Review

Endogenous and exogenous environmental hormone D (vitamin D) suppliers in autoimmune rheumatic diseases

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ABSTRACT

In addition to its involvement in bone homeostasis, a growing number of evidence support the extra-skeletal role of vitamin D_3 in modulating the immune response. In fact, the active vitamin D_3 metabolite, calcitriol ($1,25(OH)_2D_3$) is able to modulate the innate and adaptive immune system in presence of auto-immune diseases and participate to the defence against viral and bacterial pathogens. Therefore, maintaining during the year adequate levels of vitamin D_3 is crucial in preventing hypovitaminosis D, a condition associated with autoimmune rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. Vitamin D_3 can be obtained from both endogenous sources, through skin synthesis under exposure to UV-B rays from sunlight, and exogenous sources like both diet and oral supplementation. Microbiota is also regulated by calcitriol which prevents dysbiosis and abnormal immune system activation. This review mainly aims to discuss the latest updates and clinical evidence concerning the impact of endogenous and exogenous environmental vitamin D_3 sources in autoimmune rheumatic diseases.

Introduction

Vitamin D_3 (cholecalciferol) and its active form $1,25(OH)_2D_3$ (calcitriol) plays pivotal role in calcium and phosphate metabolism and skeletal mineralization, but, most interesting, as secosteroid, it also exerts pleiotropic physiological actions, including the regulation of the immune system (1). Indeed, Vitamin D_3 deficiency (25(OH) D_3 serum concentrations below 30 ng/ml) has been associated with altered immune response against pathogens and self-antigens, thereby contributing to aberrant immune response with impaired tolerogenicity predisposing to autoimmune diseases and during viral infections such as COVID-19 (2-4). In this narrative review, we aim to discuss the evidence-based interference of Vitamin D_3 on the immune system. We analyse the latest insights of Vitamin D_3 influence on pro-inflammatory pathways involved in both autoimmune conditions (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's disease (SjD) and psoriasis) bacterial and viral infective diseases (*i.e.*, tuberculosis and COVID-19) (5-7). Among immune pathways of autoimmune diseases, we provide a further update on the microbiome modulation by vitamin D_3.

The endocrine, intracrine and paracrine vitamin D_3 system

Vitamin D_3 is a secosteroid molecule derived from cholesterol with a distinctive "broken ring" structure. The skin naturally produces Vitamin D_3 through sun-mediated photosynthesis, specifically in response to ultraviolet B (UVB) radiation (290-315 nm of wavelength) (8). During the exposure to sunlight, 7-dehydrocholesterol in the dermis is isomerised to cholecalciferol (Fig. 1). Consequently, upon entering the bloodstream, cholecalciferol migrates to the liver, where it is hydroxylated to form $25(OH)D_3$ (calcidiol or calcifediol) by 25-hydroxylase enzyme (CYP2R1). Furthermore, an additional hydroxylation is needed to obtain active metabolite. Indeed, in the kidneys 1-α-hydroxylase (CYP27B1) converts $25(OH)D_3$ into $1,25(OH)_2D_3$ (calcitriol)

(9,10) (Fig. 1). Calcitriol binds vitamin D receptor (VDR) which may be found in both nuclear and intramembrane forms in target tissues. VDR interacts with retinoid X receptors to form the VDR-RXR complex able to control the function of certain transcription factors and modulates gene expression (11). Renal synthesis of calcitriol is regulated by parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23), which respectively stimulate and inhibit 1α-hydroxylase (endocrine effects of calcitriol) (12). At last, 24-hydroxylase (CYP24A1) regulates 25(OH)D_3 serum concentrations. It activates a catabolic pathway, converting calcitriol into calcitroic acid that will be eliminated into the bile through the gastrointestinal system (13). Interestingly, immune cells as well as intestinal cells express the enzyme CYP27B1 allowing the intracrine intracellular synthesis of calcitriol. Once produced, calcitriol exerts paracrine and autocrine actions on immune cells by binding to the VDR, resulting in the self-modulation of the immune response (14) (Fig. 1).

