Vitamin D affects antiphospholipid syndrome by regulating T cells (Review)

RONGXIU HUO*, YANTING YANG*, CHENGCHENG WEI*, XIAOCONG HUO, DANLI MENG, YANG YANG, YIJIA HUANG, RONGJUN HUANG, JINYING LIN and XINXIANG HUANG

Department of Rheumatology and Immunology, Guangxi Academy of Medical Sciences, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi Zhuang Autonomous Region 530016, P.R. China

Received August 28, 2024; Accepted November 28, 2024

DOI: 10.3892/ijmm.2024.5471

Abstract. Antiphospholipid syndrome (APS) is an autoimmune disease characterized by arterial and/or venous thrombosis, pathological pregnancies and persistent antiphospholipid antibodies. The occurrence and development of APS are complex and associated with immune disorders, with its prognosis remaining uncertain. Owing to its pathogenesis, anticoagulation therapy is the primary treatment for patients with APS. In recent years, with increased attention on APS, research on its treatment strategies has flourished, and preclinical and clinical relevance studies are being conducted to re-evaluate the mechanism of action of existing drugs and to develop new drugs. Recent evidence suggests that vitamin D (VD) may help improve immune disorders in patients with APS by regulating the balance between immune cells. In this review, the potential mechanistic role of VD in APS protection was discussed, highlighting the potential effects of VD as a promising adjuvant treatment option for APS.

Contents

Correspondence to: Dr Xinxiang Huang or Dr Jinying Lin, Department of Rheumatology and Immunology, Guangxi Academy of Medical Sciences, The People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Qingxiu, Nanning, Guangxi Zhuang Autonomous Region 530016, P.R. China
E-mail: nnhxx_china@163.com
E-mail: jinyinglin@sina.com

*Contributed equally

Key words: vitamin D, antiphospholipid syndrome, T cell, pathological pregnancy, thrombus

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder whose clinical manifestations are characterized by arterial and/or venous thrombosis, pathological pregnancy and persistent positive antiphospholipid antibodies (aPLs). A patient can be diagnosed with APS when at least one clinical criterion and at least one laboratory criterion are present (1). Clinical criteria include pregnancy pathology or vascular thrombosis (2). Laboratory criteria include the presence of titers or high titers of IgG and/or IgM in anti-cardiolipin (aCL) and/or lupus anticoagulants on at least two occasions, at least 6 weeks apart. The Sapporo criteria (also known as the Sydney Criteria), revised in 2006, added IgG/IgM anti-β2glycoprotein 1 (anti-β2GPI) antibody testing to the laboratory criteria, and the positive detection interval was extended from 6 weeks to 12 weeks (2). 'Non-standard' manifestations include thrombocytopenia, APS-associated nephropathy reticulum and cognitive impairment (3). In addition, 'non-standard' autoantibodies such as IgA isotypes (IgA aCL and IgA anti-β2GPI) have also been reported, but their clinical relevance is still controversial (3,4).

To date, the pathogenesis of APS has remained elusive. Although the role of T helper (Th) cells in the production of aPL antibodies has long been recognized (5), there are less data on the role of T cells in the development of APS. Studies have shown that the activation of T lymphocytes and the production of corresponding cytokines can be induced in patients with APS through different ways, which can cause an imbalance among immune cells, immune molecules and the immune system, and damage immune homeostasis *in vivo* (6), which is related to thrombosis or pathological pregnancy. It has been reported that vitamin D (VD) has a pleiotropic effect, such as anti-oxidation, preventing inflammatory response, reducing

immune-mediated damage and anticancer (7-10). Low serum VD levels are associated with autoimmune diseases (11). *In vitro* studies have shown that high VD levels directly inhibit T-cell proliferation and cell-cycle progression, inhibit the release of pro-inflammatory factors and transform the Th to the Th2 phenotype (12). This suggests that VD is essential for regulating T cells. In patients with APS, decreased serum VD levels are significantly correlated with thrombosis or obstetric complications (13-17), but their relationship with T cells remains to be further studied. Therefore, it is required to pay attention to the role of the relationship between VD and T cells in APS, which provides a relevant basis for the prevention and treatment of APS-related pathological pregnancy and thrombosis. In the present article, the relevant literature was reviewed to understand the potential mechanistic role of VD in APS protection. At the same time, this review summarizes the progress of VD in the treatment of APS and its possible adverse reactions, providing new insights for the selection of adjuvant therapy for APS.

2. Epidemiology of APS and VD insufficiency or deficiency

The estimated annual incidence of APS is 21 cases per 100,000 individuals, with a prevalence of 50 cases per 100,000 individuals (18). The male-to-female ratio of primary APS is ~1:3.5, and secondary APS is mainly systemic lupus erythematosus (SLE)-related, with a ratio of 1:7 (18). Catastrophic APS accounts for <1% of all APS cases (19). In the normal adult population, the optimal concentration of serum 25-hydroxyVD [25(OH)D] is 30-50 ng/ml (75-125 nmol/l), while concentrations indicating insufficient VD are 20-30 ng/ml (50-75 nmol/l). VD deficiency is defined as levels <20 ng/ml (<50 nmol/l) (1). The reported prevalence of 25(OH)D levels <50 nmol/l (or 20 ng/ml) is estimated to be 24% in the US population and 37% in Canada, with an even higher prevalence in Europe, reaching ~40% (20-23). In a survey of the normal adult population, 67.4% of women had VD deficiency and ~87% of women were affected by VD insufficiency, whereas ~41% of men had VD deficiency, with prevalence rates varying across studies (24). In patients with APS, the total prevalence of VD deficiency and insufficiency was reported to be 32.2 and 61.5%, respectively. The incidence of thrombotic events in VD-deficient patients with APS was 62.9% and the incidence of adverse pregnancy outcomes was 49.5% (13,25).

3. VD and its receptor

VD is a lipophilic steroid hormone, mainly in the forms of VD2 and VD3 (26). VD2 is synthesized by the ultraviolet irradiation of yeast ergosterol, a compound known as ergocalciferol (27). While it cannot be synthesized in the human body, it can be obtained through food sources, such as edible fungi and supplements (28). VD3 is synthesized in the human body by ultraviolet irradiation of 7-dehydrocholesterol in the skin into cholecalciferol. It can also be obtained from fatty fish, eggs and dairy products. VD is absorbed, transported to the liver and hydroxylated, mainly by 25-hydroxylase, and converted to 25(OH)D, which is subsequently bound to VD-binding proteins and transported to the kidney to form 1,25(OH)2D via the action of 1-α25 hydroxylase. Researchers have emphasized that 1,25(OH)2D can also be synthesized through autocrine and paracrine processes in other body tissues (25); 1,25(OH)2D is the active form of VD, which functions through diffusion or endocytosis at target organ sites (29,30). In addition, circulating 25(OH)D is moderately lipophilic, tightly binds to VD-binding proteins, is prevalent at low concentrations, and is present in two structurally similar forms: 25(OH)D3 and 25(OH)D2, but these two molecules are not as well detected as 25(OH)D because of their low levels in the blood (31).

The biological effects of VD are mainly mediated by the nuclear VD receptor (VDR), a member of the nuclear hormone receptor family and a high-affinity ligand-activated transcription factor (32). As a signaling molecule, VDR binds to 1,25(OH)2D and the heterodimer partner, the retinoid X receptor. This complex interacts with specific DNA sequences in the promoter regions of target genes, known as VD response elements, to regulate their expression (33). VDR is distributed in various cells and tissues throughout the body, such as small intestinal epithelial cells, endothelial cells, bone osteoblasts, the large intestine, distal renal tubules and parathyroid glands (34-36). VDR is expressed in almost all immune cells, including monocytes, macrophages, T and B lymphocytes and DCs, where it regulates the differentiation and proliferation of immune cells. However, its expression levels vary, which indicates that VD is involved in the regulation of inflammation and immune responses (37). T cells are one of the target cells of VD, and VD deficiency can lead to immune disorders, increasing the expression of procoagulant factors, proinflammatory cytokines, adhesion molecules and tissue factors (TF) (36). Simultaneously, all these intermediates are associated with thrombus formation and pathological pregnancy through mechanisms such as increased platelet reactivity, endothelial dysfunction and activation of the coagulation cascade and complement system (36). Therefore, VD plays an important role in the regulation of the immune balance and may have therapeutic potential in the pathophysiology of APS-related thrombosis and obstetric complications.

4. VD plays a role in maintaining immune balance in T cells and other immune cells

VD is known to differentially regulate innate immune cell subsets; influence cell maturation, metabolism and antigen presentation; and regulate cytokine production (38-40). Immature DCs usually express more VDR, whereas mature DCs show reduced VDR expression (38). This may indicate that mature DCs produce VD locally upon activation and that VD then acts on immature DCs to regulate the immune response (38,41) (Fig. 1); 1,25(OH)2D can inhibit DC maturation markers, such as CD80/CD86 and CD83 (41,42), increase the production of IL-10 and reduce proinflammatory cytokines (42,43). Thus, 1,25(OH)2D promotes an immature, tolerant DC phenotype (44,45), thereby reducing antigen presentation to T cells; 1,25(OH)2D primarily regulates the proliferation of T and B cells, but studies have found that it plays a more important role in regulating T-cell phenotypes (46,47). After binding to autoantigens,

