Review Article

Vitamin D as a Principal Factor in Mediating Rheumatoid Arthritis-Derived Immune Response

Muhammad M. Aslam,1,2 Peter John,1 Attya Bhatti,1 Sidrah Jahangir,1 and M. I. Kamboh2

1Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad, Pakistan
2Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

Correspondence should be addressed to Muhammad M. Aslam; muaazkamboh.biotech@yahoo.com

Received 5 February 2019; Revised 15 April 2019; Accepted 24 April 2019; Published 7 May 2019

Rheumatoid arthritis (RA) is a systemic multifactorial autoimmune disease. The interactions between diverse environmental and genetic factors lead to the onset of this complex autoimmune disorder. Serum levels of vitamin D (VD) are involved in the regulation of various immune responses. Vitamin D is a key signaling molecule in the human body that maintains calcium as well as phosphate homeostasis. It also regulates the functions of the immune system and, thus, can play a substantial role in the etiology of various autoimmune disorders, including RA. Low serum VD levels have been found to be associated with a higher risk of RA, although this finding has not been replicated consistently. The molecular mechanisms by which VD influences autoimmunity need to be further explored to understand how variation in plasma VD levels could affect the pathogenesis of RA. This mini-review focuses on the influence of VD and its serum levels on RA susceptibility, RA-associated complexities, treatment, and transcriptome products of key proinflammatory cytokines, along with other cytokines that are key regulators of inflammation in rheumatoid joints.

1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a systemic autoimmune multifactorial complex disease [1]. The key characteristic of this complex autoimmune disorder is the inflammation of the small joints [2–4]. Rheumatoid arthritis is associated with significant morbidity and mortality. The worldwide prevalence of RA is one percent [5]. The disease is usually more common among females than males [6, 7]. Mortality data from the United Nations Population Prospects database from 1987-2011 and World Health Organization mortality database for 31 countries show that RA accounted for almost 18 percent of all deaths caused by different forms of arthritis and other musculoskeletal disorders [8].

The interface between diverse environmental and genetic elements leads to the onset of RA [9]. The initial stages of RA are usually not evident clinically. One of the disease hallmarks of RA is the production of rheumatoid factor (RF) triggered by the autoimmunity. The imbalance of different immunological mediators leads to cellular damage, which in the case of RA manifests in bone and joint damage [10]. Cytokines are an imperative regulatory element in the pathogenesis of RA. Generally, the cytokines involved in RA can be grouped into two main categories: proinflammatory and anti-inflammatory cytokines.

Tumor necrosis factor alpha (TNFα), interleukin1 (IL-1), interleukin6 (IL-6), and interleukin17 (IL-17) are key proinflammatory cytokines that play vital regulatory roles in the chronic inflammation of joints and associated cartilage and bone deformation. TNFα is an inflammatory mediator that is arthritogenic even in its membrane-bound form [11]. IL-1 is a central cytokine in both RA and RA-mediated destruction of cartilage. IL-6 contributes to the production of autoantibodies. IL-6 also regulates the activation and differentiation of various immune cells. These cytokines have been targeted for gaining therapeutic insights into RA [12]. Proinflammatory cytokines have a significant role in the disease occurrence and severity of RA. Multiple genetic studies focusing on key proinflammatory cytokine genes have investigated the role of common genetic variation in relation to RA risk, disease
severity index, and drug response. Polymorphisms in the regulatory regions of these cytokine genes can significantly affect the binding of various transcription factors that can influence the risk of RA [13–17]. Since the focus of this short review is on the effect of VD on proinflammatory cytokines, anti-inflammatory cytokines are not discussed here.

2. Vitamin D (1,25-Dihydroxyvitamin D)

Vitamin D (VD) is a secosteroid hormone that is produced mainly by skin under the exposure of $\beta$-radiations and UV light [18]. Kidney and liver are major players for VD metabolism [19, 20]. It can also be supplemented through diet where gastrointestinal absorption takes it to blood circulation [21]. VD is considered as one of the essential nutrients in the human body. Its most significant role is to maintain calcium and phosphate homeostasis. Optimal serum VD level is 30 ng/ml [22, 23]. Different forms of VD have different activity levels [24]. Once it is generated in the body through sunlight or after body received it from food, VD is chemically converted to its active form (Figure 1). Two different enzymes generate the active form of VD. First, 25-hydroxylase, a liver enzyme, converts recently produced inactive VD to 25-hydroxyvitamin D [25(OH)D] that subsequently is activated by a kidney enzyme, 1,$\alpha$-hydroxylase, to form 1,25-dihydroxyvitamin D [1,25(OH)$_2$D$_3$] [25]. Activated VD is responsible for maintaining calcium and phosphate homeostasis by increasing intestinal phosphate and calcium absorption. VD plays an essential role in several physiological processes, including bone formation, immunity, cellular growth, and cellular differentiation [26]. Serum VD level variation has been implicated in various diseases, including cancer, metabolic syndrome, immune system disorders, frailty, cardiovascular disorders, and neurological disorders [27–31]. A microarray analysis has estimated that VD regulates 5% of the human genome either directly or indirectly and regulates the physiological behavior of more than 36 different cell types [32]. Many small scale genetic and genome-wide association studies (GWAS) have implicated multiple genetic loci (GC, DHCR7, CYP2RI, CYP24A1, SEC23A, AMDHD1, A2BPI, GPRIH4, DABI, MLL3,
FOX2A, and HMCN1) that are involved in the synthesis, transportation, metabolism, and degradation of VD [33].

Vitamin D receptor (VDR) is a member of the nuclear hormone receptors’ family [34]. VD acts as a ligand for VDR. The lipophilic 1,25(OH)2D3 can easily pass through cellular membranes and binds to its receptors without the involvement of any additional signal transduction steps, as is the case of the ligand molecules that bind to transmembrane receptors [35]. Since VDR is ubiquitously expressed, a wide range of different cell types are responsive to VD [36]. VDR is expressed in chondrocytes and synoviocytes present in inflamed joints of RA subjects. Genetic variation in the VDR gene has been linked to RA risk [37–40].

3. VD and Immunity

The discovery of the existence of VDR on peripheral blood mononuclear cells (PBMCs) and its role in the pathogenesis of RA laid down the foundation about the potentially important role of VD as an important immunity regulator [41–43]. VD plays a vital part in the regulation of various immunity mediated responses [44]. It has a significant role in controlling innate and adaptive immunity but in an antagonistic manner [45]. VD controls the innate and adaptive immune systems mainly through toll-like receptors (TLRs) and differentiation of T-cells, predominantly Th17 cells, and these Th17 cells have a crucial role in RA pathology [46]. VD modulates the regulation and differentiation of immune cells. It controls the production and secretion of autoantibody in B-cells [47]. It suppresses the proliferation and differentiation of B-cells by inducing apoptosis in activated B-cells [48]. VD obstructs the T-cells proliferation and inhibits the synthesis of IL2, INF-γ, and TNFα cytokines [49].

4. VD and Autoimmunity

In an autoimmune response, VD is involved in maintaining an optimum balance between Th1 and Th2 to suppress the autoimmune response mediated by T cells, by regulating CD4+ T cells production and activity [43]. It also halts antigen representation [50]. To overcome the effects of autoreactive T cells, VD increases the regulatory T cells activity [51]. Estrogen in RA synovial tissue boosts the immune response and VD is found to downregulate the estrogen synthetase activity, hence controlling the autoimmune response [52]. VD has an immunosuppressive effect and the physiologic concentration of VD has been shown to provide protection against autoimmune diseases [53, 54]. Changes in serum availability of VD can affect various cells and their normal signaling cascades. This can lead to disturbances in homeostasis at the molecular level, leading to onset and pathogenesis of various disorders, especially those related to calcium and bone metabolism and immune system dysfunction. Deficiency of VD has been linked to many autoimmune disorders, including insulin-dependent diabetes mellitus, systemic lupus erythematosus (SLE), and RA [55–57].

