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REVIEW

Vitamin D and inflammatory diseases

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Abstract: Beyond its critical function in calcium homeostasis, vitamin D has recently been found to play an important role in the modulation of the immune/inflammation system via regulating the production of inflammatory cytokines and inhibiting the proliferation of proinflammatory cells, both of which are crucial for the pathogenesis of inflammatory diseases. Several studies have associated lower vitamin D status with increased risk and unfavorable outcome of acute infections. Vitamin D supplementation bolsters clinical responses to acute infection. Moreover, chronic inflammatory diseases, such as atherosclerosis-related cardiovascular disease, asthma, inflammatory bowel disease, chronic kidney disease, nonalcoholic fatty liver disease, and others, tend to have lower vitamin D status, which may play a pleiotropic role in the pathogenesis of the diseases. In this article, we review recent epidemiological and interventional studies of vitamin D in various inflammatory diseases. The potential mechanisms of vitamin D in regulating immune/inflammatory responses in inflammatory diseases are also discussed.

Keywords: asthma, atherosclerosis, chronic kidney disease, inflammatory bowel disease

Introduction

Vitamin D insufficiency or deficiency has increased in the general population and become an important public health issue.[1] Vitamin D is mainly known for its favorable effects in calcium and bone metabolism. However, increasing numbers of studies have established that vitamin D insufficiency contributes to a number of diseases, suggesting a range of physiological functions of vitamin D.[2–4] Several clinical studies have confirmed that vitamin D plays a crucial role in modulating innate immune responses toward various pathogens.[5] Moreover, recent studies indicate that vitamin D can regulate the adaptive immune response in various inflammatory and autoimmune diseases.[6,7] These results suggest the beneficial effects of vitamin D supplementation in decreasing the risk and adverse outcomes of inflammatory diseases, although the precise effect remains to be elucidated in large clinical trials.

The two major physiologically relevant forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). In humans, vitamin D_3 seems to be more effective than vitamin D_2 in maintaining the circulatory level of 25-hydroxyvitamin D_3 (25[OH]D_3), a stable marker of vitamin D status.[8,9] The main sources of vitamin D_3 are endogenous production from 7-dehydrocholesterol in the skin by ultraviolet B energy and dietary intake from foods, including egg yolk, beef liver, and milk products.[8,9] Vitamin D_3 is metabolized to 25(OH)D_3 in the liver by vitamin D 25-hydroxylase and then further hydroxylated by the key enzyme 25-hydroxyl vitamin D_3-1α-hydroxylase (CYP27B1) to the biologically active form: calcitriol

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(1,25-dihydroxycholecalciferol [1,25{OH}$_2$D$_3$]).[10] 1,25(OH)$_2$D$_3$ binds and activates the vitamin D receptor (VDR), a member of the superfamily of nuclear receptors and functions as a ligand-activated transcription factor.[11] It is now well recognized that CYP27B1 and VDR are expressed in cells involved in the immune/inflammation system in the human body,[12] which provides the biological basis for the role of vitamin D in inflammatory diseases.

Most clinical studies support the view that serum 25(OH)D$_3$ levels of less than 20 ng/mL (50 nmol/L) indicate vitamin D deficiency. Serum 25(OH)D$_3$ levels below 30 ng/mL indicate insufficiency, while levels between 30 and 60 ng/mL (75 and 150 nmol/L) represent normal values.[1,13] Epidemiological studies suggest an inverse association between circulating levels of 25(OH)D$_3$ and inflammatory markers, including CRP and interleukin (IL)-6.[14] Supplemental vitamin D and calcium have been found to decrease the biomarkers of inflammation.[15,16] However, a role for supplementation of vitamin D in modifying inflammatory disease has not been well defined, and it is unclear at present whether vitamin D status is causally related to the pathogenesis of the disease or is merely a marker of health.[17] This review summarizes and critically evaluates the data from preclinical, epidemiological, and interventional studies in order to elucidate the role and mechanisms of vitamin D in inflammatory diseases.

Vitamin D signaling and immune/inflammation system

VDR expression has been documented in macrophages, a crucial cell type in the innate immune response.[18] In macrophages, activation of the toll-like receptor (TLR1/2) heterodimer by *Mycobacterium tuberculosis* results in the upregulation of VDR and CYP27B1, leading to induction of the antimicrobial peptide cathelicidin and the killing of intracellular *M. tuberculosis*.[19] In this process, IL-15 links TLR2/1-induced macrophage differentiation to the vitamin D-dependent antimicrobial pathway.[20] The increase of CYP27B1 results in the accumulation of 1,25(OH)$_2$D$_3$, which further activates VDR, leading to the target gene transcription via vitamin D response elements located in the regulatory regions of 1,25(OH)$_2$D$_3$ target genes.[21] Chen et al[22] found that 1,25(OH)$_2$D$_3$ can regulate TLR signaling via stimulating SOCS1 by downregulating miR-155 in macrophages, which provide a novel negative feedback regulatory mechanism for vitamin D to control innate immunity. In a recent study, both forms of vitamin D – 1,25(OH)$_2$D$_3$ and 25(OH)D$_3$ – dose-dependently inhibited lipopolysaccharide-induced p38 phosphorylation, IL-6, and TNFα production by human monocytes via histone H4 in an acetylation-dependent manner.[23] Moreover, 1,25(OH)$_2$D$_3$ or its analogs have been shown to initiate the differentiation of myeloid progenitors into macrophages,[24] and to reduce MCP-1 and IL-6 expression via inhibiting the activation of NF-κB in macrophages.[25] In addition, Vitamin D has been thought to be a natural endoplasmic reticulum stress reliever,[26] and can selectively suppress key effector functions of interferon (IFN)-γ-activated macrophages.[27] Interestingly, in the presence of 1,25(OH)$_2$D$_3$, VDR has also been found to repress gene transcription via displacing the deoxyribonucleic acid-bound nuclear factor of activated T-cells, thus repressing inflammatory cytokine expression[28] (Figure 1).

Dendritic cells (DCs) are the most potent antigen-presenting cells. A number of studies have shown that 1,25(OH)$_2$D$_3$ inhibits the differentiation, maturation, and immunostimulatory capacity of human DCs, characterized as the tolerogenic properties, in a VDR-dependent manner.[29,30] Molecular mechanisms underlying the modulation of tolerogenic properties of DCs by 1,25(OH)$_2$D$_3$ include decreasing surface expression of major histocompatibility complex II and costimulatory molecules (CD40, CD80, CD86), upregulating inhibitory immunoglobulin-like transcript 3 molecules, and enhancing secretion of chemokine (C–C motif) ligand 22 and IL-10[29,31] (Figure 2). The enhancement of DC tolerogenicity by 1,25(OH)$_2$D$_3$ results in the induction of T-regulatory cells, a critical event for suppressing the inflammatory response of T-effector cells.[31] 1,25(OH)$_2$D$_3$ also acts directly with VDR on the T lymphocyte to inhibit its proliferation.[32] Although native T-cells did not express VDR, VDR expression was induced by T-cell antigen-receptor signaling via the alternative p38 MAPK pathway, which is crucial for T-cell antigen-receptor responsiveness in naïve T-cells.[33] Recent work has revealed that 1,25(OH)$_2$D$_3$ inhibited production of proinflammatory cytokines, including IFNγ, IL-17, and IL-21 in CD4$^+$CD25$^-$ T lymphocytes, and promoted development of T-regulatory cells expressing cytotoxic T-lymphocyte antigen 4 and FOXP3[34] (Figure 2). T-cell cytokines also control vitamin D metabolism in macrophages. For example, IFNγ, a T-helper (Th)-1 cytokine, upregulates the macrophage CYP27B1, leading to enhanced bioconversion of 25(OH)D$_3$ to its active metabolite – 1,25(OH)$_2$D$_3$. In contrast, the Th2 cytokine IL-4 induces catabolism of 25(OH)D$_3$ to the inactive metabolite 24,25(OH)$_2$D$_3$,[35] suggesting a potential mechanism by which vitamin D metabolism links the cell-mediated immune responses to the innate immune responses, although the exact role of vitamin D in this process remains unclear.