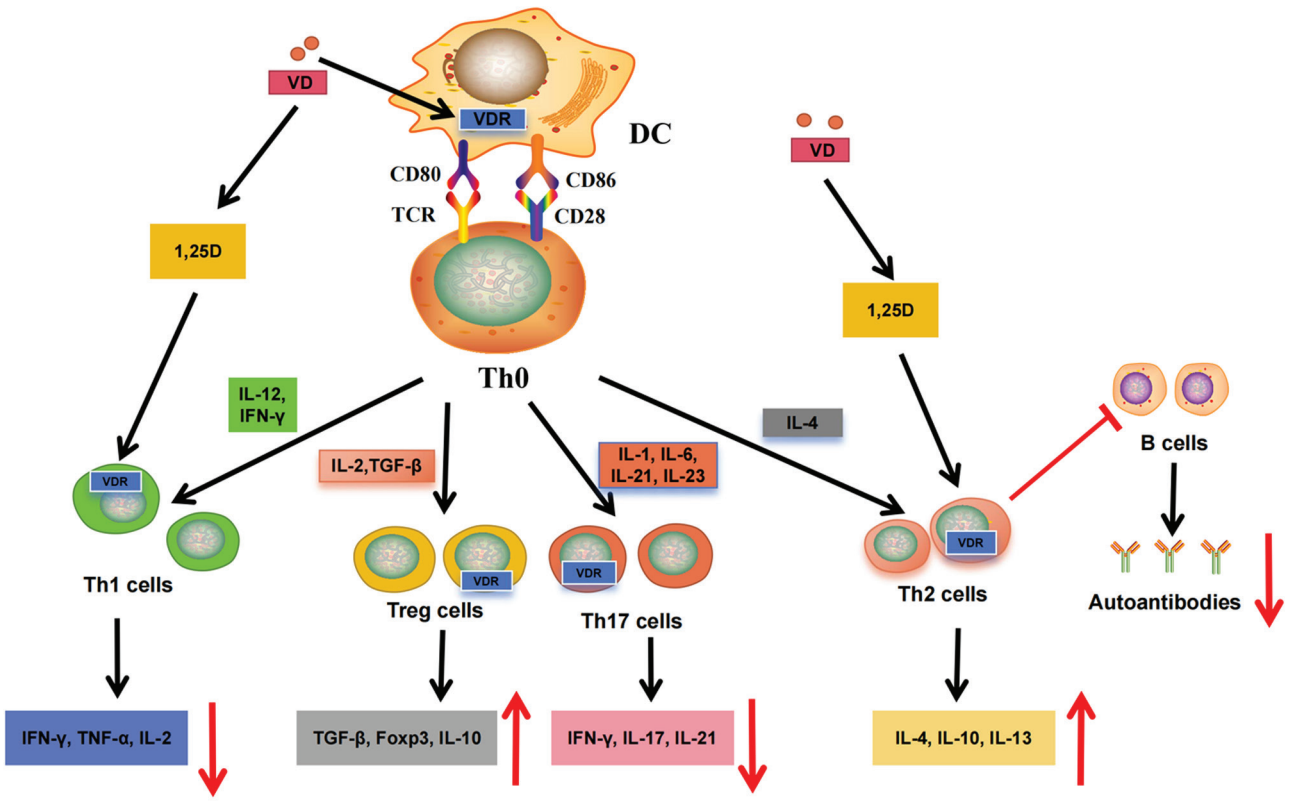

Figure 1. Immunomodulatory balance of T-cell subsets with sufficient VD. After VD and 1,25D bind to the related receptors of DCs, under the action of different cytokines, Th0 cells can promote the differentiation of Th1, Th2, Th17 and Treg cells, but Th2 and Treg cells are the most numerous. At the same time, various cytokines are secreted and the expression of Th2 cytokines and Treg cell cytokines is upregulated. The expression of Th1 and Th17 cytokines was downregulated. At the same time, Th2 cells can inhibit the overactivation of B cells and reduce the formation of autoantibodies. The red T-shaped symbol represents inhibition. The upward red arrow represents upregulation. The downward red arrow represents downregulation. Treg, T-regulatory; Th1, type I T-helper; DC, dendritic cell; VDR, VD receptor; VD, vitamin D; TCR, T-cell receptor; Fox, forkhead box; 1,25D, 1,25(OH)VD.

autoantibodies can be presented to $CD4^+$ Th cells together with major histocompatibility complex class II molecules to stimulate T-cell activation and the adaptive immune response; 1,25(OH)2D reduces the cytotoxic activity of T cells by downregulating the expression of Fas ligands (48). VD also has various effects on Th cells, such as promoting $CD4^+$ Th-cell differentiation, resulting in a reduction in Th1 and Th17 cells (49). Th1 and Th17 subgroups play key roles in different autoimmune diseases by releasing cytokines that drive inflammatory responses. In addition, 1,25(OH)2D reduces the production of Th1-related cytokines [IL-2, tumor necrosis factor (TNF)-α and interferon (IFN)-γ] and Th17-related cytokines (IL-17, IL-21, IL-22) by inhibiting Th1 and Th17 cells (50) (Fig. 1). Simultaneously, $CD4^+$ T cells are polarized toward the Th2 phenotype by upregulating cytokines, such as IL-4 and IL-5 (50). By enhancing the expression of forkhead box P3, the differentiation of Treg and $CD4^+$ T cells involved in maintaining immune tolerance is induced, while levels of IL-10 and transforming growth factor β1 (TGF-β1) are also increased (50,51), thereby reducing the inflammatory response (Fig. 1). Furthermore, Th cells reduce the formation of autoantibodies by inhibiting the differentiation and proliferation of B cells (Fig. 1). The aforementioned findings indicate that VD can prevent the development of autoimmune diseases by regulating the balance between T-cell subpopulations (Th1/Th2/Th17/Treg) (Fig. 1).

5. Potential role of T-cell imbalance caused by insufficient or absent VD in APS pathologic pregnancy

Moderate VD levels are associated not only with pathogen clearance but also with immune regulation in normal pregnancy T-cell subsets. The Th1/Th2 immune response is generally characterized by immunoinflammatory changes that occur during embryo implantation. Th1 cells migrate into the decidua, which is critical for regulating trophoblast invasion and contributes to tissue remodeling and angiogenesis, thereby supporting pregnancy (52). Th1 cells secrete various cytokines, such as IL-2, TNF-α and IFN-γ, which, in addition to providing immune surveillance, prevent excessive invasion of trophoblast cells (53). Under normal conditions, moderate levels of TNF-α protect the placental unit and modulate the adhesion of trophoblast cells to laminin, thereby regulating trophoblast cell invasion (53). In addition to downregulating protease activity and extravillous trophoblastic (EVT) cell apoptosis to prevent excessive EVT invasion, IFN-γ can induce vascular remodeling during the implantation period to better nourish implanted cells (54,55). Therefore, IFN-γ plays a key role in early placental and trophoblast invasion. Toward the end of the implantation period, Th1 immune predominance in the decidua gradually shifts to Th2 predominance. Th2 dominance has been demonstrated during normal pregnancy (56). After Th2 cells infiltrate the decidua basalis, they induce local Th2 dominance through the release of Th2

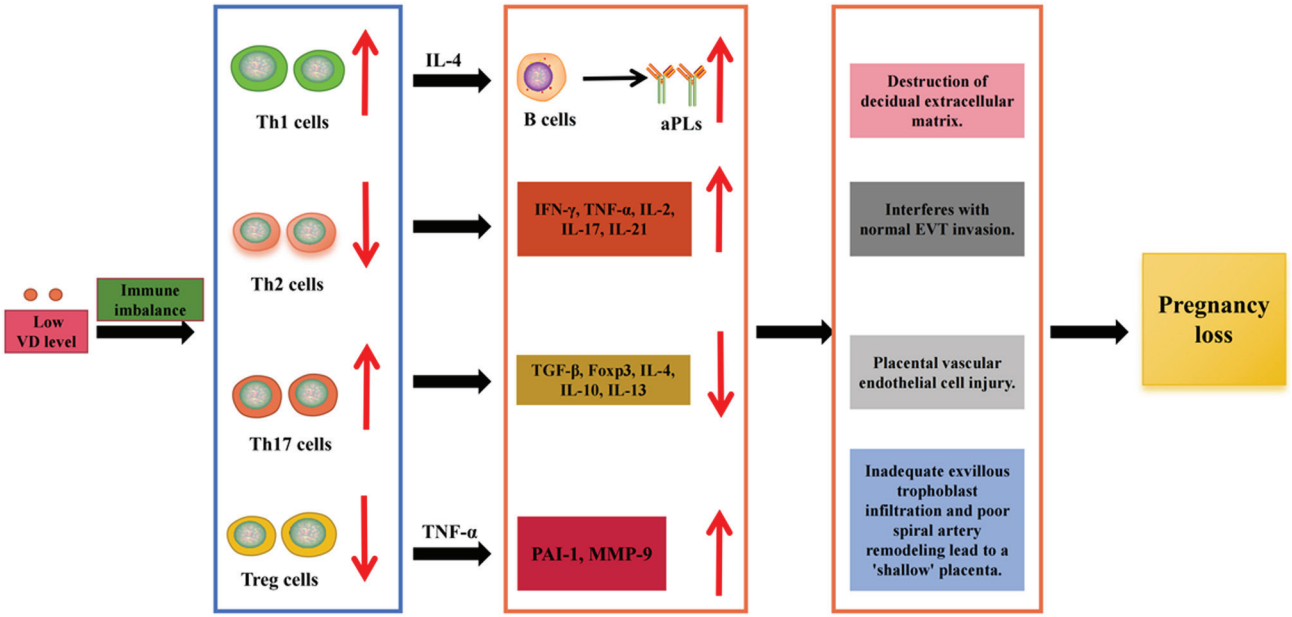

Figure 2. Potential mechanisms of pathological pregnancy caused by low VD levels in patients with antiphospholipid syndrome. When the VD level is low, it can lead to immune disorders, excessive Th1 and Th17 cells, and reduced Th2 and Treg cells, thus overactivating B cells and forming too many aPLs. At the same time, pro-inflammatory factors are too high and anti-inflammatory factors too low, and there is too much PAI-1 and MMP-9, thus leading to placental inflammation and fetal injury. This can eventually lead to loss of the fetus. The upward red arrow represents upregulation and the downward red arrow represents downregulation. PAI-1, plasminogen activator inhibitor-1. MMP-9, matrix metalloproteinase-9; VD, vitamin D; Treg, T-regulatory; Th, T-helper; Fox, forkhead box; aPLs, antiphospholipid antibodies; EVT, extravillous trophoblastic; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; TGF, transforming growth factor.

cytokines (57), such as IL-4, IL-10 and IL-13, which inhibit the development of Th1 and Th17 immunity, promoting allograft tolerance, which favors pregnancy (58). Th17 cells are relatively rare (0.64-1.4%) in the peripheral blood of healthy individuals (59). In the decidua, IL-17$^+$ T-cell counts parallel neutrophil counts, indicating that neutrophil infiltration is closely related to IL-17$^+$ T cells (60), inducing protective immunity against extracellular microorganisms in the uterus, which is associated with immune protection and pregnancy. Following implantation, sufficient VD levels in the decidua promote the differentiation of T-cell subsets into Tregs, which maintain maternal tolerance by inhibiting cytotoxic T and Th1 cells. Tregs can suppress destructive immune responses and prevent autoimmune diseases during pregnancy (61). VD enhances the immunosuppressive function of Tregs; therefore, it can inhibit proinflammatory Th17 cells and related cytokines (such as IL-17), maintaining a Th17/Treg balance (62). This balance facilitates the secretion of growth factors and extracellular matrix remodeling, which supports trophoblastic infiltration, cytotrophoblast development and decidual vessel remodeling (63), thus supporting placental development.

