

Review

Vitamin D and Rheumatic Diseases: a Review of Clinical Evidence

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Abstract: Vitamin D plays an important role in maintaining healthy mineralized skeleton. It is also considered an immunomodulatory agent that regulate the innate and adaptive immune systems. Multiple observational studies have demonstrated the association between low level of serum 25-hydroxyvitamin D [25(OH)D] and presence and severity of several rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), spondyloarthropathies and osteoarthritis (OA). Nevertheless, the specific benefits of vitamin D supplement for treatment and prevention of rheumatic diseases are less accepted as the results from randomized clinical trials are inconsistent, although some conceivable benefits of vitamin D for improvement of disease activity of RA, SLE and OA have been demonstrated in meta-analyses. It is also possible that some individuals might benefit from vitamin D differently from others since inter-individual difference in responsiveness to vitamin D supplementation has been observed in genomic studies. Although the optimal level of serum 25(OH)D is still debatable, it is advisable that patients with rheumatic diseases should maintain serum 25(OH)D level at least 30 ng/mL (75 nmol/L) to prevent osteomalacia, secondary osteoporosis and fracture, and possibly 40 – 60 ng/mL (100 – 150 nmol/L) to achieve maximal benefit from vitamin D for immune health and overall health.

Keywords: Vitamin D; 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; Rheumatic diseases; Rheumatology; Rheumatoid arthritis; Systemic lupus erythematosus; Spondyloarthropathies; Osteoarthritis; Hyperuricemia; Gout

1. Introduction

Vitamin D is a steroid hormone responsible for regulation of calcium and phosphate metabolism and maintaining a healthy mineralized skeleton [1-3]. In addition, it is known to exert various non-skeletal actions due to the presence of the vitamin D receptor (VDR) in most tissues including the skin, adipose tissue, skeletal muscle, endocrine pancreas, immune cells, breast, blood vessels and brain [1,2,4].

In rheumatology, vitamin D supplementation is recommended to prevent glucocorticoid-induced osteoporosis and to reduce the risk of fracture in patients with osteoporosis [5]. It is proposed that improvement of vitamin D status may help protect against the development and severity of rheumatic diseases given the specific actions of vitamin D on the skeletal and immune systems [2,6,7]. The purpose of this review is to provide general concepts of vitamin D for the skeletal and immune health, and summarize the mechanistic, epidemiological and clinical evidence on the relationship between vitamin D and several types of rheumatic diseases, including rheumatoid arthritis (RA), systemic

lupus erythematosus (SLE), spondyloarthropathies (SpA), gout and hyperuricemia, osteoarthritis (OA) and others.

2. Physiology of Vitamin D

Human gets vitamin D from dietary consumption, supplements and endogenous synthesis in the skin. The two major forms of vitamin D are vitamin D₂ and vitamin D₃. Vitamin D₂, synthesized from ergosterol, can be found in ultraviolet irradiated and sun-dried mushrooms, yeasts and plants. Vitamin D₃, synthesized from 7-dehydrocholesterol, can be found in animal products such as cod liver oil and oily fish, and is synthesized endogenously in the skin [1-3]. After entering the circulation, vitamin D (D₂ and D₃) is metabolized in the liver by the enzyme vitamin D-25-hydroxylase (CYP2R1) to 25-hydroxyvitamin D [25(OH)D], which is the major circulating form of vitamin D that is clinically measured to reflect vitamin D status [1,2,8]. Circulating 25(OH)D is then further metabolized by the enzyme 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) to 1,25-dihydroxyvitamin D [1,25(OH)₂D], the biologically active form. 1,25(OH)₂D exerts its functions in the target tissue by binding to the vitamin D receptor (VDR) in the nucleus where it triggers up- or down-regulation of multitudes of genes [1-3,8].

The main site of conversion of 25(OH)D into the systemically bioavailable 1,25(OH)₂D is the kidneys, where CYP27B1 is expressed and regulated by parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) [9]. CYP27B1 expressed by many other tissues (e.g., immune cells, parathyroid glands, microglia, breast, colon, and keratinocytes) can also convert 25(OH)D into 1,25(OH)₂D, resulting in intracrine and paracrine signaling without being regulated by PTH or FGF-23 [10]. Both 25(OH)D and 1,25(OH)₂D are metabolized by the enzyme 24-hydroxylase (CYP24A1) expressed mainly by the intestine, bone and kidneys into inactive water-soluble carboxylic acids, which are then excreted in the bile [11].