5. Vitamin D and Tumor Necrosis Factor-Alpha (TNFα)

Inflammation in RA occurs due to the abundant presence of inflammation-promoting cytokines [58]. TNFα is implicated in systemic inflammation. This is mainly synthesized by activated macrophages. Numerous other cell types can also produce TNFα, including fibroblast, monocytes, natural killer cells, and mast cells [59]. Most of these TNFα producing cells have VDR [60, 61]. TNFα is encoded by the TNFA gene that is present on chromosome 6p21.3. The gene is –3 kb and comprises 4 exons [62]. TNFα promotes inflammatory signaling and performs a key role in the onset and pathogenesis of RA. The level of TNFα has been shown to be higher in RA patients than controls, as TNFα is involved in inflammation followed by joint destruction [63]. However, the role of TNFα genetic variations in RA has not been established yet [64].

Studies intending to explore the effect of VD treatment on TNFα production have shown an inverse correlation between these two. This correlation has been investigated by quantification of mRNA or level of protein production and protein release in numerous studies. In PBMCs, TNFA transcriptome, as well as proteome, was reported to be inversely correlated with VD stimulation [65]. A VDR binding sequence has been found in the promoter of TNFA. VD levels can affect the binding of VDR to its target sequences in the upstream regulatory regions of the TNFA gene, which in turn can regulate the transcription of TNFA mRNA. VD levels, however, are not linked with TNFA mRNA stability. VD, therefore, regulates TNFα at transcriptional level [66]. A study conducted on a mouse model concluded that VD acts as a shield against RA because this promotes the apoptosis of fibroblast-like synoviocytes, which are key factors for cartilage destruction in RA [67]. Another study conducted on healthy women showed an inverse correlation between VD and TNFα concentration and suggested the preventive role of VD against inflammatory conditions [68].

6. Vitamin D and Interleukin-1 (IL-1)

IL-1 family is a group of 11 different cytokines [69]. Interleukin 1 alpha (IL-1α) and interleukin 1 beta (IL-1β) are the most studied members of this immunoregulatory molecular family. These cytokines are encoded by IL1A and IL1B genes that are located on 2q14. These two cytokines have a common antagonist called IL-1 receptor antagonist (IL-1Ra). The receptor for IL-1α and IL-1β is IL-1 receptor I (IL-1RI). IL-1Ra also binds to IL-1RI but it cannot induce any intracellular signaling and thus it acts to regulate the action of IL-1α and IL-1β [70]. IL-1β is produced by endothelial cells, monocytes, macrophages, activated T cells, and B cells [71]. It is expressed in mononuclear blood cells and synovial membrane [72]. It is involved in proteoglycan degradation and inhibits the synthesis of proteoglycan [73]. IL-1β has a key role in articular damage in RA and it also elicits the production of other cytokines, especially IL-6, in RA [74]. Studies of RA in animal models have shown the involvement of IL-1α and IL-1β in joint damage and cartilage degradation [75, 76].
IL-1β is found in infected cells and VD elevates IL-1β levels in macrophages during infection through direct transcription mechanism [77]. Similarly, another study showed that VD induced IL-1β production in lipopolysaccharide-treated human monocytes-derived macrophages and it also increased the production and phosphorylation of IL-1β transcriptional regulatory factor (C/EBPβ-CCAAT enhancer binding protein β) [78]. Another study conducted to find out the effect of VD on levels of proinflammatory cytokines found that VD significantly downregulated the levels of IL-1β [79]. VD has been reported to be inversely associated with IL-1α and IL-1β levels [80, 81], although a few earlier studies reported a positive correlation of VD and IL-1α and IL-1β [82-84]. Similar to IL-6 production, the levels and kind of influence VD has on IL-1 transcriptome depends on several additional factors. In human monocytic cell lines, the presence or absence of any connection between VD levels and IL-1 expression depends on the presence/absence and the nature of costimulus being present [85].

7. Vitamin D and Interleukin-6 (IL-6)

IL-6 is a monomeric glycoprotein of 26 kDa that is encoded by an interleukin-6 gene (IL6) located on 7p21. The glycoprotein is arranged into four long helical chains [86, 87]. IL-6 is a pleiotropic cytokine that is released by a range of different immune cells, including epithelial cells, fibroblasts, monocytes, and T cells [88]. The IL-6 receptor consists of two different polypeptide chains: gp130 and IL-6 receptor (IL-6R) while IL-6R specifically binds to gp130 and it serves to mediate intracellular signaling that can be either via JAK (Janus kinase)/STAT (signal transducer and activator of transcription) pathway or via mitogen-activated protein (MAP) kinase pathway [89, 90]. The STAT/JAK intracellular signaling pathway is known to play a vital role in immune-related responses that are mediated by IL-6 [91]. IL-6 is a primary mediator of inflammation. The levels of this cytokine are considerably elevated in the serum of RA patients [92-94]. IL-6 has been known to contribute towards the production of autoantibodies and it also acts as a regulator of TH-cells differentiation [95]. The signaling pathway triggered by IL-6 ultimately leads to joint inflammation and bone erosion in RA [96]. IL-6 is also involved in the initiation of the acute-phase response, the proliferation of synovial fibroblasts, and the stimulation of the precursor cells of hematopoietic lineage [97].

Serum levels of VD have been reported to be inversely related to serum IL-6 levels [98]. VD has been implicated as a downregulator of IL-6 mRNA levels in prostate cells. VD inhibits p38 molecule by the induction of MAPK phosphatase-1 (MKP1). This leads to the dephosphorylation of p38 by MKP1 and thus the activated p38 levels are reduced. p38 inhibition, in turn, is responsible for the reduction of IL-6 transcripts in the target cells [99]. IL-6 expression regulation has also been correlated with the differentiation of immune cells. The expression of IL-6 has been, therefore, linked with the degree of maturation of the immune cell, cytokine, and other signaling molecules [85]. Th17 cells are considered a crucial component of autoimmune-mediated response and 1,25(OH)₂D₃ has shown to stop the IL-6 expression, which in turn stimulate the production of Th17 cells [100, 101]. Exposure of VD reduces IL-6 levels in TNF-α stimulated synovial stroma cells (SSCs) from RA patients [102].

8. Vitamin D and Interleukin-17 (IL-17)

IL-17 is an inflammatory cytokine which is produced mainly by Th17 and other innate immune cells that have a crucial role in immune response and tissue impairment in RA [103]. It is mostly expressed in synovial fluid and synovium of RA patients [104]. Due to the immunomodulatory effect of VD on Th17 cells, it was found that active form of VD decreases the production of Th17 from CD4+T cells in humans and also it cuts down the expression of IL-17 in CD4+ T cells [105]. A recent study provides support to this observation where deficiency of VD in RA patients was found to affect Th17 cells function and, hence, IL-17 production, indicating that sufficient levels of VD may guard RA patients against IL-17 mediated immune response [106]. Some animal model studies have also reported similar findings where VD was associated with reduced production of IL-17 [107, 108]. T cells, especially Th17, are one of the main target sites for VD. VD action on T-cells halts the T-helper cells cytokines and alters the cytokine expression pattern of antigen presenting cells [109-112].