In a healthy human body, sufficient VD is important for embryo implantation, mediating immune tolerance and promoting embryo growth. However, T-cell dysregulation caused by VD insufficiency or deficiency is closely linked to adverse pregnancy outcomes in patients with APS. Insufficient or deficient VD promotes the production of aPLs by B cells and disrupts immune balance, leading to the overexpression of Th1 cytokines (IFN-γ and TNF-α) and the failure of immune tolerance after implantation (64) (Fig. 2). TNF-α increases plasminogen activator inhibitor-1 levels derived from trophoblast cells, reduces trophoblast cell invasion, activates endothelial cells, induces matrix metalloproteinase-9 expression in the decidua and degrades the decidual extracellular matrix, which interferes with normal EVT invasion (65-67) (Fig. 2). IFN-γ has a powerful proinflammatory effect, stimulating chemokine secretion, activating macrophages and increasing phagocytosis, leading to maternal inflammation and subsequent fetal loss (Fig. 2). In addition, these cytokines mediate cytotoxic activity against target cells, which may damage placental vascular endothelial cells (64,68), leading to placental microthrombus formation and subsequent pathological pregnancies (Fig. 2). The high expression of Th1 cytokines in the placentas of patients with VD insufficiency or deficiency, particularly in preeclampsia, suggests that VD exerts a protective effect at the fetomaternal interface (61). After the implantation phase, if the Th1-cell immune advantage is not transferred to a Th2-cell advantage, pathological pregnancy may ensue. However, excessive activation of Th2 cells and the subsequent release of cytokines are not beneficial. The Th2 cytokine IL-4 can induce the activation of autoreactive B cells and the exacerbation of Th2 immunity during pregnancy may worsen autoimmune diseases (69) (Fig. 2). VD deficiency can also lead to abnormal function and reduced numbers of Treg cells in the decidua. This condition is related to insufficient infiltration of extravillous trophoblastic cells and poor remodeling of spiral arteries, which, in turn, results in unstable placental development and a 'shallow' placenta (63). Simultaneously, an overly robust Th17-cell response can induce the activation of decidual natural killer cells and impair the vascular reactivity of the uterine artery, leading to embryo absorption (70). A study showed that, compared with the normal pregnancy group, the proportion of Th17 cells was significantly increased in aborted mice, whereas the proportion of Treg cells and the levels of

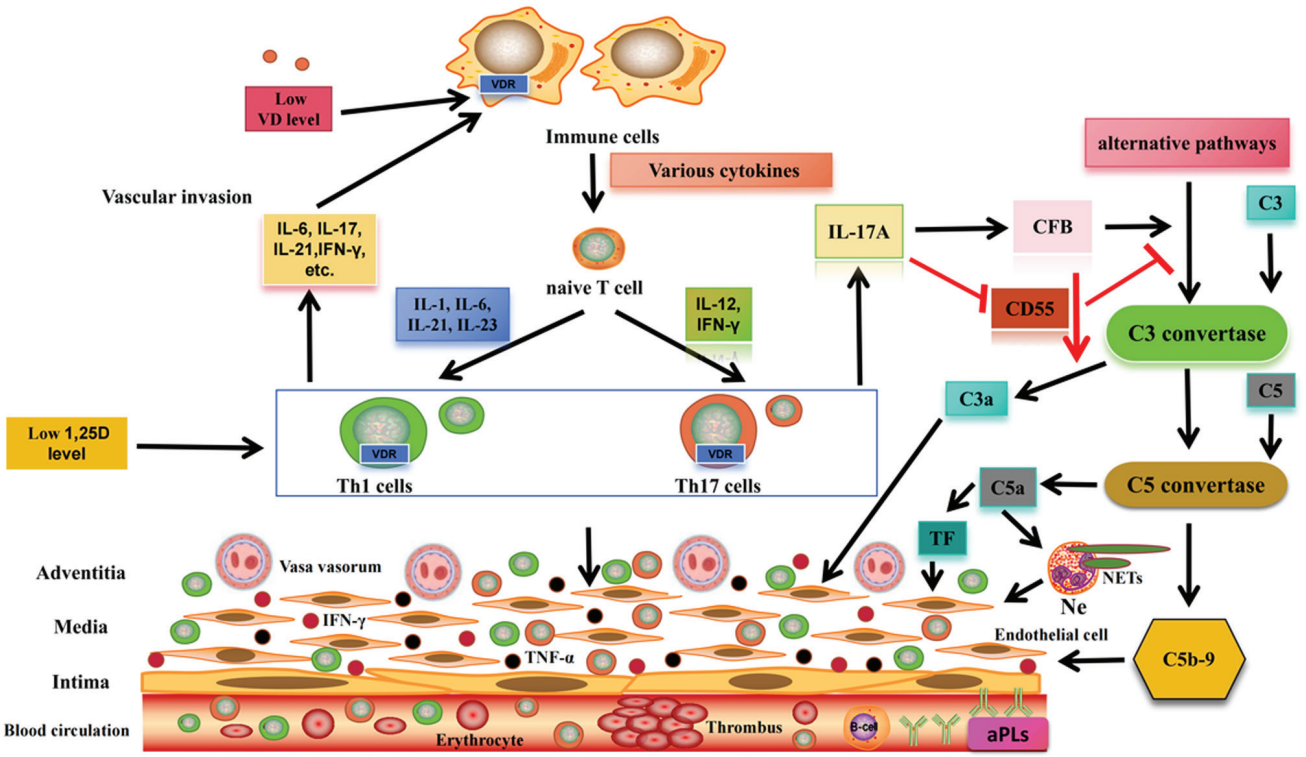

Figure 3. Potential mechanisms of thrombosis caused by low VD levels in patients with antiphospholipid syndrome. aPLs, antiphospholipid antibodies; VDR, VD receptor; VD, vitamin D; IL, interleukin; IFN, interferon; TNF, tumor necrosis factor; TGF, transforming growth factor; C, complement; 1,25D, 1,25(OH)2D; Th, T-helper; Ne, neutrophil; TF, tissue factor; NETs, neutrophil extracellular traps; CFB, complement factor B; C5b-9, complement membrane attack complex.

IL-10 and TGF-β1 were significantly decreased. Following the transplantation of Treg cells from normal pregnant mice into abortion-prone mice, the levels of TGF-β and IL-10 significantly increased, exerting a protective effect on the fetus (63). In addition, transplantation of $CD4^+$ $CD25^+$ Treg-deficient lymphocytes into pregnant T cell-deficient mice resulted in abortion (71). This finding suggests that the absence or insufficiency of Tregs can lead to abortion and that VD insufficiency or deficiency can cause an imbalance in Th1/Th2/Treg/Th17 cells and related cytokines in patients with APS, leading to adverse pregnancy outcomes (Fig. 2).

6. Potential role of T-cell imbalance in thrombosis in APS caused by VD insufficiency or deficiency

In patients with APS, VD deficiency may be closely associated with thrombosis. Normal levels of VD can inhibit endothelial cell angiogenic factors, modulate inflammatory activity, reduce endothelial damage and suppress tissue factor expression, thereby exerting antithrombotic effects. However, when VD deficiency occurs in patients with APS, B cells may become overactivated and differentiate into plasma cells, resulting in the production of more aPL (Fig. 3); aPL recognizes β2GPI and induces plaque-derived T-cell proliferation and increased IFN-γ expression, indicating Th1 cell activation in the artery walls of patients with APS. Local production of IFN-γ and TNF-α following Th1-cell activation may further stimulate these cells to present β2GPI to T cells, driving their differentiation into Th1 effector cells (72), thereby causing endothelial cell damage (Fig. 3). IFN-γ can also enhance calcium flux in neutrophils and the production of reactive oxygen species, leading to the formation of neutrophil extracellular traps and, ultimately, thrombosis (73). In a study examining inflammatory atherosclerotic infiltrates in patients with SLE-APS, researchers identified β2GPI-specific T cells. Among these, 42% were polarized Th1 cells, 38% were Th17/Th1 cells, 15% were polarized Th17 cells and 5% were Th0 cells. Notably, no T cells were polarized into Th2 cells (72). Th2-cell deficiency is an important risk factor for atherosclerosis. Furthermore, most Th cells specifically producing IL-17 in patients with APS were polarized Th17 cells. In the absence of VD, Treg cells lose their inhibitory ability and cannot control the proliferation of $IL\text{-}17^+$ T cells, leading to excessive IL-17 production. IL-17 can induce endothelial cells to secrete proinflammatory cytokines (such as IL-6) and chemokines (including IL-8) and increase adhesion molecule levels, particularly in combination with TNF-α. This promotes leukocyte recruitment and endothelial-cell invasion (73,74). In addition, IL-17A promotes thrombosis by activating tissue factors and reducing anticoagulant mediators, such as thrombomodulin and CD55 (73) (Fig. 3). Deficiency in complement inhibitor CD55 disrupts the balance of the complement system, leading to its activation. When VD levels are <40 ng/ml, CD55 expression is downregulated, whereas complement factor B expression is significantly upregulated, indicating complement system activation and readiness for the membrane attack complex formation stage (75) (Fig. 3). Complement factor B, a component of the complement alternative pathway, is responsible for C3/C5 convertase activity. Its upregulation can lead to the excessive production of complement fragments C3a and C5a. In patients with APS, C5a

mediates tissue factor expression via C5a receptors, promoting procoagulant activity (76). Simultaneously, the expression of complement component C9 is upregulated in response to reduced VD levels, and its sustained upregulation may increase the synthesis of C5b-9 (77). The release of C5a and the formation of C5b-9 result in endothelial cell activation, tissue factor expression, enhanced neutrophil-endothelial cell interactions, neutrophil extracellular trap formation and a lowered threshold for thrombosis. Severe cases may present with extensive microthrombosis, possibly associated with catastrophic APS (78,79) (Fig. 3).

The antithrombotic properties of VD have been studied previously; aPL induces endothelial cell activation through Toll-like receptor 4 (TLR-4)-mediated signal transduction and NF-κB activation, which is associated with APS thrombosis (80). Normal VD levels not only inhibit type I IFN synthesis by blocking TLR-4 signal transduction in inflammatory cells and MYD88 innate immune signal transduction adaptor (MyD88) signaling but also downregulate NF-κB and TF expression, thereby inhibiting thrombosis in APS (81,82). This evidence indicates that insufficient or deficient VD is related to APS thrombosis. In APS, aPLs can also upregulate angiogenic factors and adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1, also known as ELAM-1). VD can inhibit the expression of these molecules and reduce endothelial cell damage (83,84). To further confirm the role of VD, several studies have performed VDR knockouts in mice. After VDR knockout, platelet aggregation increased significantly, the expression of anticoagulant genes (including anticoagulant glucagon protein, antithrombin and thrombomodulin) was downregulated and the expression of the procoagulant TF gene was upregulated, increasing thrombus formation (85). In APS, the absence of VD weakens the peroxisome proliferator-activated receptor (PPAR)γ pathway, increases superoxide production and impairs endothelial progenitor cell repair capacity (86). Simultaneously, the weakened PPARγ pathway enhances angiotensin II-induced reactive oxygen species production and activates NF-κB. This activation induces cytokines, such as TNF-α, IL-6, ICAM-1, VCAM-1 and E-selectin, which promote vascular injury and thrombosis (36).

7. VD insufficiency or deficiency in autoimmune diseases

VD has immunomodulatory properties and sufficient VD generally exerts immunosuppressive effects. Autoimmune diseases are often triggered by external factors (including infections), leading to immune-cell dysregulation, particularly in T cells. This dysregulation results in an imbalance in T-cell subsets, with Th17 and Th1 cells and their associated proinflammatory cytokines becoming significantly elevated, causing excessive immune responses. This strong immune response can attack multiple organs or tissues simultaneously, causing systemic damage. When VD levels are low, autoimmune reactions may become further aggravated, leading to disease progression and exacerbation of clinical symptoms. In recent years, increasing attention has been paid to the impact of low VD levels on autoimmune diseases. Studies have demonstrated the importance of VD in diseases, such as SLE, type 1 diabetes mellitus, multiple sclerosis, autoimmune thyroid disease, rheumatoid arthritis and psoriasis (87-118). In addition to APS, the role of VD in these autoimmune diseases is summarized in Table I. It is worth noting that the type and dose of VD used in the study of different autoimmune diseases may be different (91,92,95,96,99,106,111,112,117).