3. General Concepts of Vitamin D for Skeletal and Immune Health

3.1 Effects of Vitamin D on Bone and Mineral Metabolism

Vitamin D exerts its effects on bone and mineral metabolism mainly by altering the expressions of several genes in the small intestine, kidneys, parathyroid glands and bone [2,3]. Activation of VDR by 1,25(OH)₂D promotes intestinal calcium and phosphate absorption and renal tubular calcium reabsorption that help maintain adequate calcium-phosphate product that crystallizes in the collagen matrix in the bone. 1,25(OH)₂D also has direct effects on the bone by stimulating receptor activator of nuclear factor kappa-B-dependent bone resorption and inducing the expression of osteocalcin, the major non-collagenous protein in the skeleton [12-14]. Furthermore, 1,25(OH)₂D directly inhibits PTH production, leading to decreased bone resorption, and induces FGF-23 production by the osteocytes, leading to increased urinary phosphate excretion [9,15,16].

The pathophysiology of vitamin D deficiency causing osteoporosis and osteomalacia is mainly mediated by secondary hyperparathyroidism [1,17]. Low level of serum 25(OH)D results in inadequate intestinal calcium absorption, which, in turn, leads to a transient decrease in serum ionized calcium. This subsequently results in secondary hyperparathyroidism, causing increased bone resorption which precipitates osteoporosis. Secondary hyperparathyroidism also causes increased urinary phosphate excretion leading to inadequate calcium-phosphate product, thereby precipitating rickets in children and osteomalacia in adults [1,17].

3.2 Effects of Vitamin D on the Immune System

Vitamin D is known not only for its functions in maintaining calcium and phosphate homeostasis, but also for its immunomodulatory effects on several components of the innate and adaptive immune systems [6,18]. Evidence on the effects of VDR activation on the proliferation, differentiation and function of each immune cell type is to be reviewed in this section, which is summarized in **Table 1**.

Table 1 Effects of 1,25-dihydroxyvitamin D on different types of immune cell

Immune cell type	Effect of 1,25-dihydroxyvitamin D
Macrophage & monocyte	<ul style="list-style-type: none"> • ↑ Proliferation • ↑ Cathelicidins & defensins production • ↑ IL-1β production • ↓ TLR2 & TLR4 expression
Antigen presenting cell	<ul style="list-style-type: none"> • ↓ Differentiation • ↓ Antigen presentation • ↓ Co-stimulatory molecules expression • ↑ Inhibitory molecules expression (PD-L1, ILT3) • ↓ CD40, CD80 & CD86 expression • ↓ IL-12 & IL-23 production • ↑ IL-10 production
NK cell	<ul style="list-style-type: none"> • ↓ TLR4 expression • ↓ TNF-α & IFN-γ production • ↑ Perforin granules depolarization
T lymphocyte	<ul style="list-style-type: none"> • ↓ Proliferation • ↓ CD4/CD8 ratio
T helper 1	<ul style="list-style-type: none"> • ↓ Differentiation • ↓ IL-2, TNF-α & IFN-γ production
T helper 2	<ul style="list-style-type: none"> • ↑ Differentiation • ↑ IL-4, IL-5 & IL-13
T helper 9	<ul style="list-style-type: none"> • ↓ Differentiation • ↓ IL-5, IL-8 & IL-9 • ↑ IL-13
T helper 17	<ul style="list-style-type: none"> • ↓ Differentiation • ↓ IL-17, IL-21
Regulatory T cell	<ul style="list-style-type: none"> • ↑ Differentiation • ↑ FoxP3 & CTLA-4
Cytotoxic T cell	<ul style="list-style-type: none"> • ↓ Proliferation
B lymphocyte & plasma cell	<ul style="list-style-type: none"> • ↑ Activated B cell & plasma cell apoptosis • ↑ IL-10 & CCR10 • ↓ Plasma cell & memory B cell differentiation • ↓ IgG & IgM production

Abbreviations: CCR10: C-C chemokine receptor type 10; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; FoxP3: Foxhead box P3; IFN- γ : Interferon- γ ; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IL-1 β : Interleukin-1 β ; IL-2: Interleukin-2; IL-4: Interleukin-4; IL-5: Interleukin-5; IL-8: Interleukin-8; IL-9: Interleukin-9; IL-10: Interleukin-10; IL-13: Interleukin-13; IL-17: Interleukin-17; IL-21: Interleukin-21; ILT3: Immunoglobulin-like transcript-3; PD-L1: Programmed death-ligand 1; TNF- α : Tumor necrosis factor- α ; TLR2: Toll-like receptor 2; TLR4: Toll-like receptor 4