Immunomodulatory effects of vitamin D_3

A growing amount of evidence demonstrated that the active form of vitamin D_3 modulates immune system at multiple levels (1). VDR is widely expressed in both innate and adaptive immune cells. Indeed, immune system cells, including macrophages, dendritic cells, T cells and B cells, can produce active calcitriol during inflammatory processes. Under the stimuli of calcitriol, VDR is activated and interacts with nuclear transcription factors such as NF-AT and NF-κB (15). *In vitro* studies confirmed that VDR activation in immune cells, including monocytes/macrophages, directly modulates NF-κB expression, a pivotal pro-inflammatory transcriptional factor, via upregulation of the inhibitory protein IκBα (16). Moreover, VDR directly binds promoter regions of pro-inflammatory cytokine genes (TNF-α, IL-1β, IL-6, IL-8) modulating their expression (17). Calcitriol inhibits the differentiation and maturation of monocytes and dendritic cells in a paracrine manner along with a reduced expression of co-stimulatory molecules such as CD40 and CD80–CD86. These processes impair the antigen-presenting function of innate immune cells and their subsequent activation of adaptive immune cells (T cells) (15) (Fig. 1). The paracrine hormonal activity of vitamin D_3 directly regulates adaptive immune cells as well. In fact, the highest expression of VDR has been observed in $CD8^+$ T cells compared to other cell types (18). Additionally, Vitamin D_3 can restore the immune balance repressing the self-aggressive Th1/Th17-mediated pro-inflammatory pathway and enhancing the protolerogenic Th2/Th-regulatory response (19).

Finally, VDR-mediated signalling actives immune cells toward an anti-inflammatory cell differentiation and reduces the pro-inflammatory cytokines production (17) (Fig. 1). As matter of fact, a circadian rhythm for the secosteroid vitamin D_3 synthesis might also be recognized with higher availability in presence of daily sunlight (in few hours) with related immune suppressive effects compared to daily darkness (night), as already suggested, but during the night, for circadian rhythm immune suppressive action regarding the steroid cortisol, at least in RA (20, 21).

Autoimmune diseases and vitamin D_3 endogenous deficiency

People with vitamin D_3 endogenous deficiency (25(OH)D_3 serum concentrations below 30 ng/ml) are more prone to a breakdown of tolerance toward self-antigens, increasing the incidence of autoimmune diseases (17). RA is a chronic progressive inflammatory autoimmune disease characterised by synovial hyperplasia, cartilage erosion, bone destruction with consequent joints loss of function (22). Among innate immune cells involved in RA pathogenesis, an imbalance between pro-inflammatory (M1) and anti-inflammatory (M2) monocytes/macrophages have been widely recognised (23). The action of calcitriol on the STAT-1/TREM-1 pathway regulates the transition of macrophages (inhibit macrophage transition to the M1 phenotype), which plays a role in resolving synovial inflammation in RA (24). In addition, polymorphisms of VDR gene have been reported in RA patients and might enhance, at least, osteoporosis risk rendering patients more prone to fragility fractures (25). In further confirmation, a systematic review and meta-analysis confirmed that exogenous vitamin D_3 supplementation ameliorated visual analog scale (VAS), disease activity score (DAS)-28 and tender joints count (TJC) as well as a EULAR patient reported outcome ad hoc questionnaire (D-PRO) (7, 26). Of note, epidemiological analysis demonstrated that vitamin D_3 serum concentrations are inversely related to RA activity (27). Interestingly, a study conducted in France showed that RA onset during winter seems to be associated with a worse prognosis in terms of faster erosive radiographic progression at 6 months and lower remission rate at one-year (28). An extensive literature review analysed the seasonal impact of vitamin D_3 on the clinical activity of rheumatic diseases, focusing on RA and SSc. Indeed, in autoimmune inflammatory conditions, a cyclical disease activity pattern has been proposed, with the highest burden of damage occurring during the winter, suggesting the involvement of a limited solar exposure, and reduced endogenous production of 7-dehydrocolesterol. This review concluded that a significant amount of evidence suggests the beneficial effects of vitamin D_3 supplementation on prognosis, supporting the development of randomised clinical trial placebo-control to confirm the role of vitamin D_3 supplementation as ancillary therapy in immunomodulation (29). Of note, regulatory T cells (Tregs) isolated from peripheral blood mononuclear cells of SSc patients and treated in vitro with vitamin D_3 showed enhanced IL-10 production, nonetheless, the immune suppressive activity of Tregs remained impaired (30). Similarly to RA, the impaired expression of the VDR gene may be correlated with the development of SLE, along with genetic factors and exogenous/endogenous environmental factors (epigenetic effects) (31) (Fig. 1). SLE patients are often advised to avoid sun-

