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Modulation of inflammatory and immune responses by vitamin D

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ABSTRACT

Vitamin D (VitD) is a prohormone most noted for the regulation of calcium and phosphate levels in circulation, and thus of bone metabolism. Inflammatory and immune cells not only convert inactive VitD metabolites into calcitriol, the active form of VitD, but also express the nuclear receptor of VitD that modulates differentiation, activation and proliferation of these cells. In vitro, calcitriol upregulates different anti-inflammatory pathways and downregulates molecules that activate immune and inflammatory cells. Administration of VitD has beneficial effects in a number of experimental models of autoimmune disease. Epidemiologic studies have indicated that VitD insufficiency is frequently associated with immune disorders and infectious diseases, exacerbated by increasing evidence of suboptimal VitD status in populations worldwide. To date, however, most interventional studies in human inflammatory and immune diseases with VitD supplementation have proven to be inconclusive. One of the reasons could be that the main VitD metabolite measured in these studies was the 25-hydroxyVitD (25OHD) rather than its active form calcitriol. Although our knowledge of calcitriol as modulator of immune and inflammatory reactions has dramatically increased in the past decades, further in vivo and clinical studies are needed to confirm the potential benefits of VitD in the control of immune and inflammatory conditions.

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1. Introduction

VitD was brought to the attention of the scientific and medical community after the seminal finding that rickets in children and osteomalacia in adults are caused by low levels of serum VitD [1]. It is now well known that VitD deficiency can exacerbate osteopenia and osteoporosis and increase the risk of fractures. Subsequently a growing literature has demonstrated that VitD deficiency is associated to a number of different pathological conditions of many different organs and systems in the body, including autoimmune and inflammatory diseases, infections, cancer and even neurological conditions [2,3].

Although the kidney is the main site of production of the active form of VitD $1,25(OH)_2D$ (calcitriol), many different cell types, including immune and inflammatory cells, can produce locally calcitriol thus inducing autocrine and paracrine loops of generation of and response to VitD [2,3]. Moreover, most cells in the body, including again immune and inflammatory cells, do express the nuclear receptor for VitD and thus respond to calcitriol that modulates a variety of cell functions.

In this review, we summarize the main immunomodulatory effects of $1,25(OH)_2D$ on immune cells, including signalling in both innate immunity (antimicrobial activity and antigen presentation) and adaptive immunity (T and B lymphocyte function). The recognition of the role of VitD on immune cells, and as a consequence, the possible role in inflammation and autoimmunity may have significant clinical implications. We review the potential role of VitD in asthma, inflammatory bowel disease (IBD) and respiratory infections as well as in autoimmune disease like Rheumatoid Arthritis (RA), Type 1 Diabetes (T1D), Systemic Lupus Erythematosus (SLE) and Psoriasis, discussing the biological background, evidence from animals or epidemiological studies as well as intervention studies with VitD or analogs. Collectively, these observations support the hypothesis that VitD insufficiency may be related to the dysregulation of human immune responses. In this context, we will also highlight the relevance of accurate tools for measuring VitD metabolites in human populations.

2. Sources and metabolism of VitD

2.1. Forms of VitD

VitD (calciferol) includes a number of fat soluble seco-steroids, with VitD2 (ergocalciferol) and VitD3 (cholecalciferol) representing the major forms. Whereas the D2 is human made and added to foods, the D3 form in synthetized in the skin and absorbed via animal-based food. Sources of VitD are fatty fish, fish liver oil, egg yolk and VitD-fortified foods and supplements. Human skin is the main site in which D3 is synthetized by UVB (wavelength 290–320 nm) mediated chemical modification of 7-dehydrocholesterol. Since D3 production in the skin depends upon the amount of UVB irradiating the dermis and the availability of 7-dehydrocholesterol, levels of VitD are affected by the season, latitude, clothing and skin exposure. Lower circulating VitD levels are usually found in elderly people because of lower bioavailability of 7-dehydrocholesterol and structural changes of the skin. Both D2 and D3 however act as prohormones and once activated exert the same biological activity.

VitD2 and D3 are equally efficiently metabolized by the liver to generate 25OHD (calcidiol or calcifidiol) by the cytochrome P450 enzyme CYP2R1 [4]. 25OHD circulates in the blood bound to the VitD binding protein (DBP) [5]. The next crucial step in VitD metabolism is the endocytic internalization of the complex 25OHD-DBP by the kidney proximal tubule cells mediated by the transmembrane protein megalin [5]. Subsequently, the proximal tubule cells hydroxylate 25OHD by the Cyp27B1 1α-hydroxylase to $1,25(OH)_2D$ (calcitriol) that is the active form of VitD. that also circulates in the blood bound to DBP [2,3].

DBP [6] is a multifunctional glycoprotein that in addition to bind and transport VitD metabolites modulates inflammatory and immune responses and controls bone development. Three alleles and more than 120 racial variants have been described for BNP. The main phenotypes described for BNP are DBP-1-1, DBP2-1 and DBP2-1 that have geographical and racial distribution. DBP Alleles and variants bind with different affinities VitD metabolites, influencing their circulating levels. Blood concentrations of both VitD metabolites and BNP decrease according to BNP phenotype, with DBP1-1 > DBP2-1 > DBP2-2. Many studies have shown the relationship between DBP alleles and variants with susceptibility to different diseases, including autoimmune conditions.

2.2. Synthesis of the active metabolite calcitriol

Although the kidney proximal tubule is the main site producing calcitriol, 1α-hydroxylase is present in many extra-renal tissues [7], determining intracrine and paracrine loops of calcitriol in the regulation of cell growth and activity in many different tissues. 25OHD is converted into calcitriol also in immune and

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inflammatory cells. *Cyp27b1* null mice, that have undetectable levels of 1,25$(OH)_2$D and develop rickets, low blood calcium and secondary hyperparathyroidism, represent the animal model of VitD dependent rickets type 1 (VDDRI) [8]. Human VDDRI, also termed pseudo VitD deficiency rickets, is due to inactivating mutations or deletions of CYP27B1 [9].

2.3. VitD receptors

Calcitriol exerts its multiple biological activities through the binding to the nuclear ligand binding domain (LBD) of the VitD Receptor (nVDR) [10–12] that functions as a transcription factor. The complex calcitriol-VDR binds to DNA regulatory elements termed VitD responsive elements (VDREs) in the DNA, inducing the recruitment of other DNA binding proteins (eg retinoid X receptor - RXR) and other co-regulatory elements that will exert the genomic effects of nVDR that is expressed in a multitude of different cells type, including monocytes, macrophages and activated lymphocytes [13].

Although it is well recognized that the key VitD biological activity mediated by nVDR is the regulation of calcium and phosphate metabolism [10–12], it is equally well known that VitD regulates the expression of thousands different genes involved in the regulation of differentiation, activation and proliferation of many cell types, including immune and inflammatory cells. These findings provide the biological rationale for the potential involvement of VitD in many different pathological conditions including cancer [14], chronic conditions like autoimmune and cardiovascular diseases, and infections [13,15,16].

Calcitriol may exert also non-genomic actions [17] through binding to a distinct VDR (termed membrane VDR, mVDR) [18] that is complexed to caveolin-1 at the cell surface and the perinuclear area. Binding of calcitriol to mVDR activates intracellular signalling molecules such as PKC, PI3K and MAP kinases that, in turn, activate additional transcriptional factors like SP1, SP3 and RXR.

Another mechanism of calcitriol-nVDR is modulation of target proteins (eg IFN-α and TNF-α) by binding of the calcitriol-nVDR complex to transcriptional factors as STAT1 and IKKβ, thus proving an additional mechanism by which VitD modulates inflammatory mediators [19]. Moreover, nVDR can interact, independently from calcitriol binding, with transcriptional factors and kinases to modulate immune and anti-viral responses and cell death [17].

Loss of function mutations of the nVDR generate the pathological condition known as hereditary VitD resistant rickets (HVDRR), a rare autosomal recessive disorder due to unresponsiveness to VitD [20]. Symptoms include hypocalcemia, hyperparathyroidism and early-onset rickets. The finding that administration of intravenous calcium can reverse the HVDRR phenotype confirms the crucial role played by VitD in inducing the intestinal absorption of calcium [21].

In addition to mutations associated with hereditary rickets, more than 70 different gene polymorphisms have been described for the VDR gene [22]. The most studied SNPs are BsmI, ApaI, TaqI and FokI. Cellular responses to calcitriol depend not only on the density in cells of VDR but also on the specific polymorphism of VDR. Polymorphisms of VDR have been associated with a number of pathological conditions, including inflammatory and autoimmune conditions.

3. Physiological activities of VitD

The key skeletal function of calcitriol is tight regulation of calcium and phosphate levels, primarily for mineralization of bone [23,24] (Fig. 1). Normal calcium levels are also essential for neuromuscular function, vasodilatation, nerve transmission and endocrine function and so forth.