Activated macrophages and monocytes, induced by exposure to inflammatory cytokines (e.g., IFN- γ) and toll-like receptor signaling, express CYP27B1 which converts 25(OH)D into 1,25(OH) $_2$ D that acts in an autocrine and paracrine fashion to regulate the innate and adaptive immune systems [19]. It has been shown that 1,25(OH) $_2$ D stimulates macrophage proliferation and production of the proinflammatory cytokine interleukin-1 β as well as endogenous antimicrobial peptides, cathelicidins, and defensins [20,21]. In the presence of granulomatous inflammation (e.g., TB, sarcoidosis, fungal infections and some lymphomas), an excessive amount of 1,25(OH) $_2$ D can be produced by the macrophages causing unregulated increased 1,25(OH) $_2$ D in the systemic circulation that results in hypercalcemia and hypercalciuria [22].

1,25(OH) $_2$ D regulates the functions and differentiation of antigen-presenting cells (APCs) by decreasing the antigen presentation and increasing the expression of inhibitory molecules on the cell surface causing the APCs to become tolerogenic and more immature [23-25]. It does so by decreasing the expression of MHC class II and co-stimulatory molecules, inhibiting the production of IL-12 and IL-23, and stimulating the production of IL-10, a tolerogenic cytokine [23,26,27]. 1,25(OH) $_2$ D, in addition, is shown to downregulate the expression of toll-like receptors on the monocytes and inhibit the production of proinflammatory cytokines (i.e., IL-2, IL-6 and IL-17) [6,18,28].

1,25(OH) $_2$ D is known to modulate the adaptive immune system by activating the VDR expressed by the APCs and activated T and B lymphocytes that, in general, results in a shift of immune status from proinflammatory to tolerogenic state. 1,25(OH) $_2$ D inhibits the proliferation of T lymphocytes and regulates cytokine production and differentiation with various effects on different subgroups of T lymphocytes. It promotes a shift from T helper 1 (T_{H1}), T helper 9 (T_{H9}) and T helper 17 (T_{H17}) immune profiles to T helper 2 (T_{H2}) immune profile and facilitates the differentiation of regulatory T cells (T_{reg}) [29-31]. Although little is known about the direct effect of 1,25(OH) $_2$ D on the cytotoxic lymphocytes, it is believed that 1,25(OH) $_2$ D may suppress the proliferation of cytotoxic lymphocytes based on the observation that oral administration of high-dose vitamin D $_3$ was associated with an increase in CD4/CD8 ratio [32,33].

Besides its effects on the T lymphocytes, 1,25(OH) $_2$ D is shown to have a negative effect on antibody production by the B lymphocytes when in hyperactive state via multiple mechanisms. It induces apoptosis of activated B cells and plasma cells, thereby inhibiting plasma cell formation [34,35]. Furthermore, 1,25(OH) $_2$ D directly promotes the production of anti-inflammatory cytokines such as interleukin-10 and CCR10 and inhibits the differentiation from mature B cells to memory B cells and plasma cells [36-38]. It is therefore believed that, by dampening antibody production, 1,25(OH) $_2$ D may benefit in reducing the risk and severity for autoantibody-mediated autoimmune disorders such as SLE and type 1 diabetes [39,40].

It is important to note that supplementation of vitamin D or raising serum 25(OH)D is not equivalent to activating the VDR in the immune cells, since circulating 1,25(OH) $_2$ D is regulated by PTH and FGF-23 and patients with low levels of 25(OH)D may have normal or even high level of circulating 1,25(OH) $_2$ D due to secondary hyperparathyroidism [9,41]. However, it is reasonable to postulate that circulating 25(OH)D may be converted into 1,25(OH) $_2$ D by the enzyme CYP27B1 expressed by the immune cells where it triggers intracrine and paracrine signaling, since clinical studies have demonstrated changes in immune profiles in response to vitamin D supplementation similar to what is expected from treating the immune cells with 1,25(OH) $_2$ D in vitro [42,43].