8. Benefits of VD supplementation in APS

Since the discovery of the VDR in cells across various systems, the pleiotropic effects of VD have garnered much attention. VD supplementation is important for regulating the immune system in APS. In a study, patients were divided into two groups: One received an intensive cholecalciferol regimen (300,000 IU at baseline, maintained at 50,000 IU/month and 850,000 IU/year), and the other received a standard regimen (25,000 IU/month and 300,000 IU/year). The intensive regimen improved the balance of B- and T-cell homeostasis, with an increase in Tregs and Th2 cells and a decrease in Th17, Th1 and memory B cells (111,119). VD supplementation has been shown to correct immune dysregulation in patients with autoimmune diseases. In a VDR knockout mouse model, platelet aggregation was significantly increased, the expression of anticoagulant genes (including glucagon protein, antithrombin and thrombomodulin) was downregulated and the TF gene was upregulated (120). After the injection of exogenous lipopolysaccharide, VDR-knockout mice developed multi-organ thrombosis compared to wild-type controls, suggesting VD's potential as an antithrombotic agent (120); aPL antibodies, such as anti-β2GPI-Abs, can trigger the clotting cascade through multiple mechanisms, including inducing TF expression. VD may act as an immunomodulator with antithrombotic effects. One study evaluated 179 patients with APS and found that 49.5% of patients with APS had VD deficiency (serum levels ≤15 ng/ml), which was significantly associated with thrombosis (58 vs. 42%; $P<0.05$). Neurological and ophthalmic manifestations, pulmonary hypertension, reticular skin changes and skin ulcers were also significantly associated (121). In the same study, anti-β2GPI antibodies from four patients with APS were purified and co-cultured with VD [1,25(OH)2D, 10 nm]. VD inhibited anti-β2GPI antibody-induced TF expression. Furthermore, VD reduced the overexpression of adhesion molecules, such as VCAM-1 and ICAM-1, in cultures incubated with aPL IgG antibodies (121). However, the effects of VD supplementation in thrombotic APS have remained to be studied prospectively. Clinical trials investigating VD supplementation for thrombosis prevention have yielded conflicting results. For instance, in one trial involving patients with metastatic prostate cancer, those receiving high doses of calcitriol had significantly fewer thrombotic events compared to placebo-treated patients, even after adjusting for prior thrombotic history and anticoagulation therapy (122). Conversely, in the general population, large trials have not demonstrated any significant benefits of VD supplementation in preventing venous thromboembolism (123,124).

Currently, APS-related thrombosis therapy, intensive therapy with warfarin and other vitamin K antagonists (VKA), are standard treatments. For the first thrombotic event in APS, switching from a direct oral anticoagulant to warfarin or another VKA is recommended if aPL is triple-positive and direct oral anticoagulants are already in use. The first-line

Table I. Role of VD in different rheumatic diseases.

Disease	T cells in the pathogenesis of disease	Therapeutic mechanism of VD	Dose of VD	Efficacy
T1DM	When VD levels are low, Treg cells inhibit defects in the activity and proliferation of autoreactive CD4+ and CD8+ T cells (87). Promotion of the production of Th1 and Th17 cells, reduction of the ratio of Th1/Th2 and stimulation of the release of pro-inflammatory cytokines such as IFN-γ, IL-1β and TNF-α by immune cells. The differentiation of CD4+ T cells into Th2 and Treg cells was reduced and anti-inflammatory cytokines such as IL-4, IL-10 and TGF-β were weakened (88,89). This results in autoimmune destruction of β-cells in the islets.	Promotes CD4+ T cells to differentiate into Th2 and Treg cells, reduces the production of Th1 and Th17 cells and decreases the proportion of Th1/Th2. Stimulates immune cells to release anti-inflammatory cytokines while weakening the production of proinflammatory cytokines (89,90).	Oral cholecalciferol 4,000 and 10,000 IU/d or 70 IU/kg/d (91,92)	Significant improvement in glycemic control and preservation of pancreatic β-cell function, increase in regulatory T cells. Prevention of its related micro- and macrovascular complications (91-93).
AITD	The imbalance between Th1/Th2 cells and Th17/Treg cells mediates the production of Th1 cytokines (IL-2, IFN-γ and TNF-α), promotes the proliferation and differentiation of B cells into plasma cells and induces the expression of autoantibodies (50,94).	VD inhibits Th1-cell proliferation as well as the Th1-mediated cytokine production (IL-2, IFN-γ and TNF-α) and modulates Th2 cell and cytokines production (IL-4, IL-5 and IL-10) inducing the Th2 phenotype (50). Reduces the proliferation and differentiation of B cells into plasma cells (50).	Oral cholecalciferol (4,000 IU/d) or 50,000 IU VD (95,96).	Interferes with late activation of monocytes and T cells, significantly reducing TgAb and TSH levels (95,96).
PsO	The immune complex activates resident DCs and then releases IL-23 to activate T lymphocytes, promoting differentiation into Th17. IL-16 promotes differentiation into Th1. These cells produce three major cytokines, IL-17, IL-22 and IFN, which promote the proliferation of keratinocytes (97-99).	Inhibits the production of IL-17 and directly inhibits the proliferation of keratinocytes (100).	Oral 1α(OH)D (1.0 μg/d) or VD 5,000 IU/d (99).	Promotes the expression of anti-inflammatory factor (IL-10), decreases the PASI score and plasma homocysteine level and the expression of pro-inflammatory factors (TNF-α, IL-1β and IL-6) (100). It can also significantly improve psoriatic arthritis (101,102).

Table I. Continued.

Disease	T cells in the pathogenesis of disease	Therapeutic mechanism of VD	Dose of VD	Efficacy
RA	T cells secrete cytokines to activate B cells and autoantibody production increases. The Th1- and Th17-cell response increases with the increase of the pro-inflammatory cytokine IL-17. In addition, TNF-α, IL-6 and IL-1 production increase, stimulating synovial cells (103).	VD can inhibit Th17-mediated inflammation and inhibit IL-6 and TNF-β levels, while Th17-inducing cytokines (IL-1β, IL-6 and IL-23) synergistically enhance the pro-regulatory effect of 1,25-(OH)2D3 on the T-cell phenotype (104,105). Decreased Th17-induced osteoclast activity and RA-related bone resorption (104).	8,000-50,000 IUs/wk of oral VD or equivalent or oral 1,25(OH) 2D (106).	Significant improvement in the DAS28, ESR and tender joint count but not in the pain VAS (106,107).
SLE	SLE is characterized by hyperfunction of Th1 and Th2 cells. Cytokines secreted by Th1 cells (TNF-α, IL-2, IFN-γ) participate in the activation of CD8+ T cells. Th2 cytokines (such as IL-4, IL-10, etc.) can cause excessive activation of B cells, produce autoantibodies and cause tissue damage (108,109). Th17/Treg cell imbalance allows Th17 cells to enter inflammatory tissues, such as the kidney, and promotes inflammation by increasing the production of cytokine (IL-17) (108,110).	Improved naïve CD4+ T cells, regulatory T cells; reduced Th1 and Th17 cells, memory B cells, anti-DNA antibodies (111).	Oral Cholecalciferol, 100,000 IU/wk or ergocalciferol, 50,000 IU/wk, calcium/ VD 200 IU/twice daily. (111,112).	Decreased SLE disease activity and fatigue symptoms (113,114). Reduced SELENA-SLEDAI, decreased urine protein-to-creatinine ratio (111).
MS	When the VD level is insufficient, T-cell subsets are unbalanced, Treg-cell activity is inhibited, and Th1/Th17-cell activity is enhanced, which increases the release of pro-inflammatory factors and decreases the anti-inflammatory factors. These immune cells and inflammatory factors can damage the nervous system (115).	VD upregulates Treg-cell activity, downregulates Th1/Th17-cell activity, decreases the release of pro-inflammatory factors (IL-2, IL-17, IFN-γ and TNF-α) and increases the release of anti-inflammatory factors (IL-4, IL-10 and TGF-β) (115,116).	Oral 20,000 IU/d (117).	Slight trends of reduced annual recurrence, better MRI results and lower EDSS progression (117,118).

AIH, autoimmune hepatitis; AITD, autoimmune thyroid disorders; DC, dendritic cell; RA, rheumatoid arthritis; PsO, psoriasis; MS, multiple sclerosis; T1DM, type 1 diabetes; VD, vitamin D; TgAb, antithyroglobulin; IL, interleukin; Th, T-helper; Treg. T-regulatory; TSH, thyroid-stimulating hormone; PASI, psoriasis area and severity index; TNF-α, tumor necrosis factor α; IL, interleukin; IFN, interferon; DAS28; Disease Activity Score 28; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale; SELENA-SLEDAI, safety of estrogens in lupus erythematosus national assessment-systemic lupus erythematosus disease activity index; MRI, magnetic resonance imaging; EDSS, expanded disability status scale; wk, week; d, day.

Table II. Possible manifestations of vitamin D poisoning.

Manifestations in different systems or organs	Symptoms or signs
Neuropsychiatric	Cognitive disturbances, drowsiness, confusion, apathy, psychosis, depression, stupor and coma
Gastrointestinal	Recurrent vomiting, abdominal pain, polydipsia, anorexia, constipation and peptic ulcers to pancreatitis
Cardiovascular	Hypertension, shortened QT interval, ST segment elevation, bradyarrhythmias, first degree heart block
Renal system	Polyuria, polydipsia, dehydration, hypercalciuria, nephrolithiasis, nephrocalcinosis and renal failure
Eyes	Keratopathy
Ears	Hearing impairment or loss
Joints	Periarticular calcinosis, pain, limited movement
Vascular system	Widespread vascular calcification

treatment for arterial and small-vessel thrombosis should be VKA (125). Low-dose aspirin and moderate-intensity anticoagulant therapy are recommended (126). For patients with recurrent thrombosis, heparin (including enoxaparin) at a dose of 1.5 mg/kg administered via subcutaneous injection is recommended (127), followed by anticoagulant therapy with warfarin, with a target international normalized ratio of 2.0 to 3.0 (128). Heparin not only inhibits the activation of T cells and neutrophils but also suppresses complement activation. VD has effects similar to those of an anticoagulant (including heparin), such as immune modulation, inhibition of T-cell overactivation and suppression of complement activation. In addition, supplementing VD as an adjunctive therapy for APS-related thrombosis has additional effects (125). The central role of inflammation in aPL-mediated thrombosis supports VD's potential as a treatment for APS (129). Among its many roles, VD has an immunomodulatory effect on inflammatory activity, inhibits the overactivation of monocytes, thereby reducing endothelial damage, and suppresses the expression of angiogenic factors and TF in endothelial cells (14,125). VD can also inhibit TLR-4, block the signaling pathway of the adaptor protein MyD88 and its downstream NF-κB in inflammatory cells, suppress inflammation and immune responses, and upregulate thrombomodulin (14,125), thus playing an antithrombotic role.