9. Vitamin D and Other Cytokines

Being an autocrine growth factor, IL-2 plays a significant role in optimum immune system functioning by acting as an activator, growth factor, and key component for T-cells differentiation [113, 114]. In the adaptive immune system, multiple T lymphocytes are favorite action sites for VD. VD is found to be an inhibitory factor for Th1 cells and subsequently reduced the production of INFγ and IL-2, which are important Th1 cytokines [115, 116]. In an in vitro study, it was found that VD regulated the Th2 production and Th2 cells were the main source of IL-2 and IL-10 production. Th2 cells are also involved in Th1 cells function inhibition [117]. A study conducted on human T-cell line confirmed that VD suppressed the IL-2 gene expression and reduced the IL-2 production by blocking the positive regulatory elements of transcriptional factor (NFAT) within the promoter region of the IL-2 gene [118]. In most of the cases, VD is found to downregulate the production of different cytokines, but, in case of IL-4 and IL-10, VD has an opposite effect where it upregulates the synthesis of IL-4 [119] and IL-10 [120]. An in vitro study showed that treatment of 1,25(OH)₂D₃ on CD4+Mel14+ T cells enhanced the synthesis of Th2 lymphocytes and ultimately increased the production of IL-4, IL-5, and IL-10 [121]. IL-12 determines the fate of T cells and its levels are found to be higher in RA patients [122]. In human PBMCs, VD was found to have an inhibitory effect on the production of IL-2 and IL-12 [123]. VD also blocks the differentiation of a dendritic cell and thus inhibits the IL-12 production. The complex of 1,25(OH)²D₃, VDR, and NFκB hinders with NFκB-derived transcription of IL-12 [124]. VD also downregulates the production of IL-12 and IL-23 by elevating the production of IL-10 [125, 126].
10. Connection between VD and RA

Vitamin D has been shown to act as a key player in the onset and pathogenesis of RA. In murine RA, the hormonally activated form of VD (1,25-Dihydroxyvitamin D3 [1,25(OH)2D3]) has been implicated in preventing the onset and RA pathogenesis [19]. In vitro studies in different cell lines that mimic RA like pathology have revealed that VD promotes anti-inflammatory response [127]. An In vivo study on a transgenic mouse model of RA showed that deletion of VDR was associated with inflammation followed by bone loss [128].

The prevalence of RA has been found to decrease in individuals with high intake of VD, including both dietary and supplemental forms of VD [129]. Epidemiological data have revealed that a significant number of RA patients (30-63%) have decreased VD levels [130]. VD intake is inversely associated with RA activity [131]. Distribution of serum VD levels has been examined in a number of RA case-control studies. A vast majority of these studies have found significantly different VD levels between cases and controls and these results are summarized in Table 1. Below we summarize the outcomes of significant studies.

A study conducted on RA patients that were not taking any VD supplements found a severe deficiency of VD [132]. A recent meta-analysis which combined data from fifteen different studies on a total of 1,143 RA patients and 963 controls reported the same inverse correlation between serum VD levels and disease severity [133]. A similar association between disease activity score (DAS28) and serum VD levels was found [134]. A cross-sectional study measured serum VD levels and reported VD insufficiency in a group of rheumatic patients [135]. Another study conducted on Caucasian women also reported serum VD insufficiency in RA patients as compared to controls [136]. A few other studies also reported a similar inverse association between VD levels and disease severity [137–141]. A recent meta-analysis combined results from different reports on 2,148 cases and 1,991 healthy controls, reported lower serum VD levels in RA patients as compared to healthy controls, and further reported an inverse correlation between serum VD levels and disease severity score [142]. Wang et al. [143] studied the effect of serum VD levels on 154 RA patients and reported an inverse relationship between VD levels and disease activity and anti-CCP level. A European League Against Rheumatism (EULAR) that supported a study on 625 RA patients and 276 healthy controls from 13 different European countries also reported hypovitaminosis in RA patients and inversely correlated serum VD levels with RA-associated complexities [144]. A study on a much larger sample size of 894 RA and 861 healthy controls reported an inverse correlation between serum VD levels and RA disease activity [145]. Another study on 93 RA patients and 31 healthy controls from an Iranian population also reported the inverse association between serum VD levels and RA severity and suggested VD supplementation for RA treatment along with other regular medications [146]. A study conducted on the Turkish population reported an inverse relationship between serum VD levels and RA susceptibility but did not find any association between serum VD levels and disease activity [147]. Similar results have been published by research published on Iranian population [148].

Severe deficiency of VD has been reported in early inflammatory arthritis [149]. A study conducted on 4,793 Japanese RA patients reported a severe deficiency of VD in RA patients and indicated an inverse association between levels of VD and RA related clinical symptoms [150]. Similarly, another study conducted on European RA patients reported the same results and linked VD levels inversely with RA-associated clinical symptoms, but it did not demonstrate any correlation between serum VD levels and disease severity score [151]. Studies conducted on the Italian population also reported VD deficiency in RA patients [152, 153]. In line with these results, data from North Italy rheumatology outpatients' clinic demonstrated 87% prevalence of VD deficiency in patients suffering from autoimmune rheumatic diseases [154]. Parallel to these results, almost 90% of hypovitaminosis D was reported in RA patients from the UK and Swiss outpatients clinics [155, 156]. Comorbidities in Rheumatoid Arthritis (COMORA) cohort comprising 1,431 patients from 15 different countries also found low serum VD levels with RA incidence and comorbidities [157]. A study conducted on Saudi Arabian RA patients reported VD as a good predictor of disease activity [158].

In RA treatment, combination therapy of denosumab and VD increases bilateral total hips bone mineral density (H-BMD) [159]. Another study suggested the role of VD in maintaining endothelial homeostasis in RA patients based on VD levels and CD34+ cell count in RA patients [160]. Two more studies suggested the potential immunomodulatory role of VD that can have a promising effect in RA patients [161, 162]. VD also affects other disease parameters, including Th17 cell count and incidence of anti-CCP antibodies [163]. Despite the immunomodulatory properties of VD, the beneficial role of VD supplementation as a component of RA treatment has produced inconsistent results [164–166].

11. VD and RA Related Complexities

A recent study in Northwest China found that RA patients with depression have much lower serum VD levels (mean=15.24 ± 8.78 ng/mL) as compared to RA patients without depression (mean=24.68 ± 10.98 ng/mL) and associated hypovitaminosis with depression, anxiety, and disease activity in RA patients [167]. Another study also associated low serum VD levels with increased neuropathic pain in RA patients [168]. Furthermore, low serum VD levels are inversely associated with ROS (reactive oxygen species) levels in RA patients [169]. A recent data indicate that low serum VD levels in RA patients may lead to secondary osteoporosis [170].

12. Conclusions

The human body can synthesize VD under the exposure of β-radiations and UV light or can absorb it through food. Kidney and liver metabolize the absorbed VD. VD maintains the calcium and phosphate homeostasis in the body. VD can regulate innate and adaptive immunity mainly through B and...
Table 1: Summary of the relationship between serum VD levels and RA in different populations.