Equally important is the concept of individual responsiveness to vitamin D supplementation as studies have demonstrated high inter-individual difference in genome-wide expression in human peripheral blood mononuclear cells following vitamin D supplementation. In a recent clinical trial by Shirvani et al. [44], approximately 60% of healthy adults with vitamin D deficiency or insufficiency [25(OH)D <30 ng/mL or 75

nmol/L] who received 10,000 IUs per day of vitamin D₃ for 6 months had a robust response in genome-wide expression compared to the other 40% who had mild to moderate responses although all subjects increased their serum concentrations of 25(OH)D to the same range of 60–90 ng/mL (150–225 nmol/L). Moreover, they observed that subjects with robust genomic response to vitamin D supplementation exhibited different patterns of serum metabolomic profile compared with those with lower degree of responsiveness [45]. This observation is in line with that of the prior study by Carlberg et al. [46] showing robust changes in broad gene expression in about half of the 71 patients with prediabetes who were given daily 3,200 IUs of vitamin D₃ for 5 months. Therefore, it is reasonable to postulate that vitamin D may affect the immune system differently among individuals, which is hypothesized to be due to inter-individual differences in genetic polymorphisms associated with vitamin D metabolism and signaling pathway (e.g., genes encoding VDR, vitamin D binding protein [DBP] and VDR responsive element in the target genes), as well as some undisclosed epigenetic factors [6].

3.3 Defining Optimal Serum 25-hydroxyvitamin D

It is still controversial as to what concentration of serum 25(OH)D would provide optimal benefit for bone health and overall health. Serum 25(OH)D concentration of 15 to 20 ng/mL (37.5 – 50 nmol/L) is considered sufficient for prevention of rickets and osteomalacia [17]. It is however recommended by the Endocrine Society's Clinical Practice Guideline that serum 25(OH)D concentration should be above 30 ng/mL (75 nmol/L) to maximize the calcemic effects of vitamin D and minimize the risk of secondary hyperparathyroidism that predisposes to osteoporosis [8]. According to this guideline, vitamin D deficiency and insufficiency are defined as serum 25(OH)D level of <20 ng/mL (<50 nmol/L) and 20 – <30 ng/mL (50 – <75 nmol/L), respectively [8]. On the other hand, the Institute of Medicine (IOM) concluded that serum 25(OH)D level of 20 ng/mL was the level necessary for good bone health for practically all individuals [47]. It is also worth acknowledging historical evidence to postulate vitamin D status in our hunter-gatherer ancestors. It has been reported that indigenous populations in East Africa have serum 25(OH)D in the range of 40 – 60 ng/mL (100 – 150 nmol/L) [48]. This range is consistent with that reported in populational-based studies to be associated with the lowest risk of chronic diseases and all-cause mortality [49]. However, some studies suggest that there may be a U-shaped relationship between 25(OH)D and some adverse outcomes (e.g., mortality, cardiovascular disease, falls, some cancers) at levels higher than 50 ng/mL (125 nmol/L) [50,51].

3.4 Recommended Vitamin D Intake

It is recommended by the Institute of Medicine that one should ingest at least children aged ≥1 year old and adults ingest at least 600 IUs of vitamin D per day to achieve serum 25(OH)D level of at least 20 ng/mL (50 nmol/L) [47]. The Endocrine Society Clinical Practice Guideline on vitamin D, however, recommended a higher dose of daily vitamin D intake to achieve the level of serum 25(OH)D of at least 30 ng/mL (children aged 0 – 1 year: 400 – 1,000 IUs, upper limit 2000 IUs; children aged 1 – 18 years: 600 – 1,000 IUs, upper limit 4,000 IUs; adults aged >18 years 1,500 – 2,000 IUs, upper limit 10,000 IUs) [8]. Some experts also suggested that adults should be on 4,000 – 6,000 IUs to maintain serum 25(OH)D level at the preferred range of 40 – 60 ng/mL (100 – 150 nmol/L) [52]. Notably, patients with obesity and intestinal malabsorption require 2 – 3 times higher amount of vitamin D to maintain the same serum 25(OH)D concentrations [8]. In addition, patients who receive chronic glucocorticoid therapy need 2 – 3 increased dose of vitamin D intake since glucocorticoids can cause increased catabolism of both 25(OH)D and 1,25(OH)₂D [8].