Regarding adverse pregnancies, the total prevalence of aPL was significantly higher in women with recurrent pregnancy loss (RPL) in the VD insufficiency or deficiency groups than in the normal VD group. VD deficiency is more common in patients with RPL having APS, and these patients are at greater risk of autoimmune abnormalities, including APS (130). For patients with insufficient or deficient VD combined with RPL, studies have found no significant difference in the proportion of Th1/Th2 cytokine-expressing $CD3^+/CD4^+$ Th cells when VD supplementation is administered compared with patients with normal VD levels combined with RPL (129). In another study, 35 patients with RPL and insufficient VD levels were treated with 0.5 μg/day of 1,25(OH)2D for 2 months. The proportion of TNF-α-producing Th cells decreased significantly after treatment compared with that before treatment (131); 1,25(OH)2D can reduce IFN-γ production and the number of IFN-γ^+ $CD4^+$ T cells (132). In addition, after treatment with 3.3 million IU of intramuscular VD injections in patients with RPL, the number of Th17 cells in the treatment group was significantly lower than that in the control group and the ratio of Th17/Treg cells decreased significantly more than that in the control group (133). In another study, patients with RPL having VD deficiency were administered 2,000 IU of oral VD capsules per day. After 2 months of treatment, the Treg/Th17 ratio was significantly higher than that in women who did not receive VD supplementation (134). These findings suggest that VD supplementation can provide immunomodulatory benefits in RPL and may serve as an alternative therapy for APS-related thrombosis and adverse pregnancies.

At present, there are certain limitations to the efficacy of VD supplementation in patients with ASP. First, of the existing articles, most of them focus on pre-clinical studies (*in vitro* studies and animal experiments), and there are also certain retrospective studies, but the changes in serum 25(OH)D levels after VD supplementation are mainly mentioned (135,136). There may be differences between preclinical studies and human studies, such as the impact on aPL (121,135), and retrospective studies often lack a lot of information, e.g. T-cell subsets were not reviewed to analyze which T-cell subtypes were affected by VD. Therefore, it is esteemed that there will be more large-scale prospective studies in the future to investigate the efficacy of VD in the treatment of patients with APS, particularly with regard to the effects of VD on T cells (both in thrombosis and obstetric complications). In addition, a meta-analysis was conducted on the basis of many large-scale prospective studies, so as to better evaluate the optimal dose range, safety and efficacy of VD in patients with APS, particularly the effects of correcting the T-cell imbalance after VD supplementation on thrombosis and obstetric complications, further supporting the present conclusions and making them more general.

9. VD-related adverse reactions

Due to the increasing awareness of VD's benefits, supplements are being used more widely. Currently, there is no evidence that

increasing the daily dose of VD to 50 μg (2,000 IU) causes serious adverse effects in the general population. Considering that the minimum beneficial dose for bone health is 20 μg (800 IU), it is reasonable to recommend a daily dose of 20 to 50 μg (800-2,000 IU). These recommendations are supported by scholars, with evidence levels ranging from 2 to 4 (137). In 2011, the Institute of Medicine reported the upper limits of VD intake, highlighting the possible side effects of short-term high-dose VD use and long-term VD supplementation. However, toxicity may occur when serum 25(OH)D levels in patients are ≥150 ng/ml (375 nmol/l). Acute VD toxicity is usually caused by a serum 25(OH)D concentration of >150 ng/ml (375 nmol/l) following doses >10,000 IU/day. Long-term use of doses >4,000 IU/day may lead to chronic VD toxicity, resulting in 25(OH)D concentrations ranging from 50 to 150 ng/ml (138). The manifestations of VD poisoning are typically multisystemic and are primarily due to hypercalcemia. Signs and symptoms of poisoning are presented in Table II (118,139-141). Generally speaking, the more common side effects are on the gastrointestinal tract, such as vomiting, nausea, thirst, anorexia and constipation (118,139-141).

In a study from Brazil, 21 patients who took cholecalciferol supplementation for an average of 1 year (average dose, 87,000 IU/day) were enrolled. Of note, 17 patients experienced relapses, new MRI lesions or increased disabilities. The authors also observed direct side effects of VD supplementation, including gastrointestinal symptoms, seizures, severe hypercalcemia, kidney failure, kidney stones and renal calcification (142). In another case, a patient who received high-dose cholecalciferol for 20 months (78 million IU cumulatively, 130,000 IU/day on average) developed nausea, vomiting, muscle weakness, reversible hypercalcemia and acute kidney injury (143). In addition, high VD doses and specific treatment regimens may increase adverse effects. For instance, a study of 2,256 women >70 years of age administered 500,000 IU of VD per year (~1,400 IU/day) reported a 26% increase in fracture risk within the first 3 months after dosing (144). Similarly, annual intramuscular injections of 300,000 IU of VD (~820 IU/day) were associated with a 49% increase in hip fracture risk (145). A case study from Brazil reported a 19-year-old male hospitalized for anorexia, nausea and vomiting after consuming 300 ml of an enteral formulation containing vitamin A, D and E (totaling 5,000,000 IU of VD). Laboratory tests revealed a serum 25(OH)D level of 150 ng/ml, total calcium of 14.8 mg/dl (normal reference range: 8.4-11.0 mg/dl) and serum creatinine of 2.88 mg/dl (normal reference range: 0.9-1.3 mg/dl). Hypercalcemia and acute kidney injury were treated successfully with fluid rehydration, diuretics and zoledronic acid (146). In a randomized clinical trial, participants were divided into three groups: A low-dose control group receiving 24,000 IU/month of VD3, a group receiving 60,000 IU/month and a group receiving 24,000 IU/month plus 300 μg calcifediol. Over 12 months, the group receiving 60,000 IU/month had a higher risk of falls compared with that of the control group (147). Although VD is generally safe, adverse events can occur; therefore, clinicians should carefully monitor patients receiving supplementation.

In addition, there are of course other causes of VD poisoning events, e.g., an Italian study reported 3 cases of severe hypercalcemia and renal insufficiency associated with VD poisoning. The patients had been treated with VD preparations; the prescribed dose was 600 IU, but the actual content was 52,800 IU, which was related to formulation errors and long-term use. The study highlights the need to prepare supplements such as VD according to precise rules in order to make the amount of the potentially toxic ingredient the correct and safe dose (148). The toxicity of VD has also been linked to high doses of over-the-counter supplements that are taken frequently and incorrectly prescribed by doctors as well as incorrectly instructed by pharmacists, e.g., by providing 50,00 IU prescriptions daily instead of once a week. For instance, a patient with MS who initiated a self-prescribing change increased his VD3 intake from 8,000 to 88,000 IU/day over four years, resulting in an upward trend in hypercalcaemia and creatinine rates (149).

10. Conclusion

APS is an autoimmune disease that causes pathological pregnancy and thrombosis, significantly affecting patients' quality of life and increasing their economic burden. T-cell immune disorders caused by VD deficiency are critical factors in the pathogenesis of APS thrombosis and adverse pregnancy outcomes. VD has potent immunomodulatory effects, helping to regulate T-cell subsets, exerting antithrombotic effects and preventing adverse pregnancy outcomes in APS. VD supplementation is a promising and beneficial treatment for APS. However, studies on the correction of T-cell imbalances through VD supplementation in patients with APS are still lacking, and the specific mechanisms at the molecular and signaling pathway levels remain elusive. Large-scale prospective studies are needed to confirm VD's efficacy and mechanisms in APS treatment. Furthermore, the optimal dosage and safety of VD supplementation should be further explored to develop new therapeutic strategies for APS.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