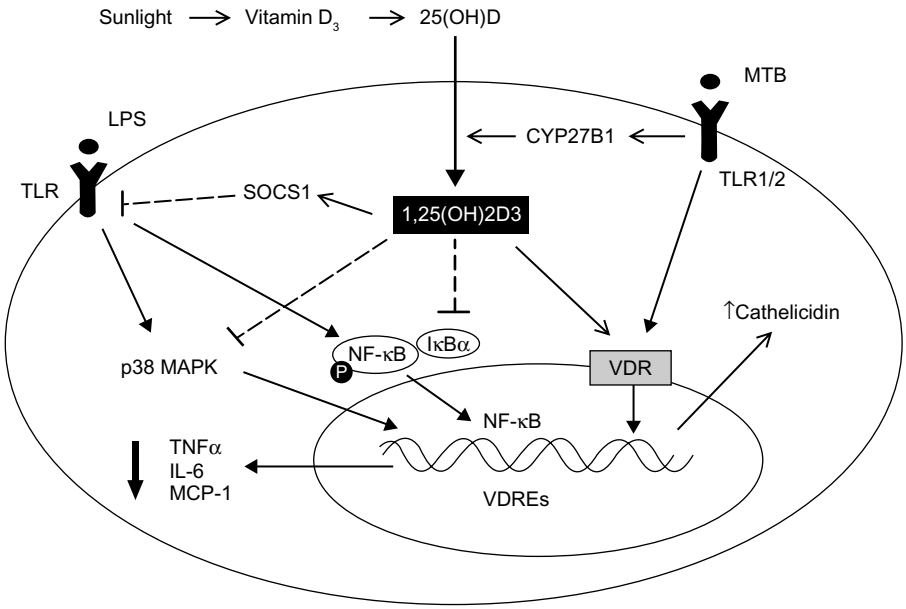

Figure 1 Schematic representation of the primary mechanisms through which vitamin D regulates macrophage-mediated innate immune response.
Notes: Vitamin D from sunlight or dietary sources is hydroxylated by the 25-hydroxylase to form its major circulating form – $25(OH)D_3$. $25(OH)D_3$ is then hydroxylated by 1α-hydroxylase (CYP27B1) to form the hormonal form of vitamin D – $1,25(OH)_2D_3$. $1,25(OH)_2D_3$ acts to modulate TLR signaling via stimulating SOCS1, inhibiting the phosphorylation of p38 MAPK and activation of NF-κB signaling in human macrophages, which reduces the gene expression and protein release of proinflammatory mediators, such as TNFα, IL-6, and MCP-1, leading to decreased recruitment of monocytes/macrophages and overall inflammation within tissue. In addition, $1,25(OH)_2D_3$ acts to increase the production of the antimicrobial peptide cathelicidin and the killing of intracellular mycobacterium tuberculosis (MTB).
Abbreviations: LPS, lipopolysaccharide; VDR, vitamin D receptor; VDREs, vitamin D response elements; IL-6, interleukin-6; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; TLR, toll-like receptor; TNFα, tumor necrosis factor-α.

Vitamin D and inflammatory diseases

Acute infections

Epidemiology studies have indicated seasonal variations in influenza and pneumococcal community-acquired pneumonia, suggesting an association between vitamin D insufficiency due to less sun exposure and acute respiratory infection (ARI).[36] A number of clinical studies have suggested an inverse association between $25(OH)D_3$ levels and ARI (Table 1).[37–42] Ginde et al[41] performed a secondary analysis

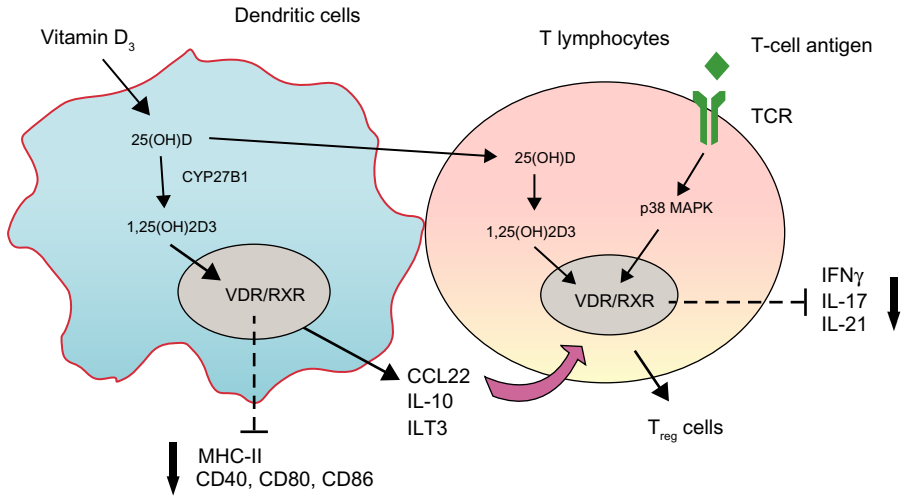

Figure 2 Schematic representation of the primary mechanisms through which vitamin D-regulated dendritic cells (DCs) and T-lymphocyte function.
Notes: Vitamin D precursors can be further processed to their active metabolite, $1,25(OH)_2D_3$, in DCs and T lymphocytes. In DCs, $1,25(OH)_2D_3$ binds to the vitamin D receptor–retinoid X receptor (VDR/RXR) complex in the nucleus, leading to a tolerogenic DC phenotype, characterized by decreased expression of major histocompatibility complex (MHC)-II, CD40, CD80, CD86, enhanced expression of immunoglobulin-like transcript (ILT)-3, and increased secretion of interleukin (IL)-10 and CCL22, which results in the induction of T-regulatory (T_{reg}) cells. The $1,25(OH)_2D_3$ signaling in T-cells is dependent on the stimulation of T-cell antigen-receptor (TCR) signaling. VDR expression can be induced by TCR signaling via the alternative p38 MAPK pathway. $1,25(OH)_2D_3$ binds to VDR, leading to inhibition of proinflammatory cytokine expression, including interferon (IFN)-γ, IL-17, and IL-21, and promotion of the development of T_{reg} cells.
Abbreviations: CCL22, chemokine (C-C motif) ligand 22; MAPK, mitogen-activated protein kinase.

Table 1 Summary of the major clinical studies evaluating the relationship between vitamin D status and acute respiratory infections

Source	Study design	Condition	Population (cases)	Main outcome(s)
Ginde et al[41]	Retrospective study (secondary analysis of the US NHANES III data)	25(OH)D_3 levels <30 ng/mL	18,883 participants	Serum 25(OH)D_3 levels were inversely associated with recent upper respiratory tract infections (URTIs)
Berry et al[39]	Retrospective study (secondary analysis of the Nationwide 1958 British Birth Cohort data)	25(OH)D_3 levels >10 ng/mL	6,789 participants	Vitamin D status had a linear relationship with respiratory infections and lung function
Sabetta et al[40]	Cross-sectional (prospective from Tromsø Study)	25(OH)D_3 levels >38 ng/mL	198 healthy adult participants	25(OH)D_3 levels >38 ng/mL were associated with reduction in risk of viral URI
Laaksi et al[42]	Cross-sectional (prospective Tromsø Study)	25(OH)D_3 levels <40 nmol/L	800 young Finnish men	Serum vitamin D concentrations with acute respiratory tract infection (ARTI) in young Finnish men
Science et al[37]	Cross-sectional (prospective cohort study)	Median serum 25(OH)D_3 level 62.0 nmol/L	743 participants (children aged 3–15 years)	Lower serum 25(OH)D_3 levels were associated with increased risk of viral RTI in children
Mohamed and Al-Shehri[38]	Cross-sectional (prospective Tromsø Study)	Cord blood 25-hydroxyvitamin D levels	206 newborns	Low cord blood 25(OH)D_3 levels were associated with increased risk of ARTI in the first 2 years of life
Camargo et al[43]	Double-blinded randomized clinical trials	Vitamin D_3 supplementation (300 IU)	744 school children	Vitamin D supplementation (300 IU/daily) significantly reduced the risk of ARTI in winter among children with vitamin D deficiency
Laaksi et al[44]	Double-blinded randomized clinical trials	Vitamin D_3 supplementation (400 IU)	164 young Finnish men	400 IU vitamin D_3 daily significantly decreased the risk of ARTI in young Finnish men