3.5 Vitamin D from Sunlight Exposure and Diets

Humans get vitamin D from sunlight exposure, diet and supplements. The amount of vitamin D synthesized by the skin is known to be dependent on the intensity and

duration of exposure to ultraviolet B radiation at wavelength of 290 – 315 nm and skin pigmentation. It is estimated that sunlight exposure 1/4 of a minimal erythema dose (MED) over 1/4 of body surface area is equivalent to ingestion of oral 1,000 IUs of vitamin D₃ [53]. People living in high-latitude regions are more susceptible to vitamin D deficiency in especially in the wintertime because of the oblique zenith angle of the sun. It is documented that when living above or below 33° latitude, little or no vitamin D can be produced in the skin during the winter. During the summertime or near the equator, vitamin D can be synthesized effectively only during 10 am – 3 pm [1,54]. Given the limited availability of vitamin D from sunlight exposure, many people would rely on oral vitamin D intake to achieve vitamin D sufficiency.

It should be noted that only few foods naturally contain vitamin D. These include oily fish (up to 1,000 IUs of D₃/3.5oz), cod liver oil (up to 1,000 IUs of D₃/tsp), sun-dried or ultraviolet-irradiated mushroom (up to 1000 IUs of D₂/3.5oz, egg yolk (20 IUs of D₂ or D₃) and meat (variable amount in the form of D₃ and 25(OH)D₃). Fortified milk, yogurt and orange juice in the US contains 100 IUs of vitamin D₂ or D₃ per serving (8 oz) [1,2]. Taken together, with minimal sunlight exposure, it is difficult to achieve adequate vitamin D intake solely from foods, and, therefore, many individuals may require vitamin D supplementation to prevent vitamin D deficiency and insufficiency.

3.6 Screening for Vitamin D Status

The Endocrine Society Clinical Practice Guideline on vitamin D recommended that screening for vitamin D deficiency should be performed in individuals who are at risk for vitamin D deficiency such as older adults with history of falls or fracture, patients with chronic illnesses, obesity, intestinal malabsorption, or individuals taking medications that interfere vitamin D metabolism (e.g., glucocorticoids, antiepileptics, antiretrovirals and antifungals) [8]. Nonetheless, the US Preventive Services Task Force reported that the evidence on the benefits of screening for vitamin D deficiency in general population is still lacking [55]. It is however advisable that patients with chronic inflammatory disorders with or without corticosteroid therapy should be screened and treated for vitamin D deficiency and supplemented with adequate calcium and vitamin D to prevent further bone resorption on top of chronic inflammation-associated bone loss.

4. Evidence on Vitamin D for Prevention and Treatment of Rheumatic Diseases

4.1 Rheumatoid Arthritis

RA is a chronic inflammatory disease characterized by synovial inflammation causing symmetrical polyarthritis affecting approximately 4 cases per 10,000 person-years [56]. RA was classically considered a T_H1-mediated disease [57]. However, recent studies have suggested that increased T_H17 and T_H22 activities and dysfunctional T_{reg} also play a role in the pathogenesis of RA [58,59]. Individuals with certain genetic variations of the human leukocyte antigen (HLA) genes are known to be susceptible to RA, while the only well-established environmental risk factor of RA is cigarette smoking [60].

Vitamin D is believed to play a role in modulating the pathogenesis and disease activity of RA based on the actions of 1,25(OH)₂D on the adaptive immune response that suppresses the proliferation and activity of T_H1 and T_H17 and enhances T_{reg} activity [61]. Furthermore, genomic studies have shown that certain polymorphisms of the gene encoding VDR and DBP were associated with susceptibility to RA, suggesting that vitamin D signaling pathway may be involved in the pathogenesis of RA [62,63].

Multiple observational studies have shown the association of vitamin D status or intake with incidence and severity of RA [64]. For example, in a prospective cohort study by Merlino et al., women in the highest tertile of vitamin D intake had a lower risk for RA by 33% compared those in the lowest tertile [65]. In the COMORbidities in Rheumatoid Arthritis (COMORA) study consisting of 1,413 patients with RA from 15 countries, serum level of 25(OH)D was inversely correlated with disease activity assessed by the Disease Activity Score-28 (DAS28) after adjusting for potential confounders [66].

Although the observed association between vitamin D status and RA incidence and severity, like in other diseases, could be partly explained by confounders such as limited physical outdoor activities and sunlight exposure, results from clinical trials have suggested that giving vitamin D to patients with RA may help mitigate the disease activity. In a meta-analysis of 6 studies including 438 RA patients, vitamin D supplementation results in a significant improvement in the DAS28 (weighted mean difference [WMD] -0.41, 95%CI: -0.59 – -0.23), erythrocyte sedimentation rate (WMD -3.40, 95%CI: -6.62 – -0.18) and tender joint count (WMD -1.44, 95%CI: -2.74 – -0.14) but not in pain visual analog scale [67]. It should however be noted that most of the individual studies included in this meta-analysis did not show statistically significant benefit of vitamin D supplementation. This could be due to difference in patient characteristics, dosing regimen of vitamin D and limited statistical power due to small sample size.

