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The Regulation of Adaptive Immunity by Vitamin D and Its Potential Role in Autoimmune Diseases

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Abstract. Besides regulating calcium and phosphate in the body, vitamin D also has some immunomodulatory effects. Some subsets of immune cells have the necessary parts for Vitamin D signalling, such as the Vitamin D receptor (VDR) and local activation enzymes. Connect the system to adaptive immunity in this paper and cover T-cell differentiation, regulatory T cells, B-cell responses, etc.; also discuss the influence of vitamin D deficiency. Then it will consider the proof of multiple sclerosis (MS), type 1 diabetes mellitus (T1DM) and rheumatoid arthritis (RA). Mechanistic and observational studies have shown that vitamin D is associated with the immune system. The clinical supplementation literature is not uniform. All the results of these studies are different, and currently, no particular disease-modifying treatment for deficiency has been found. Good trials still need to be carried out to determine when supplementation is effective, what the suitable dose is, and which patients will benefit most.

Keywords: vitamin D, adaptive immune regulation, vitamin D receptor, T cells, autoimmunity

1. Introduction

After VDR was found in cells such as dendritic cells, T lymphocytes and B lymphocytes, the immune function of vitamin D became known [1-3]. Thus, it was discovered that vitamin D has other uses in the body for long time without knowing them. Convert to 1,25-dihydroxyvitamin D3 [1,25(OH)2D3], and then vitamin D can affect the gene expression program of lymphocyte differentiation, cytokine production and immune tolerance [4-6]. At the same time, many epidemiological and experimental studies have repeatedly found associations between vitamin D deficiency and MS, T1DM and RA [7-10]. A correlation does not imply that one disease causes another or that it is severe.

Therefore, this paper will investigate how Vitamin D signalling regulates the adaptive immune system and will not focus on treating Vitamin D deficiency. Metabolism and receptor signalling lead to changes in T and B cells, and this has been observed in various diseases. The first is to regulate the activity of inflammatory effectors and the process of self-tolerance. Therefore, it will not be possible to distinguish between biological plausibility and the still-limited evidence for personalised supplementation or immune-directed clinical application [1, 8, 11, 12].

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2. Vitamin D processing in an immune context

Vitamin D reaches immune tissues largely as precursors rather than as a continuously active end product. Biological activity depends on hydroxylation, culminating in formation of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3]. The liver and kidney carry out the major systemic steps, yet the final conversion can also occur within immune cells. Thus, vitamin D signaling can be generated locally at sites of immune activity, allowing tissue-level regulation that is partly independent of circulating active hormone.

2.1. Acquisition and metabolic activation

Two routes supply the vitamin D pool. UVB irradiation of skin drives conversion of 7-dehydrocholesterol to cholecalciferol (vitamin D3), whereas food contributes vitamin D2, vitamin D3, or both. Cutaneous production varies substantially among individuals because the effective UVB dose is modified by behavior and biological factors including sun exposure, pigmentation, age, and sunscreen use [5, 13].

The first main circulating product is 25-hydroxyvitamin D [25(OH)D], produced by hepatic cytochrome P450 family 2 subfamily R member 1 (CYP2R1) hydroxylation of vitamin D. As it is relatively abundant and stable, 25(OH)D is frequently used to reflect the body's level of vitamin D. cytochrome P450 family 27 subfamily B member 1 (CYP27B1) then performs a second hydroxylation in the kidney to produce 1,25-dihydroxyvitamin D3 [1,25(OH)2D3]. Parathyroid hormone is an endocrine signal that regulates the amount of active hormones and catabolism through cytochrome P450 family 24 subfamily A member 1 (CYP24A1) [5, 13].

Immune tissue is also one of these places. Macrophages, dendritic cells and activated lymphocytes can express CYP27B1 and produce 1,25(OH)2D3 from the circulating pool of 25(OH)D at sites of immune activation [1, 10, 12]. Therefore, neighbouring cells or even the same cell can be affected by locally produced metabolites. A shortage of substrate will weaken the local regulatory circuit and thus reduce the extent of inflammation [1, 8].

2.2. VDR signaling across immune cell types

The first place Vitamin D acts in the body to influence immunity is VDR. When 1,25(OH)2D3 binds to VDR, a complex is formed between the receptor and Retinoid X Receptor (RXR). Then it will bind to the Vitamin D response elements (VDREs) and alter the expression of target genes [3]. Immune cells will change in many ways, be activated or repressed, and release Vitamin D-related factors; they are not typical extracellular cytokines.

VDR is found across much of the immune system rather than in just one cell lineage. T cells,B cells,dendritic cells,macrophages,and monocytes all express this receptor,and activation can increase its abundance in several of these cell types [3]. Therefore, the effect of vitamin D is not uniform. Different cells are in different states of activation.