| Character | Association | Population | Sample size | Reference |
|-----------|-------------|------------|-------------|-----------|
| Serum VD levels and RA | Inverse | Poland | 97 cases, 28 controls | [132] |
| Serum VD levels and RA | Inverse | Meta-analysis | 1,143 cases, 963 controls | [133] |
| Serum VD levels and RA | Inverse | South European | 120 cases, 65 controls | [134] |
| Serum VD levels and RA | Inverse | Croatia | 53 RA patients | [135] |
| Serum VD levels and RA | Inverse | Caucasian (Argentina) | 42 cases, 48 controls | [136] |
| Serum VD levels and RA | Inverse | India | 80 cases, 80 controls | [137] |
| Serum VD levels and RA, IL-17/IL-23, and bone loss | Inverse | Chinese | 130 cases, 80 controls | [138] |
| Serum VD levels and RA | Inverse | Egypt | 63 cases, 62 controls | [139] |
| Serum VD levels and RA | Inverse | Saudi Arabia | 55 cases, 40 controls | [140] |
| Serum VD levels and RA and musculoskeletal pain | Inverse | Greece | 44 cases, 44 controls | [141] |
| Serum VD levels and RA | Inverse | Meta-analysis | 3,489 RA patients | [142] |
| Serum VD levels and RA, anti-CCP antibody | Inverse | Chinese | 154 cases, 60 controls | [143] |
| Serum VD levels and RA & associated complexities | Inverse | 13 European countries | 625 cases, 276 controls | [144] |
| Serum VD levels and disease severity | Inverse | Iran | 91 cases, 31 controls | [145] |
| Serum VD levels and RA | Inverse | Japan | 4,793 RA patients | [150] |
| Serum VD levels and RA | Inverse | Italy | 1,891 cases, 1,019 controls | [152] |
| Serum VD levels and RA | Inverse | Italy | 1,168 RA patients | [153] |
| Serum VD levels and RA associated depression and anxiety | Inverse | Northwest China | 161 RA patients | [167] |
| Serum VD levels and neuropathic pain in RA patients | Inverse | Turkey | 53 RA patients | [168] |
| Serum VD levels and RA | Inverse | COMORA cohort (15 countries) | 1431 RA patients | [157] |
| Serum VD levels and ROS in RA patients | Inverse | India | 100 cases, 80 controls | [169] |
| Combination therapy of VD + denosumab and H-BMD | Positive | Japan | 22 monotherapy, 21 combination therapy | [159] |
| (i) Serum VD levels and RA | (i) Inverse | Turkey | 55 cases, 45 controls | [147] |
| (ii) Serum VD levels and disease activity | (ii) No association | | | |
| (i) Serum VD levels and disease activity | (i) No association | Iran | 99 cases, 68 controls | [148] |
| (ii) Serum VD levels and RA | (ii) Inverse | | | |
T-cell production and differentiation. It inhibits the synthesis of IL2, INF-γ, and TNFα. Immunomodulatory properties of VD have made it an important factor in multiple autoimmune conditions. VD serum levels are inversely associated with RA susceptibility, disease activity, and related pathological complexities. VD is a significant regulator of various genes involved in the immune system and plays an important role in various immune-related responses, including the expression of proinflammatory cytokines. VD, through suppression of cytokines levels, can prevent the onset and pathogenesis of RA. Therefore, VD deficiency, coupled with genetic and environmental factors, may lead to the onset of RA. Additional studies are needed to explore the precise molecular pathways and mechanisms by which VD levels mediate RA-derived immune response. Research on the potential role of VD supplementation in RA treatment has produced inconsistent results; additional large-scale pharmacological research is required to find out the effect of VD augmentation during the treatment of RA.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] P. K. Gregersen, C. I. Amos, A. T. Lee, Y. Lu et al., “REL, a member of the NF-kB family of transcription factors, is a newly defined risk locus for rheumatoid arthritis,” Nature Genetics, vol. 41, no. 7, pp. 820–823, 2009.
[2] F. A. Kurreeman, L. Padyukov, R. B. Marques et al., “A candidate gene approach identifies the TRAF1/C5 region as a risk factor for rheumatoid arthritis,” PLoS Medicine, vol. 4, no. 12, p. e358, 2007.
[3] G. S. Firestein, “Evolving concepts of rheumatoid arthritis,” Nature, vol. 423, no. 6937, pp. 356–361, 2003.
[4] H. Zhu, F. Y. Deng, X. B. Mo, Y. H. Qiu, and S. F. Lei, “Pharmacogenetics and pharmacogenomics for rheumatoid arthritis responsive to methotrexate treatment: the 2013 update,” Pharmacogenomics, vol. 15, pp. 551–566, 2014.
[5] V. Joshi, “Arthritis in the elderly,” Journal of the Indian Medical Association, vol. 101, pp. 408–412, 2003.
[6] M. Simonsson, S. Bergman, L. T. H. Jacobsson, I. F. Petersson, and B. Svensson, “The prevalence of rheumatoid arthritis in Sweden,” Scandinavian Journal of Rheumatology, vol. 28, no. 6, pp. 340–343, 1999.
[7] E. Myasoedova, C. S. Crowson, H. M. Kremers, T. M. Thornea, and S. E. Gabriell, “Is the incidence of rheumatoid arthritis rising? Results from Olmsted County, Minnesota, 1955–2007,” Arthritis & Rheumatology, vol. 62, no. 6, pp. 1576–1582, 2010.
[8] A. A. Kiadaliri, D. T. Felson, T. Neogi, and M. Englund, “Brief report: rheumatoid arthritis as the underlying cause of death in thirty-one countries, 1987–2011: trend analysis of world health organization mortality database,” Arthritis & Rheumatology, vol. 69, no. 8, pp. 1560–1565, 2017.
[9] S. Raychaudhuri, “Recent advances in the genetics of rheumatoid arthritis,” Current Opinion in Rheumatology, vol. 22, no. 2, pp. 109–118, 2010.
[10] B. Mulcahy, W. L. Frank, F. M. Michael et al., “Genetic variability in the tumor necrosis factor-lymphotoxin region influences susceptibility to rheumatoid arthritis,” American Journal of Human Genetics, vol. 59, p. 676, 1996.
[11] S. Georgopoulos, D. Plows, and G. Kollias, “Transmembrane TNF is sufficient to induce localized tissue toxicity and chronic inflammatory arthritis in transgenic mice,” Journal of Inflammation, vol. 46, no. 2, pp. 86–97, 1996.
[12] G. W. Kim, N. R. Lee, and R. H. Pi, “IL-6 inhibitors for treatment of rheumatoid arthritis: past, present, and future,” Archives of Pharmacal Research, vol. 38, no. 5, pp. 575–584, 2015.
[13] F. M. Brennan and I. B. McInnes, “Evidence that cytokines play a role in rheumatoid arthritis,” The Journal of Clinical Investigation, vol. 118, no. 11, pp. 3537–3545, 2008.
[14] J. K. Lacki, R. Moser, I. Korczowska, S. Mackiewicz, and W. Muller, “TNF-α gene polymorphism does not affect the clinical and radiological outcome of rheumatoid arthritis,” Rheumatology International, vol. 19, no. 4, pp. 137–140, 2000.
[15] J. Trifunovic Cvetkovic, S. Wallberg-Jonsson, B. Stegmayr, S. Rantapää-Dahlqvist, and A. K. Lefvert, “Susceptibility for and clinical manifestations of rheumatoid arthritis are associated with polymorphisms of the TNF-alpha, IL-1beta, and IL-1Ra genes,” The Journal of Rheumatology, vol. 29, no. 2, pp. 212–219, 2002.
[16] S. L. Ferrari, L. Ahn-Luong, P. Garnero, S. E. Humphries, and S. L. Greenspan, “Two promoter polymorphisms regulating interleukin-6 gene expression are associated with circulating levels of C-reactive protein and markers of bone resorption in postmenopausal women,” The Journal of Clinical Endocrinology & Metabolism, vol. 88, no. 1, pp. 255–259, 2003.
[17] P. Jerrard-Dunne, M. Sitzer, P. Risley et al., “Interleukin-6 promoter polymorphism modulates the effects of heavy alcohol consumption on early carotid artery atherosclerosis: the carotid atherosclerosis progression study (CAPS),” Stroke, vol. 34, no. 2, pp. 402–407, 2003.
[18] M. F. Holick, “Vitamin D deficiency,” The New England Journal of Medicine, vol. 357, no. 3, pp. 266–281, 2007.
[19] F. R. Pérez-López, “Vitamin D: The secosteroid hormone and human reproduction,” Gynecological Endocrinology, vol. 23, no. 1, pp. 13–24, 2007.
[20] M. F. Holick, “Vitamin D: a millennium perspective,” Journal of Cellular Biochemistry, vol. 88, no. 2, pp. 296–307, 2003.
[21] D. Wolpowitz and B. A. Gilchrest, “The vitamin D questions: How much do you need and how should you get it?” Journal of the American Academy of Dermatology, vol. 54, no. 2, pp. 301–317, 2006.
[22] M. Aauran and K. Briot, “Critical reappraisal of vitamin D deficiency,” Joint Bone Spine, vol. 77, no. 2, pp. 115–119, 2010.
[23] J.-C. Souberbielle, G. Friedlander, A. Kahan, and C. Cormier, “Evaluating vitamin D status. Implications for preventing and managing osteoporosis and other chronic diseases,” Joint Bone Spine, vol. 73, no. 3, pp. 249–253, 2006.
[24] M. F. Holick, “Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease,” American Journal of Clinical Nutrition, vol. 80, no. 6, pp. 1678S–1688S, 2004.
[25] A. W. Norman, “From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health,” American Journal of Clinical Nutrition, vol. 88, no. 2, pp. 491S–499S, 2008.
[26] H. F. DeLuca, “Overview of general physiologic features and functions of vitamin D,” American Journal of Clinical Nutrition, vol. 80, no. 6, pp. 1689S–1696S, 2004.
[60] M. T. Cantorna and B. D. Mahon, "D-hormone and the immune system," *The Journal of Rheumatology*, vol. 76, pp. 11–20, 2005.