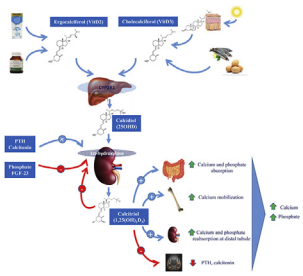

Fig. 1. Active VitD is synthetized starting from VitD2 (ergocalciferol) and VitD3 (cholecalciferol). D2 is human made and added to foods and supplements. D3 in synthetized in the skin by UVB (wavelength 290–320 nm) mediated chemical modification of 7-dehydrocholesterol and absorbed via animal-based food. VitD2 and D3 are metabolized by the liver to generate 25OHD (calcidiol or calcifidiol) by the cytochrome P450 enzyme CYP2R1. Next the renal proximal tubule cells 1α-hydroxylate 25OHD by the Cyp27B1 to 1,25$(OH)_2$D (calcitriol) that is the active form of VitD that binds to nuclear VitD receptor. Calcitriol increases circulating calcium levels by upregulating calcium absorption in the intestine, mobilizing calcium from bones, increasing calcium resorption in the kidney distal tubule and by suppressing the transcription of calcitonin and PTH. Calcitriol regulates also phosphate levels by upregulating intestinal absorption. Conversion of the inactive metabolite 25OHD to the active form calcitriol is upregulated by PTH and calcitonin, whereas downregulated by FGF-23 and phosphate.

Calcitriol increases circulating calcium levels by multiple mechanisms [23,24]: 1. Upregulation of the intestinal absorption of calcium. In the absence of calcitriol, only 10–15% of dietary calcium can be absorbed at the intestinal level [24]; 2. formation and activation of osteoclasts through the stimulation of the ligand for receptor activator for nuclear factor k B (RANKB) [25,26]; 3. Suppression of the transcription of calcitonin and PTH [27]; 4. induction of the reabsorption of calcium in the kidney distal tubule [28–31].

Calcitriol regulates also phosphate levels by upregulating intestinal absorption. In the absence of calcitriol, about 60% of dietary phosphate is absorbed. Calcitriol also induces the expression of FGF-23 in osteoclasts that results in phosphate excretion in the kidney [28–30].

Levels of 25OHD below 30 ng/ml are associated with low calcium levels that in turn activate the production of PTH (secondary hyperthyroidism), resulting in hypophosphatemia, bone loss and increased risk of fracture [32]. Inadequate levels of calcium and phosphate induce insufficient mineralization of bone collagen matrix, leading to rickets in children and osteomalacia in adults [28–30].

Optimal prevention of both nonvertebral and hip fracture occurred only in intervention trials providing a VitD supplementation sufficient to obtain concentration of 25OHD of at least 40 ng/ml, whereas little if any benefit could be found if levels of 26 ng/ml (65 nmol/L) or less were achieved [33–35].

4. VitD levels and sufficiency

4.1. VitD dietary allowance

What should be defined as an optimal intake of VitD to secure skeletal and non-skeletal beneficial effects of VitD is still debated [35–42]. The Institute of Medicine (IOM) [43] recommends 200 international units (IU) (5.0 μg) of VitD daily from birth through age 50, whereas people aged 51–70 years should take 400 IU (10 μg) and 600 IU (15 μg) are recommended after 70 years of age. The Dietary Guidelines for Americans from U.S. Department of Health and Human Services and U.S. Department of Agriculture

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[44] recommends fortified foods and supplements to older adults, people with dark skin, and people exposed to insufficient UVB radiation. Similar recommendations were issued by The American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention [45]. However, up to 800–1000 IU (20–25 μg) daily [46,47] have been also suggested by others. In spite of guidelines and recommendations, almost 1 billion people may be exposed to VitD insufficiency [3].

Supplementation can be either D2 or D3. US regulations prescribe fluid milk is fortified with 385 IU/L of VitD. In Canada, fortification of fluid milk (350–450 IU/L) is mandatory. In addition to milk, other foods are fortified with VitD, including breakfast cereals, yogurts, cheeses and juices, all of which usually contain 40–100 IU VitD per regular serving. Since the human milk is low in endogenous VitD, FDA requires that infant formula must contain 40–100 IU of VitD per 100 kcal.

4.2. VitD deficiency

No common definition exists for adequate VitD status measured as 25OHD serum concentrations. Whereas VitD deficiency in adults is defined by the IOM [43] as serum 25OHD concentrations of less than 12 ng/ml (mid-range between 8 and 15 ng/mL), sufficiency by others has been defined as serum 25OHD concentrations between 20 ng/ml (50 nmol/L) and 32 ng/ml (80 nmol/L) [48–50]. The Endocrine Society defines deficiency as 25OHD below 20 ng/ml and insufficiency 20–29 ng/ml [51].

4.3. Methods to measure circulating VitD

Typically, the form that is used for monitoring VitD status is the inactive metabolite 25OHD, that is considered an appropriate marker of total exposure (endogenous and external from food and supplements) of the body to VitD. 25OHD has a plasma half life of 3 weeks, whereas the active metabolite calcitriol has a much shorter half life, approximately 5–8 h.

Some clinical laboratories use conventional units for 25OHD (ng/ml) whereas others use international system (IS) units (nmol/L). The conversion factor to IS units is: 1 ng/ml = 2.496 nmol/L.

Availability of simple, accurate and reproducible assays to detect VitD levels in biological fluids is key to identify accurately patients that may benefit from VitD supplementation. The two main types of methods to measure serum 25OHD are respectively the competitive immunoassay and chromatographic separation followed by non-immunological direct detection (HPLC, LC-MS/MS).

Until recently, the lack of a reference standard for 25OHD has been a major issue resulting in poor comparability between methods. However, in November 2010, the National Institutes of Health Office of Dietary Supplements established the VitD Standardization Program (VDSP), an international collaborative effort to standardize the laboratory measurement of VitD status and provide commutability of results. The commutability now allows for pooling results from different studies.

Even if the standardization helped to improve the comparison among immunoassays methods, still substantial bias has been observed between some specific immunoassays and LCMS. Although different immunoassays have overall good performance, one specific immunoassay was found to be comparable to LC-MS/MS across the measuring range [52].

Of all the steroid hormones, calcitriol has represented the most difficult challenge to the analytical biochemist with respect to quantitation, inasmuch as it circulates at low picogram per milliliter concentrations (too low for direct UV quantitation), is highly lipophilic and relatively unstable, and its precursor 25OHD circulates at concentrations in excess of 1000 times that of $1,25(OH)_2D$.

Recently, we developed a simple, accurate and automated chemiluminescent immunoassay [53] that exploits the conformational change of the ligand binding domain of nVDR induced by calcitriol binding [54] for the quantitative detection of calcitriol. In the assay the recombinant LBD of nVDR is added to the patient serum. Assay reaction conditions have been defined that favour binding of calcitriol to added recombinant LBD vs. endogeneous DBP. A novel monoclonal antibody that specifically recognizes the unique recombinant LBD-calcitriol complex conformation has been generated and used to capture the complex calcitriol-LBD in a competitive fully automated immunoassay to quantify calcitriol in biological fluids. This method has been found to be superior to all previous bioanalytical assay methods, due to its enhanced precision and accuracy. The accuracy and precision of this new assay has been independently validated and has exhibited outstanding performance in the VitD External Quality Assurance Scheme (DEQAS) Scheme DVDEQA [55].

The new calcitriol assay allowed detection in clinical samples in the expected range, with a lower degree of variance as compared to LCMS [56]. Two studies [57,58] showed that the ratio $1,25(OH)_2D$/PTH(1–84) strongly and independently predicts cardiovascular mortality in chronic heart failure (HF) and might be a promising risk marker of deterioration of renal function in patients with chronic HF and mild renal impairment. This new assay for calcitriol quantitation will allow studies previously inhibited by large sample requirements, low throughput in sample processing and unreliable results, providing unprecedented simplicity, accuracy and fast results.

Below, in this Review we will cite epidemiological evidence and data from animal models that lack of VitD is correlated with different immunological disease states, and that sufficiently high VitD levels can protect against certain disease. However, the causal link between level of VitD and the susceptibility to or protection against a particular immune disease is not always evident. Moreover, even in cases where there exists an apparent causal link between VitD deficiency and a disease state, intervention studies have not always been successful, as exemplified by IBD. A possible mechanism behind this discrepancy could be that while the active molecule is calcitriol, virtually all studies on serum levels of VitD has measured the inactive precursor 25OHD. Whereas measuring 25OHD levels represents an appropriate tool to assess the total exposure of the body to endogenous and external VitD, testing the active metabolite in certain clinical conditions might help solving the discrepancies between epidemiological and interventional studies.

5. Modulation of immune and inflammatory cells by calcitriol

5.1. General effects

Calcitriol modulates activation, proliferation and differentiation of immune and inflammatory cells through the nVDR expressed in these cells [59–64]. Immune and inflammatory cells can also convert 25OHD into calcitriol [65–69]. CYP27B1 is upregulated by immune stimuli (eg IFN-γ and lipopolysaccharide (LPS)) that activate the C/EBPβ transcription factor that binds to the mouse and human CYP27B1 genes [70].

Calcitriol reduces the production of type 1 proinflammatory cytokines (IL-12, IFN-γ, IL-6, IL-8, tumor necrosis factor-α, IL-17, IL-9) and increases the production of type 2 anti-inflammatory cytokines (IL-4, IL-5, and IL-10) [71,72]. Cytokine regulation by calcitriol is mainly mediated by blocking NF-κB p65 activation via upregulation of the NF-κB inhibitory protein IκBα [73–75]. Moreover, calcitriol enhances the generation and activation of T regulatory

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(Treg) cells [76] and upregulates the generation of tolerogenic DCs [77].

In more details, here below we summarize the main activities exerted by calcitriol on the different immune and inflammatory cell populations.

5.2. Dendritic cells (DCs)

DCs are antigen-presenting cells (APCs) that patrol tissues for potential pathogens by processing foreign antigens and presenting them as peptides to T cells that subsequently differentiate into effector cells.

