REVIEWS

Role of vitamin D in autoimmune rheumatic diseases- hype or real?

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Abstract

Since the beginning of the 20th century, it has been well known that vitamin D is associated with bone and calcium metabolism. There is increasing evidence on the positive effects of vitamin D on innate and acquired immunities. Many studies have reported the relation between polymorphisms of the vitamin D receptor (VDR) and the onset of various autoimmune rheumatic diseases (AIRD). Studies conducted in animal models have reported vitamin D supplementation as an effective therapy for various autoimmune diseases. Whereas, prospective human studies have reported contradictory findings on the effect of vitamin D levels or intake on autoimmune risk. In the present review, the authors have attempted to summarize the association between vitamin D and AIRD.

Keywords: Vitamin D, immunomudulator, autoimmune, rheumatic

Introduction

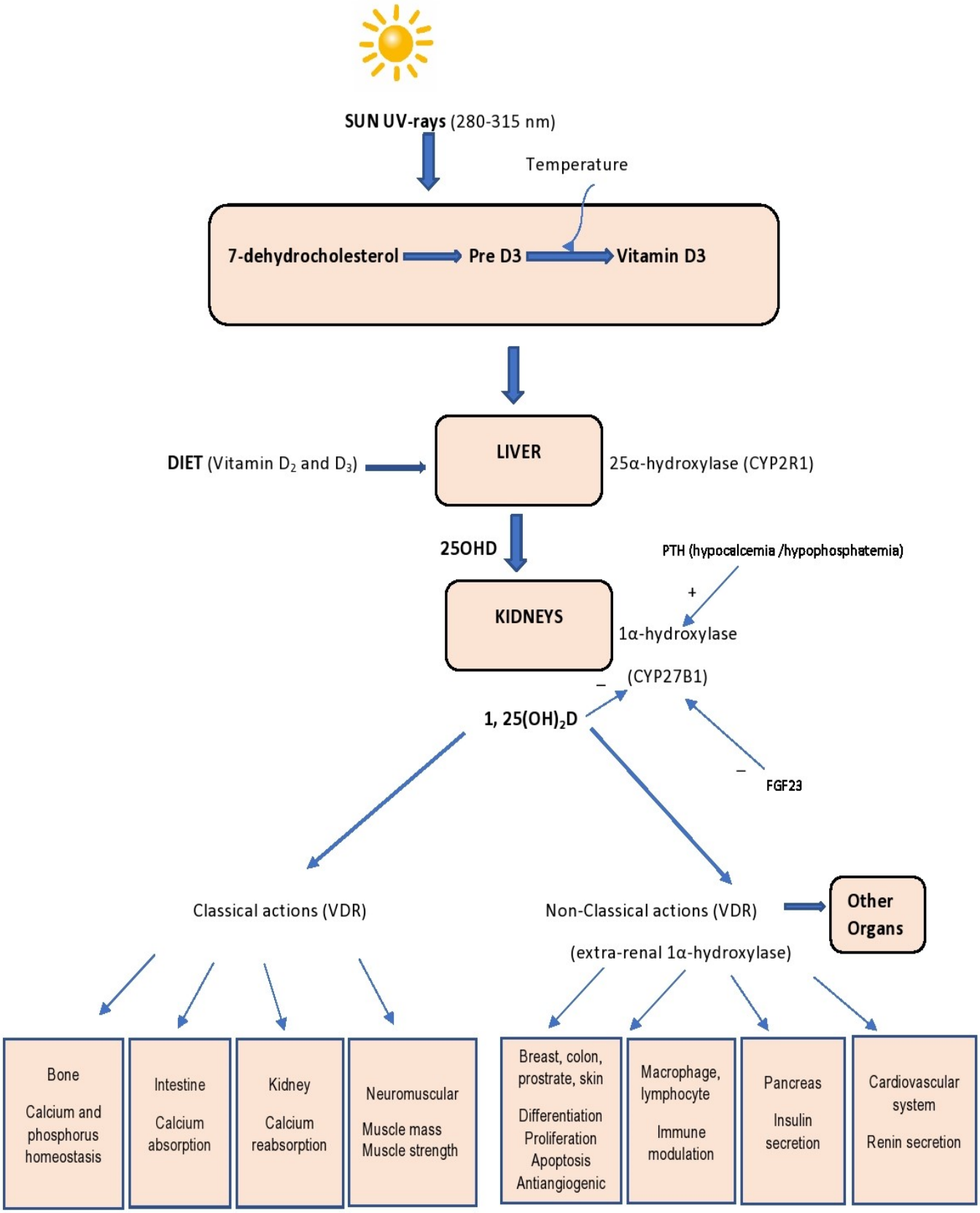
Vitamin D, 'the sunshine vitamin', is a fat-soluble derivative of steroid 7-dehydocholesterol with autocrine, paracrine and endocrine functions. Upon exposure to sunlight, vitamin D absorbs ultraviolet (UV) light (~280 to 315 nm) and gets converted to precalciferol in the skin. Most of the precalciferol eventually isomerizes into cholecalciferol (vitamin D3) through thermal conversion. Ergosterol is another commonly occurring steroid in plants, which is activated by irradiation to produce ergocalciferol (vitamin D2). Both vitamin D3 formed in the skin and absorbed from digestive tract are transported to the liver where they are hydroxylated at carbon 25 to form calcidiol (also called 25 hydroxy vitamin D3 abbreviated as 25(OH)D) by liver 25-hydroxylase, CYP2R1 and CYP27A1. 25(OH)D is the major circulating vitamin D metabolite and a reliable indicator of vitamin D status.[1] Following the hydroxylation in liver, calcidiol is further hydroxylated by 1-α-hydroxylase and CY27B1 in the proximal convoluted tubule cells of the kidney forming calcitriol (also called 1,25- dihydroxy vitamin D3, abbreviated as 1,25 (OH)2D), which is considered as the active form of vitamin D (Fig. 1).[2]