Abbreviation: US NHANES, United States National Health and Nutrition Examination Survey.

of the Third National Health and Nutrition Examination Survey, and found a strong negative association between serum 25(OH)D_3 levels (<30 ng/mL) and risk of upper respiratory tract infection, which seemed to be stronger in individuals with asthma and chronic obstructive pulmonary disease. In a large retrospective study, vitamin D status was found to have a linear association with seasonal infections and lung function, in which each 10 nmol/L increase in 25(OH)D_3 was associated with a 7% lower risk of infection and an 8 mL increase in forced expiratory volume in 1 second.[39] Several prospective cohort studies in adults and children further demonstrated that serum vitamin D concentration was associated with acute respiratory tract infection (ARTI): 25(OH)D_3 levels <38 ng/mL were associated with increased risk of ARTI.[37,40,42] Recently, Mohamed et al[38] found that low cord blood 25(OH)D_3 levels are associated with increased risk of ARTI in the first 2 years of life, suggesting a necessary early intervention for vitamin D starting from newborns.

Evidence from double-blinded randomized clinical trials (RCTs) for vitamin D interventional studies is warranted to confirm the clinically relevant effect of vitamin D in RTIs. Camargo et al[43] investigated whether vitamin D supplementation in children with vitamin D deficiency would lower the risk of ARI. Compared with controls, children receiving vitamin D (300 IU/daily) have been reported to have significantly fewer ARIs during the study period. In another placebo-controlled double-blinded study comprising 164 voluntary young Finnish men (18–28 years of age), the proportion of men remaining healthy throughout the 6-month study period was greater in the intervention group (vitamin D_3, 400 IU/daily) than in the placebo group.[44] More RCTs with larger populations, however, are warranted to investigate the role of vitamin D supplementation on respiratory health and ARI.

Studies with VDR-knockout mice have been critical in demonstrating the relationship between vitamin D and acute infections.[45–49] Compared with $VDR^{+/+}$ mice, $VDR^{-/-}$ mice exhibited significantly higher *Chlamydia trachomatis* loading and reduced clearance of chlamydial infection than wild-type $VDR^{+/+}$ mice, suggesting a vitamin D–VDR pathway involved in respiratory mucosal defense against infections.[46] VDR-knockout mice developed an unaltered Th1 response to infection due to impaired upregulation of arginase 1 expression under *Leishmania* infection.[45] Although 1,25$(OH)_2D_3$ inhibits the proliferation and differentiation of both T and B lymphocytes, the central mechanism underlying microbial eradication of vitamin D seems to be the inhibition of activation of TLRs in the host cell, which induces the formation of potent antimicrobial peptides.[19,50] The additional

anti-infection mechanism of vitamin D may be related to the ability to modulate inflammatory factor levels in ARI patients. 25(OH)D_3 levels below 21 ng/mL have an inverse relationship with CRP concentration in asymptomatic ambulatory patients.[51] However, these associations were not found in symptomatic patients.[52] In a randomized controlled trial of vitamin D supplements (1,400 IU/week) in infants, there were no differences in plasma levels of CRP or inflammatory cytokines between the treatment group and the control group.[53] The exact effects and mechanisms of vitamin D in infectious diseases therefore require further study.

The functioning of VDR is affected by gene polymorphisms, in which a start codon polymorphism (rs2228570) and three polymorphisms in the 3′ untranslated region (UTR) of the *VDR* gene (rs1544410, rs7975232, and rs731236) are the most commonly studied polymorphisms in the *VDR* gene.[54] There are reports that *VDR* polymorphism is linked to increased susceptibility to infection. Alagarasu et al have found that the frequency of the C/C genotype of rs7975232 was significantly lower in dengue virus infection patients (DEN) compared to health controls.[54] Aslan et al examined *VDR* gene polymorphisms in urinary tract infections, and found that the ff genotype in rs2228570 was significantly increased in UTI children with urinary tract infection.[55] Rathored et al have also found that the patients with ff genotypes in rs2228570 were at high risk of multidrug-resistant tuberculosis with smear-positive disease.[56] In a multicenter clinical trial, Levin et al recently investigated the relationship of common variation within genes encoding the vitamin D-binding protein, megalin, cubilin, CYP27B1, CYP24A1, and VDR with low 25(OH)D levels, and found some minor alleles at rs7968585 and rs7968585 within the *VDR* gene that were related to low 25(OH)D_3.[57] The results of these studies suggest that *VDR* gene polymorphisms can be important for the susceptibility of inflammatory diseases, which may be due to the lower 25(OH)D_3 status affected by *VDR* gene polymorphisms.

Atherosclerosis-related cardiovascular disease

It is well known that inflammation plays a key role in the development of atherosclerosis. Inflammatory cells, mainly macrophages and T lymphocytes, produce a wide range of inflammatory cytokines in atherosclerotic lesions, which are critically important in the progression of atherosclerosis-related cardiovascular disease (CVD).[58] Numerous studies have verified vitamin D deficiency (25[OH]D_3 <20 ng/mL) as one of the new risk factors for coronary heart disease (CHD).[59,60] Many potential functions of vitamin D – including protection of endothelial function, inhibition of smooth-muscle cell (SMC) proliferation, improvement of lipid profile, and others – have been thought to contribute to the antiatherogenic effect of vitamin D.[61–63]

Clinical studies have indicated an inverse association between 25(OH)D_3 levels and CHD risk (Table 2). Three large retrospective studies demonstrated that 25(OH)D_3 levels below 20 ng/mL are associated with increased risk for CHD, including hypertension, diabetes mellitus, obesity, high serum low-density lipoprotein (LDL), triglyceride (TG), and low high-density lipoprotein (HDL) levels.[17,64,65] Several cross-sectional prospective studies further strengthened this evidence, which demonstrated a significant increase for all-cause mortality when serum 25(OH)D_3 levels were less than 30 ng/mL.[66–70] In a population-based cohort study, Lim et al[71] reported that a low 25(OH)D_3 concentration had a higher risk of significant coronary artery stenosis. The odds ratios were 2.08 for 25(OH)D_3 concentration of 15–29.9 ng/mL versus at least 30 ng/mL and 3.12 for 25(OH)D_3 concentration below 15 ng/mL versus at least 30 ng/mL.

Although observational studies suggest that vitamin D deficiency or insufficiency is related to a higher risk for CVD, data from recent RCTs designed to assess the impact of vitamin D supplementation on cardiovascular outcomes are conflicting (Table 3). Some RCT results have shown that a higher intake of vitamin D is associated with a lower risk of CVD, especially in men, due to the improvement of vascular endothelial function and decrease in inflammation.[72–74] However, most evidence at present shows that vitamin supplementation has no effect on vascular disease mortality or all-cause mortality.[73–78] Since large well-controlled double-blinded RCTs aiming primarily for cardiovascular end points are still absent, whether or not vitamin D supplementation can significantly improve cardiovascular outcomes is largely unknown. At this time, larger RCTs, which can be used to evaluate the application of vitamin D in cardiology, have yet to be implemented.