Treatment of dendritic cells with calcitriol induced a decreased production of pro-inflammatory cytokines (eg IL-12 and TNF-α) and increased production of the anti-inflammatory cytokine IL-10 [78–80]. Calcitriol suppressed IL-12 expression by binding of VDR/RXR to the NF-kB site in the IL-12p40 promoter [81].

Moreover, in addition to favouring anti-inflammatory cytokine production, calcitriol reduces in dendritic cells also the expression of class II MHC and costimulatory molecules (CD40, CD80, CD86). These DCs are poor inducers of T cell proliferation and activation, induce the differentiation of Treg cells [80,82,83] and activate apoptosis in autoreactive T cells [84]. The mechanism by which calcitriol induces tolerogenic DCs is not fully understood.

5.3. Monocytes and macrophages

Activated macrophages, that are also APCs, produce inflammatory mediators to recruit additional cell types at the inflammatory site to eliminate the pathogens. Macrophages are classically divided into the M1 and M2 macrophages. M1 macrophages produce pro-inflammatory mediators (eg nitric oxide, TNF-α, IL-23, IL-12, and IL-1β), eliminate pathogens and promote the polarization to T helper 1 (Th1) and Th17 cells. M2 macrophages produce the IL-10 that has anti-inflammatory properties [85].

In monocytes, activation of Toll-like receptors and IFN-α upregulate Cyp27B1, thus inducing autocrine and paracrine production of calcitriol [86]. High levels of calcitriol produced by macrophages of patients with sarcoidosis [87] and Crohn's disease [88] are responsible for the hypercalcemia and hypercalciuria frequently observed in these patients. In monocytes and macrophages, calcitriol induces the production of cathelicidin, thus contributing to antimicrobial activity [89].

Whereas calcitriol stimulates the differentiation of monocytes to macrophages [90], available data suggest it has anti-inflammatory activity on macrophages by decreasing the production of pro-inflammatory factors such as IL-1β, IL-6, TNF-α, RANKL and COX-2, and inducing the anti-inflammatory IL-10 [72].

Calcitriol inhibits COX-2 by induction of the thioesterase superfamily member 4 (THEM4) that counteracts the binding of NFκB to the COX-2 locus, thus reducing COX-2 transcription [91]. THEM4 inhibits also IL-6 and TNF-α by preventing the NFκB mediated induction of miR-155 that suppresses SOCS1 [92]. Consistently with the data above, VDR−/− mice are less responsive to LPS stimulation [93].

5.4. B cells

B cells contribute to immune reactions by multiple ways: produce antibodies, differentiate to plasma cells, act as APCs, and secrete several cytokines modulating the activity of other immune and inflammatory cells. In antibody-mediated autoimmune conditions, B cells play a key role in generating the auto-reactive antibodies.

Calcitriol exerts different activities in the various stages of B cell differentiation. On B cells, calcitriol has inhibitory activities on proliferation, immunoglobulin class switching and antibody production, and induces apoptosis [94–96].

Calcitriol upregulates IL-10 production by B cells by binding directly to the IL-10 promoter region [97]. However, healthy controls and relapsing-remitting MS did not show any correlation between 25OHD levels and B cells producing IL-10 [98]. Calcitriol downregulates CD86 expression on B cells, suggesting a reduced stimulation of T cells [99] and the expression of CD74, that contributes to the assembly and surface exposure of MHC-II molecules [100].

Calcitriol inhibits differentiation of B cells to plasma cells [101], an effect that can be mediated by affecting the NF-kB pathway downstream to CD40 activation [102].

The absence of VitD activity in VDR KO mice is associated with increased production of IgE in vivo. In vitro, unresponsiveness of B cells (but not T cells) to VitD is also associated with augmented expression of IgE. This effect is reverted by addition of IL-10. These data might be relevant in view of the association between VitD deficiency with asthma and allergy [103].

5.5. T cells

Whereas naive T cells do not respond to VitD, nVDR expression is induced by TCR signalling [62,104,105] via MAPK p38 [106]. The effects of calcitriol on TCR-stimulated T lymphocytes are different in T cell subpopulations.

5.5.1. CD4+ T cells

Different T cells belong to the group of $CD4^+$ T cells, namely Th1, Th2, Th17, and Treg cells. Calcitriol inhibits IFN-γ production in Th1 cells [107,108] and $CD4^+$ T cells from VitD receptor KO mice produce higher levels of IFN-γ and IL-17 than their wild type counterparts [109]. Inhibition of IFN-γ expression is a consequence of VDR/RXR binding to a silencer region in the hIFN-γ promoter [110]. Calcitriol also inhibits IL-2 production in Th1 cells, by inhibition of the NFAT/AP-1 complex by VDR/RXR and Runx 1 sequestration by nVDR [111].

In Th2 cells calcitriol inhibits IL-4 production in naïve CD62 ligand-$CD4^+$ T cells during in vitro polarization [108,112], and this effect is more evident when the ligand is present from the unset of the differentiation process (108). However, in activated (CD62 ligand-$CD4^+$) T cells calcitriol does not affect IL-4 production (108). Other studies have shown that in Th2 cells cultured in the absence of polarizing cytokines calcitriol induces IL-4 and GATA3 [113,114].

In vitro Th17 cells differentiation and activation are inhibited by calcitriol. This effect is mediated by the inhibition of production of Th17-related cytokines and transcription factors such as IL-17A, IL-17F, RORC, and CCR6 [115,116]. Th17 cells in the presence of calcitriol are less effective in activating synovial fibroblasts [117] and in mediating Experimental Autoimmune Encephalitis (EAE) after adoptive transfer [74]. The VDR-RXR complex inhibits IL-17A production by multiple mechanisms: competition with NFAT binding to the IL-17A promoter [74], the inhibition of Smad7 transcription [118], sequestration of Runx1 by VDR, and induction of Foxp3 (which associates with and inhibits NFAT and Runx1 function) [78]. Calcitriol diminishes Th17 development partially through inhibition of the transcription factor RORυt, both in the presence and absence of IL-23 signalling [74].

Calcitriol also reduces the frequency of CCR6+ cells producing both IFN-γ and IL17A (non classic Th1 cells) [117].

Tregs are $CD4^+$ $CD25^+$ T cells that downregulate the activity of macrophages, DCs, $CD4^+$ and $CD8^+$ T cells, produce the anti-inflammatory cytokines IL-10 and TGFβ, and express the inhibitory co-receptor CTLA4. These cells express and are programmed by the transcriptional factor FoxP3 [119] and patients with mutated

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FoxP3 suffer from the IPEX syndrome characterized by autoimmune disorders [120].

At the molecular level, calcitriol upregulates the expression of FoxP3 by binding to the FoxP3 promoter [74,121]. Calcitriol induces Tregs differentiation in vitro and in vivo in mice [74,118]. In multiple sclerosis (MS) patients, the suppressive capacity of Tregs correlates with the serum calcitriol levels [122]. Expression of IDO, that is known to increase the number of Treg cells, is augmented by calcitriol [123].

Although in vitro calcitriol induces Treg cells, supplementation studies are inconclusive. Whereas some studies suggest calcitriol can increase Treg cell numbers [124], another study could not confirm this finding [125].

5.5.2. Cytotoxic $CD8^+$ T cells

Calcitriol inhibits in CD8 T cells the production of IFN-γ and TNF-α [126]. Data in vivo suggest that calcitriol downregulates $CD8^+$ T cells, inasmuch as VDR −/− mice show an increased number of $CD8^+$ T cells [126].

5.5.3. Unconventional T cells

TCRγδ T cell recognize phosphoantigens and are involved in the response to infections with intracellular pathogens. These cells, that produce several inflammatory cytokines (IL-17A, IL-17F, GM-CSF, TNF-α, and IFN-γ) [127], are likely to play a role in mouse autoimmune models like EAE and Collagen Induced Arthritis (CIA). Calcitriol inhibits IFN-γ production by activated TCRγδ T cells [104]. Although their main contribution to autoimmune disease might be through the production of IL17A, modulation of IL-17A production by calcitriol in these cells has not been reported.

Maturation and function of invariant NKT cells (iNKT) are modulated by calcitriol. Development of functionally mature iNKT cells depends upon the expression of functional nVDR in the thymus and VDR−/− mice express iNKT that respond poorly to TCR stimulation [128]. It has been suggested that the protective role of calcitriol in the EAE model might be mediated by the induction of production of IL-4 from iNKT cells [129].

5.5.4. Innate lymphoid cells (ILC)

ILCs include different cell types that may play a role in tissue repair and homeostasis but also in immune responses to different microorganisms. In NK cells (that belong to the group 1 of ILC) whereas some studies have shown calcitriol induces the cytolytic killing capacity [130], other studies have shown that calcitriol inhibited the development of NK cells, their cytotoxicity and IFN-γ production [131].

Increased levels of group 3 ILC cells have been found in different autoimmune conditions, including psoriasis [132], Crohn's disease [133] and MS [134]. *In vivo* absence of VitD signalling (as in VDR-KO mice) is associated with augmented levels of ILC1 and ILC3 [135]. However, on the other hand, ILC subsets were not changed in the skin lesions of psoriatic patients treated with the VitD analogue calcipotriol [136].

Table 1 recapitulates the key effects of calcitriol on immune and inflammatory cells.

6. VitD in inflammatory diseases

As summarized above, VitD has multiple regulatory effects on differentiation, proliferation and activation of different cell types belonging to both innate and acquired immune system. These studies have suggested the possibility that VitD levels might be relevant in different pathological situations in which immune and inflammatory cells play a key role.