[61] M. T. Cantorna, Y. Zhu, M. Froicu, and A. Wittke, "Vitamin D status, I, 25-dihydroxyvitamin D3, and the immune system," *The American Journal of Clinical Nutrition*, vol. 80, pp. 1717s–1720s, 2004.

[62] L. J. Old, "Tumor necrosis factor (TNF)," *Science*, vol. 230, no. 4726, pp. 630–632, 1985.

[63] A. E. Edrees, S. N. Misra, and N. I. Abdou, "Anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis: correlation of TNF-alpha serum level with clinical response and benefit from changing dose or frequency of infliximab infusions," *Clinical and Experimental Rheumatology*, vol. 23, no. 4, pp. 469–474, 2005.

[64] P. Vasanthi, G. Nalini, and G. Rajasekhar, "Role of tumor necrosis factor-alpha in rheumatoid arthritis: a review," *International Journal of Rheumatic Diseases*, vol. 10, no. 4, pp. 270–274, 2007.

[65] K. Müller and K. Bendtzen, "Inhibition of human T lymphocyte proliferation and cytokine production by 1,25-dihydroxyvitamin D3. Differential effects on CD45RA+ and CD45R0+ cells," *Autoimmunity*, vol. 14, no. 1, pp. 37–43, 1993.

[66] I. Hakim and Z. Bar-Shavit, "Modulation of TNF-α expression in bone marrow macrophages: Involvement of vitamin D response element," *Journal of Cellular Biochemistry*, vol. 88, no. 5, pp. 986–998, 2003.

[67] X. Gu, B. Gu, X. Lv et al., "I, 25-dihydroxy-vitamin D3 with tumor necrosis factor-alpha protects against rheumatoid arthritis by promoting p53 acetylation-mediated apoptosis via Sirt1 in synoviocytes," *Cell Death & Disease*, vol. 7, no. 10, Article ID e2423, 2016.

[68] C. A. Peterson and M. E. Heffernan, "Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women," *Journal of Inflammation*, vol. 5, article 10, 2008.

[69] J. Bastard, C. Jardel, J. Delattre, B. Hainque, E. Bruckert, and F. Oberlin, "Evidence for a link between adipose tissue interleukin-6 content and serum C-reactive protein concentrations in obese subjects," *Circulation*, vol. 99, no. 16, pp. 2219c–2222c, 1999.

[70] B. K. Pedersen, "Muscle as a secretory organ," *Comprehensive Physiology*, 2013.

[71] A. E. Koch, S. L. Kunkel, and R. M. Strieter, "Cytokines in rheumatoid arthritis," *Journal of Investigative Medicine*, vol. 43, no. 1, pp. 28–38, 1995.

[72] W. P. Arend, "Cytokine imbalance in the pathogenesis of rheumatoid arthritis: the role of interleukin-1 receptor antagonist," *Seminars in Arthritis and Rheumatism*, vol. 30, supplement 2, no. 5, pp. 1–6, 2001.

[73] M. J. B. M. Vervoordeldonk and P. P. Tak, "Cytokines in rheumatoid arthritis," *Current Rheumatology Reports*, vol. 4, no. 3, pp. 208–217, 2002.

[74] E. Bzustewicz and E. Bryl, "The role of cytokines in the pathogenesis of rheumatoid arthritis - Practical and potential application of cytokines as biomarkers and targets of personalized therapy," *Cytokine*, vol. 76, no. 2, pp. 527–536, 2015.

[75] E. R. Pettipher, G. A. Higgs, and B. Henderson, "Interleukin 1 induces leukocyte infiltration and cartilage proteoglycan degradation in the synovial joint," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 83, no. 22, pp. 8749–8753, 1986.

[76] D. Burger, J.-M. Dayer, G. Palmer, and C. Gabay, "Is IL-1 a good therapeutic target in the treatment of arthritis?" *Best Practice & Research Clinical Rheumatology*, vol. 20, no. 5, pp. 879–896, 2006.

[77] J. de Castro Kroner, A. Sommer, and M. Fabri, "Vitamin D every day to keep the infection away?" *Nutrients*, vol. 7, no. 6, pp. 4170–4188, 2015.

[78] B.-N. Lee, T.-H. Kim, J.-B. Jun et al., "Upregulation of interleukin-1β production by 1,25-Dihydroxyvitamin D3 in activated human macrophages," *Molecular Biology Reports*, vol. 38, no. 3, pp. 2193–2210, 2011.

[79] B. Villaggio, S. Soldano, and M. Cutolo, "1,25-dihydroxyvitamin D3 downregulates aromatase expression and inflammatory cytokines in human macrophages," *Clinical and Experimental Rheumatology*, vol. 30, no. 6, pp. 934–938, 2012.

[80] A. Neve, A. Corrado, and F. P. Cantatore, "Immunomodulatory effects of vitamin D in peripheral blood monocyte-derived macrophages from patients with rheumatoid arthritis," *Clinical and Experimental Medicine*, vol. 14, no. 3, pp. 275–283, 2014.

[81] J. Kog, S. A. Grando, and Y. C. Li, "Regulation of IL-1 family cytokines IL-1α, IL-1 receptor antagonist, and IL-18 by 1,25-Dihydroxyvitamin D3 in primary keratinocytes," *The Journal of Immunology*, vol. 176, p. 3780, 2006.

[82] D. Eklund, H. L. Persson, M. Larsson et al., "Vitamin D enhances IL-1β secretion and restricts growth of mycobacterium tuberculosis in macrophages from TB patients," *International Journal of Mycobacteriology*, vol. 2, pp. 18–25, 2013.

[83] M. Verway, M. Bouttier, T.-T. Wang et al., "Vitamin D induces interleukin-1β expression: paracrine macrophage epithelial signaling controls M. tuberculosis infection," *PLoS Pathogens*, vol. 9, no. 6, Article ID e1003407, 2013.

[84] M. Inaba, K. Yukioka, Y. Furumitsu et al., "Positive correlation between levels of IL-1 or IL-2 and 1,25(OH)2D/25-OH-D ratio in synovial fluid of patients with rheumatoid arthritis," *Life Sciences*, vol. 61, no. 10, pp. 977–985, 1997.