RH, YY and CW wrote the manuscript. XH, DM, RH, YY and YH collected the references and created the tables and figures. JL and XH conceptualised and designed the study. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Płudowski P, Kos-Kudła B, Walczak M, Fal A, Zozulińska-Ziółkiewicz D, Sieroszewski P, Peregud-Pogorzelski J, Lauterbach R, Targowski T, Lewiński A, *et al*: Guidelines for preventing and treating vitamin D deficiency: A 2023 update in Poland. Nutrients 15: 695, 2023.
2. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, Derksen RH, DE Groot PG, Koike T, Meroni PL, *et al*: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 4: 295-306, 2006.
3. Sciascia S, Amigo MC, Roccatello D and Khamashta M: Diagnosing antiphospholipid syndrome: 'extra-criteria' manifestations and technical advances. Nat Rev Rheumatol 13: 548-560, 2017.
4. Sciascia S, Sanna G, Murru V, Roccatello D, Khamashta MA and Bertolaccini ML: Anti-prothrombin (aPT) and anti-phosphatidylserine/prothrombin (aPS/PT) antibodies and the risk of thrombosis in the antiphospholipid syndrome. A systematic review. Thromb Haemost 111: 354-364, 2014.
5. Kravvariti E, Konstantonis G, Tentolouris N, Sfikakis PP and Tektonidou MG: Carotid and femoral atherosclerosis in antiphospholipid syndrome: Equivalent risk with diabetes mellitus in a case-control study. Semin Arthritis Rheum 47: 883-889, 2018.
6. Tektonidou MG, Vlachogiannis NI and Sfikakis PP: T cell involvement in antiphospholipid syndrome. Clin Immunol 263: 110218, 2024.
7. Della Nera G, Sabatino L, Gaggini M, Gorini F and Vassalle C: Vitamin D determinants, status, and antioxidant/anti-inflammatory-related effects in cardiovascular risk and disease: Not the last word in the controversy. Antioxidants (Basel) 12: 948, 2023.
8. Aggeletopoulou I, Marangos M, Assimakopoulos SF, Mouzaki A, Thomopoulos K and Triantos C: Vitamin D and microbiome: molecular interaction in inflammatory bowel disease pathogenesis. Am J Pathol 193: 656-668, 2023.
9. Muñoz A and Grant WB: Vitamin D and cancer: An historical overview of the epidemiology and mechanisms. Nutrients 14: 1448, 2022.
10. Carlberg C and Muñoz A: An update on vitamin D signaling and cancer. Semin Cancer Biol 79: 217-230, 2022.
11. Ao T, Kikuta J and Ishii M: The effects of vitamin D on immune system and inflammatory diseases. Biomolecules 11: 1624, 2021.
12. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF and O'Garra A: 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J Immunol 167: 4974-4980, 2001.
13. Zhao H, Wei X and Yang X: A novel update on vitamin D in recurrent pregnancy loss (Review). Mol Med Rep 23: 382, 2021.
14. Sayar Z, Moll R, Isenberg D and Cohen H: Thrombotic antiphospholipid syndrome: A practical guide to diagnosis and management. Thromb Res 198: 213-221, 2021.
15. Shah R, Mohammed YN, Koehler TJ, Kaur J, Toufeili M, Pulipati P, Alqaysi A, Khan A, Khalid M, Lee Y, *et al*: Antiphospholipid antibodies and vitamin D deficiency in COVID-19 infection with and without venous or arterial thrombosis: A pilot case-control study. PLoS One 17: e0269466, 2022.
16. Zhang H, Ding X, Hu X, Cai YX, Chen H, Sun C, Chen J, Li X, Zheng Z, Liao T, *et al*: Associations between 25 hydroxyvitamin D concentration and spontaneous abortion. BMC Public Health 24: 1858, 2024.
17. Chen C, Wang S, Zhang C, Wu X, Zhou L, Zou X, Guan T, Zhang Z and Hao J: Association between serum vitamin D level during pregnancy and recurrent spontaneous abortion: A systematic review and meta-analysis. Am J Reprod Immunol 88: e13582, 2022.
18. Duarte-García A, Pham MM, Crowson CS, Amin S, Moder KG, Pruthi RK, Warrington KJ and Matteson EL: The epidemiology of antiphospholipid syndrome: A population-based study. Arthritis Rheumatol 71: 1545-1552, 2019.
19. Petri M: Antiphospholipid syndrome. Transl Res 225: 70-81, 2020.
20. Cashman KD, Dowling KG, Škrabáková Z, Gonzalez-Gross M, Valtueña J, De Henauw S, Moreno L, Damsgaard CT, Michaelsen KF, Mølgaard C, *et al*: Vitamin D deficiency in Europe: Pandemic? Am J Clin Nutr 103: 1033-1044, 2016.
21. Cashman KD: Vitamin D deficiency: defining, prevalence, causes, and strategies of addressing. Calcif Tissue Int 106: 14-29, 2020.
22. Sarafin K, Durazo-Arvizu R, Tian L, Phinney KW, Tai S, Camara JE, Merkel J, Green E, Sempos CT and Brooks SP: Standardizing 25-hydroxyvitamin D values from the Canadian health measures survey. Am J Clin Nutr 102: 1044-1050, 2015.
23. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, Martucci G, Pilz S and Malle O: Vitamin D deficiency 2.0: An update on the current status worldwide. Eur J Clin Nutr 74: 1498-1513, 2020.
24. Md Isa Z, Mohd Nordin NR, Mahmud MH and Hashim S: An Update on vitamin D deficiency status in Malaysia. Nutrients 14: 567, 2022.
25. Islam MA, Ahmed S, Sultana S, Alam SS, Hossan T, Gouda W, Alsaqabi F, Hassan R and Kotyla PJ: Vitamin D status in patients with primary antiphospholipid syndrome (PAPS): A systematic review and meta-analysis. Antibodies (Basel) 13: 22, 2024.
26. Fernando M, Ellery SJ, Marquina C, Lim S, Naderpoor N and Mousa A: Vitamin D-binding protein in pregnancy and reproductive health. Nutrients 12: 1489, 2020.
27. Jäpelt RB and Jakobsen J: Vitamin D in plants: A review of occurrence, analysis, and biosynthesis. Front Plant Sci 4: 136, 2013.
28. Tsuprykov O, Chen X, Hocher CF, Skoblo R, Yin L and Hocher B: Why should we measure free 25(OH) vitamin D? J Steroid Biochem Mol Biol 180: 87-104, 2018.
29. Al-Ishaq RK, Kubatka P, Brozmanova M, Gazdikova K, Caprnda M and Büsselberg D: Health implication of vitamin D on the cardiovascular and the renal system. Arch Physiol Biochem 127: 195-209, 2021.
30. Keane JT, Elangovan H, Stokes RA and Gunton JE: Vitamin D and the liver-correlation or cause? Nutrients 10: 496, 2018.
31. de Paula FJA and Rosen CJ: Vitamin D safety and requirements. Arch Biochem Biophys 523: 64-72, 2012.
32. Zmijewski MA and Carlberg C: Vitamin D receptor(s): In the nucleus but also at membranes? Exp Dermatol 29: 876-884, 2020.
33. Arora J, Wang J, Weaver V, Zhang Y and Cantorna MT: Novel insight into the role of the vitamin D receptor in the development and function of the immune system. J Steroid Biochem Mol Biol 219: 106084, 2022.
34. Khundmiri SJ, Murray RD and Lederer E: PTH and vitamin D. Compr Physiol 6: 561-601, 2016.
35. Li YC, Chen Y and Du J: Critical roles of intestinal epithelial vitamin D receptor signaling in controlling gut mucosal inflammation. J Steroid Biochem Mol Biol 148: 179-183, 2015.
36. Mohammad S, Mishra A and Ashraf MZ: Emerging role of vitamin D and its associated molecules in pathways related to pathogenesis of thrombosis. Biomolecules 9: 649, 2019.
37. Battault S, Whiting SJ, Peltier SL, Sadrin S, Gerber G and Maixent JM: Vitamin D metabolism, functions and needs: From science to health claims. Eur J Nutr 52: 429-441, 2013.
38. Hewison M, Freeman L, Hughes SV, Evans KN, Bland R, Eliopoulos AG, Kilby MD, Moss PA and Chakraverty R: Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J Immunol 170: 5382-5390, 2003.
39. Fritsche J, Mondal K, Ehrnsperger A, Andreesen R and Kreutz M: Regulation of 25-hydroxyvitamin D3-1 alpha-hydroxylase and production of 1 alpha,25-dihydroxyvitamin D3 by human dendritic cells. Blood 102: 3314-3316, 2003.
40. Harrison SR, Li D, Jeffery LE, Raza K and Hewison M: Vitamin D, autoimmune disease and rheumatoid arthritis. Calcif Tissue Int 106: 58-75, 2020.
41. Hewison M, Zehnder D, Chakraverty R and Adams JS: Vitamin D and barrier function: A novel role for extra-renal 1 alpha-hydroxylase. Mol Cell Endocrinol 215: 31-38, 2004.
42. Penna G and Adorini L: 1 Alpha,25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. J Immunol 164: 2405-2411, 2000.

43. Bartels LE, Jørgensen SP, Agnholt J, Kelsen J, Hvas CL and Dahlerup JF: 1,25-dihydroxyvitamin D3 and dexamethasone increase interleukin-10 production in CD4+ T cells from patients with Crohn's disease. Int Immunopharmacol 7: 1755-1764, 2007.
44. Széles L, Keresztes G, Töröcsik D, Balajthy Z, Krenács L, Póliska S, Steinmeyer A, Zuegel U, Pruenster M, Rot A and Nagy L: 1,25-dihydroxyvitamin D3 is an autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. J Immunol 182: 2074-2083, 2009.
45. Piemonti L, Monti P, Sironi M, Fraticelli P, Leone BE, Dal Cin E, Allavena P and Di Carlo V: Vitamin D3 affects differentiation, maturation, and function of human monocyte-derived dendritic cells. J Immunol 164: 4443-4451, 2000.
46. Hewison M: Vitamin D and immune function: An overview. Proc Nutr Soc 71: 50-61, 2012.
47. Cantorna MT, Snyder L, Lin YD and Yang L: Vitamin D and 1,25(OH)2D regulation of T cells. Nutrients 7: 3011-3021, 2015.
48. Cippitelli M, Fionda C, Di Bona D, Di Rosa F, Lupo A, Piccoli M, Frati L and Santoni A: Negative regulation of CD95 ligand gene expression by vitamin D3 in T lymphocytes. J Immunol 168: 1154-1166, 2002.
49. Xie Z, Chen J, Zheng C, Wu J, Cheng Y, Zhu S, Lin C, Cao Q, Zhu J and Jin T: 1,25-dihydroxyvitamin D3-induced dendritic cells suppress experimental autoimmune encephalomyelitis by increasing proportions of the regulatory lymphocytes and reducing T helper type 1 and type 17 cells. Immunology 152: 414-424, 2017.
50. Bellan M, Andreoli L, Mele C, Sainaghi PP, Rigamonti C, Piantoni S, De Benedittis C, Aimaretti G, Pirisi M and Marzullo P: Pathophysiological role and therapeutic implications of vitamin D in autoimmunity: Focus on chronic autoimmune diseases. Nutrients 12: 789, 2020.
51. Zhou Q, Qin S, Zhang J, Zhon L, Pen Z and Xing T: $1,25(OH)_2D_3$ induces regulatory T cell differentiation by influencing the VDR/PLC-γ1/TGF-β1/pathway. Mol Immunol 91: 156-164, 2017.
52. Germain SJ, Sacks GP, Sooranna SR, Sargent IL and Redman CW: Systemic inflammatory priming in normal pregnancy and preeclampsia: The role of circulating syncytiotrophoblast microparticles. J Immunol 178: 5949-5956, 2007.
53. Torchinsky A, Shepshelovich J, Orenstein H, Zaslavsky Z, Savion S, Carp H, Fain A and Toder V: TNF-alpha protects embryos exposed to developmental toxicants. Am J Reprod Immunol 49: 159-168, 2003.
54. Piccinni MP, Raghupathy R, Saito S and Szekeres-Bartho J: Cytokines, hormones and cellular regulatory mechanisms favoring successful reproduction. Front Immunol 12: 717808, 2021.
55. Casazza RL, Lazear HM and Miner JJ: Protective and pathogenic effects of interferon signaling during pregnancy. Viral Immunol 33: 3-11, 2020.
56. Yang X, Tian Y, Zheng L, Luu T and Kwak-Kim J: The update immune-regulatory role of pro- and anti-inflammatory cytokines in recurrent pregnancy losses. Int J Mol Sci 24: 132, 2022.
57. Michimata T, Tsuda H, Sakai M, Fujimura M, Nagata K, Nakamura M and Saito S: Accumulation of CRTH2-positive T-helper 2 and T-cytotoxic 2 cells at implantation sites of human decidua in a prostaglandin D(2)-mediated manner. Mol Hum Reprod 8: 181-187, 2002.
58. Mitchell RE, Hassan M, Burton BR, Britton G, Hill EV, Verhagen J and Wraith DC: IL-4 enhances IL-10 production in Th1 cells: Implications for Th1 and Th2 regulation. Sci Rep 7: 11315, 2017.
59. Nakashima A, Ito M, Yoneda S, Shiozaki A, Hidaka T and Saito S: Circulating and decidual Th17 cell levels in healthy pregnancy. Am J Reprod Immunol 63: 104-109, 2010.
60. Cua DJ and Tato CM: Innate IL-17-producing cells: The sentinels of the immune system. Nat Rev Immunol 10: 479-489, 2010.
61. Cyprian F, Lefkou E, Varoudi K and Girardi G: Immunomodulatory effects of vitamin D in pregnancy and beyond. Front Immunol 10: 2739, 2019.
62. Minton K: Vitamin D shuts down T cell-mediated inflammation. Nat Rev Immunol 22: 1, 2022.
63. Zhang H, Wang S, Tuo L, Zhai Q, Cui J, Chen D and Xu D: Relationship between maternal vitamin D levels and adverse outcomes. Nutrients 14: 4230, 2022.
64. Schröder-Heurich B, Springer CJP and von Versen-Höynck F: Vitamin D effects on the immune system from periconception through pregnancy. Nutrients 12: 1432, 2020.
65. Renaud SJ, Postovit LM, Macdonald-Goodfellow SK, McDonald GT, Caldwell JD and Graham CH: Activated macrophages inhibit human cytotrophoblast invasiveness in vitro. Biol Reprod 73: 237-243, 2005.
66. Seki H, Matuoka K, Inooku H and Takeda S: TNF-alpha from monocyte of patients with pre-eclampsia-induced apoptosis in human trophoblast cell line. J Obstet Gynaecol Res 33: 408-416, 2007.
67. Lockwood CJ, Oner C, Uz YH, Kayisli UA, Huang SJ, Buchwalder LF, Murk W, Funai EF and Schatz F: Matrix metalloproteinase 9 (MMP9) expression in preeclamptic decidua and MMP9 induction by tumor necrosis factor alpha and interleukin 1 beta in human first trimester decidual cells. Biol Reprod 78: 1064-1072, 2008.
68. Raphael I, Nalawade S, Eagar TN and Forsthuber TG: T cell subsets and their signature cytokines in autoimmune and inflammatory diseases. Cytokine 74: 5-17, 2015.
69. Jara LJ, Medina G, Cruz-Dominguez P, Navarro C, Vera-Lastra O and Saavedra MA: Risk factors of systemic lupus erythematosus flares during pregnancy. Immunol Res 60: 184-192, 2014.
70. Travis OK, White D, Pierce WA, Ge Y, Stubbs CY, Spradley FT, Williams JM and Cornelius DC: Chronic infusion of interleukin-17 promotes hypertension, activation of cytolytic natural killer cells, and vascular dysfunction in pregnant rats. Physiol Rep 7: e14038, 2019.
71. Idali F, Rezaii-Nia S, Golshahi H, Fatemi R, Naderi MM, Goli LB, Zarnani AH and Jeddi-Tehrani M: Adoptive cell therapy with induced regulatory T cells normalises the abortion rate in abortion-prone mice. Reprod Fertil Dev 33: 220-228, 2021.
72. Benagiano M, Borghi MO, Romagnoli J, Mahler M, Bella CD, Grassi A, Capitani N, Emmi G, Troilo A, Silvestri E, *et al*: Interleukin-17/Interleukin-21 and interferon-γ producing T cells specific for β2 glycoprotein I in atherosclerosis inflammation of systemic lupus erythematosus patients with antiphospholipid syndrome. Haematologica 104: 2519-2527, 2019.
73. Robert M, Miossec P and Hot A: The Th17 pathway in vascular inflammation: Culprit or consort? Front Immunol 13: 888763, 2022.
74. Cremoni M, Brglez V, Perez S, Decoupigny F, Zorzi K, Andreani M, Gérard A, Boyer-Suavet S, Ruetsch C, Benzaken S, *et al*: Th17-immune response in patients with membranous nephropathy is associated with thrombosis and relapses. Front Immunol 11: 574997, 2020.
75. Rawal N and Pangburn MK: Formation of high affinity C5 convertase of the classical pathway of complement. J Biol Chem 278: 38476-38483, 2003.
76. Liu X, Hu Y, Yu X, Tan Y, Yu F, Chen M and Zhao M: Differential contributions of the C5b-9 and C5a/C5aR pathways to microvascular and macrovascular thrombosis in complement-mediated thrombotic microangiopathy patients. Clin Immunol 259: 109871, 2024.
77. Li H, Xie X, Bai G, Qiang D, Zhang L, Liu H, He Y, Tang Y and Li L: Vitamin D deficiency leads to the abnormal activation of the complement system. Immunol Res 71: 29-38, 2023.
78. Skendros P, Mitsios A, Chrysanthopoulou A, Mastellos DC, Metallidis S, Rafailidis P, Ntinopoulou M, Sertaridou E, Tsironidou V, Tsigalou C, *et al*: Complement and tissue factor-enriched neutrophil extracellular traps are key drivers in COVID-19 immunothrombosis. J Clin Invest 130: 6151-6157, 2020.
79. Chen Y, Li X, Lin X, Liang H, Liu X, Zhang X, Zhang Q, Zhou F, Yu C, Lei L and Xiu J: Complement C5a induces the generation of neutrophil extracellular traps by inhibiting mitochondrial STAT3 to promote the development of arterial thrombosis. Thromb J 20: 24, 2022.
80. Borghi MO, Raschi E, Grossi C, Chighizola CB and Meroni PL: Toll-like receptor 4 and β2 glycoprotein I interaction on endothelial cells. Lupus 23: 1302-1304, 2014.
81. Matias ML, Romao-Veiga M, Ribeiro VR, Nunes PR, Gomes VJ, Devides AC, Borges VT, Romagnoli GG, Peracoli JC and Peracoli MT: Progesterone and vitamin D downregulate the activation of the NLRP1/NLRP3 inflammasomes and TLR4-MyD88-NF-κB pathway in monocytes from pregnant women with preeclampsia. J Reprod Immunol 144: 103286, 2021.
82. Martinez-Moreno JM, Herencia C, Montes de Oca A, Muñoz-Castañeda JR, Rodríguez-Ortiz ME, Díaz-Tocados JM, Peralbo-Santaella E, Camargo A, Canalejo A, Rodriguez M, *et al*: Vitamin D modulates tissue factor and protease-activated receptor 2 expression in vascular smooth muscle cells. FASEB J 30: 1367-1376, 2016.