The potential role of VitD in inflammatory and autoimmune diseases is also underlined by the correlations between DBP or VDR polymorphisms and the susceptibility to autoimmune and inflammatory disease [6 and 22 for reviews]. Frequently such associations with specific clinical conditions have a racial distribution, underlying the importance of other genetic factors in determining susceptibility to diseases. Meta-analysis methods are usually used to balance the recruitment bias and low numbers usually found in single epidemiologic genetic studies.

DBP polymorphisms have been found to correlate with some inflammatory and autoimmune conditions, like asthma, RA and IBD. A significant association was detected between RA and a specific SNP in the DBP gene. The haplotype DBP2 was more frequent in the non-IBD population. Although not confirmed in other populations, a strong association was found between the DBP2-2 group and susceptibility to active tuberculosis in Gujarati Asians. However the association could be observed only in VitD deficient patients. DBP2 carriers may have especially low levels of circulating VitD. On the contrary, genetic studies could not find an association of DBP polymorphisms and MS and T1D.

As to VDR, an association between VDR polymorphisms and susceptibility to UC and Crohn'n disease has been found. A recent meta-analysis from 13 case-control studies showed that there were no significant associations between TaqI and BsmI polymorphisms, whereas a significant association was described with the ApaI group. A meta-analysis confirmed that the VDR FokI polymorphism contributes to the risk of tuberculosis, especially in HIV-negative and in the Asian group. The VDR BsmI allele was associated with T1D in Asians but not in the overall population. A meta-analysis of psoriasis patients revealed no significative correlation with VDR polymorphisms.

6.1. Asthma (Tables 2 and 3)

Asthma is a chronic inflammatory condition characterized by reversible obstruction, cellular infiltration and inflammation of airways. The overall effects of calcitriol on the different cell types involved in asthma are decreased airway hyper-responsiveness, inflammation and remodelling [137,138].

In airway muscle cells, calcitriol reduces proliferation, production of inflammatory cytokines, matrix metalloproteases and mucus secretion [139,140]. In innate immunity, calcitriol inhibits differentiation, migration and cytokine production from different cell types involved in asthma including mast cells, neutrophils and eosinophils [141].

Epidemiological studies have correlated VitD levels with asthma symptoms and progression in different populations. Low maternal VitD intake and levels during pregnancy are correlated to wheezing in offspring [142]. In children, low serum levels of 25OHD are associated with an increased risk for asthma, along with increased symptoms and exacerbations, and reduced lung function [reviewed in [143]]. In VitD sufficient children a positive correlation was found between serum 25OHD levels and control of asthma [144]. However, another study found there is no correlation between VitD levels and airway reactivity and inflammation, and allergy [145]. In a meta-analysis, World Allergy Organization found no support for VitD supplementation to reduce the risk for allergic conditions in children [146].

In adults some studies found VitD insufficiency is associated with severe or uncontrolled asthma [147] and patients with low 25OHD levels had greater decline in lung function compared to high VitD levels especially in never smokers and non inhaled corticosteroids patients [148]. Elderly asthmatics are frequently VitD deficient or insufficient [149]. VitD deficiency in adults with asthma was a significant baseline predictor of all-cause mortality [150], although the reduced exposure of old people to UVB radiation must

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Table 1
Summary table on effects of calcitriol on immune and inflammatory cells.

Target cells	Effects		References
	Suppression	Induction	
Dendritic Cells.	Pro-inflammatory cytokines. Class II MHC and costimulatory molecules (CD40, CD80, CD86).	Anti-inflammatory cytokine IL-10. Tolerogenicity.	[78–80,82–84]
Monocytes and macrophages.	Pro-inflammatory cytokines IL-1β, IL-6, TNFα, RANKL and COX-2.	Anti-inflammatory cytokine IL-10. Cathelicidin (anti-microbial).	[72,88]
B-cells.	Proliferation, immunoglobulin class switching & production. CD 86 and CD74 (reduced T-cells stimulation and MHC-II assembly). B-cells to plasma cells.	Apoptosis. Anti-inflammatory cytokine IL-10.	[94–96,98–101]
$CD4^+$ T cells.	IFN γ and IL-2 in Th1 cells. Th17 differentiation and activation by the inhibition of IL-17A, IL-17F, RORC, and CCR6. IL-4 in naïve CD62 ligand + $CD4^+$ T cells during in vitro polarization.	IL-4 and GATA3 in cultures driven by Ag, anti-CD3 and CD28. FoxP3 and Tregs differentiation in vitro and in vivo in mice.	[74,107,108,111–116,121]
$CD8^+$ T cells.	IFNγ and TNFα.		[126]
Unconventional T Cells.	IFN-γ.	Invariant NKT cells (iNKT).	[104,128]
Innate Lymphoid Cells.	NK development.	Cytolytic killing capacity.	[130,131]

be taken into account. Other studies suggest there is no correlation between VitD status and asthma severity and control [151,152].

Whereas supplementation with VitD of pregnant women did not reduce significantly wheezing episodes, asthma diagnosis and number of upper and lower respiratory tract infections of offspring [137,153–156], promising results were obtained in VitD deficient children in which the VitD supplementation reduced respiratory infections and asthma symptoms [157–159]. The ongoing VITALITY trial will provide more answers to the role of postnatal VitD supplementation in infant immune health [160]. However, the data in children were not confirmed in VitD deficient adults, in which VitD supplementation did not reduce asthma exacerbations, although when the analysis was restricted to patient achieving 30 ng/ml 25OHD or higher there was a significant reduction [161,162]. No effects in adults were also observed when VitD was administered in bolus [163]. Further studies are needed to unequivocally define the utility of VitD supplementation in asthma.

6.2. *Inflammatory bowel disease (IBD)*

IBD, that includes Crohn's disease and ulcerative colitis (UC), is a chronic remittent or progressive inflammation of the gastrointestinal tract. IBD patients are at increased risk for developing colon cancer compared to the general population [164], in line with the general concept that inflammation can play a role in cancer development through promotion of angiogenesis and production of tumor-promoting cytokine and chemokines [165].

In addition to modulating many of the inflammatory and immune cells involved in IBD [166,167], VitD also affects intestinal cell integrity and functionality. VDR KO mice show impaired epithelial cell tight junctions that result in increased susceptibility to and severity of colitis [168] and also an increase of *Bacteroides fragilis*, that has been associated with IBD in humans [169,170]. Conversely, mice overexpressing VDR in intestinal mucosal cells have preserved tight junctions and are protected against colitis [171]. Along the same line, dextran sulfate sodium (DSS) colitis is more severe in mice lacking CYP27B1 [172].

Mice fed a VitD deficient diet are more susceptible to DSS-induced colitis [173]. IL10−/− mice exposed to a VitD deficient diet or lacking VDR or CYP27B1 show more severe disease compared to VitD sufficient animals [174,175].

Supplementation studies gave inconsistent results using different animal models of IBD. Whereas VitD supplementation proved to be beneficial in Smad −/− mice and DSS colitis [176], supplementation of mice in an adoptive T cell transfer model of colitis [177] and in infection with *Citrobacter rodentium* [178] did not induce any improvement. In IL10−/− mice fed either 25 IU or 5000 IU VitD per kg diet in the food throughout life until 3 mo of age, there were no differences in incidence or severity of disease [179]. Whereas VitD treatment attenuated 2,4,6-trinitrobenzene sulphonic acid (TNBS)-induced colitis, oxazolone-induced colitis did not benefit [180].

Human epidemiological studies [166 for review] have shown that low VitD levels from low UVB exposure at northern latitudes correlate with increased risk of IBD both in the United States and in Europe [181]. VitD deficiency has also been associated with onset of IBD [182], increased clinical disease activity [183], and risk of malignant transformation [184] and UC [185]. Intestinal VDR expression was lower in patients with active Crohn's disease compared to those with quiescent disease [186]. A key limitation of epidemiological studies is that they cannot discriminate if VitD deficiency is a cause or consequence of IBD.

In intervention studies [166 for review], oral supplementation (1200 IU VitD3) increased serum 25OHD levels but insignificantly reduced the risk of relapse from 29% to 13% [187] in human IBD. However, in another study, after 24 weeks supplementation with up to 5000 IU VitD decreased the Crohn's Disease Activity Index scores [188].

6.3. *Respiratory tract infections (RTI) (Table 4)*

Human airway epithelial cells express both VDR and 1α-hydroxylase [189]. Calcitriol produced by airway epithelial cells and locally by inflammatory cells can induce the production of the antimicrobial peptides cathelicidin and defensin β4. Cathelicidin has also antiviral activity on influenza and respiratory syncytial virus (RSV) [189–191]. The innate immune protein hCAP-18, which is capable of killing viruses and bacteria, is upregulated by calcitriol [192].

Experimental animal models of infection have generated contrasting results. Whereas VitD-deficient mice are more susceptible to *Mycobacterium bovis* infection than WT mice due to an effect on NO production [193], VDR KO can clear *Listeria monocytogenes* following either primary or secondary infection as well as wild type animals [194]. As mentioned above, calcitriol inhibits production of IL-17, an effect that can be beneficial in inflammation but detrimental in infections inasmuch as IL-17 may also plays a protective role against infection by induction of antimicrobial peptides and neutrophil chemokines [195–198]. Along this line, $1,25(OH)_2D$ may impair host defense against *Citrobacter rodentium* by suppressing Th17 T cell responses in vivo [178].

Epidemiological studies in pregnancy and newborns have

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Table 2
Asthma - Epidemiological studies.