[85] M. Di Rosa, G. Malaguarnera, C. De Gregorio, M. Palumbo, G. Nunnari, and L. Malaguarnera, "Immuno-modulatory effects of vitamin D3 in human monocyte and macrophages," *Cellular Immunology*, vol. 280, no. 1, pp. 36–43, 2012.

[86] N. Nishimoto and T. Kishimoto, "Interleukin 6: from bench to bedside," *Nature Clinical Practice Rheumatology*, vol. 2, no. 11, pp. 619–626, 2006.

[87] P. E. Lipsky, "Interleukin-6 and rheumatic diseases," *Arthritis Research and Therapy*, vol. 8, p. S4, 2006.

[88] T. Kishimoto, S. Akira, M. Narazaki, and T. Taga, "Interleukin-6 family of cytokines and gp130," *Blood*, vol. 86, no. 4, pp. 1243–1254, 1995.

[89] T. Taga, M. Hibi, Y. Hirata et al., "Interleukin-6 triggers the association of its receptor with a possible signal transducer, gp130," *Cell*, vol. 58, no. 3, pp. 573–581, 1989.

[90] A. Desgeorges et al., "Concentrations and origins of soluble interleukin 6 receptor-alpha in serum and synovial fluid," *The Journal of Rheumatology*, vol. 24, pp. 1500–1516, 1997.

[91] J. J. O’Shea and P. J. Murray, "Cytokine signaling modules in inflammatory responses," *Immunity*, vol. 28, no. 4, pp. 477–487, 2008.

[92] T. Hirano, "Cytokines in autoimmune disease and chronic inflammatory proliferative disease," *Cytokine & Growth Factor Reviews*, vol. 13, no. 4-5, pp. 297–298, 2002.

[93] K. R. Prowse and H. Baumann, "Interleukin-1 and interleukin-6 stimulate acute-phase protein production in primary mouse
hapatocytes,” *Journal of Leukocyte Biology*, vol. 45, no. 1, pp. 55–61, 1989.

[94] F. A. Houssiau, J.-P. Devogelaer, J. van Damme, C. N. de Deuxchaisnes, and J. van Snick, “Interleukin-6 in synovial fluid and serum of patients with rheumatoid arthritis and other inflammatory arthritides,” *Arthritis & Rheumatism*, vol. 31, no. 6, pp. 784–788, 1988.

[95] S. Suematsu, M. Hashizume, H. Yoshida, M. Shina, and M. Mihara, “IL-6 and IL-1 synergistically enhanced the production of MMPs from synovial cells by up-regulating IL-6 production and IL-1 receptor I expression,” *Cytokine*, vol. 51, no. 2, pp. 178–183, 2010.

[96] J. Van Snick, “Interleukin-6: an overview,” *Annual Review of Immunology*, vol. 8, pp. 253–276, 1990.

[97] Y. Zhang, D. Y. M. Leung, B. N. Richers et al., “Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1.” *The Journal of Immunology*, vol. 188, no. 5, pp. 2127–2135, 2012.

[98] L. Nonn, L. Peng, D. Feldman, and D. M. Pechl, “Inhibition of p38 by vitamin D reduces interleukin-6 production in normal prostate cells via mitogen-activated protein kinase phosphatase 3: implications for prostate cancer prevention by vitamin D,” *Cancer Research*, vol. 66, no. 8, pp. 4516–4524, 2006.

[99] M.-L. Xue, H. Zhu, A. Thakur, and M. Wilcox, “1α,25-Dihydroxyvitamin D inhibits pro-inflammatory cytokine and chemokine expression in human corneal epithelial cells colonized with *Pseudomonas aeruginosa*,” *Immunology & Cell Biology*, vol. 80, no. 4, pp. 340–345, 2002.

[100] B. Stockinger, “Th17 cells: an orphan with influence,” *Immunol-ogy & Cell Biology*, vol. 85, no. 2, pp. 83–84, 2007.

[101] J. A. Huhtakangas, J. Veijola, S. Turunen et al., “1,25(OH)2D3 and calcipotriol, its hypocalcemic analog, exert a long-lasting anti-inflammatory and anti-proliferative effect in synovio-cytes cultured from patients with rheumatoid arthritis and osteoarthritis,” *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 173, pp. 13–22, 2017.

[102] N. Y. Hemdan, G. Birkenmeier, G. Wichmann et al., “Interleukin-17-producing T helper cells in autoimmunity,” *Autoimmunity Reviews*, vol. 9, no. 11, pp. 785–792, 2010.

[103] J. P. van Hamburg, P. S. Asmawidjaja, N. Davelaar et al., “Th17 cells, but not Th1 cells, from patients with early rheumatoid arthritis are potent inducers of matrix metalloproteinases and proinflammatory cytokines upon synovial fibroblast interaction, including autocrine interleukin-17A production,” *Arthritis & Rheumatism*, vol. 63, pp. 73–80, 2010.

[104] U. Ikeda, D. Wákita, T. Ohkuri et al., “1α,25-Dihydroxyvitamin D3 and all-trans retinoic acid synergistically inhibit the differentia-tion and expansion of Th17 cells,” *Immunology Letters*, vol. 134, no. 1, pp. 7–16, 2010.

[105] P. Ranganathan, S. Khalatbari, S. Yalavarthi, W. Marder, R. Brook, and M. J. Kaplan, “Vitamin D deficiency, interleukin 17, and vascular function in rheumatoid arthritis,” *The Journal of Rheumatology*, vol. 40, no. 9, pp. 1529–1534, 2013.

[106] C. Daniel, N. A. Sarty, N. Zahn, H. H. Radeke, and J. M. Stein, “Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile,” *The Journal of Pharmacology and Experimental Therapeutics*, vol. 324, no. 1, pp. 23–33, 2008.

[107] J. Tang, R. Zhou, D. Lager et al., “Calcitriol suppresses antirenal autoimmunity through inhibitory effects on the Th17 effector response,” *The Journal of Immunology*, vol. 182, no. 8, pp. 4624–4632, 2009.

[108] J. R. Mora, M. Iwata, and U. H. Von Andrian, “Vitamin D effects on the immune system: vitamins A and D take centre stage,” *Nature Reviews Immunology*, vol. 8, pp. 685–698, 2008.

[109] S. H. Chang, Y. Chung, and C. Dong, “Vitamin D suppresses Th17 cytokine production by inducing C/EBP homologous protein (CHOP) expression,” *Journal of Biological Chemistry*, vol. 285, pp. 38751–38755, 2010.

[110] M. R. Von Essen, M. Kongsbak, P. Schjerling, K. Olgaard, N. Ørum, and C. Geisler, “Vitamin D controls T cell antigen receptor signaling and activation of human T cells,” *Nature Immunology*, vol. 11, no. 4, pp. 344–349, 2010.

[111] E. M. Colin, P. S. Asmawidjaja, J. P. van Hamburg et al., “1,25-dihydroxyvitamin D3 modulates Th17 polarization and interleukin-22 expression by memory T cells from patients with early rheumatoid arthritis,” *Arthritis & Rheumatism*, vol. 62, no. 1, pp. 132–142, 2010.

[112] G. S. Buchan, K. Barrett, T. Fujita, T. Taniguchi, R. Maini, and M. Feldmann, “Detection of activated T cell products in the rheumatoid joint using cDNA probes to Interleukin-2 (IL-2) IL-2 receptor and IFN-gamma,” *Clinical and Experimental Immunology*, vol. 71, pp. 295–301, 1988.

[113] A. Takeuchi, G. S. Reddy, T. Kobayashi, T. Okano, I. Park, and S. Sharma, “Nuclear factor of activated T cells (NFAT) as a molecular target for 1a, 25-dihydroxyvitamin D3-mediated effects,” *Journal of Immunology*, vol. 160, pp. 209–218, 1998.

