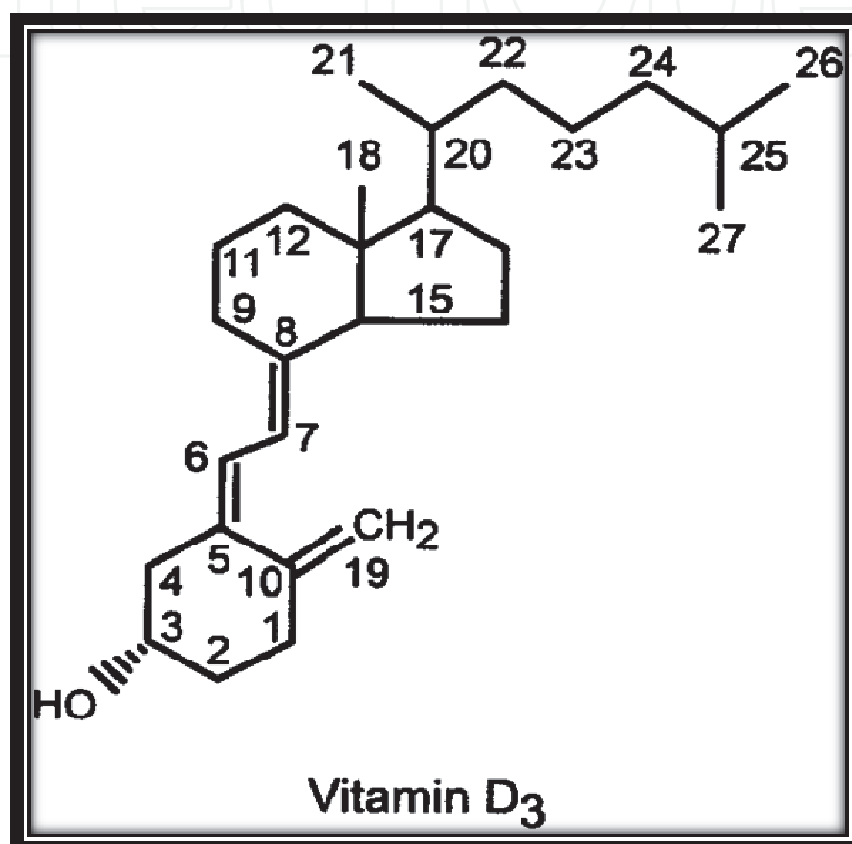


Fig. 1. Structure of vitamin D<sub>3</sub>, or cholecalciferol

### 4. Source of vitamin D

The main source of vitamin D is *de novo* synthesis in the skin. Although vitamin D is present in food, dietary intake alone is often insufficient, supplying only 20% of the body's requirements (3). It is not found in plant materials (eg, vegetables, fruits, or grains) and is present in low levels in meats and other animal food sources, except in rare cases such as fish liver oils (2).

### 5. Metabolism of vitamin D

The terminology related to the biochemistry of vitamin D can be confusing. Vitamin D has 2 forms and several metabolites. The 2 forms are vitamin D<sub>2</sub> and vitamin D<sub>3</sub>, also called ergocalciferol and cholecalciferol, respectively (4).

Both forms of vitamin D undergo identical metabolism (Figure 2). Some evidence indicates that vitamin D<sub>2</sub> may be metabolized more rapidly than vitamin D<sub>3</sub>, but with regular daily intake they can be considered bioequivalent. Both forms of vitamin D are converted to 25-hydroxyvitamin [25(OH)D] in the liver, and the serum level of 25(OH) D is measured to determine the adequacy of vitamin D status. In the kidney, 25(OH)D is hydroxylated to 1, 25-dihydroxyvitamin D [1, 25(OH)<sub>2</sub> D], which is the only biologically active form of vitamin D. Acting principally on the duodenum, 1, 25(OH)<sub>2</sub> D increases calcium absorption. It also acts on bone cells, both osteoblasts and osteoclasts, to mobilize calcium. The synthesis of 1, 25(OH)<sub>2</sub> D is tightly regulated and stimulated primarily by serum parathyroid hormone (PTH) (4).

