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The Multifaceted Effects of Vitamin D and Its Potential Contribution to Rheumatoid Arthritis

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Author's contribution

This whole work was carried out by the author.

Mini-review

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ABSTRACT

Vitamin D (VD) is known to have pleiotropic effects on various tissues and organs including those of the immune and musculoskeletal systems. VD deficiency has been suggested to trigger the onset of autoimmune diseases including rheumatoid arthritis (RA), although the significance of this finding remains controversial. Conversely, patients with RA often have VD deficiency, and it may modify the pathophysiology of the disorder. This review summarizes recent findings on the multiple roles of VD that may modulate the clinical course of RA. The possibility of administering VD as a therapeutic option for RA is also explored.

Keywords: Vitamin D; rheumatoid arthritis; review.

1. INTRODUCTION

Vitamin D (VD) is a secosteroid that regulates calcium and phosphate absorption in the intestine. In humans, the most important forms of VD are VD2 and VD3. The body can obtain these compounds through the diet or can synthesize these compounds from cholesterol when exposed to sunlight. Specifically, VD2 (ergocalciferol) is produced when ergosterol or provitamin D2, a type of cholesterol found in fungi or plants, is exposed to UV radiation. Animals and fish undergo a similar process where 7-dehydrocholestrol (related to cholesterol and also known as provitamin D3) is converted to previtamin D3 upon exposure

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to UV rays from the sun. Finally, previtamin D3 is isomerized to its active form, VD3 (cholecalciferol).

Irrespective of their origin, the D2 and D3 forms have to be converted to active compounds through a 2-step enzymatic hydroxylation process to exert their effects. First, VD2 and VD3 are converted to 25-hydroxyvitamin D (25[OH]D; calcifediol) by 25-hydroxylase in the liver; 25(OH)D is stored in the liver, and when necessary, released into the circulation and converted to its most active form, 1,25-dihydroxyvitamin D ($1,25[OH]_2D$; calcitriol), in the kidney or skin. The rate of the conversion is determined by the serum levels of calcium and parathyroid hormone.

2. SERUM LEVELS OF VD

Clinically, the serum level of 25(OH)D has been accepted as the best index of VD status. The levels of 25(OH)D can be affected by multiple factors including smoking, exposure to sunlight, age, gender, and dietary consumption [1-3]. First, given that UV rays or sunlight is essential for producing VD naturally, factors that affect the amount of sunlight exposure to the skin are major regulators of VD production. Examples of these factors include lifestyle (i.e., the amount of time spent participating in outdoor activities), the incident angle of the sun, latitude position, clothing styles, season of the year, and time of day. For example, several studies have shown that residents in northern countries have lower levels of VD [4,5]; however, the use of cod liver oil or vitamin supplements can also affect VD levels in people living in northern countries [1,3]. Clothing with different amounts of skin exposure also affects VD status [6]. In addition, elderly people often have low serum VD levels due to reduced exposure to sunshine, decreased expression of VD receptors (VDR) in the peripheral tissues, and impaired intestinal absorption or renal activation of VD [7]. As for differences in gender, a Japanese study demonstrated that VD levels were higher in men than in women during the summer and winter seasons and that VD deficiency was more common in both sexes during late autumn than in the summer season [8].

Habitual intake of VD-rich foods (e.g., mushrooms and fish such as salmon or mackerel), or VD-fortified foods and supplements can help to prevent VD deficiency [9,10]. In fact, intake of fish and shellfish is associated with higher serum 25(OH)D levels in Japanese women during the summer season [8]. The active form of VD3 is the most potent supplemental form for increasing serum VD levels, especially during the winter season [11]. Therefore, the active VD3 compound is currently considered as the most effective for improving VD deficiency [9].

3. THE IMMUNOMODULATORY FUNCTION OF VD

Studies have identified VD, particularly $1,25(OH)_2D_3$, as an immunomodulatory compound that activates VDRs expressed in various immune cells [12-14]. VD regulates the differentiation and activation of $CD4^+$ and $CD8^+$ T cells as well as natural killer cells [15-17] and modulates the cytokine profiles of T cell subpopulations by inhibiting nuclear factor-κB signalling [14,18]. In addition, VDR expression occurs, not only in the “conventional” T cells, but also in the $\gamma\delta$ T cells, and the ligand VD has been shown to inhibit $\gamma\delta$ T cell activation [19]. Further, B cell proliferation, plasma cell differentiation, and immunoglobulin production are inhibited by VD [14]. Antigen-presenting cells such as monocytes, macrophages, and dendritic cells, are also affected by VD. For example, VD treatment inhibits the expression of the toll-like receptor in monocytes and attenuates the expressions of the major