83. Chen SF: 1 alpha, 25-Dihydroxyvitamin D3 decreased ICAM-1 and ELAM-1 expressions on pulmonary microvascular endothelial cells and neutrophil motivation. J Steroid Biochem Mol Biol 52: 67-70, 1995.
84. Jamali N, Song YS, Sorenson CM and Sheibani N: 1,25(OH)2D3 regulates the proangiogenic activity of pericyte through VDR-mediated modulation of VEGF production and signaling of VEGF and PDGF receptors. FASEB Bioadv 1: 415-434, 2019.
85. Aihara K, Azuma H and Matsumoto T: Vitamin D-vitamin D receptor system regulates antithrombogenicity in vivo. Clin Calcium 16: 1173-1179, 2006 (In Japanese).
86. Han T, Liu M and Yang S: DJ-1 alleviates angiotensin II-induced endothelial progenitor cell damage by activating the PPARγ/HO-1 pathway. J Cell Biochem 119: 392-400, 2018.
87. Haseda F, Imagawa A, Murase-Mishiba Y, Terasaki J and Hanafusa T: $CD4^+$ $CD45RA^-$ FoxP3high activated regulatory T cells are functionally impaired and related to residual insulin-secreting capacity in patients with type 1 diabetes. Clin Exp Immunol 173: 207-216, 2013.
88. He LP, Song YX, Zhu T, Gu W and Liu CW: Progress in the relationship between vitamin D deficiency and the incidence of type 1 diabetes mellitus in children. J Diabetes Res 2022: 5953562, 2022.
89. Rak K and Bronkowska M: Immunomodulatory effect of vitamin D and its potential role in the prevention and treatment of type 1 diabetes mellitus-A narrative review. Molecules 24: 53, 2018.
90. Roep BO: The role of T-cells in the pathogenesis of type 1 diabetes: From cause to cure. Diabetologia 46: 305-321, 2003.
91. Felício KM, de Souza ACCB, Neto JFA, de Melo FTC, Carvalho CT, Arbage TP, de Rider Brito HA, Peixoto AS, de Oliveira AF, de Souza Resende F, *et al*: Glycemic variability and insulin needs in patients with type 1 diabetes mellitus supplemented with vitamin D: A pilot study using continuous glucose monitoring system. Curr Diabetes Rev 14: 395-403, 2018.
92. Treiber G, Prietl B, Fröhlich-Reiterer E, Lechner E, Ribitsch A, Fritsch M, Rami-Merhar B, Steigleder-Schweiger C, Graninger W, Borkenstein M and Pieber TR: Cholecalciferol supplementation improves suppressive capacity of regulatory T-cells in young patients with new-onset type 1 diabetes mellitus-A randomized clinical trial. Clin Immunol 161: 217-224, 2015.
93. Giri D, Pintus D, Burnside G, Ghatak A, Mehta F, Paul P and Senniappan S: Treating vitamin D deficiency in children with type I diabetes could improve their glycaemic control. BMC Res Notes 10: 465, 2017.
94. Janyga S, Marek B, Kajdaniuk D, Ogrodowczyk-Bobik M, Urbanek A and Bułdak Ł: CD4+ cells in autoimmune thyroid disease. Endokrynol Pol 72: 572-583, 2021.
95. Chahardoli R, Saboor-Yaraghi AA, Amouzegar A, Khalili D, Vakili AZ and Azizi F: Can supplementation with vitamin D modify thyroid autoantibodies (Anti-TPO Ab, Anti-Tg Ab) and thyroid profile (T3, T4, TSH) in hashimoto's thyroiditis? A double blind, randomized clinical trial. Horm Metab Res 51: 296-301, 2019.
96. Penna-Martinez M, Filmann N, Bogdanou D, Shoghi F, Huenecke S, Schubert R, Herrmann E, Koehl U, Husebye ES and Badenhoop K: High-dose vitamin D in Addison's disease regulates T-cells and monocytes: A pilot trial. Nutrition 49: 66-73, 2018.
97. Lynde CW, Poulin Y, Vender R, Bourcier M and Khalil S: Interleukin 17A: Toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol 71: 141-150, 2014.
98. Kjær TN, Thorsen K, Jessen N, Stenderup K and Pedersen SB: Resveratrol ameliorates imiquimod-induced psoriasis-like skin inflammation in mice. PLoS One 10: e0126599, 2015.
99. Navegantes KC, de Souza Gomes R, Pereira PAT, Czaikoski PG, Azevedo CHM and Monteiro MC: Immune modulation of some autoimmune diseases: The critical role of macrophages and neutrophils in the innate and adaptive immunity. J Transl Med 15: 36, 2017.
100. Balato A, Schiattarella M, Lembo S, Mattii M, Prevete N, Balato N and Ayala F: Interleukin-1 family members are enhanced in psoriasis and suppressed by vitamin D and retinoic acid. Arch Dermatol Res 305: 255-262, 2013.
101. Prtina A, Rašeta Simović N, Milivojac T, Vujnić M, Grabež M, Djuric D, Stojiljković MP, Soldat Stanković V, Čolić MJ and Škrbić R: The effect of three-month vitamin D supplementation on the levels of homocysteine metabolism markers and inflammatory cytokines in sera of psoriatic patients. Biomolecules 11: 1865, 2021.
102. Brożyna AA, Slominski RM, Nedoszytko B, Zmijewski MA and Slominski AT: Vitamin D signaling in psoriasis: Pathogenesis and therapy. Int J Mol Sci 23: 8575, 2022.
103. Weyand CM and Goronzy JJ: The immunology of rheumatoid arthritis. Nat Immunol 22: 10-18, 2021.
104. van Hamburg JP, Asmawidjaja PS, Davelaar N, Mus AMC, Cornelissen F, van Leeuwen JPTM, Hazes JM, Dolhain RJ, Bakx PA, Colin EM and Lubberts E: TNF blockade requires 1,25(OH)2D3 to control human Th17-mediated synovial inflammation. Ann Rheum Dis 71: 606-612, 2012.
105. Jeffery LE, Qureshi OS, Gardner D, Hou TZ, Briggs Z, Soskic B, Baker J, Raza K and Sansom DM: Vitamin D antagonises the suppressive effect of inflammatory cytokines on CTLA-4 expression and regulatory function. PLoS One 10: e0131539, 2015.
106. Guan Y, Hao Y, Guan Y, Bu H and Wang H: The effect of vitamin D supplementation on rheumatoid arthritis patients: A systematic review and meta-analysis. Front Med (Lausanne) 7: 596007, 2020.
107. Nguyen Y, Sigaux J, Letarouilly JG, Sanchez P, Czernichow S, Flipo RM, Soubrier M, Semerano L, Seror R, Sellam J and Daïen C: Efficacy of oral vitamin supplementation in inflammatory rheumatic disorders: A systematic review and meta-analysis of randomized controlled trials. Nutrients 13: 107, 2020.
108. Pan L, Lu MP, Wang JH, Xu M and Yang SR: Immunological pathogenesis and treatment of systemic lupus erythematosus. World J Pediatr 16: 19-30, 2020.
109. Berthelot JM, Le Goff B, Neel A, Maugars Y and Hamidou M: NETosis: At the crossroads of rheumatoid arthritis, lupus, and vasculitis. Joint Bone Spine 84: 255-262, 2017.
110. Shan J, Jin H and Xu Y: T cell metabolism: A new perspective on Th17/Treg cell imbalance in systemic lupus erythematosus. Front Immunol 11: 1027, 2020.
111. Terrier B, Derian N, Schoindre Y, Chaara W, Geri G, Zahr N, Mariampillai K, Rosenzwajg M, Carpentier W, Musset L, *et al*: Restoration of regulatory and effector T cell balance and B cell homeostasis in systemic lupus erythematosus patients through vitamin D supplementation. Arthritis Res Ther 14: R221, 2012.
112. Petri M, Bello KJ, Fang H and Magder LS: Vitamin D in systemic lupus erythematosus: Modest association with disease activity and the urine protein-to-creatinine ratio. Arthritis Rheum 65: 1865-1871, 2013.
113. Ruiz-Irastorza G, Egurbide MV, Olivares N, Martinez-Berriotxoa A and Aguirre C: Vitamin D deficiency in systemic lupus erythematosus: Prevalence, predictors and clinical consequences. Rheumatology (Oxford) 47: 920-923, 2008.
114. Lima GL, Paupitz J, Aikawa NE, Takayama L, Bonfa E and Pereira RMR: Vitamin D supplementation in adolescents and young adults with juvenile systemic lupus erythematosus for improvement in disease activity and fatigue scores: A randomized, double-blind, placebo-controlled trial. Arthritis Care Res (Hoboken) 68: 91-98, 2016.
115. Galoppin M, Kari S, Soldati S, Pal A, Rival M, Engelhardt B, Astier A and Thouvenot E: Full spectrum of vitamin D immunomodulation in multiple sclerosis: Mechanisms and therapeutic implications. Brain Commun 4: fcac171, 2022.
116. Peelen E, Muris AH, Damoiseaux J, Knippenberg S, Broens K, Smolders J, Cohen Tervaert JW, Hupperts R and Thewissen M: GM-CSF production by CD4+ T cells in MS patients: Regulation by regulatory T cells and vitamin D. J Neuroimmunol 280: 36-42, 2015.
117. Soilu-Hänninen M, Aivo J, Lindström BM, Elovaara I, Sumelahti ML, Färkkilä M, Tienari P, Atula S, Sarasoja T, Herrala L, *et al*: A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β-1b in patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 83: 565-571, 2012.
118. Feige J, Moser T, Bieler L, Schwenker K, Hauer L and Sellner J: Vitamin D supplementation in multiple sclerosis: A critical analysis of potentials and threats. Nutrients 12: 783, 2020.
119. Piantoni S, Andreoli L, Scarsi M, Zanola A, Dall'Ara F, Pizzorni C, Cutolo M, Airò P and Tincani A: Phenotype modifications of T-cells and their shift toward a Th2 response in patients with systemic lupus erythematosus supplemented with different monthly regimens of vitamin D. Lupus 24: 490-498, 2015.
120. Kello N and Cho YM: Natural supplements in antiphospholipid syndrome: A case for further study. Clin Immunol 258: 109848, 2024.