The regulation of the immune/inflammatory response is one of the most verified mechanisms of the antiatherogenic effect of vitamin D. First, vitamin D exerts protective effects against endothelial dysfunction, an inflammatory process that precedes atherosclerosis, via multiple mechanisms, including stimulating nitric oxide production and inhibiting oxidative stress.[59,79] Vitamin D has been found to inhibit contractions, which were endothelium-dependent through inhibiting cyclooxygenase-1 expression and reactive oxygen species production.[59,79] In addition, calcitriol significantly repressed the expression of cyclooxygenase 2 and promoted

Table 2 Summary of major clinical studies evaluating the relationship between vitamin D status and cardiovascular disease (CVD) risk

Source	Study design	Condition	Population (cases)	Main outcome(s)
Martins et al[65]	Retrospective study (secondary analysis of the US NHANES III data)	Mean $25(OH)D_3$ levels =30 ng/mL	15,088 participants in the US	Serum $25(OH)D_3$ levels were negatively associated with important CVD risk factors, including hypertension, diabetes mellitus, obesity, and high serum TG levels
Ponda et al[17]	Cross-sectional (retrospective study)	$25(OH)D_3$ levels <20 ng/mL	107,811 participants in the US	Vitamin D deficiency was associated with an unfavorable lipid profile, including higher TC, LDL, TG, and lower HDL
Park and Lee[64]	Cross-sectional (retrospective study)	$25(OH)D_3$ levels <25 nmol/L	5,559 Korean participants	Vitamin D insufficiency was associated with increased prevalence of CVD, accompanied by higher waist circumference, fasting glucose, LDL, and TG levels and lower HDL cholesterol levels
Wang et al[69]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <15 ng/mL	1,739 Framingham offspring	Vitamin D deficiency was associated with incident CVD
Dobnig et al[70]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <13.3 ng/mL	3,258 participants in Austria	Low $25(OH)D_3$ and $1,25(OH)_2D_3$ levels were independently associated with all-cause and cardiovascular mortality
Semba et al[68]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <10.5 ng/mL	1,006 participants in Italy	Older community-dwelling adults with low serum $25(OH)D_3$ levels were at higher risk for all-cause and CVD mortality
Zhao et al[66]	Cohort study (prospective study)	$25(OH)D_3$ levels <29 ng/mL	2,609 participants with hypertension in the US	Concentrations of $25(OH)D_3$ were inversely associated with all-cause and CVD mortality among adults with hypertension in the US
Wasson et al[67]	Cross-sectional (prospective study)	The $25(OH)D_3$ levels <15 ng/mL	1,844 ischemic heart disease (IHD) patients	Vitamin D Levels of <15 ng/mL were associated with a hazard ratio of 2.30 (P=0.035) for IHD events compared to levels ≥30 ng/mL
Lim et al[71]	Cross-sectional (prospective study)	$25(OH)D_3$ levels <30 ng/mL	921 participants with hypertension in the US	Low $25(OH)D_3$ concentrations were independently associated with higher risk of coronary artery stenosis

Abbreviations: TC, total cholesterol; LDL, low-density lipid; TG, triglyceride; HDL, high-density lipid; US NHANES, United States National Health and Nutrition Examination Survey.

prostaglandin catabolism, both of which reduce the level of prostaglandins and suppress proinflammatory cytokine expression in endotheliocytes.[80] Second, $1,25(OH)_2D_3$ may alter macrophage function and gene expression, which is crucial in the formation of foam cells and vascular inflammation response that promote the process of atherosclerosis.[26] In patients with type 2 diabetes mellitus, $1,25(OH)_2D_3$ can inhibit foam-cell formation, and suppresses macrophage cholesterol uptake via reducing peroxisome proliferated-activated receptor-γ-dependent CD36 expression.[81] In addition, vitamin D induces an antiatherogenic monocyte/macrophage phenotype via regulating endoplasmic reticulum stress.[26] Previous studies by our group have found vitamin D deficiency causes increased proinflammatory cytokine expression in epicardial adipose tissue, which is coupled with increased inflammatory cellular infiltrate, suggesting the anti-inflammation effect of vitamin D in epicardial adipose tissue is a novel mechanism for atheroprotection.[82] Third, $1,25(OH)_2D_3$ inhibits the proliferation of vascular SMCs (VSMCs),[83] and exerts protective effects against VSMC morphological changes, which further inhibit the secretion of inflammatory molecules.[84]

In a hypercholesterolemic swine model, our group has found that vitamin D deficiency significantly increases the expression of TNFα in neointimal lesions after balloon angioplasty and that calcitriol has antiproliferative properties in TNFα-stimulated human VSMCs.[85] Besides the direct antiatherogenic effect, vitamin D has a variety of indirect effects on the systemic pathophysiological conditions that promote atherosclerosis, such as improving insulin resistance and hypertension.[59] However, Ponda et al[17,77] recently reported repletion of $25(OH)D_3$ levels in the short term does not correct or even ameliorate dyslipidemia, suggesting that the definitive role of vitamin D in CVD remains to be elucidated.

Asthma

Asthma is a disorder characterized by varying and recurring symptoms of airflow obstruction and bronchial hyperresponsiveness in the setting of inflammation.[86] Epidemiologic studies suggest an association between vitamin D deficiency

Table 3 Summary of interventional studies evaluating the effect of vitamin D supplements on cardiovascular disease (CVD) risk

Source	Study design	Condition	Population (cases)	Main outcome(s)
Harris et al[72]	Randomized, placebo-controlled trial	Vitamin D (2,000 IU/day) for 16 weeks	57 African American adults	Vitamin D supplements (2,000 IU/day) for 16 weeks were effective at improving vascular endothelial function in African American adults
Zittermann et al[73]	Randomized, placebo-controlled trial	Vitamin D (83 μg/day) for 1 year	200 overweight subjects (mean 25[OH]D_3 levels =12 ng/mL)	Vitamin D supplements enhanced the beneficial effects of weight loss on CVD risk, including decreasing lipid levels and inflammation
Sun et al[74]	Cross-sectional (prospective study)	Vitamin D (≥600 IU/day) or vitamin D (<100 IU/day)	2,280,324 person-years of follow-up	Higher intake of vitamin D was associated with a lower risk of CVD in men but not in women
Cauley et al[75]	Cross-sectional (prospective study)	Calcium plus vitamin D supplementation	29,862 postmenopausal women	There was no difference in CVD morbidity between groups
Ponda et al[77]	Randomized, placebo-controlled trial	Vitamin D (50,000 IU/week) for 8 weeks	151 vitamin D-deficient (25[OH]D levels <20 ng/mL) patients	Correcting vitamin D deficiency in the short term did not improve the lipid profile
Yiu et al[78]	Randomized, placebo-controlled trial	Vitamin D (5,000 IU/day) for 12 weeks	100 type 2 diabetes mellitus patients	12 weeks of oral supplementation with vitamin D did not significantly affect vascular function or serum biomarkers of inflammation and oxidative stress
Stricker et al[168]	Randomized, placebo-controlled trial	Vitamin D (100,000 IU/single oral dose)	76 patients with peripheral arterial disease	Vitamin D supplementation did not influence endothelial function, arterial stiffness, coagulation, or inflammation parameters
Gepner et al[76]	Randomized, placebo-controlled trial	Vitamin D (2,500 IU/day) for 4 months	114 subjects	Vitamin D supplementation did not improve endothelial function, arterial stiffness, or inflammation

and asthma (Table 4).[87–92] Some prospective studies and case-control studies have shown the majority of asthmatic children to be vitamin D-deficient.[91,93] Vitamin D deficiency has been found to increase the risk of severe asthma exacerbation, defined as the need for emergency room evaluation or hospitalization.[94] A prospective study of adults and children found that low serum 25(OH)D_3 levels were associated with increased requirement of steroids in the pediatric asthma group.[90] Higher maternal circulating 25(OH)D_3 concentrations in pregnancy were independently associated with lower risk of asthma at 5 years old in offspring.[92] However, another study showed that high 25(OH)D_3 levels in pregnant women could pose an increased risk of asthma in offspring,[95] indicating a reasonable level of vitamin D in pregnant women is crucial for maintaining normal bronchial responsiveness in offspring.