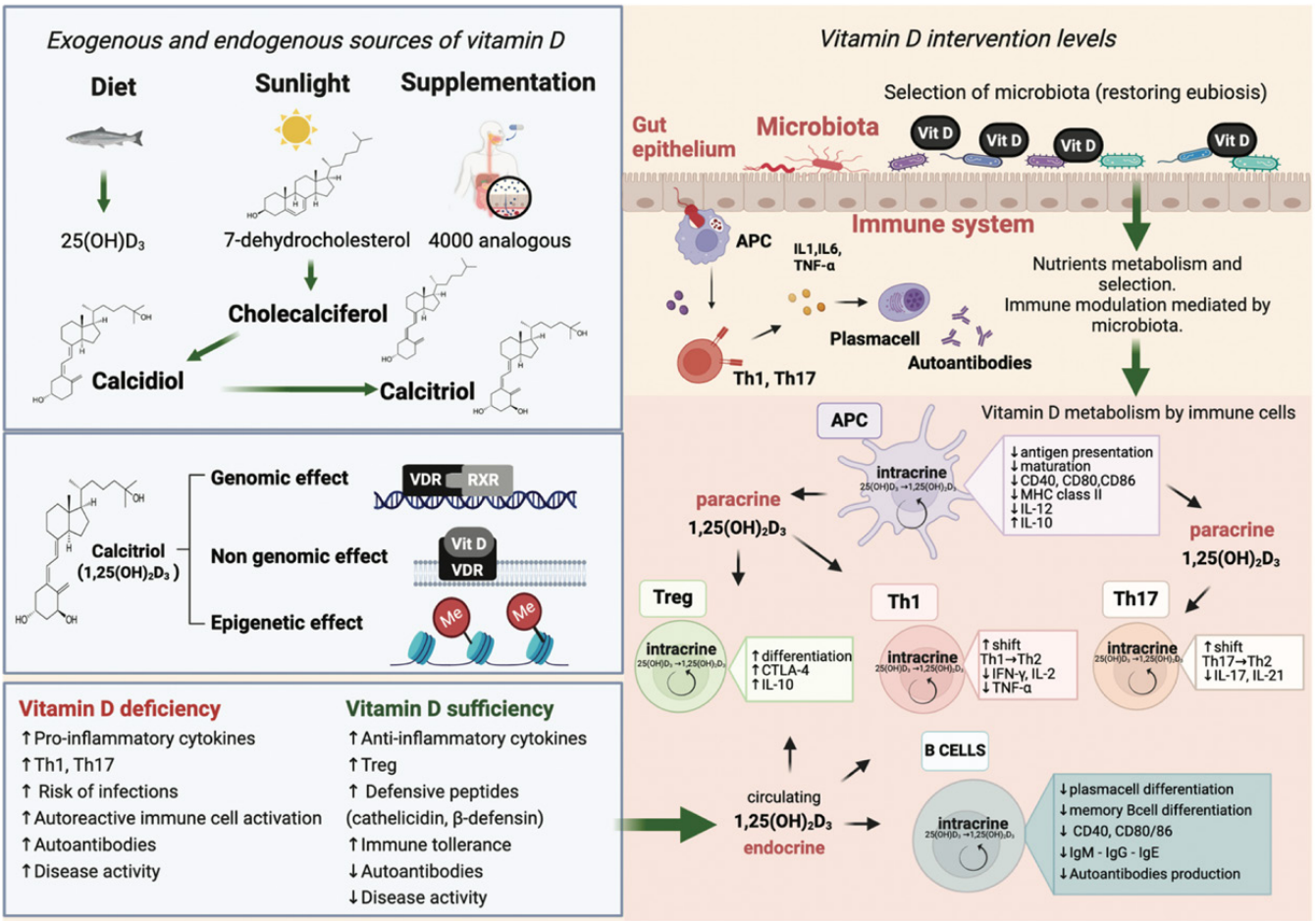

Fig. 1. The effects of vitamin D_3 on the immune system and gut microbiota: exogenous and endogenous sources of vitamin D_3 with synthesis steps. The regulatory role of this molecule has been shown to affect the innate and acquired immune system due to exemplification of endocrine, paracrine and intracrine effect of vitamin D_3 on the innate and acquired immune system (see text for additional details).
VitD: vitamin D_3; VDR: vitamin D receptor; RXR: retinoid X receptor; APC: antigen presenting cell; Th: T helper cell; Treg: T regulatory cell; IL: interleukin; IFN- γ: interferon-γ; TNF-α: tumour necrosis factor alpha; Met: methylated DNA.
(The original figure was created by co-author R. Campitiello with www.biorender.com).