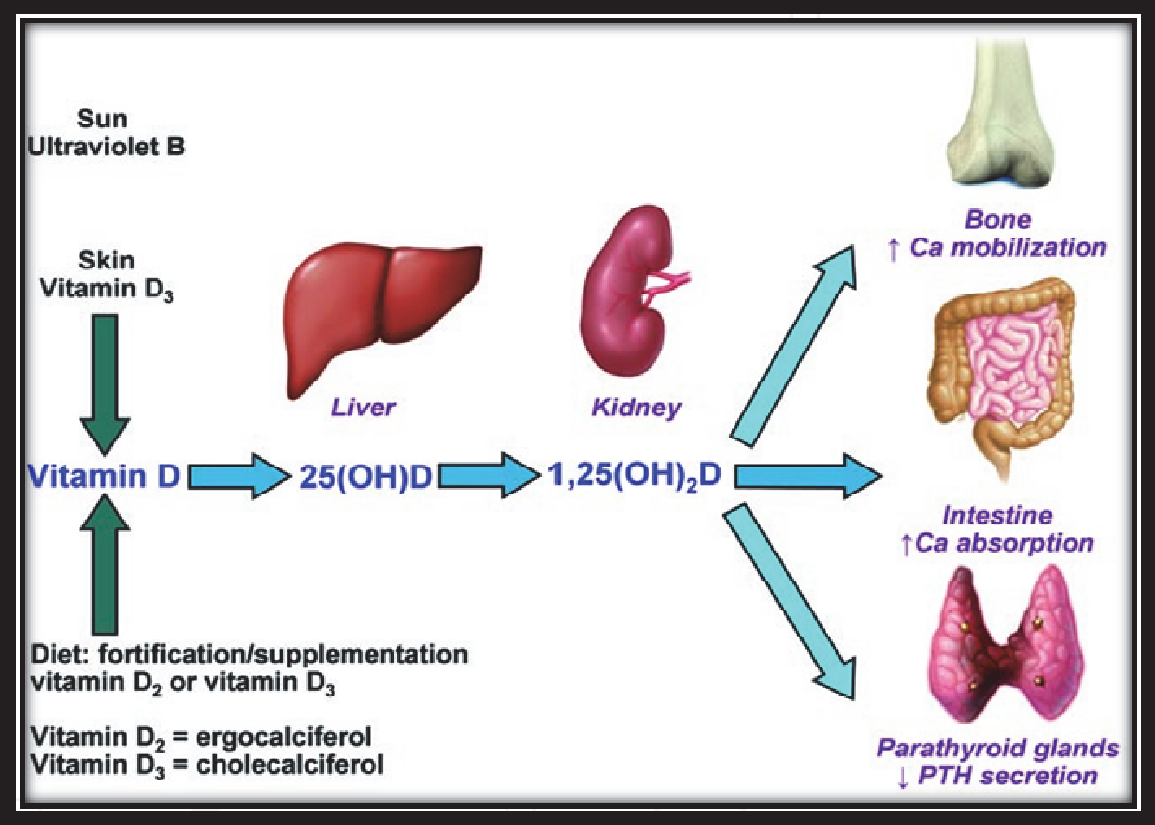


Fig. 2. Vitamin D metabolism. Ca = calcium; 1, 25(OH)<sub>2</sub>D = 1, 25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; PTH = parathyroid hormone.

6. Vitamin D and autoimmune disease

Vitamin D and its prohormones have been the focus of a growing number of studies in past years, demonstrating their function not only in calcium metabolism and bone formation, but also their interaction with the immune system. This is not surprising, since vitamin D receptors (VDR) are expressed in different tissues, such as brain, heart, skin, bowel, gonads, prostate, breasts, and the immune cells(3).

Epidemiological studies have linked vitamin D status with autoimmune disease susceptibility and severity (5). Potentially, vitamin D deficiency could be a clinical problem of global proportions.

