

## REVIEW ARTICLE

# IMMUNOMODULATORY ROLE OF VITAMIN D: CLINICAL IMPLICATIONS IN INFECTIONS AND AUTOIMMUNE DISORDERS

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Vitamin D exerts its well-known effects on bone health and calcium-phosphate homeostasis primarily through the vitamin D receptor signaling pathway. Vitamin D also has several extra-skeletal actions and its deficiency is not only implicated in musculoskeletal disorders, but also cardiovascular disorders, diabetes, neurodegenerative conditions and cancers. There is a growing body of research highlighting the link of vitamin D deficiency and alterations in vitamin D signaling with certain infections and autoimmune disorders; although the evidence is inconsistent and inconclusive. Vitamin D has been suggested to play a fundamental role in curbing infections and mitigating autoimmune disease processes. The present review was undertaken to explore the promise of vitamin D as a protective agent and a clinically useful therapeutic adjunct against infections and autoimmune diseases and identify knowledge gaps and limitations of the available data for informing future work. An exhaustive search was conducted in established databases including Google Scholar, PubMed, ScienceDirect and Springer for articles published on vitamin D, immunity, infection and autoimmune disorders. All relevant articles published in the English language between the year 2000 and 2020 were retrieved for writing the review. Although a considerable body of evidence highlighting the potential clinical benefits of vitamin D against the development of various autoimmune conditions and for the prevention of infections has emerged over the last decade, the findings are limited by the lack of appropriately designed randomized controlled trials which are needed to formulate precise clinical recommendations.

**KEY WORDS:** Vitamin D; Immunity; Infection; Vitamin D Receptors; Vitamin D Deficiency; Autoimmune Diseases; Calcitriol; Cholecalciferol; Multiple Sclerosis; Neuroprotection.

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**INTRODUCTION**

Vitamin D (calciferol), a fat-soluble vitamin, is primarily involved in the maintenance of skeletal health and mineral homeostasis. Vitamin D is a steroidal organic compound having two major naturally occurring forms, ergocalciferol in plants and cholecalciferol in animals. Vitamin D has hormone-like actions and its chief target organs are the bone, kidney and small intestine where it regulates calcium and phosphorus absorption and metabolism.<sup>1</sup> Endogenous dermal

production is the principal human source of vitamin D while exogenous dietary contribution is much smaller.<sup>2</sup> Skin exposure to natural sunlight leads to conversion of the cholesterol derivative 7-dehydrocholesterol into vitamin D<sub>3</sub>. Vitamin D<sub>3</sub> then undergoes hydroxylation in the liver at position 25 and then in the kidney at position 1 to form the active metabolite 1,25-dihydroxy D<sub>3</sub> (calcitriol).<sup>3</sup>

Besides skeletal mineral balance, vitamin D has been shown to be involved in multiple extra skeletal functions including neuroprotection, xenobiotic detoxification, cell proliferation, cellular differentiation and immunomodulation.<sup>4</sup> These findings have highlighted the potential of vitamin D as an antioxidant, anticancer, antimicrobial and anti-inflammatory agent having a tremendous impact on the health of the musculoskeletal, cardiovascular, nervous and immune systems. These pleiotropic actions of vitamin D are carried out via the vitamin D receptors (VDR) that belong to the nuclear hormone receptor

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family and are present on various cell types such as cells involved in immune functions.<sup>5,6</sup> Vitamin D has important functional roles in immunity, at the level of both innate and adaptive immune systems. The suppression of antigen-presenting cell (APC) maturation and reduction of pro-inflammatory cytokines are few of the well-known immunomodulatory features of vitamin D.<sup>7</sup> The deficiency of vitamin D has been related to many immune diseases like asthma, psoriasis, rheumatic diseases, and multiple sclerosis. Normal vitamin D levels have been reported to play part in protection against certain viral and bacterial infections.

### **VITAMIN D AND INFECTION**

Vitamin D deficiency is reported to be associated with an increased risk of infections. Seasonal changes in the levels of vitamin D are associated with an increased incidence of several infections, particularly respiratory infections, in many epidemiologic studies. Moreover, considering the emerging evidence on the modulatory mechanisms employed by vitamin D on immune functions, the benefits of vitamin D supplementation against infectious processes come as no surprise.<sup>8</sup>

#### ***Influenza A viral infection***

Low serum levels of vitamin D during winter are reported to be associated with the increased occurrence of epidemic influenza.<sup>9</sup> Low incidence of influenza A viral infection has been shown in school-going children upon supplementation with 1200 IUs of vitamin D3 daily.<sup>10</sup> However, in other populations, the amount of vitamin D needed to derive clinical benefits remains rather vague.<sup>11</sup> Some clinical practices have reported complete resolution of influenza symptoms within two to three days of a one-time 50,000 IU dose of vitamin D3.<sup>12</sup> Supplementation with vitamin D3 is potentially advantageous in conditions in which influenza vaccine is contraindicated such as in patients receiving immunosuppressive therapy.<sup>13</sup> Therefore, it is not too early to suggest health care providers to promptly diagnose and treat vitamin D deficiency in deficient patients.<sup>14</sup>