light exposure to prevent DNA damage, formation of immune complexes, and disease progression. In fact, hypovitaminosis D is a common comorbidity in SLE patients induced by the indoor lifestyle (32). Therefore, endogenous Vitamin D_3 serum levels should be checked at least every 6 months in SLE patients, and hypovitaminosis should be promptly corrected. A large body of epidemiological data revealed that also SSc patients suffer of vitamin D_3 deficiency (33). SSc is a rare and complex disease, and its pathogenesis is influenced by several environmental factors, including professional occupation, and disease-related features (34). Firstly, SSc gastrointestinal involvement decrease the absorption of several nutrients, including the exogenous vitamin D_3 introduced by foods (that is only 20% of daily needs), which can result in malnutrition, hypovitaminosis and small intestinal bacterial overgrowth (SIBO) (35, 36). Secondly, in SSc endogen natural production of vitamin D_3 is impaired by skin fibrosis, which makes the skin resistant to UV-B radiation (33). Notably, several studies have attempted to investigate the association between vitamin D_3 and SSc pathogenesis. Remarkably, VDR and low calcitriol serum levels can interfere with SSc fibrotic process, acting on the TGF-β/Smad signalling (37). Calcitriol seems to ameliorate fibroblasts-induced fibrosis reducing extracellular deposition of collagen, fibronectin, and stress fibres in animal models (38). A transactional study confirmed the vitamin D_3 deficiency burden in SSc patients, notably, a significant correlation has been found between 25(OH)D_3 serum concentrations and SSc clinical parameters (interstitial lung disease, peripheral vascular, kidney and gastrointestinal items of Medsger's disease severity scale) (39). Skin psoriasis is one of the immune mediated diseases that most benefit from solar exposition. To date, UVA irradiation (PUVA) therapy remains the first-line treatment in a various of skin diseases including psoriasis (40). Calcipotriol, a synthetic analogue of calcitriol is used in clinical practice as topic treatment of cutaneous psoriasis (41). Of note, intra-articular injection of calcipotriol ameliorates histological synovitis in arthritic murine model showing good safety profile (42). Moreover, calcipotriol exerts anti-proliferative and anti-inflammatory effects on synovial stromal cells sug-

gesting a potential role in local treatment of arthritis. Interestingly, both calcitriol and calcipotriol inhibited the migration of synovial stromal cells in a wound healing similarly to glucocorticoids (43). Focusing on SjD, a meta-analysis revealed a higher prevalence of hypovitaminosis D in patients compared to healthy controls. Furthermore, within the cohort of patients diagnosed with SjD and hypovitaminosis D, a shorter tear breakup time and poorer Schirmer's test scores were observed, indicating more severe sicca syndrome compared to patients with normal serum concentrations of vitamin D_3 (44). Of note, in an Italian cohort of SjD patients, reduced serum concentrations of vitamin D_3 have been observed already at the onset of the disease (45). Additionally, a lower level of vitamin D_3 has been found in SjD patients with peripheral neuropathy compared to those not presenting this symptom, suggesting a role of vitamin D_3 in SjD extraglandular manifestations (46). Furthermore, based on an observational study, it has been hypothesized a possible correlation between anti-Ro and anti-La positive congenital cardiac block and low serum concentrations of vitamin D_3, especially during weeks 18 to 24 of pregnancy in women diagnosed with SjD (47). It is notable that SjD increases the incidence of lymphoma, however, there appears to be a correlation between insufficient vitamin D_3 serum concentrations and lymphoma clinical manifestations and prognosis in SjD patients (48). Finally, a recent Mendelian randomization study using two genetic databases "GWAS" and "25OHD", counting respectively 6098 cases of SjD patients and 417,580 patients with hypovitaminosis D, highlighted that higher serum concentrations of vitamin D_3 may reduce the risk of primary SjD (49).

In conclusion, vitamin D_3 supplementation is recommended for the general population and particularly for patients affected by autoimmune diseases, leveraging its anti-inflammatory modulatory effect and high tolerability (toxicity has been reported for supra-physiological 25(OH)D_3 serum concentrations above 150 ng/ml).