Trial Design	Measurements	Results	Reference
1194 mother-child pairs.	Maternal intake of vitamin D during pregnancy assessed from a validated food-frequency questionnaire. Recurrent wheeze, ie, a positive asthma predictive index (≥2 wheezing attacks among children with a personal diagnosis of eczema or a parental history of asthma).	Compared with mothers in the lowest quartile of daily intake (median: 356 IU VitD), those in the highest quartile (724 IU) had a lower risk of having a child with recurrent wheeze (odds ratio (OR): 0.39; 95% CI: 0.25, 0.62; *P* for trend <0.001). A 100-IU increase in vitamin D intake was associated with lower risk (OR: 0.81; 95% CI: 0.74, 0.89). Adjustment for 12 potential confounders, including maternal intake of other dietary factors, did not change the results.	[142]
102 pre-school children, aged 1−4 years with asthma and 102 healthy controls in winter.	Asthma control classified according to the Global Initiative for Asthma (GINA) guidelines and the Test for Respiratory and Asthma Control in Kids (TRACK) in 1−4 years-old children	Serum vitamin D levels: - 22.64 ng/ml in the asthma group - 32.11 ng/ml in the control group (p = 0.001). Total number of exacerbations during the previous year significantly lower in the vitamin D sufficient group, compared to the deficient and insufficient groups (p = 0.03). Frequency of patients with controlled asthma higher in the sufficient group compared to the deficient and insufficient groups (p = 0.001 and p = 0.001, respectively).	[144]
71 non-obese children (6−18 y old) with asthma who were not receiving anti-inflammatory treatment.	Spirometry with a methacholine challenge test, fractional exhaled nitric oxide (F_{ENO}), serum vitamin D levels, total immunoglobulin E (IgE) levels, blood eosinophil counts, and high-sensitivity C-reactive protein levels.	No correlation between vitamin D level and response to the methacholine challenge test, F_{ENO}, high-sensitivity C-reactive protein levels and IgE levels	[145]
280 adult asthma patients.	Clinical parameters of asthma control.	25OHD concentrations in adult asthmatics were low (25.6 ±11.8 ng/ml) and vitamin D insufficiency or deficiency (vitamin D < 30 ng/ml) found in 67% of asthma patients. 25OHD levels were related to asthma severity (intermittent: 31.1 ± 13.0 ng/ml, mild: 27.3 ± 11.9 ng/ml, moderate: 26.5 ± 12.0 ng/ml, severe: 24.0 ± 11.8 ng/ml, p = 0.046). 25OHD levels were related to asthma control (controlled: 29.5 ± 12.5 ng/ml, partly controlled 25.9 ± 10.8 ng/ml, uncontrolled: 24.2 ± 11.8 ng/ml, p = 0.030). The frequency of vitamin D insufficiency or deficiency significantly higher in patients with severe or uncontrolled asthma and was associated with a lower forced expiratory volume in 1 s (FEV1) (vitamin D < 30 vs. ≥30 ng/ml 2.3 ± 0.9 L vs. 2.7 ± 1.0 L, p = 0.006) and sputum eosinophilia (5.1± 11.8% vs. 0.5± 1.0%, p = 0.005). The use of oral corticosteroids or sputum eosinophilia associated with a 20% or 40% higher risk of vitamin D insufficiency or deficiency.	[147]
395 adults with asthma.	VitD levels and lung function parameters assessed at baseline and 11 years later.	Participants with low 25OHD (<50 nmol/L) had more decline in lung function measurements for FEV1 (388 mL), forced vital capacity (298 mL), and the FEV1/forced vital capacity ratio (3.7%) over the follow-up, compared with those with high 25(OH)D (≥50 nmol/L) who declined 314 mL, 246 mL, and 3.0%, respectively (P = 0.08, 0.30, and 0.23, respectively). The associations were stronger in never smokers and non-inhaled corticosteroids (ICS) users. In never smokers, low 25OHD levels were associated with more decline in FEV1 (445 vs. 222 mL) (P = 0.01). In non-ICS users, low 25OHD levels were associated with more decline in FEV1 (467 vs. 320 mL) (P = 0.02).	[148]
28 asthmatic, 65 years old and older.	VitD assessed at baseline.	Twenty nine percent of subjects were deficient and 50% insufficient in serum vitamin D at baseline.	[149]
9,566,000 adults with current asthma.	VitD assessed after median follow-up of 15 years.	VitD levels were a significant baseline predictors of higher all-cause mortality (vitamin D level <30 vs ≥50 nmol/L: adjusted HR, 2.19; 95% CI, 1.05−4.58).	[150]
Multi-centre cross-sectional study in 297 adults with a medical record diagnosis of inhaled corticosteroids-treated asthma.	Serum 25(OH)D concentration. Fractional exhaled nitric oxide concentration (FeNO), spirometry and sputum induction for determination of lower airway eosinophil counts (n = 35 sub-group).	No association between vitamin D status and markers of asthma severity or control.	[151]
Random sample of 3471 persons. Of these, 2308 were re-examined 5 years later.	25OHD and specific IgE against four common inhalant allergens. Wheezing and asthma assessed from questionnaires. Lung function measured by spirometry.	No statistically significant associations between 25OHD and prevalence or incidence of asthma or wheezing. Associations with lung function were inconsistent.	[152]

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Table 3
Asthma - Intervention studies.

Trial Design	Measurements	Dosage	Results	Reference
Randomized controlled, ethnically stratified, 180 pregnant women at 27 weeks gestation administered with either no vitamin D or VitD. 158 offspring assessed at 3 years.	Primary outcome in offspring was any history of wheeze assessed by validated questionnaire. Secondary outcomes in offspring included atopy, respiratory infection, impulse oscillometry and exhaled nitric oxide.	800 IU ergocalciferol daily until delivery or single oral bolus of 200,000 IU cholecalciferol.	No difference between supplemented and control groups in risk of wheeze [no vitamin D: 14/50 (28%); any vitamin D: 26/108 (24%) (risk ratio 0.86; 95% confidence interval 0.49, 1.50; P = 0.69)]. There was no significant difference in atopy, eczema risk, lung function or exhaled nitric oxide between supplemented groups and controls.	[154]
Randomized, double-blind, placebo-controlled trial. 881 pregnant women between the ages of 18 and 39 years at high risk of having children with asthma randomized at 10–18 weeks' gestation to placebo or VitD. 806 infant born were included in the analyses for the 3-year outcomes.	Incidence of asthma and recurrent wheezing in children from VitD or placebo treated mothers.	440 women → daily 4000 IU vitamin plus prenatal vitamin containing 400 IU vitamin D. 436 women → placebo plus a prenatal vitamin containing 400 IU vitamin D.	The incidence of asthma and recurrent wheezing in children born from the 4000 IU Vitamin D group at age 3 years was lower by 6.1%, but this did not meet statistical significance.	[155]
623 women recruited at 24 weeks of pregnancy. Follow-up of the children (N = 581).	Age at onset of persistent wheeze in the first 3 years of life. Secondary outcomes included number of episodes of troublesome lung symptoms, asthma, respiratory tract infections, and neonatal airway immunology.	Vitamin D3 (2400 IU/d; n = 315) or matching placebo tablets (n = 308) from pregnancy week 24 to 1 week postpartum.	The use of 2800 IU/d of vitamin D3 during the third trimester of pregnancy compared with 400 IU/d did not result in a statistically significant reduced risk of persistent wheeze in the offspring through age 3 years.	[156]
Randomized, double-blind, placebocontrolled trial comparingvitamin D(3) supplements with placebo in schoolchildren.	The primary outcome was the incidence of influenza A, diagnosed with influenza antigen testing with a nasopharyngeal swab specimen.	1200 IU/d.	vitamin D(3) supplementation during the winter may reduce the incidence of influenza A which occurred in 18 of 167 (10.8%) children in the vitamin D(3) group compared with 31 of 167 (18.6%) children in the placebo group [relative risk (RR), 0.58; 95% CI: 0.34, 0.99; P = 0.04].	[157]
Randomized, double-blind, parallel-group, 6-month trial studying the effects of inhaled budesonide with or without vitamin D on 48 children from 5 to 18 years of age with newly diagnosed asthma and sensitive only to house dust mites.	clinical parameters of asthma control in children.	vitamin D-500 IU cholecalciferol.	during 6 months of treatment, the number of children who experienced asthma exacerbation was significantly lower in the steroid + D3 group than in the steroid group (n [%], 4 [17] vs 11 [46]; *P* = 0.029. In children with a decrease of 25(OH)D, the risk of asthma exacerbation was 8 times higher than in children with a stable or increased 25(OH)D serum level (odds ratio, 8.6; 95% CI, 2.1–34.6).	[159]
Randomized, double-blind, parallel, placebo-controlled trial studying adult patients with symptomatic asthma and a serum 25-hydroxyvitamin D level of less than 30 ng/mL 408 patients randomized.	The primary outcome was time to first asthma treatment failure (a composite outcome of decline in lung function and increases in use of β-agonists, systemic corticosteroids, and health care).	Oral vitamin D3 (100,000 IU once, then 4000 IU/d for 28 weeks; n = 201) or placebo (n = 207).	Vitamin D3 did not reduce the rate of first treatment failure or exacerbation in adults with persistent asthma and vitamin D insufficiency.	[161]
Randomized, controlled trial 250 adults with asthma	Prevention of asthma, exacerbation and upper respiratory infections.	Six 2-monthly oral doses of 3 mg vitamin D3 (n = 125) or placebo (n = 125) over 1 year.	Bolus-dose vitamin D3 supplementation did not influence time to exacerbation or URI in a population of adults with asthma with a high prevalence of baseline vitamin D insufficiency.	[163]

shown that VitD insufficiency is associated with respiratory infections [198]. Newborns with levels of 25OHD <20 ng/ml in the cord blood are more likely to develop respiratory syncytial virus (RSV) infection in the first year of life as compared with those with >30 ng/ml 25OHD [199]. Unlike the risk of wheezing (see above), higher maternal circulating 25OHD concentrations in pregnancy correlated with reduced risk of lower respiratory tract infections (LRTI) in offspring in the first year of life, although higher maternal midpregnancy 25OHD levels were associated with only a modestly reduced risk of recurrent LRTI by 36 months [200].