At the cellular level, 1,25(OH)2D interacts with nuclear vitamin D3 receptor (VDR) also known as NR1I1 (nuclear receptor 1, group I, member 1), a member of the nuclear receptor family of transcription factors. Upon activation by vitamin D, the VDR forms a heterodimer with retinoid X receptor (RXR). After the heterodimerization of VDR-1, 25 (OH) 2D complexes with RXR, the complex binds to vitamin D3 response elements (VDREs) and recruits numerous nuclear co-activator or compressor proteins. The transcription of mRNA is either enhanced or inhibited by this ligand-activated transcription factor.[3] The VDR helps in controlling calcium and phosphate absorption and other processes through activation and deactivation of these genes. Four polymorphisms implicated in the development of autoimmune diseases have been identified as *Apa1, Bsm1, Taq1 and Fok1*.[4] We have tried to review the role of vitamin D as an anti-inflammatory, anti-proliferative, pro-differentiative and immunomodulator in various autoimmune rheumatic diseases based on the evidence till date, so as to aid in the treatment of various autoimmune rheumatic diseases.

Vitamin D levels

Though vitamin D deficiency has been recognized as pandemic, it is the most underdiagnosed and undertreated deficiency across the world. Vitamin D deficiency is widely prevalent in India with a prevalence of 70-100% in the