In addition, some studies have also shown that giving 1,25(OH)₂D can also help improve the outcomes of RA. In an open-labeled randomized clinical trial by Gopinath et al. [68], 59 RA patients who received 1,25(OH)₂D₃ along with disease-modifying antirheumatic drugs (DMARDs) and calcium demonstrated a significantly higher pain relief compared with 62 patients receiving DMARDs and calcium alone. Another phase II clinical trial by Li et al. [69] gave 22-oxa-1,25(OH)₂D₃ or 1,25(OH)₂D₃ or placebo to 369 RA patients and observed a significant reduction in swollen joints and improved Health Assessment Questionnaire Disease Activity Index scores in the groups receiving two active treatment compared with the placebo group.

In summary, there is suggestive observational evidence that increasing vitamin D intake to raise serum 25(OH)D may reduce the risk of developing RA. However, there is no demonstration from a clinical trial that vitamin D supplementation can reduce the risk of incident RA. There is moderate evidence that vitamin D supplement or oral administration of 1,25(OH)₂D can mitigate the disease severity of RA. Further large-scale of randomized clinical trials are required before any form of vitamin D or 1,25(OH)₂D can be recommended as an adjunctive treatment for RA in clinical practice.

4.2 Systemic Lupus Erythematosus

SLE is an autoimmune disorder with a broad variety of clinical presentations including but not limited to constitutional symptoms, arthralgias, arthritis, glomerulonephritis, serositis, vascular phenomenon, skin rashes and hematologic cytopenias [70]. The reported incidence of SLE ranges from 0.3/100,000 person-years in Africa to 23.2/100,000 person-years in North America [71]. The pathogenesis of SLE is not fully understood, but it is hypothesized to involve genetic predisposition and environmental predisposing factors such as cigarette smoking, Epstein-Barr virus infection and silica exposure [72]. Patients with SLE have been shown to have dysregulated the immune profiles characterized by increased T_H17 and decreased T_{reg} activities with variable T_H1 and T_H2 activities as well as development of autoantibodies (e.g., ANA, anti-Sm/RNP, anti-Ro/La, anti-dsDNA, etc.) [73-76].

Low level of serum 25(OH)D has been shown to be associated with presence of SLE in several case-control studies [77,78]. In addition, there is evidence from population genetic studies that individuals carrying some genetic polymorphisms of VDR (i.e., BsmI and FokI polymorphic variants) were at an increased risk for SLE [79]. It has also been shown that expression of VDR in 20 renal biopsy specimens was negatively associated with the Systemic Lupus International Collaborating Clinics (SLICC) renal activity scores and the SLE disease activity index scores (SLEDAI) [80]. Therefore, it can be postulated that activation of vitamin D signaling pathway may help mitigate the autoinflammatory process in SLE and lupus nephritis via its immunomodulatory effects on T_H17, T_{reg} and B cells and possibly the direct effects on renal tissue.

Nevertheless, in the Nurses' Health Studies I and II of 186,389 women and 190 incident SLE cases, there was no association between vitamin D intake and risk of incident

SLE, indicating that the association between vitamin D status/intake and SLE may not be causal as no temporal association was demonstrated [81]. On the other hand, evidence on the benefit of vitamin D for alleviating disease activity of SLE seems to be more recognized as low levels of 25(OH)D have been shown to be associated with disease activity of SLE indicated by the SLE disease activity index scores (SLEDAI), anti-dsDNA positivity and rate of remission [78]. Moreover, in a meta-analysis of 5 randomized controlled trials with a total of 490 patients with SLE, vitamin D₃ supplementation was found to decrease the fatigue severity scale scores in patients with SLE (2 trials with 79 patients; standard mean difference -1.179, 95% CI: -1.90 – -0.46), although no significant changes in the SLEDAI and positivity of anti-dsDNA was observed [82].

Taken together, it is well-documented that low level of 25(OH)D is associated with SLE occurrence and disease severity. There is evidence from a few clinical trials that vitamin D supplement may improve disease activity in SLE patients. However, whether improving vitamin D status/intake can reduce the risk of developing SLE needs further investigation.