Vitamin D_3 endogenous effects on intestinal microbiota: an intriguing relationship

The human intestinal microbiota is shaped before birth and an early colonisation is pivotal for the development and maturation of the immune system. Microbiota is approximately composed by 3.8×10^{13} bacterial cells and the most representative phyla are Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria (50). Indeed, intestinal microbiota plays a crucial role in the immune system homeostasis and may be involved in the pathogenesis of autoimmune disease such as RA, SLE and inflammatory bowel diseases (IBD) (51).

In modern society, dysbiosis is commonly observed, primarily due to the Western dietary regimen, which typically consists of refined sugars, saturated fats, and inadequate intake of fruits, vegetables, and whole grains. Additionally, excessive antibiotic administration and sanitation practices contribute to this phenomenon. (52, 53). Bowel mucosal integrity is vital to prevent bacterial dissemination into the bloodstream. Indeed, damaged intestinal epithelium may facilitate microbial translocation. In individuals with genetic susceptibility, this can contribute to the development of autoreactive immune cells, disease onset, or new flares (54). Interestingly, lactobacillus treatment shifted the Treg-Th17 balance towards a Treg phenotype in SLE-murine model (55).

Furthermore, it has been suggested that oral bacterial DNA intake might induce Breg cells and ameliorate lupus-like symptoms (56). Novel evidence documented the vitamin D_3 role in maintaining eubiosis and gut homeostasis via VDR activation (57). Vitamin D_3 response elements are in the promoter region of nucleotide binding oligomerisation domain containing Nucleotide Binding Oligomerization Domain Containing 2 (NOD2) which is a pattern recognition receptor genetically linked to the pathogenesis of IBD such as Crohn's disease (58). NOD2 is a transcriptional factor involved in bacterial peptidoglycans recognition enhancing bacterial killing through autophagy of intracellular pathogens and promotes antimicrobial peptide production interacting with the TGFβ-activated kinase 1 (TAK1), activating MAPK (mitogen-activated protein kinase) and NF-κB (nuclear factor kappa B) and consequent pro-inflammatory cytokines production (IL-1, IL-6, IL-12, IL-23, TNF-α) (59). Indeed, calcitriol induced NOD2 production has been demonstrated in human monocytes, while VDR activation reduces bacterial-stimulated NF–κB activity, supporting the host's defensive mechanisms against bacterial invasion and infection (60, 61). Calcitriol also plays a protective effect on the integrity of the gut epithelial barrier, reducing bacterial translocation from the gastrointestinal mucosa to mesenteric lymph nodes and ameliorating histological features of the colon epithelium in an acute colitis murine model (62). Vitamin D_3 potentiates the tight junction protein claudin-2 in intestinal epithelial cells, as the CLDN2 gene is a direct target of the VDR signalling pathway (63). In addition, calcitriol protects the gut barrier function maintaining the integrity of tight junction complexes (occludin, zonula occludens (ZO)-1 and -2, and claudin-2, -7 and -12) and adherents junctions' proteins (E-cadherin) (64). A genome-wide association study demonstrated that VDR influences the gut microbiome, as confirmed by significant shifts in the microbiota observed in VDR -/- mice compared to controls (65). Indeed, the absence of VDR leads to the depletion of Lactobacillus and enrichment of Clostridium and Bacteroides in faecal stool, altering pathways of the intestinal microbiota. These endogenous changes may collectively affect the immune response to infections, cancer, and autoimmune diseases (66). Furthermore, a cross-sectional analysis of 150 young healthy subjects showed that vitamin D_3 was inversely related to inflammatory markers (PCR; $r = -0.170$, $p=0.039$), cell adhesion protein (E-selectin; $r = -0.220$, $p=0.007$) and presence of Coprococcus ($r = -0.215$, $p=0.008$) and Bifidobacterium ($r = -0.269$, $p=0.001$) (67). It should be noted that Bifidobacterium abundance in gut microbiota has been

linked to autoimmune diseases onset (68). A monocentric pilot study revealed that an 8-week supplementation with high doses of vitamin D_3 strongly modifies the upper gastrointestinal tract microbiome in healthy volunteers preventing opportunistic pathogens invasion and increasing bacterial richness (69). Notably, immunomodulation treatment with methotrexate, hydroxychloroquine in RA exhibits the capacity to reinstate gut microbiome diversity which is often altered in RA cohorts. Analogous findings have been documented regarding TNF-α inhibitors in the treatment of ankylosing spondylitis (70). Available data suggest a complex mutual relation between the vitamin D_3 system and intestinal microbiota.
Therefore, the impact in restoring eubiosis might be an additional beneficial effect of vitamin D_3 in regulating autoimmune response, restoring healthy microbe-host interactions (Fig. 1).