#### ***Tuberculosis***

Heliotherapy (sunlight exposure) and subsequently cod liver oil and vitamin D (following its isolation from cod liver oil almost a century ago) were historically used as therapy and prophylaxis for tuberculosis.<sup>8,15</sup> Tuberculosis has been linked with vitamin D deficiency and VDR polymorphisms which make these populations particularly susceptible to the ailment.<sup>16-18</sup> Progression of TB in affected individuals has a strong correlation with serum vitamin D levels.<sup>19</sup> This may be explained by the bactericidal action of vitamin D against *Mycobacterium tuberculosis* such as reversal of mycobacterium tuberculosis-induced inhibition of phagosome maturation, which is an important element of progression of tu-

berculosis.<sup>15</sup> Vitamin D may serve as a beneficial adjunct to antibiotic regimens aimed against *Mycobacterium tuberculosis* and its multi-drug resistant form.<sup>20,21</sup>

#### ***Other bacterial infections***

Keeping in view the antimycobacterial actions and inhibitory effect of vitamin D on the pathogenesis of tuberculosis, it is safe to assume a role of vitamin D in the prevention, inhibition and treatment of other infections. Vitamin D3 has been shown to control pulmonary inflammation by inducing the production of cathelicidin, which is dubbed as the natural broad-spectrum antimicrobial peptide.<sup>13</sup> Acute respiratory infections, particularly in children, are reported to be more commonly seen with vitamin D deficiency, and supplementation has not been clearly indicated as an effective prevention strategy against acute respiratory infections.<sup>22</sup> Seasonal disparities in circulating vitamin D parallel those of sepsis.<sup>23</sup> Vitamin D has also been reported as an effective intervention in treating *Helicobacter pylori* infections.<sup>24</sup> Such studies thus highlight the need to verify and establish additional correlates of vitamin D, and investigate it in the context of infectious processes.

Sufficient information is not there about the immunomodulatory potential of vitamin D in fungal, protozoal, or parasitic infections. Low dose vitamin D is reported to reduce fungal burden and improve survival in candida-infected mice but higher doses were associated with poor outcomes.<sup>25</sup> Emerging evidence alludes to the fact that vitamin D status has a significant contribution to the overall immune response and vitamin D repletion can potentially offer favorable outcomes against multiple microbial pathogens.<sup>8</sup>

### **VITAMIN D AND AUTOIMMUNE DISEASE**

The involvement of vitamin D in immune response modulation makes it a pivotal element in some autoimmune diseases like multiple sclerosis, type 1 diabetes mellitus, psoriasis, inflammatory bowel disease, systemic lupus erythematosus and rheumatoid arthritis.<sup>26</sup> Patients having autoimmune diseases have been revealed to have lower serum concentrations of vitamin D than the general population.<sup>27-30</sup> This suggests that vitamin D, in contrast to genetic and some environmental factors, may be a modifiable element in the development of autoimmunity. Here, we review some of the well-known autoimmune conditions which have been associated with vitamin D deficiency.

#### ***Systemic lupus erythematosus***

Systemic lupus erythematosus (SLE), an autoimmune disorder with a chronic course, is capable of affecting virtually any organ system.<sup>31</sup> Although the exact underlying mechanism for SLE development is not yet fully understood, mounting evidence sug-

gests an association between SLE and hypovitaminosis D.<sup>32-34</sup> Other studies also report quicker SLE progression in patients having low serum levels of vitamin D.<sup>35-37</sup> This is especially discommodious for SLE patients who are required to avoid sun exposure, thus worsening the already present vitamin D deficiency. Lower disease activity has been witnessed in patients given vitamin D supplements.<sup>38,39</sup> However, a practical strategy to integrate vitamin D supplementation into SLE treatment has not been developed so far.

### **Multiple sclerosis**

The autoimmune diseases multiple sclerosis (MS) is a chronic debilitating condition targeting the nervous system. MS has previously been linked with vitamin D in several epidemiologic and observational studies.<sup>40-42</sup> Better exposure to the sun and higher vitamin D levels in childhood and adolescence are reported to decrease the risk of developing MS later in life.<sup>43-47</sup> Low serum vitamin D levels at the time of diagnosis has been shown to be affiliated with early conversion of relapsing-remitting course to secondary progressive disease.<sup>48</sup> Vitamin D supplementation causes significant alleviation of symptoms and improvement of overall health in patients with relapsing-remitting MS.<sup>49</sup> Vitamin D thus appears to have the potential to improve MS prognosis.