4.3 Spondyloarthropathies

SpA are a family of autoinflammatory diseases that share certain genetic predisposing factors and clinical characteristics [83]. These include ankylosing spondylitis (AS), reactive arthritis, psoriatic arthritis (PsA), inflammatory bowel disease (IBD) and undifferentiated spondyloarthropathy. These diseases are grouped based on their association with the human leukocyte antigen-B27 (HLA-B27) gene and presence of enthesitis as a common clinical feature. Other clinical features include dactylitis, back pain, uveitis and skin rash [83]. The pathogenesis of SpA is still poorly understood; however, it is hypothesized to involve nonantigen-presenting properties of HLA-B27, self- or bacterial-derived antigenic peptides and gut dysbiosis that trigger autoimmunity [84].

Low levels of serum 25(OH)D have been observed in patients with AS [85], PsA [86] and IBD [87] compared with healthy individuals. Moreover, vitamin D insufficiency [25(OH)D <30 ng/mL] and deficiency [25(OH)D <20 ng/mL] have been found to predict all-cause mortality among patients with AS in a populational based study of 919 Israeli patients [88]. It is also worth noting that vitamin D supplementation has been shown in randomized clinical trials to improve outcomes in patients with IBD and alter the composition of gut microbiota towards genera associated lower inflammatory burden [89,90]. Thus, vitamin D is believed to play a role in modulating the disease severity of SpA by its effects not only on the immune cells but also on gut microbiota, which is thought to play a role in the pathogenesis of SpA. Nevertheless, clinical trials investigating the effect of vitamin D supplementation in patients with SpA are still lacking.

Interestingly, DBP gene polymorphisms have been shown to be associated with the development of peripheral arthritis and uveitis in 223 Korean patients with AS [91]. There is also a case report of a patient who had concomitant homozygous deletion of the DBP and deliberating AS with relatively mild disruption of bone metabolism [92]. Provided the evidence that DBP has pleiotropic functions in sequestration of actin and a variety of less-defined roles in modulating immune responses [93], DBP may be a more significant mediator of the disease and that the observed association between AS and vitamin D is, in fact, due to the variation in circulating DBP that is correlated with measured serum 25(OH)D.

4.4 Gout and Hyperuricemia

Gout is a systemic disease characterized by the deposition of monosodium urate crystals in tissues. This condition requires increased serum uric acid above a specific threshold to form uric acid crystals [94]. Although hyperuricemia is the major predisposing factor in gout, only about 5% of individuals with hyperuricemia above 9 mg/dL develop gout [94]. In a meta-analysis of 7 cross-sectional studies, individuals with vitamin D deficiency [25(OH)D <20 ng/mL] and insufficiency [25(OH)D 20 – <30 ng/mL] have

been shown to have increased serum uric acid in a dose-dependent manner compared with vitamin D-sufficient individuals (pooled mean differences 0.45 and 0.33 mg/dL, respectively) [95]. The association is thought to be due not only to the fact that both vitamin D deficiency/insufficiency and hyperuricemia share common comorbidities such as obesity and metabolic syndrome, but also a direct causal association between the two conditions. This is supported by the study of 71 patients with prediabetes who were randomized to receive weekly doses of 20,000 IUs of vitamin D₂, 15,000 IUs of vitamin D₃ or no vitamin D that vitamin D supplementation was associated with a reduction in mean serum uric acid level by 0.6 mg/dL in those with baseline uric acid level of >6 mg/dL [96]. It has been suggested that the mild uric-lowering effect of vitamin D is mediated by suppression of PTH, which is known to downregulate the ATP-binding cassette transporter G2 (ABCG2) in the kidneys, leading to a reduction in renal clearance of uric acid [97,98]. Furthermore, studies have shown that patients with primary hyperparathyroidism had increased serum uric acid [99] and that those who underwent parathyroidectomy had decreased serum uric acid levels postoperatively [100,101], indicating a significant effect of PTH on serum uric acid. However, there has been no demonstration if vitamin D supplementation can reduce urinary uric acid excretion. Despite the causal link between vitamin D and uric acid, vitamin D status was not found to be associated with gout in the populational-based data from the US National Health and Nutrition Examination Survey (NHANES) [102].

Based on the current evidence, correcting vitamin D deficiency/insufficiency has a mild uric-lowering effect (~ 0.3 – 0.6 mg/dL), which is thought to be mediated by suppression of PTH. However, no direct association between vitamin D and gout has been demonstrated.