Vitamin D_3 and viral infections, including COVID-19 and similarities with autoimmune rheumatic diseases

Active form of vitamin D_3 modulates the innate immune response to infections. This statement has been known since ancient times, however recently it has been observed a growing interest in investigating the molecular basis behind this mechanism (71, 72). It is widely acknowledged that respiratory infections exhibit a recurring pattern, with peak occurrences typically observed during winter months when solar exposure is inadequate for the endogenous synthesis of vitamin D_3. Of note, natural sunlight exposure (and UV effects) has been shown to rapidly neutralise viruses on surfaces, including SARS-CoV-2, thereby mitigating exposure risks in outdoor settings (73). Vitamin D_3 contributes to orchestrate the complex immune response to bacterial and viral infections at different levels. VDR contributes to microbial sensing and effector responses modulating NF-κB, NOD2 and NLRP3 pathways (74). Human macrophage toll-like receptors (TLRs), upon antimicrobial peptides stimulation, upregulate VDR gene expression, which through a complex vitamin D_3/VDR signalling activates the innate immunity against infection (75, 76). Optimal serum concentrations of 25(OH)D_3 enhances the synthesis of antimicrobial defensive peptides (cathelicidin/LL-37, β-defensin) by immune cells, which in turn inhibit the replication of Mycobacterium tuberculosis in vitro (77) (Fig. 1). Meta-analyses highlighted that low 25(OH)D_3 serum concentration is associated with a more severe clinical manifestation of COVID-19 (78, 79). Many similitudes have been highlighted between COVID-19 infection and autoimmune rheumatic diseases in terms of pathological mechanism and similar pro-inflammatory cytokine profile (TNF-α, IL-6, IL-8, IL-17, GM-CSF) (80).
Interestingly, however, contrary to RA, in viral infections, including SARS-CoV-2, females usually present with less severe inflammation showing even a protective role of oestrogen on B cells and antibody production (3, 80, 81). Low serum presence of Treg have been reported in patients infected with SARS-CoV-2, while optimal serum concentrations of vitamin D_3 may be beneficial in equilibrating Treg levels (82). Recent publications recommended a daily vitamin D_3 supplementation rather that sporadic intake able to effectively modulate the immunity and lowering the severity of respiratory tract infections (83, 84). Indeed, a literature review illustrated that patients experiencing severe COVID-19 symptoms reported low serum level of vitamin D_3 (<12 ng/mL), additionally, in patients with mild to moderate symptoms, it is recommended a daily supplementation of 1000 – 2000 U.I. of vitamin D_3 in order to reduce cytokine storms and morbidity (85). A retrospective study showed a lower COVID-19-related incidence and mortality in tropical countries compared to non-tropical countries. These results underlined the beneficial effects of solar exposure, thus vitamin D_3 production, in regulating immune response and ameliorate clinical outcomes (86). Nevertheless, conflicting data on the matter emerged. In fact, "CORONAVIT Study", a randomised trial conducted in UK enrolling 6200 healthy subjects aimed to test if daily intake of cholecalciferol at high and low dose (800 IU or 3200 IU) for six months might reduce the risk of SARS-CoV-2 infection. The results did not show any statistically significant difference with the placebo group (87). Considering the most recent insights, we may deduct that vitamin D_3 influence in the immune system is a powerful tool in infectious disease settings, and this is by preventing excessive and harmful cytokine storms (*e.g.*, SARS-CoV-2 infection) while allowing the clearance of pathogens through the production of antimicrobial peptides (88).
In conclusion, vitamin D_3 supplementation to standard antiviral/antibacterial therapy may represent an additional factor in boosting the immune system's ability to mount an effective response to pathogens, thereby mitigating the damages caused by cytokine storms.