Fig. 1: Conversion of vitamin D and its actions



general population, despite abundant sunshine.[5] Moreover, there is no clear consensus on the optimum serum levels of vitamin D needed for the proper functioning of the immune system. Vitamin D deficiency is defined as the presence of serum levels of 25(OH) D <20 ng/ml (50nmol/l) with consistent elevation of parathyroid hormone (PTH) and reduction in intestinal calcium absorption. An inverse association has been noted between 25(OH)D levels and parathyroid hormone (PTH). The PTH levels will start stabilizing at the point where the former reaches 30 to 40 ng/ml. Vitamin D insufficiency is defined as serum 25(OH) D levels in the range of 20-29 ng/ml, and the desirable and safe range is 30-100 ng/ml.[5] Vitamin D intoxication has been noted in subjects who consume 40, 000 IU/day of vitamin D and when serum levels of 25(OH)D are >150 ng/ml.[6] Vitamin D intoxication (VDI) due to supplementation has been reported more frequently in recent years. The understanding of the role of vitamin D (25OHD) in the pathogenesis of several diseases would have contributed to increase in vitamin D intake. There are studies relating the close association of symptoms and findings of VDI with serum calcium concentration and duration of hypercalcemia. The altered hormonal and mineral levels commonly noted in patients with VDI include high serum phosphorus and calcium, low alkaline phosphatase (ALP), high serum 25OHD, low serum parathyroid hormone (PTH) and high urine calcium/creatinine.

Immunomodulatory effect of vitamin D

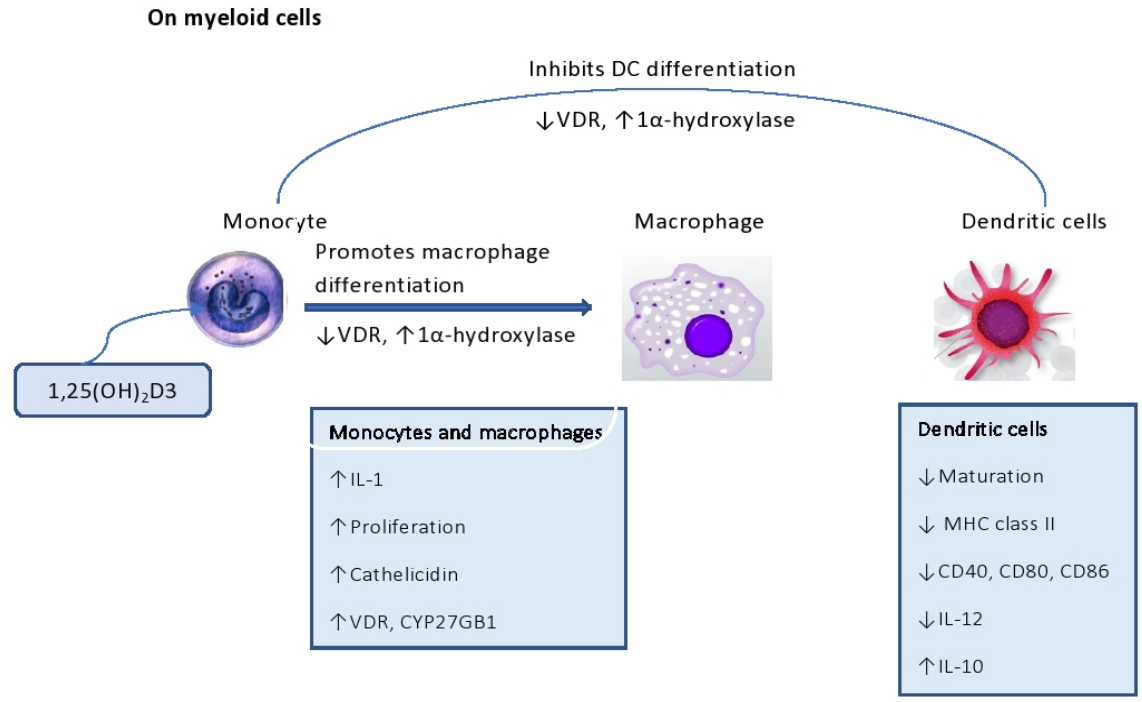
The beneficial effects of vitamin D on the immune regulatory cells are innumerable. In the 1980s, the vitamin D receptor (VDR) was found to be located in human peripheral blood monocytes, activated B- and T-cells, and in all major T-cell lineages as well as macrophage/monocytes. More recently, vitamin D has been shown to be an inhibitor of dendritic cell maturation, T-cell stimulatory function, and B-cell differentiation and proliferation. It acts by inhibiting B cell proliferation and differentiation and immunoglobulin secretion. The suppression of T cell proliferation results in a shift from Th1 (IFN-gamma production) to Th2 (with IL-4, IL-5, and IL-10 production) phenotype.[8] It also affects T cell maturation, thus inhibiting Th17 development and facilitates the induction of T regulatory cells (Treg). These effects reduce the production of inflammatory cytokines (IL-17, IL-21) with increased production of anti-inflammatory cytokines such as IL-10.[9] Active vitamin D has also shown to increase the production of FOXP3 + Treg *in vitro* through direct interaction of the VDR with the *FOXP3* gene.[10] It also inhibits production of inflammatory cytokines IL-1, IL-6, IL-8, IL-12, and TNFα by monocytes. Additionally, it inhibits dendritic cell differentiation and maturation with preservation of an immature phenotype, as demonstrated by a decreased expression of MHC class II molecules, co-stimulatory molecules and IL-12. Research on murine bone-marrow-derived dendritic cells (BMDCs) has demonstrated similar findings. Vitamin D exposure altered the BMDCs to promote Treg (T regulatory cells) production over cytotoxic T-cells.[9] Additionally, vitamin D has also been found to regulate the production of anti-microbial peptides namely cathelicidin and beta-2 defensin.[11] Cathelicidin is an enhancer of the epithelial barrier providing an additional mechanism by which vitamin D might promote homeostasis by repairing damaged epithelial barriers (Fig.2).