4.5 Osteoarthritis

OA is the most common degenerative joint disease and a major cause of pain and disability affecting more than 25% of adults aged 65 years or more [103]. The interplaying mechanisms of OA include articular cartilage degradation, osteophyte formation, subchondral sclerosis and synovial hyperplasia [104]. Risk factors of OA include joint injury, aging, obesity and genetics [105].

Given that low level of serum 25(OH)D has been shown in some studies to be associated with presence and severity of knee osteoarthritis in both younger and older individuals [106,107], it is estimated that vitamin D may affect the development and progression of OA due to its impacts on not only bone quality but also pain reduction due to reduced inflammation and improved skeletal muscle function of the lower extremities. This can be supported by the evidence from clinical trials showing the benefit of vitamin D for improvement of muscle strength, body sway and physical performance, which is thought to be due to the genomic and non-genomic actions of 1,25(OH)₂D on energy metabolism and function of the skeletal muscle [108,109].

A randomized controlled trial by Sanghi et al. [110] in 107 patients with knee OA demonstrated that giving daily 60,000 IUs followed by monthly 60,000 IUs of oral vitamin D₃ for 12 months results in a significant decrease in visual analog scale pain (between-group mean difference [MD] -0.39, 95%CI: -0.71 – -0.08) and total Western Ontario and McMaster Universities Arthritis Index (WOMAC) (MD -3.53, 95%CI: -4.39 – -2.71) compared with placebo. In a study by Jin et al. [111], 413 patients with knee OA were randomized to receive either 50,000 IUs of vitamin D₃ per month or placebo for 2 years. Compared with the placebo group, the group receiving vitamin D₃ was found to have significantly decreased WOMAC function (MD -72.9, 95%CI: -126.4 – -19.4) and total WOMAC (MD -91.4, 95%CI: -165.1 – -17.7). However, no significant difference between groups in tibial cartilage volume or WOMAC pain was observed in this study. In other clinical trials no significant effect of vitamin D on outcomes of knee OA was observed [112,113]. In sum, vitamin D supplement may have modest effect on improving pain and function in patient with knee OA; however, it does not reverse the disease process.

4.6 Other Rheumatic Diseases

Multiple observational studies have revealed association between low level of serum 25(OH)D and presence and/or severity of several rheumatic diseases, including systemic sclerosis, inflammatory myopathies and vasculitis [114-118]. However, evidence from clinical trials demonstrating the impact of any form of vitamin D on most of these diseases is still lacking. It is therefore still unclear if the association between vitamin D and these conditions is causal or more likely explained by confounders and reverse causation such as limited physical activity or corticosteroid use. In a pilot clinical trial of 20 patients with localized scleroderma, 9-month oral calcitriol therapy (0.75 µg/day for 6 months followed by 1.25 µg/day for 3 months) was not more effective than placebo in improvement of skin score [119]. It should be noted that patients presenting with chronic widespread pain due to osteomalacia caused by vitamin D deficiency can often fulfill the clinical criteria for diagnosis fibromyalgia [120]. This may partially explain the observed pain reduction benefit of vitamin D in some but not all clinical trials [121] as some of the patients who had osteomalacia mimicking fibromyalgia might have been treated.

5. Conclusion

Vitamin D plays an essential role in not only maintaining healthy mineralized skeleton but also modulating the innate and adaptive immune systems in a way that is thought to benefit as an adjunctive treatment for many immune-mediated diseases. Low level of 25(OH)D is associated with presence and severity of most if not all rheumatic diseases, such as RA, SLE, SpA and OA. However, the benefits of vitamin D supplement for treatment and prevention of these diseases are relatively unclarified as the results from existing clinical trials are inconsistent. Many of them are small in sample size and likely underpowered; however, when those results were pooled in meta-analyses, there were conceivable signals of benefits of vitamin D for improvement of disease activity, especially in RA and SLE. It is also worth noting that, based on recent genomic studies on vitamin D, there might be inter-individual difference in responsiveness to vitamin D supplementation that needs further investigations, suggesting that some individuals might be able to benefit from vitamin D more or less than others. Regardless of the evidence on disease-specific benefit of vitamin D, it is advisable that patients with rheumatic disease with or without corticosteroid therapy should have sensible sunlight exposure and adequate vitamin D intake to maintain serum 25(OH)D level at least 30 ng/mL (75 nmol/L) in order to prevent osteomalacia, secondary osteoporosis and fracture, and possibly 40 – 60 ng/mL (100 – 150 nmol/L) to achieve maximal benefit from vitamin D for immune health and overall health.

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