The mechanisms of vitamin D deficiency in asthma pathophysiology are not fully understood. Many researchers have focused on the potential effect of vitamin D in inflammatory response that inhibits the progress of asthma.[86] Vitamin D has been found to increase the production of IL-10, an anti-inflammatory cytokine, while decreasing the expression of proinflammatory cytokines in airway SMCs.[96,97] In a mouse model, Gorman et al[98] recently examined asthma-like responses 24 hours after airway challenge with the experimental allergen ovalbumin in adult offspring born to vitamin D_3-replete and vitamin D_3-deficient mothers. They found the ability of airway-draining lymph-node cells to proliferate and secrete cytokines in response to ovalbumin ex vivo was significantly enhanced by vitamin D deficiency.[98] In a mouse model of allergic airway inflammation, our group has previously found vitamin D deficiency causes an increase in the expression of TNFα, which decreases the expression of VDR and prohibitin, a vitamin D target gene.[95] Vitamin D supplementation reduces the levels of TNFα, thereby increasing the expression of VDR and prohibitin, which could be responsible for reducing allergic airway inflammation.[99]

Inflammatory bowel diseases

Vitamin D deficiency is common in patients with inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD)[100–105] (Table 5). Several retrospective and cross-sectional studies have reported a high prevalence of vitamin D deficiency in patients with IBD, which was associated with disease activity and quality of life.[101–105] Recently, a prospective cohort study of 72,719 women enrolled in the Nurses' Health Study examined the relationship between vitamin D status and risk of CD and UC.[100]

Table 4 Summary of major clinical studies evaluating the relationship between vitamin D status and asthma risk

Source	Study design	Condition	Population (cases)	Main outcome(s)
Korn et al[91]	Prospective study	25(OH)D_3 levels <30 ng/mL	280 adult asthma patients	Severe and uncontrolled adult asthma was associated with vitamin D insufficiency and deficiency
Brehm et al[169]	Cross-sectional study	25(OH)D_3 levels <30 ng/mL	616 children (6–14 years)	Vitamin D insufficiency was relatively frequent in an equatorial population of children with asthma; lower vitamin D levels were associated with increased markers of allergy and asthma severity
Bener et al[93]	Randomized compared trial	25(OH)D_3 levels <30 ng/mL	483 children with asthma and 483 healthy controls	The majority of asthmatic children had vitamin D deficiency compared to control children
Freishtat et al[89]	Cross-sectional case-control study	25(OH)D_3 levels <30 ng/mL	92 asthma and 21 controls in African American youths	The prevalence of vitamin D insufficiency and deficiency was significantly greater among asthma cases than control subjects
Brehm et al[94]	Prospective study	25(OH)D_3 levels <30 ng/mL	1,024 children with asthma	Vitamin D insufficiency was associated with higher odds of severe exacerbation over a 4-year period
Morales et al[92]	Prospective cohort study	Maternal circulating 25(OH)D_3 levels	1,724 children	Maternal vitamin D intake resulted in a lower risk of asthma in children at 5 years of age
Gale et al[95]	Prospective cohort study	25(OH)D_3 levels >75 nmol/L	596 pregnant women and 466 children	High vitamin D levels in pregnant women could pose an increased risk of asthma in offspring
Goleva et al[90]	Prospective cohort study	25(OH)D_3 levels <20 ng/mL	205 adults and children	Significant associations between serum vitamin D status and steroid requirement in the pediatric asthma group

Table 5 Summary of major clinical studies evaluating the role of vitamin D status and vitamin D supplementation in inflammatory bowel disease (IBD)

Source	Study design	Condition	Population (cases)	Main outcome(s)
Ananthakrishnan et al[100]	Prospective cohort study	25(OH)D_3 levels <20 ng/mL	72,719 women	Higher predicted plasma levels of 25(OH)D_3 significantly reduced the risk for incident Crohn's disease (CD) and insignificantly reduced the risk for ulcerative colitis (UC) in women
Pappa et al[103]	Cross-sectional study	25(OH)D_3 levels <15 ng/mL	130 IBD patients (UC =36, CD =94)	Vitamin D deficiency was highly prevalent among pediatric patients with IBD
Jahnsen et al[105]	Cross-sectional study	25(OH)D_3 levels <30 nmol/L	120 IBD patients (UC =60, CD =60)	Hypovitaminosis D was common in IBD patients
Sentongo et al[104]	Cross-sectional study	25(OH)D_3 levels <38 nmol/L	112 CD patients	Hypovitaminosis D was common in CD patients
Ulitsky et al[102]	Retrospective cohort study	25(OH)D_3 levels <20 ng/mL or <10 ng/mL (deficiency or severe deficiency)	504 IBD patients (UC =101, CD =403)	Vitamin D deficiency was common in IBD, and was independently associated with lower health-related quality of life and greater disease activity in CD
Levin et al[101]	Retrospective cohort study	25(OH)D_3 levels <50 nmol/L or <30 nmol/L (deficiency or severe deficiency)	78 children with IBD	A high proportion of children with IBD were vitamin D-deficient; treating vitamin D deficiency is important for the management of pediatric IBD
Jørgensen et al[106]	Randomized double-blind placebo-controlled trial	Oral vitamin D with 1,200 IU daily for 12 months	108 patients with CD	Oral supplementation with 1,200 IU vitamin D_3 significantly reduced the risk of relapse from 29% to 13%
Yang et al[107]	Randomized, controlled clinical trial	Oral vitamin D with 5,000 IU daily for 24 weeks	18 mild-to-moderate patients with CD	24 weeks' supplementation with up to 5,000 IU/day vitamin D_3 effectively raised serum 25(OH)D_3 and reduced CD activity index scores in a small cohort of CD patients
Pappa et al[108]	Randomized, controlled clinical trial	Vitamin D_2 2,000 IU/day (arm A) or vitamin D_3 2,000 IU/day (arm B) or vitamin D_2 50,000 IU/week (arm C) for 6 weeks	61 children with IBD (25[OH]D level <20 ng/mL)	Oral doses of 2,000 IU vitamin D_3 daily and 50,000 IU vitamin D_2 weekly for 6 weeks was superior to 2,000 IU vitamin D_2 daily for 6 weeks in raising serum 25(OH)D concentration, and was well tolerated among children and adolescents with IBD
Miheller et al[109]	Randomized, controlled clinical trial	1,25$(OH)_2D_3$ (active vitamin D or plain vitamin D [pVD])	37 inactive CD patients	1,25$(OH)_2D_3$ had a more prominent short-term beneficial effect than pVD on disease activity of CD

In this study, researchers used Cox proportional hazard modeling to examine the hazard ratio (HR) for incident CD or UC after adjusting for potential confounders. Compared with women with a predicted 25(OH)D_3 level less than 20 ng/mL, the multivariate-adjusted HR was 0.38 (95% confidence interval 0.15–0.97) for CD and 0.57 (95% confidence interval 0.19–1.70) for UC for women with a predicted 25(OH)D_3 level greater than 30 ng/mL, suggesting higher predicted plasma levels of 25(OH)D_3 significantly reduce the risk for incident CD.[100]

Vitamin D supplementation has shown potential therapeutic benefit for IBD in some small, randomized, double-blind studies (Table 5). Jørgensen et al[106] reported that oral supplementation with vitamin D_3 (1,200 IU/day for 12 months) significantly reduced the risk of IBD relapse from 29% to 13%. Yang et al[107] investigated the effect of high-dose vitamin D_3 on serum vitamin D levels and CD activity index. They found supplementation of vitamin D_3 (5,000 IU/day for 24 weeks) effectively raised serum 25(OH)D_3 and reduced CD activity index scores. Pappa et al[108] reported oral doses of 2,000 IU vitamin D_3 daily or 50,000 IU vitamin D_2 weekly seem to be superior to 2,000 IU vitamin D_2 daily in raising serum 25(OH)D_3 concentration, and was tolerated among children and adolescents with IBD. Another study has shown that 1,25$(OH)_2D_3$ (active form of vitamin D) has a more prominent short-term beneficial effect than 25(OH)D_3 (plain vitamin-D) on CD activity.[109] Although most studies have now shown vitamin D_3 treatment might be effective in IBD, larger, randomized, double-blind, placebo-controlled trials needed to elucidate this correlation are lacking.