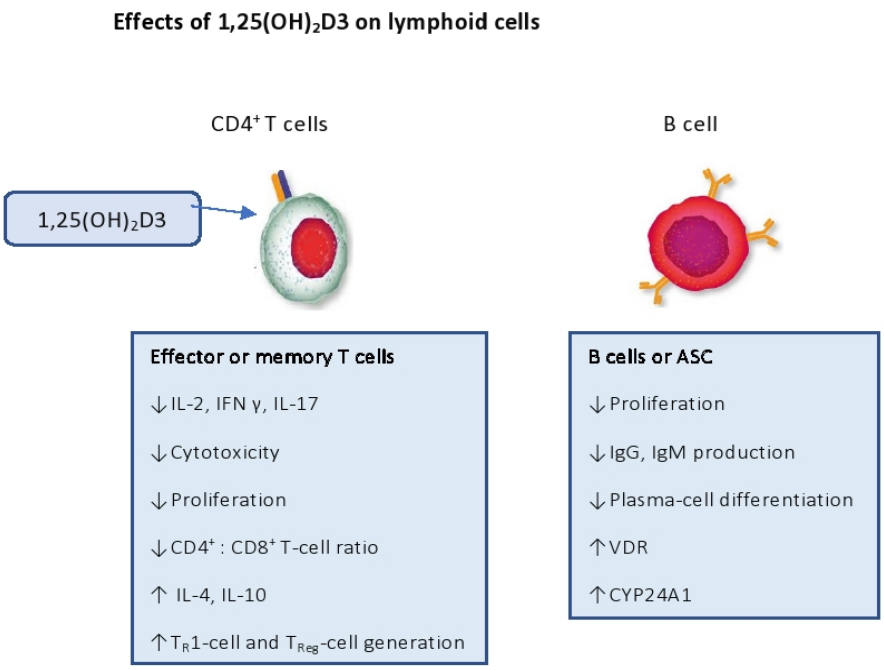
Systemic lupus erythematosus (SLE)