7. The mechanisms of vitamin D immunomodulation

Dendritic cells (DCs) are primary targets for the immunomodulatory activity of 1, 25(OH)2D3, as indicated by inhibited DC differentiation and maturation, leading to down-regulated expression of MHC-II, costimulatory molecules (CD40, CD80 and CD86) and decreased production of IL-12. Moreover, 1, 25(OH)2D3 enhances IL-10 production and promotes DC apoptosis. Together, these effects of 1, 25(OH)2D3 inhibit DC-dependent T-cell activation. In particular, the active synthesis of 1, 25(OH)2D3 seems to exert an autoregulatory function by inhibiting the differentiation of monocyte precursors into immature DCs and the subsequent ability of the immature DCs to undergo terminal differentiation in response to maturation stimuli (Fig. 3).

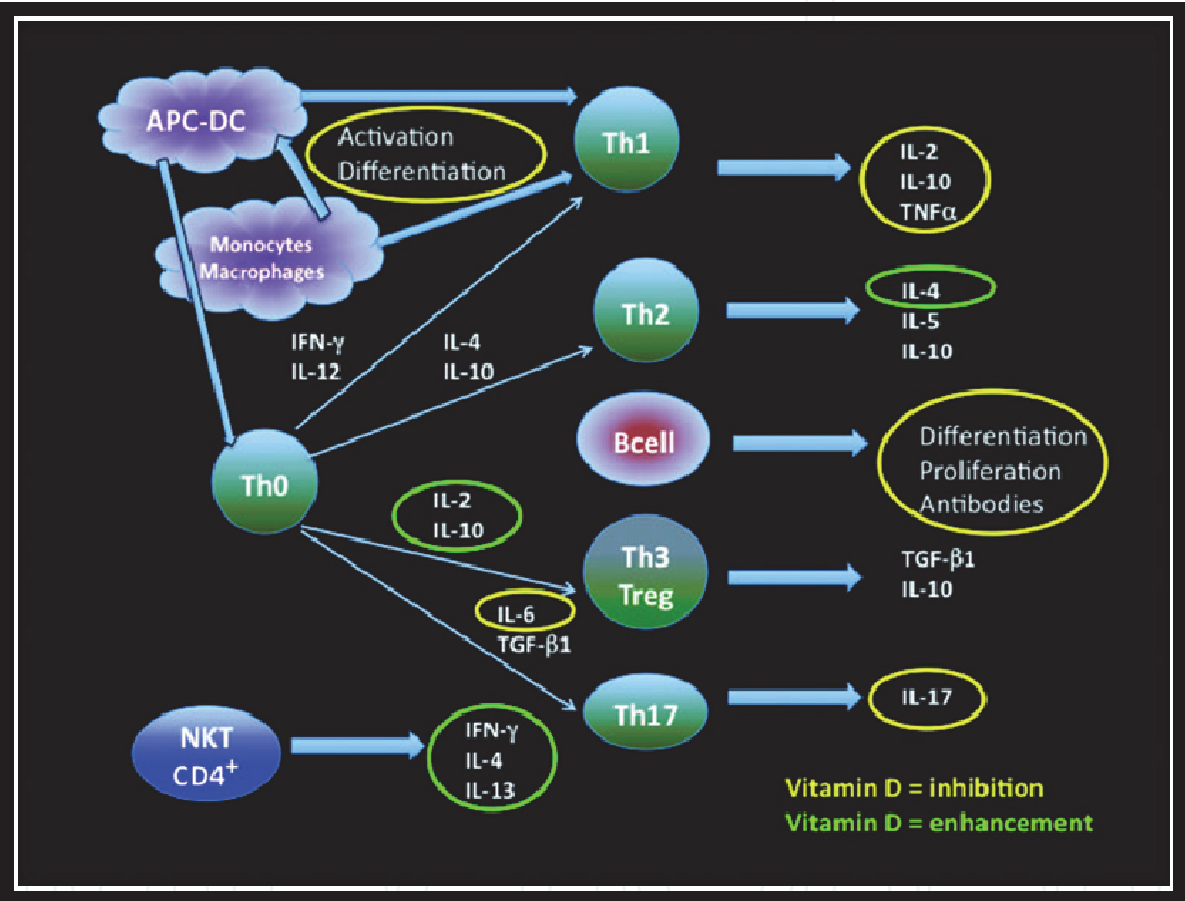


Fig. 3. Mechanisms involved in vitamin D modulation of the immune responses. DCs are primary targets for the immunomodulatory activity of 1, 25(OH)2D3, as indicated by inhibited DC differentiation and maturation, together with inhibition of differentiation of monocyte precursors into immature DCs. 1, 25(OH)2D3 suppresses Th1 (and Th17) driven cytokine responses, induces Treg cells, induces IL-4 production (Th2) and enhances NKT-cell function. Differentiation and maturation of B cells is also inhibited. Th are CD4+ helper cell subsets (Th1, Th2, Th3-Treg, Th17) originating from naive T cell (Th0). Thin arrows (left) indicate cytokines that induce differentiation of Th0 cells and thicker arrows (right) indicate cytokines produced by activated Th cell subsets. All T cells that have been tested express the VDR. B cells and NKT cells are also reported. The yellow circles indicate the cytokines/activities inhibited by vitamin D. On the contrary, the green circles indicate the cytokines enhanced by vitamin D.

Target cell population	Actions mediated by 1. 25(oH)3 D3
APCs (monocytes, macrophages, dendritic cells)	inhibits the expression of class II MHC molecules inhibits the expression of costimulating molecules (CD40, CD80, and CD86) and other maturation inducing proteins (CD1a, CD83) increases chemotaxis and phagocytosis of monocytes and cytotoxicity against tumor cells and bacteria inhibits the maturation of dendritic cells induces tolerogenic dendritic cells capable of inducing Treg cells inhibits the release of IL-12 p70 inhibitsproinflammatory cytokines (IL-1 and TNF) by monocytes and macrophages.