In VDR-knockout mice models, vitamin D deficiency increases susceptibility to dextran sodium sulfate-induced colitis.[110] Histological examination revealed the disruption in the epithelial junctions in dextran sodium sulfate-treated $VDR^{-/-}$ mice. 1,25$(OH)_2D_3$ preserved the integrity of the tight junctions in Caco-2 cell monolayers.[110] Ryz et al[111] found that 1,25$(OH)_2D_3$ treatment increases host susceptibility to *Citrobacter rodentium*, an extracellular microbe that causes acute colitis, by suppressing mucosal Th17 immune responses. Taken together, these observations suggest that vitamin D plays a critical role in mucosal barrier homeostasis by preserving the integrity of junctions via regulating the host immune/inflammatory response, leading to decreased susceptibility to mucosal damage and decreased risk of IBD.

Chronic kidney disease

Normal renal function is crucial for vitamin D metabolism.[1] Vitamin D deficiency is highly prevalent among patients with chronic kidney disease (CKD; 20%–85%).[112,113] Studies have demonstrated a strong association between vitamin D deficiency and increased all-cause and CKD mortality in the general population (Table 6).[113–118] Chronic low-grade inflammation is a hallmark of CKD, and has been disclosed as one important factor contributing to the progression of CKD and high cardiovascular mortality.[10] A prospective cohort study of 444 patients with eGFR <60 mL/min/1.73 m^2 (follow-up time 9.4 years) showed that most patients died from cardiovascular causes.[116] Cox proportional hazard modeling has shown multivariate-adjusted HRs (with 95% confidence intervals) in severely vitamin D-deficient (25[OH]D_3 <10 ng/mL) compared to vitamin D-sufficient patients (25[OH]D_3 ≥ 30 ng/mL) were 3.79 (1.71–8.43) for all-cause and 5.61 (1.89–16.6) for cardiovascular mortality, suggesting low 25(OH)D_3 levels are a crucial factor linking CKD to CVD.[116] Another cross-sectional study strengthened this evidence, demonstrating that higher vascular stiffness and endothelial dysfunction were associated with low levels of 25(OH)D_3 and 1,25$(OH)_2D_3$ in CKD patients.[119] Vitamin D intake for more than 12 months can significantly reduce the probability of cardiovascular events.[117] Low 25(OH)D_3 and 1,25$(OH)_2D_3$ levels are independently associated with albuminuria, a major risk factor for the progression of renal disease linked to all-cause mortality and cardiovascular mortality.[114] Treatment with active vitamin D preparations also has a beneficial effect in decreasing albuminuria.[120] Besides regulating inflammation and proteinuria, vitamin D has been found to improve aerobic capacity and increase the level of fetuin-A, an important protective factor for cardiovascular morbidity in pediatric CKD patients.[115,121]

Several randomized, double-blind, placebo-controlled studies have examined the role of vitamin D as a therapeutic agent for CKD (Table 7).[120,122–127] High-dose cholecalciferol supplementation (50,000 IU/week for 12 weeks) was safe and sufficient to maintain serum 25(OH)D_3 concentrations (≥ 30 ng/mL) and simultaneously decreased serum MCP-1 concentrations in early CKD.[122–124] In moderate CKD patients, both cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2) are effective in increasing 25(OH)D_3 and decreasing parathyroid hormone and inflammatory cytokine levels.[125,127] In nonhemodialysis patients, supplementation of cholecalciferol with 40,000 IU/week for 8 weeks significantly increased the level of 1,25$(OH)_2D_3$ and decreased serum parathyroid hormone and inflammatory cytokine levels.[126] However, this effect was not observed in end-stage renal disease (ESRD) patients.[126] As patients with CKD progress to ESRD, renal CYP27B1 activity decreases, resulting in

Table 6 Summary of major clinical studies evaluating the relationship between vitamin D status and chronic kidney disease (CKD) risk

Source	Study design	Objective	Population (cases)	Main outcome(s)
Pilz et al[116]	Prospective cohort study	To investigate the relationship between the vitamin D status and mortality of CKD	444 CKD patients	Low $25(OH)D_3$ levels were associated with increased all-cause and cardiovascular mortality in CKD patients
Santoro et al[117]	Cross-sectional study	To investigate the relationship between the vitamin D status and mortality of CKD	104 CKD patients	Vitamin D has been shown to reduce the probability of cardiovascular or renal events; vitamin D intake for more than 12 months can reduce the probability of such events by 11.42%
London et al[119]	Cross-sectional study	To investigate the relationship between vitamin D status and cardiovascular risk factors	104 CKD patients (end stage)	Vitamin D deficiency and low $1,25(OH)_2D_3$ could be associated with arteriosclerosis and endothelial dysfunction in hemodialysis patients
Isakova et al[114]	Cross-sectional study	To investigate the relationship between vitamin D level, inflammation, and albuminuria	1,847 participants	Low $25(OH)D_3$ and $1,25(OH)_2D_3$ levels were independently associated with albuminuria; vitamin D deficiency may contribute to inflammation and subsequent albuminuria
Petchey et al[115]	Cross-sectional study	To investigate the relationship between vitamin D status and maximum aerobic-exercise capacity in patients with CKD	85 CKD participants	Vitamin D was independently associated with aerobic capacity in CKD patients
Satirapoj et al[113]	Cross-sectional study	To investigate the relationship between vitamin D status and the staging of CKD	2,895 CKD patients	$25(OH)D_3$ insufficiency and deficiency were more common and associated with level of kidney function in the Thai CKD population, especially in advanced-stage CKD
Schaible et al[121]	Cross-sectional study	To investigate the effect of vitamin D status on fetuin-A in CKD patients	112 pediatric patients	Cumulative intake of $25(OH)D_3$ and calcitriol were significantly correlated with fetuin-A in CKD patients
Seeherunvong et al[118]	Cross-sectional, retrospective study	To assess the prevalence of abnormal vitamin D status in children and adolescents with CKD	258 patients with early CKD	Vitamin D insufficiency and deficiency may contribute to growth deficits during the earliest stages of CKD

the impaired formation of $1,25(OH)_2D_3$ in many of these patients.[128] Previous attempts to counteract these changes in mineral metabolism with nutritional vitamin D therapy have been unsuccessful.[129] For this reason, most therapeutic approaches to treat vitamin D deficiency in ESRD patients favor the use of calcitriol or its associated analogs instead of the use of nutritional vitamin D forms.[128,130] Interestingly, in an uncontrolled trial of seven ESRD patients, Stubbs et al[128] reported significant and favorable effects after 8 weeks of cholecalciferol supplementation on circulating monocytes and concentration of inflammatory cytokines, which may be have been due to extrarenal production of calcitriol in the setting of minimal renal CYP27B1 activity in ESRD patients.

Experimental studies have demonstrated that vitamin D can control inflammation and oxidative stress that prevent CKD progress.[131,132] Using a mouse model of obstructed nephropathy, Tan et al[132] reported that the synthetic vitamin D analog paricalcitol reduced the infiltration of inflammatory T-cells and macrophages in the obstructed kidney, which was accompanied by a decreased expression of RANTES and TNFα. In a human proximal tubular cell line (HKC-8), paricalcitol inhibited RANTES messenger ribonucleic acid and protein expression and abolished the ability of tubular cells to recruit lymphocytes and monocytes after TNFα stimulation.[132] In a study using a uremic rat model, paricalcitol significantly decreased cardiac oxidative stress. When combining with the angiotensin-converting enzyme inhibitor enalapril, paricalcitol further prevented inflammation and oxidative injury in uremic rats.[131] These studies provide experimental evidence supporting the role of inflammation in providing a pathological link between vitamin D and CKD.