Epidemiological studies have shown a significant correlation between VitD levels and respiratory infections in children. Serum VitD below 50 nmol/L increased the risk of (RTI) in children by 70% [201] and serum 25OHD levels above 30 ng/ml are associated with better respiratory outcomes. Also in healthy adults, levels of 25OHD below 30 ng/ml were associated with an increased risk of RTI [202,203].

Significantly lower VitD levels were found in Tuberculosis (TB) patients vs controls. A recent meta-analysis of 25 studies involving 3599 TB cases and 3063 controls [204] shows that VitD deficiency is

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Table 4
RTI - Epidemiological studies.

Patient population	Measurements	Results	Reference
922 newborns.	Cord blood VitD levels. History of respiratory infection at 3 months of age. History of wheezing at 15 months of age and then annually thereafter. Incident asthma defined as doctor diagnosed asthma by the time the child was 5 years old and reported inhaler use or wheezing since the age of 4 years.	Follow-up was 89% at the age of 5 years. Adjusting for the season of birth, 25OHD in cord blood had an inverse association with risk of respiratory infection by 3 months of age (odds ratio: 1.00 [reference] for ≥75 nmol/L, 1.39 for 25–74 nmol/L, and 2.16 [95% confidence interval: 1.35–3.46] for <25 nmol/L). Cord-blood 25OHD levels were inversely associated with risk of wheezing by 15 months, 3 years, and 5 years of age (all $P < 0.05$).	[198]
156 neonates.	Parent-reported LRTI symptoms in a daily log and simultaneous presence of RSV RNA in a nose-throat specimen.	Concentrations of 25-OHD were lower in neonates who subsequently developed RSV LRTI compared with those who did not (65 nmol/L versus 84 nmol/L, $P = 0.009$). Neonates born with 25-OHD concentrations <50 nmol/L had a sixfold (95% confidence interval: 1.6–24.9; $P = 0.01$) increased risk of RSV LRTI in the first year of life compared with those with 25-OHD concentrations ≥ 75 nmol/L.	[199]
1248 children.	Mid-pregnancy VitD levels and respiratory disorders in children evaluated by maternal reporting through questionnaires.	Higher maternal mid-pregnancy 25OHD level was associated with a reduced risk of three or more LRTIs by 36 months vs. none, adjusted risk ratio 0.74 [95% confidence interval (CI): 0.58, 0.93] per 20 nmol/L increase. Associations were similar when examining the frequency of LRTIs by 18 months, and the frequency of LRTIs between 18 and 36 months.	[200]
6789 participants in the nationwide 1958 British birth cohort.	VitD levels and lung function (forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and respiratory infections from the age of 45 years.	Each 10 nmol/l increase in 25(OH)D was associated with a 7% lower risk of infection (95% CI 3, 11%).	[202]
14,108 individuals over 16 years of age.	VitD levels and ARI.	After adjusting for season, demographic factors, and clinical data, 25OHD levels <30 ng/mL were associated with 58% higher odds of ARI (OR 1.58; 95% CI: 1.07–2.33) compared to levels ≥30 ng/mL.	[203]

a risk factor for TB rather than a consequence, although such an association was lacking in normal and HIV-infected African population. VitD deficiency correlates also with increased risk to progress from latent to active tuberculosis.

A recent meta-analysis showed that VitD supplementation protected against acute respiratory tract infections, especially in VitD deficient patients at baseline, but administration of VitD by bolus was not beneficial [205].

Although a meta-analysis failed to demonstrate a benefit in VitD supplementation to TB treatment, no study has addressed the possibility that VitD might be beneficial in preventing TB, especially in latent TB [206].

7. VitD and autoimmunity

Abnormal activation of the immune system may generate autoimmune disorders in which the immune response is directed against harmless self-antigens, resulting in inflammation, tissue damage, and loss of function. Since autoimmune patients are frequently VitD deficient and VitD has been shown to affect several cellular populations involved in the physiopathology of autoimmune diseases, a number of studies have addressed the potential role of VitD in autoimmune conditions.

7.1. Biological plausibility

Immune cells involved in pathogenesis of diverse models of autoimmune diseases are modulated by VitD. Among the different cell populations mediating autoimmune disease, $CD4^+$ T cells may represent a target of the beneficial effects of VitD in some experimental models of autoimmune diseases. When the VDR is not expressed in $CD4^+$ cells, calcitriol cannot suppress EAE [207], and $1,25(OH)_2D$ prevents $CD4^+$ Th cell migration into the CNS [208]. The conclusion that $CD4^+$ T cells may represent a relevant target of VitD in autoimmune diseases is also suggested by the finding that VDR binds near to SNPs that have been associated with autoimmune diseases in human $CD4^+$ T cells [209].

IL-17 is believed to play a key role in autoimmune diseases. In mice, an arthritis phenotype associated with inflammation and bone erosion is correlated with IL-17 overexpression in joints [210]. In EAE a key cell population that seems to mediate the disease are Th17-derived cells expressing IFN-γ and T-bet [211]. Also in humans, Th17 cells are increased in RA and SLE [212,213] and CCR6+ memory Th cells, which include Th17 cells, activate synovial fibroblasts [214]. In consideration of the role of Th17 cells in autoimmunity and the beneficial effect of calcitriol on autoimmune diseases, it seems reasonable to suggest that inhibition of Th17 activity may represent a major mechanism by which $1,25(OH)_2D$ suppresses autoimmunity.

Since Th2 cells might exert a protective role in Th17-driven autoimmune diseases [215] and VitD upregulates IL-4 production in these cells, also Th2 cells may represent an important target of calcitriol in autoimmune diseases. In EAE calcitriol upregulates also NKT cell-derived IL-4.

The finding that $CD8^+$ T cells have higher levels of VDR than $CD4^+$ T cells [105] suggests that $CD8^+$ T cells may represent a target for calcitriol in autoimmune diseases. Actually $CD8^+$ T cells are believed to play a role in autoimmune diseases at least in certain models. The EAE model in mice induced by myelin-specific $CD8^+$ cells has some characteristics more similar to MS than $CD4^+$ T cells, [216,217]. A model of autoimmune intestinal inflammation [218] can be induced by hsp60-specific IL-8+ T cells. In humans, IL-17A + $CD8^+$ T cells are well represented in the synovial fluid of psoriatic arthritis patients. However, the attenuation of EAE by calcitriol does not seem to target $CD8^+$ T cells [219].

7.2. Experimental models of autoimmune diseases

Administration of VitD has beneficial effects in a number of experimental models of autoimmune disease. In EAE, VitD has protective effects in preventing and also in reversing paralysis [74,220,221]. Also high dose dietary VitD has been shown to have

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beneficial effects in EAE. Interestingly, the combination of high dietary VitD and IFN-β is more effective than the two agents alone [222]. The suppressive effects of calcitriol seem to require dietary calcium [222]. The protective effect of 1,25$(OH)_2$D in EAE is associated with inhibition of IL-12 and IL-17 and requires IL-10 signalling [72,223,224].

VitD proved to be protective also in autoimmune diabetes in nonobese diabetic (NOD) mice. The mechanisms underlying this protection might be represented by the induction of Treg cells and by a decreased numbers of effector T cells [225–227]. Calcitriol also reduces the severity of SLE in MRL/1 mice [228] and the incidence of arthritis and hind paw swelling in an experimental rat model of RA [229].

7.3. Multiple sclerosis (MS) (Table 5)

In addition to above reported considerations of VitD activity on immune and inflammatory cells, 1,25$(OH)_2$D also modulates the functions of brain pericytes. The pericytes in the brain line the epithelial cells of blood vessels, and maintain the blood–brain barrier and neuron functioning. 1,25$(OH)_2$D treatment of brain pericytes down regulates pro-inflammatory gene expression and up regulates anti-inflammatory genes [230]. Since TNF and IFN-γ stimulate brain pericytes to express Cyp27B1 [230], it is likely that this may represent a feedback mechanism to limit inflammation by local production of calciferol.

A classical observation is that low levels of VitD at higher latitudes are associated with an increased risk of MS and other autoimmune diseases [231,232]. Conversely, a 50% reduced risk of MS has been described for those living below 35° latitude for the first 10 years of life [233]. The risk of MS is also reduced by increasing VitD levels and decreased by 41% for every increase of 25OHD 20 ng/ml above 24 ng/ml [234] and administration of more than 400 IU of VitD per day reduced risk by 42% [235].

Remission in MS patients was associated with higher serum levels of VitD when compared to relapses [236] and MS disease activity as assessed by magnetic resonance imaging was less severe in patients with high VitD levels [237]. Efficacy of IFN-β treatment in MS correlates with high levels of VitD, whereas IFN-β-treated patients with low levels of VitD had an increased risk of relapses [238].