T lymphocytes	inhibits T cell proliferation, secretion of cytokines, and progression of the cellular cycle from G1a to G1b increases the production of IL-4, IL-5, IL-10 inhibits IL-12, INF-γ, and IL-2 inhibits activation of antigenspecific T lymphocytes inhibits the expression of FasL by activated T lymphocytes
B cells	Expresses vDR Suppresses IgE secretion
NK cells	inhibits INF-γ

Table 1. Actions of vitamin D in the immune system

Tolerogenic DCs induced by a brief treatment with1, 25(OH)2D3or its analogues can induce CD4+ CD25+ T regulatory (Treg) cells that are able to mediate transplantation tolerance and arrest the development of autoimmunity (i. e. autoimmune diabetes). Tolerogenic DCs, however, may not always be necessarily involved in the generation of T-reg cells by VDR agonists and a combination of 1, 25(OH)2D3 and dexamethasone has been shown to induce naïve CD4+ T cells (Th0) to differentiate in vitro into IL-10-producing Treg cells, even in the absence of antigen-presenting cells. VDR agonists not only favour induction of CD4+CD25+ Treg cells and enhance their suppressive activity, but can also promote their recruitment at inflammatory sites. Furthermore, 1, 25(OH)2D3 treatments induced natural killer (NK) T-cell functions *in vitro* and *in vivo*. NKT cells are early innate regulatory cells that can alter the outcome of autoimmunity. Therefore, two types of cells are induced by 1, 25(OH)2D3; the Treg and the NKT cells; induction of these regulatory cells and direct inhibition of Th1 cells are the mechanisms by which 1, 25(OH)2D3 suppresses experimental autoimmunity. In addition, treatment with VDR agonists inhibits the T-cell production of IL-17, a pro-inflammatory cytokine that is produced by pathogenic T cells (Th17) in various models of organ-specific autoimmunity in the brain, heart, synovium and intestines.



nmol/L	ng/mL	Health status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30–50	12–20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

Table 2. Classification of Vitamin D Status by 25(OH)D Concentration

Interestingly, IL-17 production is sustained by IL-23, an IL-12 family member consisting of p19 and p40 chains, the latter of which is strongly inhibited by VDR agonists. Recently, 1, 25(OH)2D3 treatment induced a significant inhibition of normal lymphoid cell progenitors growth of both T and B lineage and inhibited significantly also the growth of malignant Bcell lineage lymphoid progenitors, without inducing cytotoxic effect. More recently, by testing the effects of 1, 25(OH)2D3 on B-cell responses, it was found that it inhibited the ongoing proliferation of activated B cells and induced their apoptosis, whereas initial cell division was unimpeded.