Liver inflammatory disease

Nonalcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis without significant alcohol use or other known liver disease, and is characterized by chronic portal inflammation.[133] Recent studies emphasize the role of insulin resistance, metabolic syndrome, and proinflammatory cytokines in the development and progression of NAFLD.[134,135] Vitamin D serum levels negatively correlate with insulin resistance and metabolic syndrome. Supplementation of vitamin D has been found to reduce

Table 7 Summary of interventional studies evaluating the effect of vitamin D supplements on chronic kidney disease (CKD) risk

Source	Study design	Objective	Population (cases)	Main outcome(s)
Alvarez et al[122]	Randomized, double-blind, placebo-controlled trial	To investigate the effect and safety of high-dose cholecalciferol (50,000 IU/week for 12 weeks followed by 50,000 IU every other week for 40 weeks) on serum parathyroid hormone (PTH) in CKD patients	46 subjects with early CKD (stage 2–3)	After 1 year, this oral cholecalciferol regimen was safe and sufficient to maintain serum 25(OH)D_3 concentrations (≥30 ng/mL) and prevent vitamin D insufficiency in early CKD; furthermore, serum PTH improved after cholecalciferol treatment
Alvarez et al[123]	Randomized, double-blind, placebo-controlled trial	To investigate the effect and safety of high-dose cholecalciferol (50,000 IU/week for 12 weeks followed by 50,000 IU every other week for 40 weeks) on circulating markers of inflammation in CKD patients	46 subjects with early CKD (stage 2–3)	High-dose cholecalciferol decreased serum MCP-1 concentrations by 12 weeks in patients with early CKD
Shroff R et al[127]	Randomized, placebo-controlled, double-blind study	To investigate the effect of ergocalciferol supplementation on the onset of secondary hyperparathyroidism in children with CKD stage 2–4	72 children with CKD (stage 2–4)	Ergocalciferol is an effective treatment that was effective in increasing 25(OH)D_3 and decreasing PTH levels in patients with moderate chronic kidney disease
Kooienga et al[125]	Randomized, placebo-controlled, double-blind study	To investigate the effects of vitamin D_3 supplementation on secondary hyperparathyroidism in patients with moderate CKD	639 elderly women (moderate CKD)	Vitamin D_3 was effective in increasing 25(OH)D_3 and decreasing PTH levels in patients with moderate CKD
Chandra et al[124]	Randomized, placebo-controlled, pilot study	To investigate the effect and safety of high-dose cholecalciferol (50,000 IU/week for 12 weeks) in CKD patients	34 subjects with CKD (stages 3 and 4)	Weekly cholecalciferol supplementation appeared to be an effective treatment to correct vitamin D status and PTH in CKD
Marckmann et al[126]	Randomized, placebo-controlled, double-blind study	To investigate the effect and safety of cholecalciferol (40,000 IU/week for 8 weeks) in hemodialysis (HD) and non-HD CKD patients	52 subjects with CKD (stages 3 and 4)	This oral cholecalciferol regimen was safe, and had favorable effects on 1,25$(OH)_2D_3$ and PTH in non-HD patients
Molina et al[120]	Randomized, placebo-controlled, double-blind study	To investigate the effect of vitamin D (666 IU/day for 6 months) on albuminuria in proteinuric CKD patients	101 nondialysis CKD patients with albuminuria	Vitamin D supplementation with daily cholecalciferol had a beneficial effect in decreasing albuminuria, with potential effects on delaying the progression of CKD
Moe et al[170]	Randomized, double-blind study	To investigate the effect and safety of cholecalciferol (4,000 IU/day ×1 month, then 2,000 IU/day ×2 months) or doxercalciferol (1 μg/day ×3 months) in CKD patients	47 subjects with CKD (stages 3 and 4)	Both cholecalciferol and doxercalciferol decreased PTH; there was no significant difference between groups
Stubbs et al[128]	Uncontrolled study	To investigate whether 25(OH)D repletion affects vitamin D-responsive monocyte pathways in vivo	7 patients with HD	Vitamin D therapy had a biologic effect on circulating monocytes and associated inflammatory markers in end-stage renal disease patients
Albalate et al[130]	Randomized, double-blind study	To investigate drug or dosing regiments in CKD patients	217 HD patients	In HD patients, calcifediol increased 25(OH)D_3, serum calcium, and phosphates and lowered PTH

Abbreviation: HD, hemodialysis.

insulin resistance in obese children.[134] Recently, lower vitamin D levels were found to be independently associated with increased severity of steatosis, necroinflammation, and fibrosis in NAFLD.[136,137] Furthermore, serum vitamin D levels that could predict the severity of NAFLD independently of other metabolic characteristics and relate vitamin D to NAFLD are largely unknown. Considering that inflammation is followed by steatosis in most NAFLD patients,[138] vitamin D may be involved in NAFLD through its ability to modulate the immune/inflammation system. Recently, Roth et al[139] fed young (25-day-old) Sprague Dawley rats with a low-fat diet alone, with vitamin D depletion, or with a Westernized diet, and found that vitamin D-depleted animals fed a Westernized diet exhibited significantly greater hepatic steatosis and inflammation compared to low-fat diet groups, which may be related to the upregulation of TLR2, TLR4, TLR9, and endotoxin receptor CD14 in the liver, suggesting vitamin D depletion exacerbates NAFLD, possibly by way of endotoxin exposure in a Westernized diet rat model. Low vitamin D serum levels have also been found to correlate with the severity of inflammation and fibrosis in chronic hepatitis B and C viruses, where cellular immunity played crucial roles in the progress of diseases.[140,141] In hepatitis B, *VDR* polymorphisms have been associated with infection susceptibility and clinical course in different populations.[142] Taken together, these data indicate a potential link between vitamin D and viral hepatitis.

Multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, which affects more than 2 million individuals worldwide. Growing evidence suggest that vitamin D deficiency might be one of the most important environmental factors for the prevalence, relapse rate, and progression of MS[143–146] (Table 8). In a large prospective case-control study of 7 million US military personnel, high circulating levels of 25(OH)D_3 were found to be associated with a lower risk of MS, in which every 50 nmol/L increase in serum 25(OH)D_3 led to a 41% decrease in MS risk.[145] Another prospective study of 35,794 mothers of participants in the Nurses' Health Study II has shown that the relative risk of MS was lower among women born to mothers with high milk or vitamin D intake during pregnancy.[147] In addition, serum 25(OH)D_3 concentrations in patients with MS were also found to be related to the relapse of the disease. Mowry et al found that each 10 ng/mL increase in 25(OH)D_3 level was associated with a 15% lower risk of a new T_2 lesion and a 32% lower risk of a gadolinium-enhancing lesion. Each 10 ng/mL increase in vitamin D level was associated with lower subsequent disability, suggesting higher vitamin D levels were associated with lower relapse risk.[143]

Although a link between vitamin D supplementation and decreased risk of MS has been widely assumed, present vitamin D-repletion therapies have not yet shown a significant effect on the progress of MS (Table 8). In a retrospective cohort study of 116,671 female registered nurses, intake of vitamin D (≥400 IU/day) from multivitamins was not been found to statistically reduce the risk of MS.[145] Moreover, no published RCTs of vitamin D repletion so far – low dose or high dose – have shown any benefit on relative risk of MS relapse.[148–150] However, in a high-dose vitamin D_3-supplementation RCT (20,000 IU/day for 12 weeks) in MS patients, vitamin D was found to increase proportion of IL-10^+ $CD4^+$ T-cells and decrease the ratio between IFNγ^+ and IL-4^+ $CD4^+$ T-cells.[151] Moreover, in a myelin oligodendrocyte glycoprotein-induced animal model of MS, vitamin D significantly attenuated central nervous system inflammation and demyelination, accompanied by a lower amount of IFNγ-producing myelin oligodendrocyte glycoprotein-specific T-cells via a developmental stage-dependent manner.[152]

These results suggest the exact effect of vitamin D repletion on the risk of MS remains to be clarified, since large, high-quality, randomized trials are still lacking.