Results of VitD administration in MS patients have been contradictory. Cholecalciferol supplementation improved the Expanded Disability Status Scale [EDSS], reduced MRI lesions and relapse rate, and increased functionality [239,240]. These effects were even higher when VitD was used as a supplement to IFN-β treatment [240]. On the opposite, two other trials reported no difference in any of these parameters [241,242]. Most notably however, VitD supplementation decreased the evolution of a pre-MS condition like optic neuritis to MS [243].

7.4. Rheumatoid Arthritis (RA) (Tables 6 and 7)

In addition to the above mentioned studies on the multiple effects of VitD on immune and inflammatory cells involved in RA physiopathology, one study has also shown that in an in vitro model of a collagen-rich barrier, fibroblast-like synoviocytes purified from rats with arthritis and RA patients were less invasive of the barrier in the presence of VitD [244]. Similarly to other autoimmune conditions, low levels of VitD have been correlated with an augmented risk of RA [245] and osteoarthritis [246]. These data are summarized in the Table here below.

Results obtained in studies aimed at assessing the reduction of the RA risk after VitD supplementation are controversial. While some studies found an inverse correlation between the risk of developing RA and VitD intake [247,248], others did not [249]. Disease activity was reduced in two supplementation open-label trials [250,251], but no positive effect on disease activity in two subsequent double-blind, placebo-controlled trials [252,253] was described.

A study designed to test the effects of VitD administration on RA relapse rate did not reach statistical significance [254], showing however that in one out of 10 patients the relapse would be prevented. As for MS studies, the number of patients enrolled is too low to draw any conclusion from these intervention studies. Data are summarized in Table 7.

7.5. Type 1 Diabetes (T1D)

Studies of VitD supplementation in T1D are inconclusive. Some studies have shown a beneficial effect of VitD administration in adults [255–257], but two other studies failed to show any benefit [258,259]. Since destruction of β cells cannot be reversed, it might be tempting to speculate that VitD should be administered in the earliest phases of the disease, as also suggested by the finding that the protective effect is only visible when the disease lasted for less than 1 year [255].

More encouraging results were obtained in children, in which VitD deficiency was associated with an increased risk of T1D and VitD supplementation during the first year of life reduced the risk to develop T1D by 80% [260]. Also in pregnant women, VitD administration reduced the development of islet autoantibodies in

Table 5
MS - Epidemiological studies.

Trial Design	Measurements	Results	Reference
White: 148 cases, 296 controls. Black and Hispanics: 109 cases, 218 controls.	Odds ratio (OR) of MS associated with serum levels (quintiles) of 25OHD in each racial/ethnic group.	White ethnicity: A 41% decrease in MS risk found for each 50 nmol/L increase in serum 25OHD. OR = 0.59, (95% CI = 0.36–0.97, p = 0.04). Black/Hispanic ethnicity: Among these groups, there were no statistically significant association between low 25OHD levels and risk for MS.	[234]
NHS: 92,253 women followed during 20 years. NHS II: 95,310 women followed during 10 years.	Dietary vitamin D was related to MS cases. Diet was assessed at baseline and updated every 4 years. Relative risk (RR) of development of MS.	A total of 173 MS cases with onset after baseline was confirmed. Pooled, age-adjusted RR in the highest quintile vs the lowest was 0.67 (95% CI 0.40–1.12, p-value for trend 0.03). RR comparing supplement of ≥400 IU/day with no supplement was 0.59 (95% CI 0.38–0.91, p for trend = 0.006).	[235]
Prospective study of 178 persons with clinically definite MS, followed for 4 years.	Serum 25OHD was measured biannually and linked to other factors, e.g. IFN-β treatment.	25OHD associated with a reduced relapse risk only in patients on IFN-β treatment (p < 0.001). IFN-β associated with reduced relapse risk in patients with higher 25OHD hazard ratio (HR), 0.58 (95% CI 0.38–0.98). IFN-β associated with increased relapse risk in patients with lower 25OHD HR = 2.01 (95% CI 1.22–3.32).	[238]

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Table 6
RA - Epidemiological studies.

Trial Design	Measurements	Results	Reference
556 participants in the Framingham Heart Study followed for 8–9 years.	Serum 25OHD. Knee radiographs scored for severity of OA (ostheoarthritis).	Incident OA occurred in 75 knees, progressive OA in 62 knees. Risk for progression had OR = 2.9 (95% CI 1.0–8.2) for the lowest tertile of serum 25OHD compared to the highest tertile	[245]
Prospective cohort study of 29,368 women 55–69 y.o. w/o RA history followed for 11 years.	Vitamin D intake Risk ratios (RR)	Intake of Vitamin D was inversely associated with risk of RA; RR highest vs lowest tertile = 0.67 (95% CI 0.44–1.00, p for trend = 0.05) Both dietary vitamin D and supplemental intake showed this trend.	[247]
Female RA patients (54 Italian, 64 Estonian) vs normal controls (35 Italian, 30 Estonian).	Serum 25OHD and Disease Activity Score (DAS28) during winter and summer.	Negative correlation between serum 25OHD level and DAS28 was found in summer in Italian RA patients, $r = -0.57$, $p < 0.0001$ and in winter in Estonian RA patients, $r = -0.40$, $p < 0.05$. No significant differences were found between RA patients and their controls, in either country	[246]

Table 7
RA - Intervention studies.

Trial Design	Measurements	Dosage	Results	Reference
Open label trial, 19 RA patients. Standard therapy (DMARD) plus alphacalcidol.	Therapy results were evaluated by ESR, Richie index, Lee index and other parameters.	Alphacalcidol, 2 μg/day orally for 3 months.	After 3 months: Significant decrease in number of painful joints, 38.22 v 16.4; $p < 0.01$. Significant decline in ESR, 41.71 v 17.76, $p < 0.05$. 89% of RA patients experienced a positive effect on disease activity. No side effects.	[250]
Open label randomized trial comparing DMARD with (n = 59) and without (n = 62) $1,25(OH)_2D$ + Calcium.	Time to pain relief by patients' VAS (visual analogue scale).	500 IU $1,25(OH)_2D3$ and calcium.	Patients in the Vitamin D group had higher pain relief at 3 months, 50% v 30%, $p = 0.006$.	[251]
Randomized, double blind, placebo-controlled study. 1 year, n = 22.	Primary outcome: Change in plasma PTH. Secondary: Change in BMD, DAS28, SF-36 (Short Form 36).	50,000 IU D2 3 times a week for 4 weeks, then twice monthly for 11 months. + 500 mg Calcium 3 times per day.	Vitamin D had no significant effect on PTH. DAS28 scores were unaffected, but the patients RA assessment worsened. The physical function domain in the SF-36 declined 6 points ($p = 0.03$).	[253]

offspring [255].

7.6. Systemic Lupus Erythematosus (SLE) (Tables 8 and 9)

Some in vitro evidence (summarized above) implies that VitD modulates the differentiation and activity of T and B-lymphocytes and, therefore, the production of autoantibodies [261].

Epidemiological studies have reported that VitD deficiency is more prevalent in SLE patients than in the general population [262–266]. It has been suggested however that such association might be the consequence of the recommendation that SLE patients should avoid sunlight exposure [267] and of the administration of drugs (eg glucocorticoids) usually used in SLE [268]. Such hypothesis is also corroborated by the finding that VitD intake was not associated with the risk of SLE development in a prospective study [269].

Contradictory results have been obtained when the association between high disease activity in SLE with low VitD serum concentrations has been investigated [270,271], although in children with juvenile SLE an inverse correlation between 25OHD serum levels and disease activity has been described [272]. Although one study found that low VitD levels correlate with flare-up in SLE [273], another study could not confirm these data [274]. Overall, it is not possible to firmly establish a causal relationship between VitD serum concentrations and disease activity in SLE patients.

Interestingly, even in healthy people without SLE [261] low levels of VitD have been correlated with the presence of ANA antibodies and cholecalciferol supplementation decreased autoantibody titers [275].

Inconsistent results were obtained with VitD supplementation, with studies showing no benefits [276,277] whereas others have shown improved disease activity [278] and proteinuria [279], and reduced production of pro-inflammatory cytokines [278]. A study with 158 SLE patients treated with cholecalciferol and 89 placebo SLE controls demonstrated an improved disease activity score and fatigue, and decreased auto-antibody levels [270]. Similar results were obtained in another study [280].

7.7. Psoriasis

Psoriasis is a chronic autoimmune inflammatory condition characterized by keratinocyte hyper proliferation and abnormal differentiation [281]. Since VDR is expressed in keratinocytes, calcitriol exerts certain biological activities in these cells. Calcitriol can induce keratinocyte differentiation, and whereas picomolar physiological doses calcitriol promotes proliferation, supraphysiological concentrations inhibit keratinocyte proliferation. Also VitD analogs exert pro-differentiating and antiproliferative effects on keratinocytes and anti-inflammatory properties [282].

Pro-inflammatory cytokines TNF-α, IFN-γ, IL-2, and IL-8 are known to play a critical role in the T-cell-mediated inflammatory process in the psoriatic skin [281]. Topical treatment with the VitD analogue calcipotriol modulates the expression of cytokines and the presence of cell populations known to play a role in psoriasis. Calcipotriol treatment reduced the expression of the inflammatory cytokine IL-8 [283] and the expression of the antimicrobial

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Table 8
SLE - Epidemiological studies.