VDR-dependent transcription in T lymphocytes can affect differentiation and cytokine production, change the balance of inflammation and regulation [3]. Dendritic cells also have an indirect effect. Vitamin D deficiency can hinder their development and affect antigen-presentation/inflammatory cytokine production. Therefore, there are fewer signals for strong T-cell activation and tolerance is more likely [2].

Monocytes and macrophages have a combined receptor signal and local activation of CYP27B1. Thus, they can produce and respond to active vitamin D at the site of inflammation. In fact, it is

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known that Vitamin D can regulate inflammation locally [1, 7]. All of the above show that vitamin D and immunity are not merely correlated. Vitamin D affects inflammation and tolerance at the level of receptor expression and local metabolic activation in the cells of the innate and adaptive immune systems.

3. How Vitamin D shapes adaptive immune responses

Adaptive immunity depends on clonal T- and B-cell responses that are highly effective against specific antigens. The same specificity becomes harmful when self-reactive clones escape control. Vitamin D does not appear to act at a single checkpoint; instead, available evidence places it at several regulatory steps, including helper-T-cell polarization, Treg function, dendritic-cell support of lymphocyte activation, and B-cell differentiation.

3.1. Effects on Th1/Th17 inflammatory pathways

Th1 and Th17 responses are frequently implicated in chronic autoimmune inflammation, but their mediator profiles differ. Th1 cells characteristically produce interferon-gamma (IFN-γ) and interleukin-2 (IL-2), whereas Th17 cells are major producers of interleukin-17 (IL-17). Sustained activity of these pathways can maintain inflammatory signaling and contribute to tissue injury [1, 6].

1,25(OH)2D3 can act directly on VDR-expressing T cells, changing transcription programs associated with lineage commitment and cytokine production. Under these conditions, development of Th1 and Th17 responses is reduced and output of IFN-γ and IL-17 falls [4]. A second pathway involves dendritic cells: vitamin D lowers IL-12 and IL-23 production, removing cytokine signals that normally support Th1 and Th17 differentiation [3]. Thus, the same metabolite can influence inflammatory T-cell responses both directly and through antigen-presenting cells.

This mechanism is relevant to MS, RA, and T1DM because IL-17-associated inflammation has been implicated in each. The implication is not that vitamin D deficiency alone causes these disorders, but that inadequate vitamin D may remove one of several restraints on inflammatory polarization. A shift away from regulatory control could then make maintenance of self-tolerance more difficult [1, 8].

3.2. Support for regulatory T-cell responses

Regulatory T cells (Tregs), especially CD4+Foxp3+ cells, provide an important counterweight to autoreactive effector cells. Their suppressive activity includes production of interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) and other mechanisms that limit inappropriate activation [1, 6]. Vitamin D signaling can support the Treg program, including increased Foxp3 expression, and thereby strengthen suppression of autoreactive responses [1, 4].

An additional effect arises upstream at the dendritic-cell level. When vitamin D promotes a less inflammatory, more tolerogenic dendritic-cell phenotype, conditions become more favorable for regulatory rather than inflammatory T-cell responses [3]. The net result may be a more stable balance between Th1/Th17 activity and Treg-mediated control; low vitamin D status has been associated with disturbance of this balance in autoimmune settings [1, 8, 9].

3.3. Effects on B-cell activity

The contribution of B cells to autoimmunity extends beyond antibody secretion. They also present antigen and cooperate with T cells, while differentiated plasma cells can generate antibodies against

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self-antigens. If these processes are insufficiently controlled, B-cell responses become another source of sustained inflammation and tissue injury [7, 8].

As B cells are VDR, allowing 1,25(OH)2D3 can bind to them directly. Experimental work suggests that vitamin D signaling slows B-cell proliferation, blueuces plasma-cell differentiation,and lowers immunoglobulin output. Therefore, it is expected that the production of autoantibodies will decrease [1, 6]. Vitamin D can affect helper-T cell activity in a different way, and these helper-T cells are required for proper activation of B cells and antibody production [4].

Reports of low vitamin D levels are associated with an increased risk of autoimmune diseases and other features of autoimmunity. It will not be the same as before, however. Based on the above evidence, we believe that sufficient vitamin D levels can help maintain the regulation of B-cell responses in a healthy state [7, 8].

4. Vitamin D across selected autoimmune disorders

Mechanistic studies provide several routes by which vitamin D could alter the threshold between immune tolerance and autoimmunity. Whether those routes have measurable clinical consequences depends on the disease and on the type of evidence considered. MS, T1DM, and RA illustrate this distinction particularly well because all three have observational, experimental, and intervention data, but these lines of evidence do not always point with equal strength in the same direction.