The generation of plasma cells and post-switch memory B cells was significantly inhibited by 1, 25(OH)2D3 although the up-regulation of genetic programs involved in B-cell differentiation was only modestly affected. B cells expressed mRNAs for proteins involved in vitamin D activity, including 1α-hydroxylase, 24-hydroxylase and the VDR, each of which was regulated by 1, 25(OH)2D3 and/or activation. Interestingly, 1, 25(OH)2D3 up-regulated the expression of p27, but not of p18 and p21, which may be important in regulating the proliferation of activated B cells and their subsequent differentiation in plasma cells.

The net effect of 1, 25(OH)2D3 is enhancement of the innate immune system (protective) and down regulation of the adaptive immune system(acquired). Therefore, 25(OH)D deficiency may theoretically lead to autoimmune diseases.

8. The optimum serum level of vitamin D for skeletal health

Determination of vitamin D status is not based on measurement of serum 1, 25(OH)D concentrations. It is assessed by measuring the prohormone 25(OH)D, which is an indicator of supply rather than function. The most stable and plentiful metabolite of vitamin D in human serum, 25(OH)D, has a half-life of about 3 weeks, making it the most suitable indicator of vitamin D status (4). Using PTH elevation as a biomarker reflecting physiologic low levels of vitamin D, recent reports indicate that vitamin D deficiency would be more accurately defined as a 25D concentration of less than 32 ng/ml (80 nmol/l). The optimal serum concentrations of 25(OH)D begin at 75 nmol/L (30 ng/mL), and the best are between 90-100 nmol/L (36–40 ng/mL) (7). Whether 'normal' serum levels of vitamin D are sufficient for immune homeostasis is not known. In 2009, a standard reference material for 25(OH)D became available that permits standardization of values across laboratories and may improve method-related variability.

9. Vitamin D and autoimmune diseases

Observational studies in humans suggest an association between vitamin D deficiency and many rheumatological and non-rheumatological disorders, listed in Table 3.

Rheumatological	Non Rheumatologicl
1. Rheumatoid Arthritis "RA" (3, 7, 8).	1. Multiple Sclerosis "MS" (7, 8, 12, 14).
2. Undifferentiated Connective tissue (8).	2. Independent Diabetes Mellitus "IDDM" (6, 8, 12).
3. SLE (8).	3. Allergic asthma in children (9, 10).
4. Scleroderma (11).	4. Allergic rhinitis (10).
5. Ankylosing spondylitis (12).	5. Grave's disease (13).
6. Behcet's disease (15).	
7. Psoriasis (16).	
8. Fibromylgia (17)	

SLE: Systemic lupus erythematosus, 25(OH)D: serum vitamin D level

Table 3. Disorders that have been linked to 25(OH)D

10. Vitamin D level and vitamin D supplementation in autoimmune diseases

10.1 Rheumatoid Arthritis (RA)

Rheumatoid arthritis is an immune-mediated disease, mainly driven by Th1 cells. The characteristic features of the disease are erosive arthritis and joint destruction, which lead to severe disability and increased mortality. In various animal models of RA, such as CIA in mice, the disease-modifying effect of VDR ligands has been widely investigated. With 1, 25(OH)2D3 vitamin treatment in the early phase, collagen-induced arthritis was preventable to a certain extent and the progression of arthritis decreased (18).

In the last few years, the possible role of vitamin D in the pathogenesis, activity, and treatment of RA has been raised based on the results and observations of clinical and laboratorial studies(3). There have been 7case control studies evaluating vitamin D in RA patients. Two studies showed lower level of 25(OH)D than controls but 5 did not. In these studies the prevalence of low 25(OH)D was found to be between 30-63%. *The rationale for relating vitamin D deficiency and RA is based on two facts:* evidence indicate that patients with RA have vitamin D deficiency and the presence of 1, 25(OH) and VDR in macrophages, chondrocytes, and synovial cells in the joints of these patients with RA (3).