[114] J. M. Lemire and D. Clay Archer, “1,25-dihydroxyvitamin D3 prevents the in vivo induction of murine experimental autoim-mune encephalomyelitis,” *The Journal of Clinical Investigation*, vol. 87, no. 3, pp. 1103–1107, 1991.

[115] P. Szodoray, B. Nakken, J. Gaal et al., “The complex role of vitamin D in autoimmune diseases,” *Scandinavian Journal of Immunology*, vol. 68, no. 3, pp. 261–269, 2008.

[116] E. Van Etten and C. Mathieu, “Immunoregulation by 1,25-dihydroxyvitamin D3: basic concepts,” *The Journal of Steroid Biochemistry and Molecular Biology*, vol. 97, no. 1-2, pp. 93–101, 2005.

[117] I. Alroy, T. L. Towers, and L. P. Freedman, “Transcriptional repression of the interleukin-2 gene by vitamin D3: direct inhibition of NFATp/AP-1 complex formation by a nuclear hormone receptor,” *Molecular and Cellular Biology*, vol. 15, no. 10, pp. 5789–5799, 1995.

[118] M. T. Cantorna, C. E. Hayes, and H. F. DeLuca, “1,25-dihydroxycholecalciferol inhibits the progression of arthritis in murine models of human arthritis,” *Journal of Nutrition*, vol. 128, no. 1, pp. 68–72, 1998.

[119] J. Correale, M. C. Ysraeedit, and M. I. Gain, “Immunomodula-tory effects of vitamin D in multiple sclerosis,” *Brain*, vol. 132, no. 5, pp. 1146–1160, 2009.

[120] A. Boonstra, F. J. Barrat, C. Crain, V. L. Heath, H. F. J. Savelkoul, and A. O’Garra, “1α,25-Dihydroxyvitamin D3 has a direct effect on naive CD4+ T cells to enhance the development of Th2 cells,” *The Journal of Immunology*, vol. 167, no. 9, pp. 4974–4980, 2001.

[121] L. Petrovic-Rackov and N. Pejnovic, “Clinical significance of IL-18, IL-15, IL-12 and TNF-alpha measurement in rheumatoid arthritis,” *Clinical Rheumatology*, vol. 25, pp. 448–452, 2006.
[123] X. Rausch-Fan, F. Leutmezer, M. Willheim et al., "Regulation of cytokine production in human peripheral blood mononuclear cells and allergen-specific Th cell clones by 1α,25-dihydroxyvitamin D3," *International Archives of Allergy and Immunology*, vol. 128, no. 1, pp. 33–41, 2002.

[124] D. D’Ambrosio, M. Cippitelli, M. G. Cocciolet al., "Inhibition of IL-12 production by 1,25-dihydroxyvitamin D3. Involvement of NF-κB downregulation in transcriptional repression of the p40 gene," *The Journal of Clinical Investigation*, vol. 101, no. 1, pp. 252–262, 1998.

[125] G. Penna and L. Adorini, "I Alpha, 25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation," *The Journal of Immunology*, vol. 164, pp. 2405–2411, 2000.

[126] H. J. Wu, Y. Lo, D. Lük, C. S. Lau, L. Lu, and M. Y. Mok, "Alternatively activated dendritic cells derived from systemic lupus erythematosus patients have tolerogenic phenotype and function," *Clinical Immunology*, vol. 156, no. 1, pp. 43–57, 2015.

[127] L. E. Jeffery, K. Raza, and M. Hewison, "Vitamin D in rheumatoid arthritis towards clinical application," *Nature Reviews Rheumatology*, vol. 12, p. 201, 2015.

[128] K. Zwerina, W. Baum, and R. Axmann et al., "Vitamin D receptor regulates TNF-mediated arthritis," *Annals of the Rheumatic Diseases*, vol. 70, no. 6, pp. 1122–1129, 2011.

[129] L. A. Merlini, J. Curtis, T. R. Mikuls, J. R. Cerhan, L. A. Griswell, and K. G. Saag, "Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa women’s health study," *Arthritis & Rheumatism*, vol. 50, pp. 72–77, 2004.

[130] X. Feng, C. Lv, F. Wang, K. Gan, M. Zhang, and W. Tan, "Modulatory effect of 1,25-dihydroxyvitamin D$_3$ on IL-β-induced RANKL, OPG, TNFα, and IL-6 expression in human rheumatoid synoviocyte MH7A,” *Clinical and Developmental Immunology*, vol. 2013, Article ID 160123, 8 pages, 2013.

[131] G. G. Song, S.-C. Bae, and Y. H. Lee, "Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis," *Clinical Rheumatology*, vol. 31, pp. 1733–1739, 2012.

[132] A. Raczkiewicz, B. Kisiel, M. Kulig, and W. Tlstochowicz, "Vitamin D status and its association with quality of life, physical activity, and disease activity in rheumatoid arthritis patients," *Journal of Clinical Rheumatology*, vol. 21, 2015.

[133] Y. H. Lee and S. C. Bae, "Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: a meta-analysis," *Clinical and Experimental Rheumatology*, vol. 34, pp. 827–833, 2016.

[134] M. Cutolo, K. Otsa, K. Laas et al., "Circannual vitamin D serum levels and disease activity in rheumatoid arthritis: Northern versus Southern Europe," *Clinical and Experimental Rheumatology*, vol. 24, pp. 702–704, 2006.

[135] S. Grazio, D. B. Naglić, B. Anić et al., "Vitamin D serum level, disease activity and functional ability in different rheumatic patients," *The American Journal of the Medical Sciences*, vol. 349, no. 1, pp. 46–49, 2015.

[136] M. L. Brance, L. R. Brun, S. Lioi, A. Sánchez, M. Abdala, and B. Oliveri, "Vitamin D levels and bone mass in rheumatoid arthritis," *Rheumatology International*, vol. 35, no. 3, pp. 499–505, 2015.

[137] R. Sharma, R. Saigal, L. K. Goyal et al., "Estimation of vitamin D levels in rheumatoid arthritis patients and its correlation with the disease activity," *The Journal of the association of Physicians of India*, vol. 62, pp. 678–681, 2014.

[138] Q. Hong, J. Xu, S. Xu, L. Lian, M. Zhang, and C. Ding, "Associations between serum 25-hydroxyvitamin D and disease activity, inflammatory cytokines and bone loss in patients with rheumatoid arthritis," *Rheumatology*, vol. 53, no. 11, pp. 1994–2001, 2014.

[139] T. A. Gheita, S. Sayed, H. A. Gheita, and S. A. Kenawy, "Vitamin D status in rheumatoid arthritis patients: relation to clinical manifestations, disease activity, quality of life and fibromyalgia syndrome," *International Journal of Rheumatic Diseases*, vol. 19, pp. 294–299, 2014.

[140] M. A. Atwa, M. G. Balata, A. M. Hussein, N. I. Abdelrahman, and H. H. Elminshawy, "Serum 25-hydroxyvitamin D concentration in patients with psoriasis and rheumatoid arthritis and its association with disease activity and serum tumor necrosis factor-alpha," *Saudi Medical Journal*, vol. 34, no. 8, pp. 806–813, 2013.

[141] I. Kostoglou-Athanassiou, P. Athanassiou, A. Lyraiki, I. Raftakis, and C. Antoniadis, "Vitamin D and rheumatoid arthritis," *Therapeutic Advances in Endocrinology and Metabolism*, vol. 3, no. 6, pp. 181–187, 2012.

[142] J. Lin, J. Liu, M. L. Davies, and W. Chen, "Vitamin D level and rheumatoid arthritis disease activity: review and meta-analysis," *PLoS One*, vol. 11, Article ID e0146351, 2016.