SLE is a systemic autoimmune disease that may cause chronic inflammation and damage to multiple organs and tissues. Environmental factors and genetic susceptibility are responsible for the pathogenesis of SLE. SLE patients tend to have vitamin D deficiency, since most of them are photosensitive to UV radiation and unable to expose themselves to sunlight. The correlation between vitamin deficiency/insufficiency and SLE has been documented in multiple studies. Kim *et al.* and Ruiz *et al.* have concluded that serum 25(OH) D titers were significantly lower in SLE patients than controls.[12, 13] An Indian data by Mandal *et al.* concluded that vitamin D deficiency is prevalent among healthy Indians as well as SLE patients.[14] The direct role of vitamin D in modulating lupus activity has been demonstrated in animal models.[15] Lemire *et al*. showed that supplementation of 25(OH)D for 18 weeks reduced dermatologic lesions, proteinuria, and anti-dsDNA antibodies in the MRL/1 SLE mouse models.[16]

The relation between 25 (OH) D and lupus remains unclear. An Indian study has shown an inverse correlation between vitamin D3 and SLE Disease Activity index (SLEDAI) scores, anti-dsDNA and IFN-α.[14] One of the largest studies by Amital *et al.*, comprising of 378 patients from several European and Israeli cohorts, has shown an association between the vitamin D level at a single time point and disease activity.[17] But certain limitations of this study hamper the generalization of the study findings. The disease activity was not defined using a standardized scoring and no attempt was made to adjust for important cofounders such as the use of corticosteroids, immunosuppressant drugs, vitamin D supplements and body mass index (BMI). It is

Fig.2 Effect of vitamin D3 on myeloid and lymphoid cells





therefore difficult to conclude any causative association from this observation. Two other studies also showed an inverse relation between vitamin D levels and lupus flares.[18, 19] In contrast, no relation between low 25(OH) D levels and disease activity has been noted in Spanish and Korean studies. [20, 21] Although increase in fatigue was noted in patients with low vitamin D levels. A study by Susan *et.al* has concluded that vitamin D deficiency was more frequently associated with the presence of disease activity, low complement levels and azathioprine level.[22]

Bogaczewi *et al.* have observed that SLE patients, especially those with renal impairment, are at higher risk of vitamin D deficiency and require vitamin D supplementation.[23] The study by Abou-Raya *et al.* substantiated that vitamin D supplementation has contributed to a significant improvement in disease activity scores as well as significant reduction in the levels of autoantibodies (anti-Sm, anti-dsDNA) and ESR with a rise in the levels of C4. The intervention group subjects showed mild/low disease activity and a trend towards improved SLEDAI scores.[24] A study, which examined the potential impact of vitamin D3 supplementation on the overexpression of interferon (IFN) inducible genes (the IFN Signature) in patients with SLE and vitamin D deficiency, did not observe any difference in the IFN signature response after 12 weeks of supplementation with vitamin D3 as compared to placebo.[25] Another study in SLE patients has demonstrated that a 20 ng/ml increase in 25(OH)D levels was associated with a 21% decrease in the odds of having high disease activity score and a 15% decrease in the odds of having clinically important proteinuria.[26]

The identification of an association between polymorphisms in various vitamin D genes has further substantiated the causal association between vitamin D and lupus risk or disease activity. A number of association between *VDR* gene polymorphisms have been reported, which showed a significant association between *Bsm1* polymorphism of the B allele and susceptibility to SLE in Asians.[27, 28] There are ongoing clinical trials testing the safety and efficacy of different doses of vitamin D in SLE patients. Some studies are also investigating whether vitamin D can be used for treatment and/or prevention of SLE.[29] A similar study is evaluating the impact of different doses of vitamin D3 on the expression of interferon alpha (IFN-alpha).