Patient population	Measurements	Results	Reference
36 SLE patients.	Vit D levels Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) in high activity (group I: 12 patients, mean age 29.6 years) or in minimal activity (group II: 24 patients, mean age 30.0 years), compared to normal controls (group III: 26 women, 32.8 years).	In group I, 25OHD levels were lower ($P < 0.05$), which was related to the SLEDAI ($R = -0.65$, $P < 0.001$). In multiple regression analysis, the 25OHD level was associated with SLEDAI, osteocalcin and bone-specific alkaline phosphatase	[264]
378 SLE patients.	VitD levels SLE disease activity scores (SLEDAI-2K and ECLAM)	Significant negative correlation between the serum concentration of vitamin D and the standardised values (z-scores) of disease activity scores (Pearson's correlation coefficient $r = -0.12$, $p = 0.018$).	[265]
38 premenopausal SLE patients.	VitD levels BMD SLE activity index (SLEDAI)	Patients with high SLEDAI scores had significantly lower 25(OH)D levels ($P = 0.033$). Left femoral neck BMD was significantly lower in the deficient compared to insufficient group ($P = 0.042$). Trend toward better BMD gain at 2 years in the vitamin D insufficient compared to the deficient group, which did not reach statistical significance.	[266]
Incident cases of SLE and RA among 186,389 women followed from 1980 to 2002 → 190 incident cases of SLE and 722 of RA.	Dietary intake of VitD	Vitamin D intake was not associated with risk of SLE or RA	[269]
Forty SLE patients with mean age of 25.3 ± 4.2 years.	SLE disease activity - British Isles Lupus Assessment Group (BILAG) Index Score.	Serum 25[OH]D concentration inversely correlated with the BILAG index score ($r = -0.486$, $p = 0.001$). Those with a more severe vitamin D deficiency had also higher concentrations of liver enzymes ($p < 0.05$), lower serum albumin and hemoglobin concentrations ($p < 0.05$), and higher titers of antibodies to double-stranded DNA (ds-DNA) ($p < 0.001$).	[270]
159 SLE patients.	Disease activity was measured by the SLE Disease Activity Index 2000 (SLEDAI-2K).	Levels of 25(OH) D were not associated with lupus activity score, disease duration, sun exposure, vitamin D supplementation, or use of corticosteroids.	[271]
SLE ($n = 38$) and healthy controls ($n = 207$), ages 5–21 years.	SLE activity.	Severe vitamin D deficiency (25(OH)D < 10 ng/ml) was observed in a significantly higher proportion of subjects with SLE (36.8% vs 9.2%, $P < 0.001$). In SLE, the odds ratio (OR) for severe deficiency was 2.37 ($P = 0.09$), adjusting for age, sex, race, and season. However, for each 1 SD greater body mass index (BMI) z-score, 25(OH)D levels were 4.2 ng/mL lower ($P = 0.01$) in SLE, compared with controls. Adjusting for 25(OH)D levels, SLE associated with significantly lower 1,25(OH)2D ($P < 0.001$) and intact PTH levels ($P = 0.03$). Greater SLE disease activity index scores were observed in those with 25(OH)D < 20 ng/mL ($P = 0.01$).	[272]
82 flares from 46 patients that were separated by at least 8 months from previous flares. Serum 25(OH)D levels were measured at 4 and 2 months before flare, and at the time of flare (a flare interval).	Correlation between flares and VitD levels.	Flares occurring during low daylight months (LDM, Oct–Mar), 25(OH)D levels were decreased at the time of flare, but only in non-African American (non-AA) patients (32% decrease at flare, compared to 4 months prior, $p < 0.001$). In non-AA SLE patients, unusually large declines in 25(OH)D during LDM may be mechanistically related to SLE flare, whereas relatively high 25(OH)D levels during HDM may protect against flares.	[273]
170 patients with SLE who were prospectively followed up for 6 months.	SLEDAI	lower 25(OH)D levels were associated with high SLE activity ($p = 0.02$) No association between baseline vitamin D levels and relapse-free survival rate.	[274]

chemoattractant psoriasin and koebnerisin that amplify the inflammatory reactions in psoriasis [284]. Conversely, calcipotriol augmented in psoriatic plaques the anti-inflammatory cytokines IL-10 [283] and lymphopoietin which induces Th2 differentiation and inhibits IL-12/23 production [285].

From the clinical point of view, topical treatment with VitD analogs have been proven to be effective and safe [286]. In a double-blind, placebo controlled study, Maxacalcitol reduced erythema and scaling [287]. Topical tacalcitol ointment reduced the psoriasis area severity index (PASI) without calcemic side effects [288]. Skin irritation is the most relevant adverse side effect described for topical VitD analogs.

8. Concluding remarks

There is a growing body of evidence that VitD, especially its active metabolite, plays a key role in modulating the physiological activity of the immune system. This emergent role has stimulated a florid line of research aimed at associating the level of VitD with pathological situations wherein the immune system may be altered, such as in autoimmunity and inflammation.

In these studies, 25OHD, the actual precursor of the active hormone calcitriol, is what has been routinely measured, circulating in the blood at ng/mL concentrations. This measurement, performed with either LCMS or immunoassay, has recently become

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Table 9
SLE - Intervention studies.

Patient population and treatment	Measurements	Results	Reference
57 SLE patients, stable, inactive disease, randomized into a 12-week double-blind, placebo-controlled trial of vitamin D3 at doses of 2000 IU or 4000 IU.	IFN signature (as determined by measuring the expression levels of 3 IFN response genes).	Vitamin D3 supplementation up to 4000 IU daily was safe and well-tolerated but failed to diminish the IFN signature in vitamin D-deficient SLE patients.	[276]
24-month prospective study, 34 SLE women randomized to receive, together with their ongoing treatment, a standard regimen (SR) of cholecalcipherol (25,000 UI monthly) or an intensive regimen (IR) (300,000 UI initial bolus followed by 50,000 UI monthly) for one year and then switched to the other regimen in the second year.	Quarterly assessment of 25OHD levels, disease activity, SLE serology and bone metabolism markers.	No significant differences in disease activity and SLE serology found at any time point between SR and IR. No changes in the mineral metabolism.	[277]
267 SLE patients randomized 2:1 to receive either oral cholecalciferol 2000 IU/day or placebo for 12 months.	Disease activity before and after 12 months of supplementation. Disease activity measured by the SLE Disease Activity Index.	Lower 25(OH)D levels correlated significantly with higher SLE disease activity. At 12 months of therapy, there was a significant improvement in levels of inflammatory and hemostatic markers as well as disease activity in the treatment group compared to the placebo group.	[278]
1006 SLE patients monitored over 128 weeks. SLE patients with low levels of 25-hydroxyvitamin D (25[OH]D; <40 ng/ml) were given supplements of 50,000 units of vitamin D2 weekly plus 200 units of calcium/vitamin D3 twice daily	VitD levels, disease activity.	20-ng/ml increase in the 25OHD level was associated with a 21% decrease in the odds of having a high disease activity score and a 15% decrease in the odds of having clinically important proteinuria. Although these associations were statistically significant, the clinical importance is relatively modest. There was no evidence of additional benefit of 25(OH)D beyond a level of 40 ng/ml.	[279]
40 juvenile-onset SLE patients randomized (1:1) to receive oral cholecalciferol 50,000 IU/week (juvenile-onset SLE-VitD) or placebo (juvenile-onset SLE-PL), for 24 weeks.	Disease activity assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the EuropeanConsensus Lupus Activity Measurement (ECLAM). Fatigue assessed using the Kids Fatigue Severity Scale (K-FSS).	At the end of the intervention, a significant improvement in SLEDAI ($P = 0.010$) and in ECLAM ($P = 0.006$) observed in the juvenile-onset SLE-VitD group compared to the juvenile-onset SLE-PL group. Reduction of fatigue related to social life found in the juvenile-onset SLE-VitD group compared to the juvenile-onset SLE-PL group ($P = 0.008$).	[280]

significantly more reliable consequent to marked gains in commutability enabled by the broad acceptance of and adherence to an international standardization program.

Several epidemiological studies of observational nature have been conducted to correlate circulating levels of 25OHD with autoimmune and inflammatory disease parameters. Overall, the studies have shown an inverse relationship between 25OHD and the clinical manifestations of a given disease. At the same time, circulating levels of sufficiency/insufficiency have been proposed by major medical organizations such as the Institute of Medicine (IOM) [43] and Endocrine Society [51], with different thresholds belying slightly different demographic perspectives. While associations with the disease are strong and potential mechanisms tractable, still the role of the VitD in inflammation and autoimmunity deserve large and well controlled clinical studies.

VitD supplementation has not always diminished the severity of clinical manifestations. A likely explanation of these perceptually negative outcomes, is that the majority of these studies attempted correlations with measured levels of precursor 25OHD and not the active hormone *per se*. Testing circulating levels of calcitriol might support the establishment of more robust disease correlates between the biologically active VitD metabolite and pathological conditions.

9. Personal note

This review was written to honor Prof. Alberto Mantovani for his seminal contribution to the current understanding to different fields of immunology and inflammation, especially the complex interplay between immunity, inflammation and tumor growth. Francesco Colotta was privileged to work with Alberto for more than 12 years during his PhD and post-PhD period at Mario Negri Institute in Milan, describing under Alberto's support and inspiration, among the others, the novel and unprecedented decoy function of IL-1R type II, a new isoform of IL-1R Antagonist and regulation of cellular apoptosis by cell shape. It was an extraordinary and unique period of Francesco's life spent enjoying and sharing not only the excitement and beauty of science and discovery but also the pleasure of extraordinary personal relationships with Alberto and many other people in Alberto's Lab, to whom Francesco is and will be sincerely grateful forever. It was really The Dream Team.

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