Vitamin D_3 and exogenous sources: sun and diet

The beneficial effects of solar exposition have been studied since ancient times in the prevention of diseases such as rickets, osteomalacia, and osteoporosis (89). Epidemiological studies highlighted that in Northern European countries, around 20% of the population registered a vitamin D_3 deficiency of less than 20 ng/mL, while in other European regions are estimated 30-60% and the Middle East 80%. Populations at major risk includes young children, pregnant women and especially elderly which not only are commonly institutionalised, but they also suffer of malnutrition (90). Nevertheless, data show that photochemical UV excessive exposure over the years contributes to cumulative DNA photodamage which may lead to increased risk of skin disease such as keratinocytes carcinomas and melanoma (91). On the other hand, regular sun exposure seems to be protective for non-communicable diseases such as cancer (colon, breast, prostate), non-Hodgkin lymphoma, hypertension and diabetes, and this phenomenon has been partially recognized to adequate vitamin D_3 photosynthesis (92). The precise amount of solar exposure in the Mediterranean basin required to meet

daily endogenous need for optimal levels of vitamin D_3 has been elucidated. Indeed, the analysis proved that the period of active vitamin D_3 synthesis lasts from the beginning of March until the third week of October while UVB time zone goes from 10:00 until 16:00. Moreover, according to skin type it has been estimated the approximate amount of exposition time (minutes) required to produce 1000 IU vitamin D_3: 5.05 for type I, 6.3 for type II, 7.6 for type III, 11.35 for type IV, 15.15 for type V and 25.25 for type VI (93). It is noteworthy that solar exposition is not the only way to prevent hypovitaminosis D: diet plays a contribution. However, only a limited selection of alimentary products naturally contains vitamin D_3. This vitamin is found in animal-source (fish liver oil, salmon, sardines, herring and mackerel) and in a smaller amount it is also present in dairy products (butter), egg yolk and nuts (peanuts) (94). Indeed, Northern countries compensate the scarcity of sunlight with exogenous sources of vitamin D_3 adopting a diet rich in short chain fatty acids and fat-soluble vitamins. Interestingly, in fish oil are also found in high quantities essential lipids with anti-inflammatory effects such as eicosapentaenoic acid and docosahexanoic acid (95) (Fig. 1). Similarly, to vitamin D_3, short chain fatty acids can block NF-κB and coxgenes reducing the expression of prostaglandin E2, Leukotriene B4, IL-1β and IL-6 (96-98). Moreover, short chain fatty acids enhance macrophages phagocytosis, efferocytosis and promoting their shift to anti-inflammatory M2 macrophages (99). A Danish study demonstrated that vitamin D_3 levels in dairy products are subject of seasonal variation (100). Further complicating the scenario are the comorbidities such as body mass index, IBD, microbiota dysbiosis, cancer, pregnancy and autoimmune disease that influence the needed daily intake of vitamin D_3 (101-104). Therefore, relying solely on diet may not be an effective strategy for maintaining consistent 25(OH)D_3 serum concentrations in the long term. A recent randomised double-blind, placebo-controlled clinical trial "VITAL" investigated in a large cohort of healthy subjects the potential beneficial effect of daily supplementation with 2000 IU/day of cholecalciferol and/or 1 g/day of n-3 fatty acids in reducing incidence of autoimmune disease. Indeed, the vitamin D_3 arm showed a statistically significant effect, reducing the incidence rate of autoimmune diseases onset by 22%. A similar trend has been highlighted in the omega 3 fatty acid group, although statistical significance was not reached (105). After two years from "VITAL" trial termination, data show that cholecalciferol protective effects vanish after discontinuation underlining the importance of constant long-term supplementation (106). In summary, the precise dosage and manner of administration of vitamin D_3 supplementation should be patient tailored preferring a daily intake. This statement is supported by the fact that high exogenous exaggerated amounts of vitamin D_3 stimulates the inactivating enzyme CYP24A1 (107).

The interest in vitamin D_3 and anti-inflammatory activities is now moving also to chronic osteoarthritis where recently it has been shown that vitamin D_3 can activate chondrocyte autophagy (108).

Conclusion

Vitamin D_3 is a secosteroid hormone with a plethora of biological effects in human body. In autoimmune disease patients, it is highly recommended to monitor serum concentrations of vitamin D_3 and promptly correct deficiencies through daily supplementation. To date, a growing amount of evidence elucidated the mechanisms underlying the beneficial role of vitamin D_3 in optimizing the immune response in autoimmune diseases as well as in viral or bacterial infections. Moreover, the interaction between calcitriol and microbiota and the gut immune system, is an area of growing interest in research. Indeed, data suggest that calcitriol plays a role in modulating the composition and function of the gut microbiota, while the gut microbiota influences the metabolism and absorption of vitamin D_3 and in turn, the immune responses by considering that almost 70-75% of the immune system is located in the gut.

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