4.1. Multiple sclerosis

In MS, immune-mediated injury within the central nervous system (CNS) targets myelin and produces demyelination that can accumulate as neurological disability [14]. This makes the disease a useful model for examining whether an environmental factor such as vitamin D can modify both peripheral immune activation and inflammatory processes within nervous tissue.

The epidemiological signal is consistent but not definitive. Lower vitamin D concentrations and reduced sun exposure are repeatedly associated with higher MS risk, while MS prevalence increases at higher latitudes where cutaneous vitamin D synthesis is more limited by lower UVB exposure [10, 11]. Associations have also been reported for low vitamin D during early life or pregnancy. Because these studies are observational, however, they cannot by themselves separate causation from correlated environmental or behavioral factors [11].

Preclinical findings are more mechanistic. Administration of vitamin D in experimental autoimmune encephalomyelitis (EAE) can reduce clinical severity and inflammatory damage in neural tissue [4]. Vitamin D-related pathways have also been linked to oligodendrocyte biology, maintenance of myelin, and regulation of CNS inflammation, providing possible routes to neuroprotection in addition to systemic immune effects [11, 15].

Translation to patients has been less straightforward. Supplementation studies differ in dose, duration, baseline status, disease stage, and participant characteristics, and their outcomes are not uniform. For that reason, current trial evidence is insufficient to conclude that vitamin D supplementation prevents MS or materially changes its long-term course [11, 14].

4.2. Type 1 diabetes mellitus

T1DM develops when autoimmune destruction progressively reduces the pancreatic beta-cell mass and, consequently, endogenous insulin secretion. Its central mechanism is therefore immune-mediated beta-cell loss rather than the insulin resistance that dominates type 2 diabetes [9].

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Interest in vitamin D as a modifier of T1DM arises from receptor expression in both beta cells and immune populations involved in the autoimmune attack. Population studies have associated low vitamin D status, particularly early in life, with increased risk of later T1DM [9, 12]. These data are compatible with an effect on susceptibility, although they do not establish vitamin D deficiency as a sufficient cause.

During disease development, self-reactive lymphocytes recognize beta-cell antigens and drive islet inflammation. Vitamin D could theoretically influence this process through its effects on inflammatory-regulatory balance. Its actions on B cells also provide a route by which production of beta-cell-related autoantibodies, including glutamic acid decarboxylase (GAD) antibodies and insulin autoantibodies, might be moderated [1, 7].

Non-obese diabetic (NOD) mouse experiments support a preventive hypothesis: supplementation can reduce immune-cell infiltration of pancreatic islets and postpone diabetes onset. Human data are much weaker, and vitamin D is not an established independent therapy for diagnosed T1DM. Because considerable beta-cell destruction precedes clinical diagnosis, any benefit may be more plausible before or early in overt disease, a possibility that remains to be tested adequately [9, 12].

4.3. Rheumatoid arthritis

RA is driven by persistent inflammation of the synovium, followed over time by cartilage degradation and bone erosion. The inflammatory network in affected joints involves several immune populations, including T cells, B cells, macrophages, and dendritic cells [8].

Cross-sectional and clinical studies often find lower serum vitamin D in people with RA, and lower concentrations have been related to greater disease activity and higher inflammatory markers [8, 16]. A mechanistic interpretation is also plausible: vitamin D can reduce pro-inflammatory signaling while supporting tolerance, and its effects on autoreactive B cells may influence production of rheumatoid factor and anti-citrullinated protein (anti-CCP) antibodies [1, 6, 8].

The intervention literature is less consistent than the observational literature. Differences among studies in starting vitamin D status, disease duration, concurrent immunosuppressive treatment, and supplementation regimens make direct comparison difficult and may account for some of the heterogeneous outcomes.

Accordingly, correcting vitamin D deficiency in an RA patient may be clinically appropriate for general health, but available evidence does not establish supplementation as a therapy that alters the underlying disease process. Trials designed around baseline status, dose, duration, and patient subgroup are needed before a disease-specific benefit can be defined [8].

5. Conclusion

Current evidence supports an immunological role for vitamin D that is distinct from, but connected to, its classical endocrine function. Local activation of vitamin D and VDR signaling occur in immune cells, and these pathways can influence helper-T-cell polarization, Treg activity, dendritic-cell behavior, and B-cell differentiation. Those effects provide a coherent mechanism for the recurrent association between inadequate vitamin D status and autoimmune conditions such as MS, T1DM, and RA.

The clinical interpretation must nevertheless remain cautious. Mechanistic experiments and observational cohorts show biological plausibility, whereas supplementation trials have produced variable results and do not consistently demonstrate disease modification. Future studies should stratify participants by baseline vitamin D status and disease stage, use well-defined dosing

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regimens, and identify outcomes relevant to prevention or adjunctive treatment. Until then, vitamin D should be viewed as a potential modifier of immune regulation rather than a proven stand-alone therapy for autoimmune disease.

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