histocompatibility complex (MHC) and costimulatory molecules in dendritic cells [14]. Overall, VD has a suppressive effect on immune responses. In fact, cells isolated from patients with autoimmune diseases who were treated with $1,25(OH)_2D_3$ secreted fewer proinflammatorycytokines (interferon-γ tumour necrosis factor [TNF]-α),) and more of the immunosuppressive cytokines (interleukin-5 and tissue growth factor [TGF]-β)) [16]. Pender [20] hypothesized that the potential protective effect of VD against autoimmune diseases such as RA might be mediated by an increase in the number of $CD8^+$ T cells. However, the pathogenic link between VD and $CD8^+$ T cells is still not completely understood and needs further clarification [21].

Khoo et al. [22] reported that the seasonal variation in serum $25(OH)D_3$ and $1,25(OH)_2D_3$ levels was associated with a higher number of peripheral $CD4^+$ and $CD8^+$ T cells. This change was also observed in regulatory or memory T cells and T cell functions. Zwerina et al*.* [23] crossed human TNF transgenic mice, an animal arthritis model, with VDR-deficient mice and reported increased arthritic symptoms and joint damage. This suggests that VDR signalling plays a key role in limiting the proinflammatory phenotype of monocytes or macrophages.

A number of epidemiological studies have suggested an association between VD deficiency and autoimmunity via the alteration of both innate and acquired immunity [24-26]. People living at latitudes above 37º have an increased risk of developing multiple sclerosis (a neurological autoimmune disease), whereas consumption of VD supplements has been reported to reduce this risk [12]. Similarly, the risk of rheumatoid arthritis (RA) may be reduced by VD supplementation [27]. However, Costenbader et al*.* [28], who assessed VD intake using a food frequency questionnaire in prospective cohorts of women in the Nurses' Health Study and Nurses' Health Study II (from 1980 to 2002), concluded that VD intake was not associated with the risk of either systemic lupus erythematosus (SLE) or RA. Therefore, the epidemiological significance of a potential relationship between VD deficiency andthe onsetof RA remains controversial [29,30]. On the other hand, Haga [30] suggested that $25(OD)D_3$ levels might decrease during the acute phase response (APR), which may explain its low levels in patients with increased disease activity. In this regard, potential modulation of the APR by VD has been suggested, such as that observed in patients receiving their first nitrogen-containing bisphosphonate infusion [31,32]. A negative correlation between serum 25(OH)D levels and APR severity (e.g., increased body temperature and C-reactive protein [CRP]) has been reported in adults [31] and children [32] alike. Therefore, VD may be clinically useful in the prevention of APR.

More recently, the role of T helper 17 (Th17) cells in RA has gained interest [33], and several studies have suggested that the Th17 population is modulated by VD [34,35]. *In vitro* treatment of human RA synovial fibroblasts with $1,25(OH)_2D_3$ resulted in suppressed IL-17 production, suggesting that VD suppresses Th17-mediated synovial inflammation in RA [35].

4. MUSCLE FUNCTION AND VD

VD has a well-known role in muscle function [36]. VD directly binds to skeletal muscle tissues that express VDRs and activates intracellular signalling pathways. Therefore, VD deficiency impairs signalling in muscle cells, resulting in myopathy or muscle dysfunction, which may increase the risk of falls. In fact, a strong inverse association between 25(OH)D levels and sarcopenia has been reported [37,38]. Marantes et al*.* [39] reported a significant

association between low VD levels and low skeletal mass as well as low isometric knee extension moments in subjects aged >65 years.

A meta-analysis of clinical trials for VD supplementation revealed that increased VD levels (combined with calcium intake) reduce the risk of falls [40]. VD supplementation has been reported to normalize the muscle strength in patients with myopathy [41]. These findings collectively indicate that adequate nutritional intake is important to preserve muscle mass and strength during aging [42]. Therefore, further research is required to determine whether VD supplementation would be beneficial to RA patients who are considered to be at risk of muscle weakness and falls [43,44].

5. CARDIOVASCULAR RISK AND VD

The incidence and severity of cardiovascular events such as myocardial infarction depend primarily on the associated major risk factors that include high blood pressure, serum lipid levels, insulin resistance or diabetes, and renal function as well as age and smoking. In addition to these factors, low levels of VD might be an important risk factor for cardiovascular disease; an inverse relationship between 25(OH)D levels and hypertension has previously been reported [45].