Low sun exposure and reduced body mass index (BMI) are well established risk factors for vitamin D deficiency in RA patients (19). Few studies have examined dietary or nutritional intake prior to RA onset, and none have assessed the association of vitamin D with disease onset. *Linda et al.* found that greater intake (highest versus lowest tertile) of total daily vitamin D was inversely associated with risk of RA. Inverse associations were apparent for both dietary and supplemental vitamin D. (20). The relationship between polymorphisms of the VDR gene and the onset of RA activity has been demonstrated in a study in which patients with BB or Bb genotypes for VDR had higher indices in the health assessment questioner (HAQ), erythrocyte sedimentation rate (ESR), cumulative dose of corticosteroids, and number of disease-modifying anti-rheumatic drugs (DMARDs) when compared to patients with the BB genotype (3).



In collagen-induced arthritis models, dietarian supplementation or oral administration of vitamin D prevented the development or delayed the progression of arthritis(3). In an open labeled study with 19 patients with RA treated with traditional DMARDs, oral supplementation with high doses of alfacalcidol for three months reduced the severity of the symptoms in 89% of the patients, 45% of which achieved complete remission and 44% had satisfactory results. Higher incidence of side effects, such as hypercalcemia, was not observed (3).

There also seem to be an inverse relationship between disease activity and the concentration of vitamin D metabolites in patients with inflammatory arthritis. A UK study that involved 206 patients demonstrated that at baseline in the pre-treatment patients, there was an inverse association between levels of 25(OH)D and the number of painful joints, DAS28, and HAQ. For each increase in 10 ng/mL in vitamin D serum levels, the DAS28 reduced by 0.3 points and the levels of CRP by 25%. But at 1 year the only observation is the inverse association with HAQ score (3).

## 10.2 Systemic Lupus Erythematosus (SLE)

Several studies have demonstrated a higher prevalence of vitamin D deficiency in SLE patients when compared to individuals with other rheumatologic diseases and healthy controls(3). *Huisman et al.* observed that 50% of SLE patients had vitamin D deficiency (cut off <50 nmol/L or 20 ng/mL) (21).

### **Patients with systemic lupus erythematosus have multiple risk factors for 25(OH)D deficiency:(3)**

#### 1. Photosensitivity:

Is the characteristic of the disease, and the recommendation to apply sunscreen are responsible for lower sun exposure, decreasing the production of vitamin D in the skin.

#### 2. Chronic treatment with corticosteroids and hydroxychloroquine:

These medications seem to affect vitamin D metabolism, although the evidence for this is not yet clear.

#### 3. Severe renal involvement:

This affects the hydroxylation step of 25(OH)D.

#### 4. African descent:

Severe lupus is more prevalent in people of African descent. It is believed that vitamin D deficiency in this group is a consequence of not only genetic factors, but it is speculated that lower serum concentrations of 25(OH)D, due to the lower cutaneous conversion rate secondary to skin color, would be another important factor.

It has been observed that critical levels of vitamin D (<10 ng/mL) are more common in patients with renal involvement and photosensitive skin lesions (4).

The association between low 25(OH)D and disease activity scores, according to the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) and ECLAM (European Consensus Lupus Activity Measurement) has been documented (3).

*Thudi et al.* demonstrated that functional assessment using combined scores (modified HAQ, global VAS by the patient, and fatigue scale) was worse in patients with probable or confirmed diagnosis of lupus and vitamin D deficiency. However, this study did not demonstrate an association between vitamin D deficiency and the levels of auto-antibodies, including anti-DNA (22).

*Carvalho et al.* investigated the presence of anti-vitamin D antibodies in the serum of SLE patients to better explain vitamin D deficiency in autoimmune diseases. One-hundred and seventy-one SLE patients were investigated and 4% of them had vitamin D antibodies but the levels of 25(OH)D were similar in patients with or without those autoantibodies. Among the clinical and laboratorial associations investigated, the presence of anti-dsDNA was the only one that showed a strong relationship with anti-vitamin D antibodies (23).

### 10.3 Ankylosing Spondylitis AS

Osteoporosis is frequent in AS and high disease activity which assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is associated with an alteration in vitamin D metabolites and increased levels of bone resorption (11).