Other inflammation/ immune-related disorders

Inflammation has also been found to play an important role in other chronic diseases, including hypertension, diabetes, chronic lower-back pain (CLBP), and congestive heart failure (HF). Several reviews have thoroughly discussed the relationship between vitamin D and hypertension or diabetes.[153,154] There is clear evidence to support an association between low plasma levels of 25(OH)D_3 and hypertension and type 2 diabetes.[153,154] Furthermore, clinical trials aimed at testing the effect of vitamin D supplementation on hypertension and type 2 diabetes documented a dose-dependent blood pressure-lowering and insulin sensitivity-increasing effect of vitamin D in patients.[155–157] However, in a recent randomized, double-blind, placebo-controlled clinical trial, high-dose oral vitamin D_3 (100,000 IU) for 6 months seemed not to reduce blood pressure or left ventricular mass in patients with resistant hypertension.[158] Because the 6-month period used in this study may have been too short a period to detect meaningful effects of vitamin D on left ventricular mass and function, longer trials and detailed studies are needed to better

Table 8 Summary of the major clinical studies evaluating the relationship between vitamin D status and multiple sclerosis (MS) risk

Source	Study design	Objective	Population (cases)	Main outcome(s)
Martinelli et al[144]	Retrospective study	To investigate the relationship between the vitamin D status and MS risk	100 clinically isolated syndrome (CIS) patients	CIS patients with very low (<10th percentile) and low (<25th percentile) 25(OH)D_3 levels were particularly at risk of clinically definite MS
Munger et al[145]	Prospective, nested case-control study	To investigate the relationship between 25(OH)D_3 levels and MS risk	7 million US military personnel	High circulating levels of vitamin D were associated with a lower risk of MS
Runia et al[171]	Prospective longitudinal study	To investigate the relationship between 25(OH)D_3 levels and exacerbation risk in MS	73 patients with relapsing–remitting MS (RRMS)	Higher vitamin D levels were associated with decreased exacerbation risk in RRMS
Mirzaei et al[147]	Prospective study	To investigate the effect of gestational vitamin D on adult-onset MS	35,794 mothers of participants of the Nurses' Health Study II	Higher maternal milk and vitamin D intake during pregnancy may be associated with a lower risk of developing MS in offspring
Mowry et al[143]	5-year longitudinal cohort study	To investigate whether vitamin D status is associated with relapse of MS	469 MS patients	Higher vitamin D levels were associated with lower relapse risk
Munger et al[172]	Retrospective cohort study	To evaluate the effect of dietary intake of vitamin D on risk of MS	116,671 female registered nurses	Intake of ≥400 IU/day of vitamin D from multivitamins was associated with a non-statistically significant reduced MS risk
Shaygannejad et al[149]	Randomized, double-blind, placebo-controlled clinical trial	To evaluate the effect of low-dose oral vitamin D on the prevention of progression of RRMS	50 RRMS patients	Adding low-dose vitamin D to routine disease-modifying therapy had no significant effect on Expanded Disability Status Scale score or relapse rate
Kampman et al[150]	Randomized, double-blind study	To evaluate the effect of vitamin D (20,000 IU weekly for 96 weeks) on the clinical outcome of MS	35 MS patients	Supplementation with 20,000 IU vitamin D weekly did not result in beneficial effects on MS-related outcomes
Burton et al[148]	Randomized, prospective, controlled study	To evaluate the effect of vitamin D (40,000 IU/day over 28 weeks) on the clinical outcome of MS	49 MS patients	The trial lacked the statistical precision and design requirements to adequately assess changes in clinical disease measures
Smolders et al[151]	Randomized, double-blind study	To evaluate the toleration and immunoregulatory effect of vitamin D (20,000 IU/day vitamin D_3 for 12 weeks) in MS	15 RRMS patients	Vitamin D supplementation increased proportion of IL-10^+ $CD4^+$ T-cells and decreased the ratio between interferon-γ^+ and interleukin 4^+ $CD4^+$ T-cells

investigate the definite role of vitamin D supplementation in various forms of hypertension.

Nonspecific lower-back pain is one of the most common reasons for CLBP that burdens health care systems with high cost. Human population studies have shown that plasma levels of vitamin D are inversely associated with risk for CLBP.[159] However, results from a double-blind RCT of 53 patients aged 18–40 years with nonspecific CLBP showed no significant effect of vitamin D supplementation (50,000 IU) in decreasing the pain visual analog scale score of the patients.[160] Vitamin D deficiency is associated with loss of muscle strength and poor outcomes in patients with HF. In a double-blind RCT in 31 patients (25[OH]D_3 levels $\leq$37.5 ng/mL), vitamin D_3 repletion (50,000 IU) decreased aldosterone in patients with HF and low serum vitamin D, suggesting that vitamin D may be an important adjunct to standard HF therapy.[161]

Apart from inflammatory disorders, vitamin D deficiency has been found to be associated with immune-related disorders, such as rheumatoid arthritis and systemic lupus erythematosus.[162,163] Randomized placebo-controlled trials have shown that vitamin D supplementation seems to ameliorate inflammatory and hemostatic markers and show a tendency toward subsequent clinical improvement in these diseases.[146,163,164] In a healthy population, vitamin D levels were significantly higher in antinuclear antibody-negative individuals than antinuclear antibody-positive individuals.[165] Along with this finding is the additional observation that vitamin D deficiency is associated with certain immune abnormalities in such autoimmune disorders as systemic lupus erythematosus and rheumatoid arthritis.[163,166] Recently, a retrospective cross-sectional study showed the risk of auto- and cellular immune abnormalities is increased in women with recurrent pregnancy losses and vitamin D deficiency.[167]

Conclusion

The remarkable expression of the *CYP27B1* and *VDR* genes by macrophages, DCs, and T lymphocytes suggests that the immune/inflammation system could be a target for the effect of vitamin D. Emerging evidence from clinical studies has indicated that vitamin D deficiency is associated with several inflammatory diseases; however, the question remains whether or not vitamin D deficiency contributes to the etiology of inflammatory disease or if vitamin D deficiency is simply a manifestation of these diseases. In acute infection and autoimmune disorders, preliminary evidence suggests an important role of vitamin D supplementation in decreasing the risk of disease. The pathophysiological process in many chronic inflammatory diseases, including atherosclerosis, is complex and confounded by various metabolic factors. Whether vitamin D supplementation is beneficial in the prognosis of these diseases requires further evaluation in larger prospective trials with a focus on major outcome events. In addition, dose-response randomized trials are necessary to identify threshold effects and possible adverse effects in vitamin D therapy. Future studies should aim to characterize optimal ranges of vitamin D status following vitamin D therapy, and should focus on determining the exact relationship between vitamin D dose and outcomes during the progression of diseases.

The identification and characterization of the molecular mechanisms responsible for recognizing and responding to vitamin D in the immune/inflammation system has widened our view of the essential components of a healthy immune response. Nonetheless, many key questions remain to be addressed. These include the cell type-specific roles of VDR in the progression of inflammatory diseases and the mechanisms of cross talk between VDR and other nuclear receptors, such as the retinoid X receptor and liver X receptor, which stimulate the intracellular pathway to exert the anti-inflammation effect. In addition, a single measurement of serum vitamin D status or the current standard value is unlikely to be valid in all situations. The development of research to refine existing biomarkers or establish new indicators that takes many factors into account and to identify useful functional biomarkers of vitamin D status in specific tissues will offer key insights into the development of targeted therapies for individuals with functional vitamin D insufficiency or deficiency in inflammatory diseases, though the research methodology for these potential biomarkers remains to be elucidated.

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Disclosure

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