VD levels of RA patients are inversely correlated with low-density lipoprotein and triglyceride levels and the incidence of metabolic syndrome [46]. Haque et al. [47] also reported an association between VD deficiency and cardiovascular risk in RA patients; they found that the VD level was significantly associated with high-density lipoprotein cholesterol and inversely associated with HOMA-IR (a marker of insulin resistance). Sen et al. [48] found serum levels of 25(OH)D in VD-deficient patients (25[OH]D <20 ng/mL) to be positively associated with microvascular function.

Some studies have suggested that VD supplementation might be protective against cardiovascular risk [41,49,50]. However, this finding is controversial, and strong evidence to support the role of VD supplementation for cardiovascular protection is needed.

6. PAIN AND VD

There has been growing interest in the association between VD status and chronic pain [51-53]. VD deficiency is reportedly linked to an increased sensitivity to pain, potentially because the “pain-sensing” neurons produce and respond to active VD metabolites; thus, VD deficiency might induce nociceptor hyper-innervation and hypersensitivity [54].

VD levels might predict pain sensitivity in osteoarthritis (OA), a degenerative joint disease. However, the results are conflicting, and the ameliorating effect of VD supplementation in pain control has not yet been established [55,56]. As for RA, it has been reported that VD supplementation reduces pain when VD is administered to “disease-modifying anti-rheumatic drugs (DMARDs)-naïve” patients during the early stages of the disease [57]. For example, Higgins et al. measured VD levels in 176 RA patients and found a significant inverse relationship between VD and a visual analogue scale (VAS) score that reflected the patients’ symptoms. They also reported that there was no significant correlation between VD and disease activity score 28 (DAS28) scores. However, the mean DAS28 score was higher in VD-deficient patients who also had higher VAS scores [58]. Nevertheless, the evidence for the use of VD for chronic pain in adults is insufficient, and further controlled studies are required [55].

7. VD AND RA: IS VD SUPPLEMENTATION BENEFICIAL?

The relationship between VD deficiency and RA incidence remains unclear; further, it has not been determined if VD levels can modulate RA severity.

RA patients often have low levels of serum VD, irrespective of supplementation. In addition, VD levels may vary according to the patient's residential location or ethnicity. In any case, hypovitaminemia in patients may not always be recognized [59,60].

VD deficiency or low serum levels of VD have been correlated with RA activity. Kostoglow-Athanassiou et al. [61] investigated 25(OH)D_3 levels in a cohort of 44 RA patients and reported that the VD level was negatively correlated with the DAS28 score, CRP level, and erythrocyte sedimentation rate. However, VD did not significantly contribute to disease activity in a larger study of 499 RA patients [62]. In addition, the potential role of VD supplementation in RA may vary among different ethnic groups; the association of RA with VD deficiency in African American patients was not as strong as that in European patients [63] or in Chinese patients [64]. Thus, the results of studies on the association between VD status and RA are still inconclusive.

Nevertheless, the potential contribution of VD, or VD deficiency, in modulating RA pathophysiology may involve a wide range of factors from innate immunity to pain control and may vary between patients (Fig. 1). The critical role of VD in bone metabolism is well recognized and continues to be supported. A study conducted recently by Chen et al. [64] provided *in vitro* evidence that VD interacts with bone morphogenetic protein-2 to promote osteogenesis and bone mineralization. Further, VD modulates the PI3K/Akt/mTOR (the mammalian target of rapamycin) pathway, which provides important intracellular signalling for osteoclastogenesis. Kim et al. [65] presented an interesting hypothesis that VD has a synergistic therapeutic effect with mTOR inhibitors (e.g. rapamycin) on bone destruction in RA.

Therefore, the immune-mediated chronic inflammatory arthritis, muscle weakness and falls, osteoporosis, cardiovascular comorbidities, and chronic pain that are often present in RA patients might be controlled, in part, by the appropriate control of serum VD levels using exogenous VD administration. In fact, a number of studies have suggested that maintaining adequate serum levels of VD is important in preventing or improving cardiovascular risks, autoimmune diseases, and other diseased conditions. However, whether VD supplementation actually improves outcomes or prognosis is still controversial needs further investigation [27,36,41,47,66,67].

Of note, VD deficiency increases the risk for infections, particularly opportunistic infections such as tuberculosis [68,69]. VD regulates T cell-mediated immune responses (as described above) as well as innate immunity by inducing the expression of antimicrobial peptides (e.g., cathelicidin and defensin) via toll like receptor-mediated signals [70,71]. Therefore, VD deficiency may be linked to a decreased immunological defence against many infections, including mycobacterial infections [70,72].