Rheumatoid arthritis (RA)

The association between vitamin D deficiency and RA has not yet clearly established. Some studies find no correlation between vitamin D deficiency and risk of developing RA and disease activity.[30, 31] Whereas, certain studies have found an inverse correlation between the two.[32, 33] A cross-sectional study by Grazio *etal.* have found no difference in 25(OH) D levels between RA patients and controls, but an increased incidence of deficiency in undifferentiated arthritis was noted.[34] Rai *et al.* evaluated the status of vitamin D in RA patients and proved that neither the serum vitamin D levels nor vitamin D deficiency in RA patients were significantly different from controls, probably as the vitamin D levels are significantly low among the general Indian population.[35] Another study has reported an inverse relationship at baseline between 25(OH) D levels and the tender joint count, DAS28 score and Health Assessment Questionnaire (HAQ) score in RA patients. Increase in the level of 25(OH) D by 10 ng/ml was found to be associated with a decrease in the DAS28 score by 0.3 and at the CRP level by approximately 25%. An inverse association between baseline vitamin D metabolite levels and the HAQ score was noted at 1 year. An association between increased risk of RA and *VDR Fok1* gene polymorphism of the B allele has been demonstrated in whites and native American population.[36] An Indian study by Rajeev *et al.* demonstrated that vitamin D deficiency or insufficiency is more common in RA as compared to healthy controls, which may be one of the causes leading to the development or worsening of RA. DAS28 score also had a negative correlation with serum vitamin D levels.[37] Though there are studies suggesting that vitamin D supplementation reduces disease activity in RA patients, evidence is insufficient to support this hypothesis.

Juvenile idiopathic arthritis

There are limited studies on juvenile idiopathic arthritis and vitamin D. Around 20% of the pediatric rheumatology patients are vitamin D deficient. As shown by Pelajo e*t al.*, patients with autoimmune disorders are more likely to be vitamin D deficient than patients with non-autoimmune conditions.[38] In a US study, a subset of new-onset patients with juvenile idiopathic arthritis has shown a non-significant negative correlation between 25(OH) D levels and disease activity.[39]

Psoriatic arthritis

Two studies from Spain and Canada have shown low 25(OH) D levels in patients with psoriatic arthritis.[40, 41] The Spanish study has also suggested an association with activity and obesity. Touma *et al.* reported a high prevalence

of vitamin D insufficiency among psoriatic arthritis (PsA) patients.[42] However, a study from Israel did not replicate these findings.[43]

Behcet's disease

Studies from Brazil and Tunisia have reported an association between Behcet's disease and low vitamin D status, with the latter study suggesting an association with disease activity. [44,45]

Spondyloarthropathy (SpA)

Similar to other autoimmune diseases, patients with ankylosing spondylitis (AS) are found to have lower vitamin D levels than healthy controls, however the etiology is not clearly elucidated. No consistent link between vitamin D levels and disease activity in AS has been reported. There is no evidence to justify the use of serum 25-hydroxyvitamin D3 levels as a marker of disease activity.[46] But a cross-sectional study by Zhao *et al*., which demonstrated an association between vitamin D deficiency and both higher disease activity and functional impairment in axial SpA, supports the hypothesis that vitamin D has an immunomodulatory role.[47] A study conducted on Chinese patients showed a significantly lower vitamin D levels in Chinese axial SpA patients as compared to the control group.[48]

Conclusion

Recent research has contributed to the better understanding of the immunomodulating and anti-inflammatory effects of vitamin D. Apart from the *in vitro* and animal studies suggesting the potential of vitamin D in decreasing systemic inflammation and preventing AIRD in humans, the evidence from human epidemiological and interventional studies is inadequate. Though lower vitamin D levels have been noted in individuals with AIRD, very few studies have evaluated the causal relationship. Further research, especially in the Indian scenario, should focus on conducting randomized controlled trials to evaluate the type and dose of the compound to be administered to attain pharmacological and clinical efficacy as well as the duration of the period of supplementation and any side effects of the treatment. However, with the available data, it is advisable that vitamin D-deficient patients should be adequately treated for more successful treatment outcome of rheumatic disorders.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Citation

Oommen R, Shenoy P. Vitamin D in autoimmune rheumatic diseases- hype or real? IJRCI. 2017;5(1):R1.

Submitted: 23 March 2017; **Accepted:** 30 August 2017, **Published:** 21 September 2017

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