121. Agmon-Levin N, Blank M, Zandman-Goddard G, Orbach H, Meroni PL, Tincani A, Doria A, Cervera R, Miesbach W, Stojanovich L, *et al*: Vitamin D: An instrumental factor in the anti-phospholipid syndrome by inhibition of tissue factor expression. Ann Rheum Dis 70: 145-150, 2011.
122. Beer TM, Venner PM, Ryan CW, Petrylak DP, Chatta G, Dean Ruether J, Chi KN, Curd JG and DeLoughery TG: High dose calcitriol may reduce thrombosis in cancer patients. Br J Haematol 135: 392-394, 2006.
123. Keaney JF Jr and Rosen CJ: VITAL signs for dietary supplementation to prevent cancer and heart disease. N Engl J Med 380: 91-93, 2019.
124. Cannegieter SC, Doggen CJ, van Houwelingen HC and Rosendaal FR: Travel-related venous thrombosis: Results from a large population-based case control study (MEGA study). PLoS Med 3: e307, 2006.
125. Cohen H, Cuadrado MJ, Erkan D, Duarte-Garcia A, Isenberg DA, Knight JS, Ortel TL, Rahman A, Salmon JE, Tektonidou MG, *et al*: 16th International congress on antiphospholipid antibodies task force report on antiphospholipid syndrome treatment trends. Lupus 29: 1571-1593, 2020.
126. Ruiz-Irastorza G, Crowther M, Branch W and Khamashta MA: Antiphospholipid syndrome. Lancet 376: 1498-1509, 2010.
127. Chighizola CB, Ubiali T and Meroni PL: Treatment of thrombotic antiphospholipid syndrome: The rationale of current management-an insight into future approaches. J Immunol Res 2015: 951424, 2015.
128. Uludag G, Onghanseng N, Tran ANT, Hassan M, Halim MS, Sepah YJ, Do DV and Nguyen QD: Current concepts in the diagnosis and management of antiphospholipid syndrome and ocular manifestations. J Ophthalmic Inflamm Infect 11: 11, 2021.
129. García-Carrasco M, Jiménez-Herrera EA, Gálvez-Romero JL, Mendoza-Pinto C, Méndez-Martínez S, Etchegaray-Morales I, Munguía-Realpozo P, Vázquez de Lara-Cisneros L, Santa Cruz FJ and Cervera R: The anti-thrombotic effects of vitamin D and their possible relationship with antiphospholipid syndrome. Lupus 27: 2181-2189, 2018.
130. Ota K, Dambaeva S, Han AR, Beaman K, Gilman-Sachs A and Kwak-Kim J: Vitamin D deficiency may be a risk factor for recurrent pregnancy losses by increasing cellular immunity and autoimmunity. Hum Reprod 29: 208-219, 2014.
131. Chen X, Yin B, Lian RC, Zhang T, Zhang HZ, Diao LH, Li YY, Huang CY, Liang DS and Zeng Y: Modulatory effects of vitamin D on peripheral cellular immunity in patients with recurrent miscarriage. Am J Reprod Immunol 76: 432-438, 2016.
132. Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, Walker LS, Lammas DA, Raza K and Sansom DM: 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J Immunol 183: 5458-5467, 2009.
133. Rafiee M, Gharagozloo M, Ghahiri A, Mehrabian F, Maracy MR, Kouhpayeh S, Pieper IL and Rezaei A: Altered Th17/Treg ratio in recurrent miscarriage after treatment with paternal lymphocytes and vitamin D3: A double-blind placebo-controlled study. Iran J Immunol 12: 252-262, 2015.
134. Ji J, Zhai H, Zhou H, Song S, Mor G and Liao A: The role and mechanism of vitamin D-mediated regulation of Treg/Th17 balance in recurrent pregnancy loss. Am J Reprod Immunol 81: e13112, 2019.
135. Piantoni S, Andreoli L, Allegri F, Meroni PL and Tincani A: Low levels of vitamin D are common in primary antiphospholipid syndrome with thrombotic disease. Reumatismo 64: 307-313, 2012.
136. Bećarević M, Sarić M, Stojanovich L, Mirković D, Dopsaj V and Ignjatović S: Anti-annexin A5 antibodies and 25-hydroxycholecalciferol in female patients with primary antiphospholipid syndrome. Clin Rheumatol 37: 3359-3364, 2018.
137. Hanley DA, Cranney A, Jones G, Whiting SJ, Leslie WD, Cole DE, Atkinson SA, Josse RG, Feldman S, Kline GA, *et al*: Vitamin D in adult health and disease: A review and guideline statement from Osteoporosis Canada. CMAJ 182: E610-E618, 2010.
138. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, *et al*: The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: What clinicians need to know. J Clin Endocrinol Metab 96: 53-58, 2011.
139. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, Płudowski P and Jones G: Vitamin D toxicity-A clinical perspective. Front Endocrinol (Lausanne) 9: 550, 2018.
140. Rolf L, Muris AH, Bol Y, Damoiseaux J, Smolders J and Hupperts R: Vitamin D_3 supplementation in multiple sclerosis: Symptoms and biomarkers of depression. J Neurol Sci 378: 30-35, 2017.
141. Alkundi A, Momoh R, Musa A and Nwafor N: Vitamin D intoxication and severe hypercalcaemia complicating nutritional supplements misuse. BMJ Case Rep 15: e250553, 2022.
142. Fragoso YD, Adoni T, Damasceno A, de Albuquerque Damasceno CA, Ferreira ML, Finkelzstejn A, Gomes S, Goncalves MV, Grzesiuk AK, Lins S, *et al*: Unfavorable outcomes during treatment of multiple sclerosis with high doses of vitamin D. J Neurol Sci 346: 341-342, 2014.
143. De Vincentis S, Russo A, Milazzo M, Lonardo A, De Santis MC, Rochira V, Simoni M and Madeo B: How much vitamin D is too much? A case report and review of the literature. Endocr Metab Immune Disord Drug Targets 21: 1653-1659, 2021.
144. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D and Nicholson GC: Annual high-dose oral vitamin D and falls and fractures in older women: A randomized controlled trial. JAMA 303: 1815-1822, 2010.
145. Smith H, Anderson F, Raphael H, Maslin P, Crozier S and Cooper C: Effect of annual intramuscular vitamin D on fracture risk in elderly men and women-a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford) 46: 1852-1857, 2007.
146. Rocha PN, Santos CS, Avila MO, Neves CL and Bahiense-Oliveira M: Hypercalcemia and acute kidney injury caused by abuse of a parenteral veterinary compound containing vitamins A, D, and E. J Bras Nefrol 33: 467-471, 2011.
147. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, Dick W, Willett WC and Egli A: Monthly high-dose vitamin D treatment for the prevention of functional decline: A randomized clinical trial. JAMA Intern Med 176: 175-183, 2016.
148. Benemei S, Gallo E, Giocaliere E, Bartolucci G, Mennini-Ippolito F, Firenzuoli F, Mugelli A and Vannacci A: It's time for new rules on vitamin D food supplements. Br J Clin Pharmacol 76: 825-826, 2013.
149. Kimball S and Vieth R: Self-prescribed high-dose vitamin D3: Effects on biochemical parameters in two men. Ann Clin Biochem 45: 106-110, 2008.