The inflammatory activity in AS itself plays a major role in the pathophysiology of bone loss, this may be mediated in AS by substances regulating both the inflammatory process and bone turnover. High levels of proinflammatory cytokines such as interleukin-1 and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) are thought to play a major role in chronic inflammation and act on osteoblasts and osteoclasts (12). A prospective study demonstrated a significant loss of bone mass in early AS with a strong association with inflammatory activity (24).

#### Factors may contribute to the development of osteopenia/osteoporosis in AS: (12)

1. Treatment of AS.
2. Hormone disorder.
3. Decreased mobility or physical activity.

Patients with AS and osteoporosis had significantly higher values for ESR, CRP, and urine-cross-links, and significantly decreased results in 1, 25 D<sub>3</sub>, 25 D<sub>3</sub> and PTH, but no differences in serum calcium, serum calcium corrected for albumin, bone-AP and daily renal calcium excretion were observed (12).

Clinical studies have reported the impact of vitamin D in AS as an endogenous immune modulator, suppressing activated T cells and cell proliferation that may accelerate the inflammation process (25).

### 10.4 Undifferentiated Connective Tissue Disease (UCTD)

A study by *Zold et al.* demonstrated the presence of a seasonal variation in the levels of 25(OH)D in patients with UCTD and that those levels were lower in this population than in the control population. In this same study, 21.7% of patients with UCTD and vitamin D deficiency developed established connective tissue disease (especially RA, SLE, Sjgren's syndrome, and mixed connective tissue disease); their mean 25(OH)D was lower than that of patients who remained with undifferentiated disease,  $14.7 \pm 6.45$  ng/mL vs  $33.0 \pm 13.4$  ng/mL,  $P = 0.0001$  respectively (26). The presence of dermatological symptoms

(photosensitivity, erythema, and chronic discoid rash) and pleuritis was associated with low levels of vitamin D.

### 11. The immunological basis for the vitamin D role in preventing autoimmunity

Prospective studies available for the 4 major autoimmune diseases: RA, SLE, MS, and type 1 DM, have demonstrated the beneficial effects of vitamin D supplementation in modulating the components of the immune system responsible for the inflammation, such as the expression of cytokines, growth factors, nitrous oxide, and metalloproteinase(3). A recent systematic review concluded that total number of studies are small, so no conclusion could be made with regards to the importance of 25(OH)D in preventing autoimmune disease.

### 12. Summary

The vitamin D endocrine system is recognized as an important immune modulatory factor involved in autoimmune diseases. VDR agonists seem primarily to inhibit DC differentiation, pathogenic pro-inflammatory T cells such as Th1 and Th17 cells and, under appropriate conditions, they seem to favour a deviation to the Th2 pathway. These immunomodulatory and anti-inflammatory activities might be particularly efficient in RA, SLE, Ankylosing spondylitis and UCTD patients and support a therapeutic role of 1, 25(OH)<sub>2</sub>D in such a disease.

In addition, vitamin D may play an important role in the maintenance of B-cell homeostasis, and the correction of vitamin D deficiency may be useful in the treatment of B cell-mediated autoimmune rheumatic disorders such as SLE.

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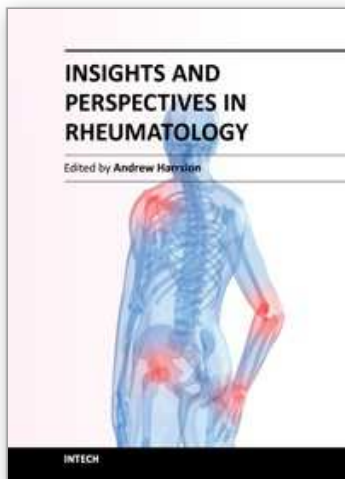
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This book offers a range of perspectives on pathogenesis, clinical features and treatment of different rheumatic diseases, with a particular focus on some of the interesting aspects of Sjögren's syndrome. It contains detailed and thorough reviews by international experts, with a diverse range of academic backgrounds. It will also serve as a useful source of information for anyone with a passive interest in rheumatology, from the genetic and molecular level, through to the psychological impact of pain and disability.

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