### **Type 1 diabetes mellitus**

Association of vitamin D status with type 1 diabetes mellitus (T1DM) is well-documented, with early vitamin D supplementation in genetically predisposed infants and children possibly reducing the risk of developing T1DM.<sup>50-52</sup> Some studies have found vitamin D to be a useful adjunct to insulin therapy in T1DM patients.<sup>53-55</sup> Randomized controlled trials (RCTs) with supplementary vitamin D have reported positive short-term effects in recently diagnosed T1DM patients.<sup>56</sup> Vitamin D is most certainly a valuable area of research in the context of T1DM treatment and warrants further research.

### **Inflammatory bowel disease**

Inflammatory bowel disease (IBD), a Th1-immune mediated autoimmune disorder, is characterized largely by vitamin D deficiency.<sup>57</sup> However, this deficiency does not indicate a cause and effect relationship, and may just be a result of malabsorption or decreased vitamin D intake secondary to IBD. Although, some murine models have shown promising effects on IBD symptoms and complications upon vitamin D supplementation,<sup>58-60</sup> human based studies have yet to confirm these hypotheses.<sup>61</sup>

### **Rheumatoid arthritis**

Rheumatoid arthritis (RA) is a multifactorial chronic inflammatory and autoimmune condition characterized by articular and extra-articular destruction that can lead to dysfunction and permanent disability. Some studies have demonstrated serum vitamin D

to be inversely correlated with RA susceptibility and disease activity.<sup>62</sup> Vitamin D deficiency alongside other genetic and environmental determinants may trigger the onset and progression of RA but conclusive evidence is lacking.<sup>63-68</sup> Results from a recent study did not indicate a link between circulating vitamin D levels and future risk of RA.<sup>69</sup> Further data need to be gathered and analyzed in order to consider vitamin D as a low-risk and cost-effective adjunct to RA treatment.

### **Uveitis**

Uveitis is an inflammatory ophthalmologic disease which affects the retina and uvea, and its etiopathogenesis predominantly involves T-lymphocyte mediated autoimmune damage.<sup>70</sup> The potential benefits of vitamin D have been highlighted in the context of this sight-threatening autoimmune condition. Serum vitamin D levels within the normal range are associated with a reduced incidence of noninfectious uveitis, suggesting an increased risk of uveitis with hypovitaminosis D.<sup>71</sup> Inadequate vitamin D status predisposes to a higher risk of autoimmune anterior uveitis, with a 4% risk reduction for every 1 ng/mL rise in serum vitamin D.<sup>71</sup>

Another recent study by Chiu, et al. showed that patients having active uveitis had lower circulating vitamin D than those having inactive uveitis. Supplementation with vitamin D and solar exposure were shown to decrease uveitis activity in patients with hypovitaminosis D.<sup>72</sup> Supplementary vitamin D also offers beneficial effects in the course of autoimmune uveitis, regardless of circulating vitamin D levels.<sup>73</sup> Vitamin D deficiency is a common finding in juvenile idiopathic arthritis (JIA), and it is associated with higher disease activity and risk of uveitis.<sup>74</sup> Future prospective studies are required to inform about the potential use of vitamin D supplementation as an adjunctive therapy in the community prevention and/ or clinical treatment of autoimmune uveitis.

### **Dermal autoimmune conditions**

Topical vitamin D analogues combined with corticosteroids, and otherwise, have long been used safely and effectively for treating inflammatory skin diseases such as psoriasis.<sup>29,75,76</sup> Low serum vitamin D levels are also been linked to atopic dermatitis and vitiligo.<sup>77,78</sup> However, further evidence from multi-nuclear case-control studies is needed to ascertain whether vitamin D contributes to the increased risk of developing these conditions, and whether or not supplementation can be used in disease treatment.

## **CONCLUSION**

Vitamin D, through its regulatory effects on immunity, shows irrefutable promise in the context of autoimmune and infectious disease treatment and prevention. However, current studies are limited by compromised study designs, small sample

sizes, selection bias, time constraints and lack of resources, among others. Investigation of the immune mechanisms activated by vitamin D is needed to emphasize its potential immunomodulatory benefits. Furthermore, the clinical utility of vitamin D in the setting of immune disorders needs to be substantiated through randomized controlled trials. This review highlights viable evidence that necessitates conducting more comprehensive studies that may allow vitamin D supplementation to be used as a safe, effective and inexpensive tool for curbing and mitigating a plethora of infectious and autoimmune diseases.

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#### CONFLICT OF INTEREST

Authors declare no conflict of interest.  
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#### AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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