[143] Y. Wang, F. Zhang, S. Wang et al., "Serum vitamin D level is inversely associated with anti-cyclic citrullinated peptide antibody level and disease activity in rheumatoid arthritis patients," *Archives of Rheumatology*, vol. 31, no. 1, pp. 64–70, 2016.

[144] J. Vojinovic, A. Tincani, A. Sulli et al., "European multicentre pilot survey to assess vitamin D status in rheumatoid arthritis patients and early development of a new patient reported outcome questionnaire (D-PRO)," *Autoimmunity Reviews*, vol. 16, no. 5, pp. 548–554, 2017.

[145] S. Coccetti, Z. Tatar, P. Galan et al., "Prevalence of vitamin D deficiency in rheumatoid arthritis and association with disease activity and cardiovascular risk factors: data from the COMEDRA study," *Clinical and Experimental Rheumatology*, vol. 34, pp. 984–990, 2016.

[146] E. Rajae et al., "The relationship between serum level of vitamin D3 and the severity of new onset rheumatoid arthritis activity," *Journal of Clinical and Diagnostic Research*, vol. 11, pp. Oc28–Oc30, 2017.

[147] T. Baykal, K. Senel, F. Alp, A. Erdal, and M. Uğur, "Is there an association between serum 25-hydroxyvitamin D concentrations and disease activity in rheumatoid arthritis?" *Bratislava Medical Journal*, vol. 113, pp. 610–611, 2012.

[148] M. Sahebargi, Z. Mirfeizi, Z. Rezaieyazdi, H. Rafatpanah, and L. Goharyeshi, "25(OH) vitamin D serum values and rheumatoid arthritis disease activity (DA S28 ESR)," *Caspian Journal of Internal Medicine*, vol. 5, pp. 148–155, 2014.

[149] Y.-E. Park, B.-H. Kim, S.-G. Lee et al., "Vitamin D status of patients with early inflammatory arthritis," *Clinical Rheumatology*, vol. 34, no. 2, pp. 239–246, 2015.

[150] T. Furuya, T. Hosoi, E. Tanaka et al., "Prevalence of and factors associated with vitamin D deficiency in 4,793 Japanese patients with rheumatoid arthritis," *Clinical Rheumatology*, vol. 32, no. 7, pp. 1081–1087, 2013.

[151] H. J. Haga, A. Schmedes, Y. Naderi, A. M. Moreno, and E. Peen, "Severe deficiency of 25-hydroxyvitamin D$_3$ (25-OH-D$_3$) is associated with high disease activity of rheumatoid arthritis," *Clinical Rheumatology*, vol. 32, no. 5, pp. 629–633, 2013.

[152] M. Rossini, S. M. Bongi, G. Ia Montagna et al., "Vitamin D deficiency in rheumatoid arthritis: prevalence, determinants..."
and associations with disease activity and disability,” *Arthritis Research & Therapy*, vol. 12, no. 6, article R216, 2010.

[153] M. Varenna, M. Manara, F. P. Cantatore et al., “Determinants and effects of vitamin D supplementation on serum 25-hydroxy-vitamin D levels in patients with rheumatoid arthritis,” *Clinical and Experimental Rheumatology*, vol. 30, pp. 714–719, 2012.

[154] P. P. Sainaghi, M. Bellan, S. Carda et al., “Hypovitaminosis D and response to cholecalciferol supplementation in patients with autoimmune and non-autoimmune rheumatic diseases,” *Rheumatology International*, vol. 32, no. II, pp. 3365–3372, 2012.

[155] M. Moubis, A. J. Ostor, A. J. Crisp, A. Ginawi, D. J. Halsall, and N. Shenker, “Hypovitaminosis D among rheumatology outpatients in clinical practice,” *Rheumatology*, vol. 47, no. 9, pp. 1348–1351, 2008.

[156] D. Stoll, J. Dudler, O. Lamy et al., “High prevalence of hypovitaminosis D in a Swiss rheumatology outpatient population,” *Swiss Medical Weekly*, vol. 141, Article ID w13196, 2011.

[157] N. Hajjaj-Hassouni, N. Mawani, F. Allali et al., “Evaluation of vitamin D status in rheumatoid arthritis and its association with disease activity across 15 countries: the comora study,” *International Journal of Rheumatology*, vol. 2017, Article ID 5491676, 8 pages, 2017.

[158] F. S. Azzeh and O. A. Kensa, “Vitamin D is a good marker for disease activity of rheumatoid arthritis disease,” *Disease Markers*, vol. 2015, Article ID 260725, 6 pages, 2015.

[159] Y. Nakamura, T. Suzuki, T. Yoshida, H. Yamazaki, and H. Kato, “Vitamin D and calcium are required during denosumab treatment in osteoporosis with rheumatoid arthritis,” *Nutrients*, vol. 9, no. 5, 2017.

[160] A. Lo Gullo, G. Mandraffino, G. Bagnato et al., “Vitamin D status in rheumatoid arthritis: inflammation, arterial stiffness and circulating progenitor cell number,” *PLoS ONE*, vol. 10, no. 8, Article ID e0134602, 2015.

[161] A. S. Bansal, F. Henriquez, N. Sumar, and S. Patel, “Thelper cell subsets in arthritis and the benefits of immunomodulation by 1,25(OH)2 vitamin D,” *Rheumatology International*, vol. 32, no. 4, pp. 845–852, 2012.

[162] J. P. Van Hamburg, P. S. Asmawidjaja, N. Davelaar et al., “TNF blockade requires 1,25(OH)2D3 to control human Th17-mediated synovial inflammation,” *Annals of the Rheumatic Diseases*, vol. 71, no. 4, pp. 606–612, 2012.

[163] Y. Liu and H. Wen, “Impact of vitamin deficiency on clinical parameters in treatment-naive rheumatoid arthritis patients,” *Zeitschrift für Rheumatologie*, vol. 77, pp. 833–840, 2018.

[164] N. L. Bragazzi, A. Watad, S. G. Neumann et al., “Vitamin D and rheumatoid arthritis: an ongoing mystery,” *Current Opinion in Rheumatology*, vol. 29, no. 4, pp. 378–388, 2017.

[165] N. Maruotti and F. P. Cantatore, “Vitamin D and the immune system,” *The Journal of Rheumatology*, vol. 37, p. 491, 2010.

[166] G. Adami, M. Rossini, L. Bogliolo et al., “An exploratory study on the role of vitamin D supplementation in improving pain and disease activity in rheumatoid arthritis,” *Modern Rheumatology*, pp. 1–4, 2018.

[167] D. Pu, J. Luo, Y. Wang et al., “Prevalence of depression and anxiety in rheumatoid arthritis patients and their associations with serum vitamin D level,” *Clinical Rheumatology*, vol. 37, no. 1, pp. 179–184, 2018.

[168] H. Yesil, U. Sungur, S. Akdeniz, G. Gurer, B. Yalcin, and U. Dundar, “Association between serum vitamin D levels and neuropathic pain in rheumatoid arthritis patients: a cross-sectional study,” *International Journal of Rheumatic Diseases*, vol. 21, no. 2, pp. 431–439, 2018.

[169] S. Mateen, S. Moin, S. Shahzad, and A. Q. Khan, “Level of inflammatory cytokines in rheumatoid arthritis patients: Correlation with 25-hydroxy vitamin D and reactive oxygen species,” *Plos One*, vol. 12, Article ID e0178879, 2017.

[170] L.-M. Tan, T.-T. Long, X.-L. Guan et al., “Diagnostic value of vitamin D status and bone turnover markers in rheumatoid arthritis complicated by osteoporosis,” *Annals of Clinical and Laboratory Science*, vol. 48, pp. 197–204, 2018.