RA patients undergo immunosuppressive treatment and are at increased risk for tuberculosis or other serious infections; hence, their serum VD levels, together with serum calcium levels, phosphate levels, and bone mineral density, should be monitored. Recent studies have suggested a beneficial or essential role of VD for patients who are treated using immunosuppressive or anti-TNF-α strategies [23,35].

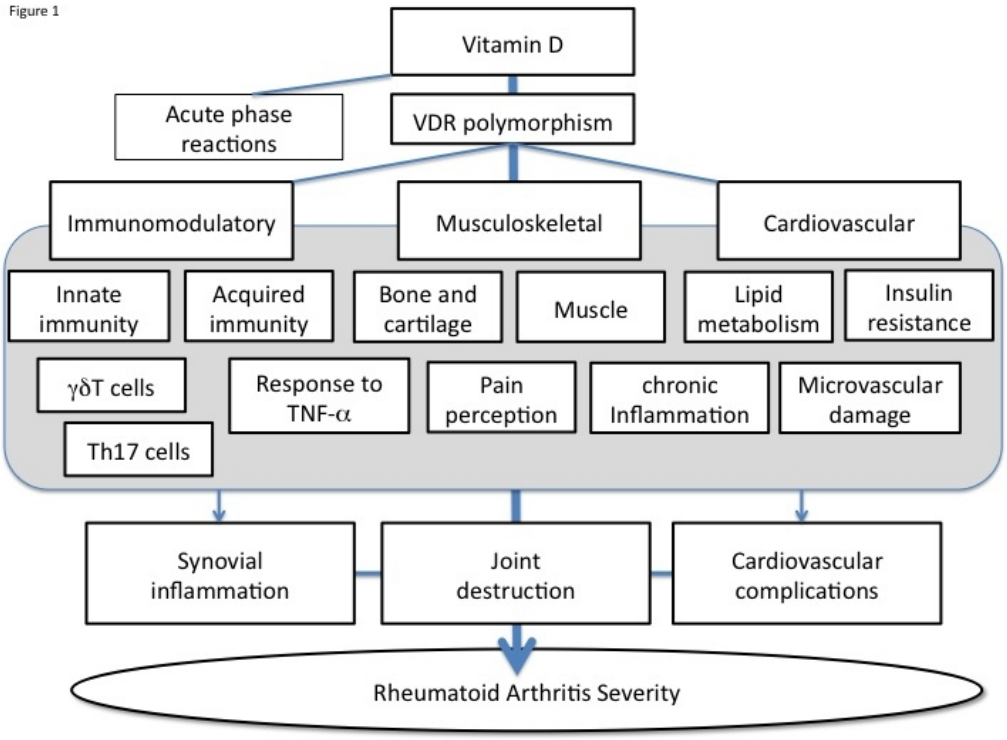

Fig. 1. Potential contribution of vitamin D to rheumatoid arthritis

It should be noted that mild VD deficiency may not be apparent, and there may not be any immediate symptoms; further, serum VD (or calcium/phosphate) levels may not be monitored in all patients. Thus, it may be difficult to identify VD deficiency in a patient. Therefore, it is essential to be aware of the patient's calcium intake or daily lifestyle as well as serum VD levels and to promote nutritional education highlighting the importance of a balanced diet, including an appropriate intake of VD. In regards to nutritional intake, we previously reported that the younger generation does not always recognize the importance of VD and other minerals or nutrients in bone metabolism or that of VD- or calcium-rich foods [73]. Supporting this fact, a large, Australian cohort study by Vu et al. [74] summarized the results of a questionnaire revealing a "lack of knowledge about VD" and found that 18% of the participants were unaware of the beneficial effects of VD on bones.

8. CONCLUDING REMARKS

Although the direct causal effect of VD deficiency on RA pathogenesis remains controversial, as summarized by Cantorna et al. [15], VD may be an environmental factor that affects the prevalence of autoimmune diseases. Conversely, a number of studies reported that polymorphisms of VDR genotypes, such as the *TaqI* and *BsmI* alleles, could be linked to disease susceptibility and bone loss in RA [75,76]. Thus, VD would be present and activated at a different degree in each environment, and the response to VD would differ among individuals depending on their genotype [77,78]. This would result in unique VD-mediated responses in each individual, some of which may trigger autoimmune reactions and/or altered bone metabolism related to RA. Observation and careful interventions with respect to patients' diet, supplement use, and lifestyle, along with medication, surgical

manipulation, rehabilitation, and genetic assessment, if applicable, may be important for promoting a better understanding of the outcomes of rheumatic diseases such as RA.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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