Commentary

Vitamin D Status and the Host Resistance to Infections: What It Is Currently (Not) Understood

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ABSTRACT

Purpose: Vitamin D is increasingly thought to play a role in regulating immunity. This comprehensive review updates the current understanding regarding ways in which we believe that vitamin D regulates responsiveness of the immune system and how serum status modulates the host defense against pathogens.

Methods: The literature was searched by using PubMed and Scopus with the following key words: *vitamin D*, *immunity*, *innate and adaptive immunity*, *infectious disease*, and *vaccine response*.

Findings: Vitamin D deficiency remains a major public health concern worldwide. The overall body of evidence confirms that vitamin D plays an important role in modulating the immune response to infections. Epidemiologic studies suggest a clear association between vitamin D deficiency and susceptibility to various pathogens. However, translation of vitamin D use into the clinic as a means of controlling infections is fraught with methodologic and epidemiologic challenges. The recent discovery of alternative activation pathways, different active forms of vitamin D, and possible interaction with non–vitamin D receptors provide further complications to an already complex interaction between vitamin D and the immune system. Moreover, it has become apparent that the individual responsiveness to supplementation is more dynamic than presumed from the static assessment of 25-hydroxy vitamin D status. Furthermore, the epigenetic response at the level of the individual to environmental changes and lifestyle or health conditions provides greater variation than those resulting from vitamin D receptor polymorphisms.

Implications: To understand the future of vitamin D with respect to clinical applications in the prevention and better control of infectious diseases, it is necessary to determine all aspects of vitamin D metabolism, as well as the mechanisms by which active forms interact with the immune system globally. For the most part, we are unable to identify tissue-specific applications of supplementation except for those subjects at high risk of osteomalacia and osteoporosis. (*Clin Ther.* 2017;39:930–945)

Key words: immunity, immune response, infections, vitamin D, vitamin D status, vitamin D supplementation, vaccine.

INTRODUCTION

Vitamin D is an essential dietary component for which biological effects occur only as a consequence of its metabolism into a family of daughter metabolites. Two of these are important for human health, vitamin D_2 (which is synthesized in plants and fungi) and vitamin D_3 (which is made in skin exposed to sunlight).[1] This fat-soluble molecule is biologically inert in humans and needs to be activated by 2 successive hydroxylations at positions 25 and 1 via reactions of the cytochrome P450 (CYP) enzymes CYP2R1 and CYP27B1, respectively (Figure 1). These components are hydroxylated primarily in the liver to form the main circulating form, 25-hydroxy vitamin D (25[OH]VitD), and then by the kidney or cells expressing the vitamin D–activating enzyme CYP27B1. The final active metabolite 1α,25-dihydroxy vitamin D (1α,25

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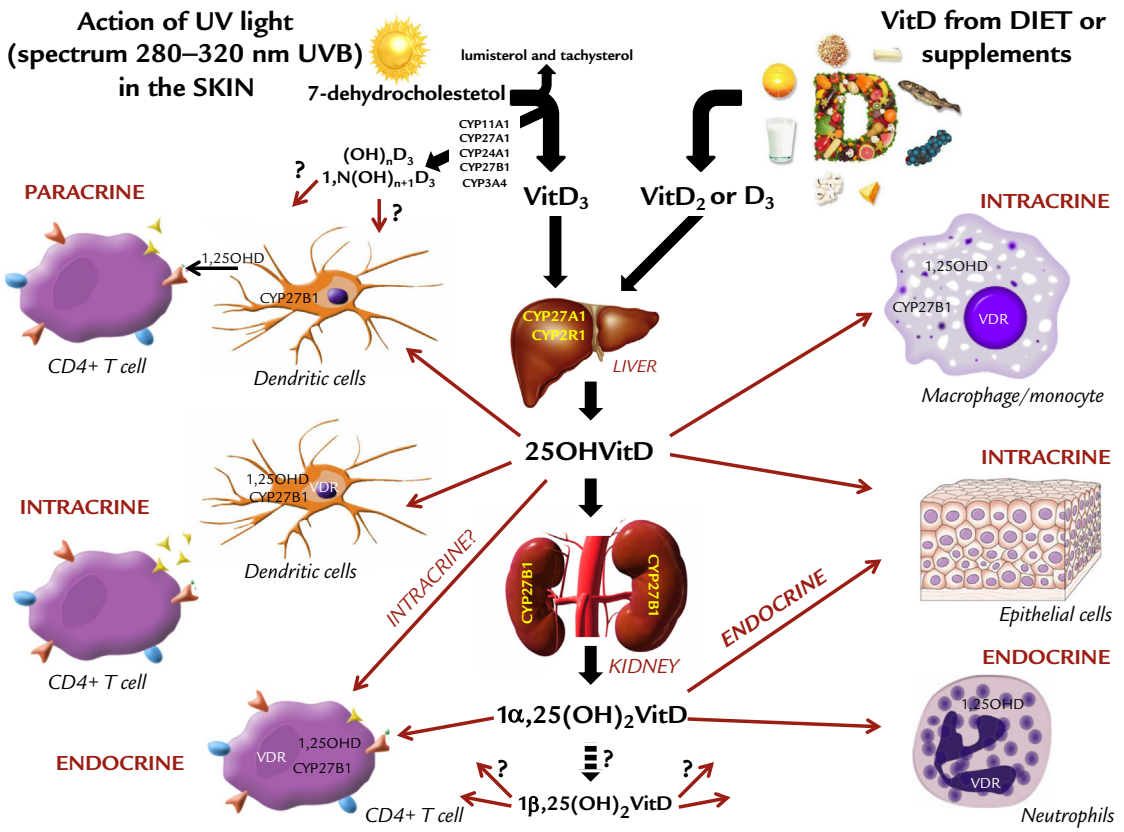

Figure 1. This figure shows how daughter metabolites of vitamin D are produced and interact with innate cells. The 2 main forms are 25-hydroxy vitamin D (25[OH]VitD; ie, the main circulating form) and 1α,25-dihydroxy vitamin D (1α,25[OH]$_2$VitD; ie, the main active form). In addition to the classic activating pathways through the 2 hydroxylations at the liver (via cytochrome P450 [CYP] 2R1 for vitamin D_2 and CYP27A1 for vitamin D_3) and then at kidney levels (via CYP27B1), alternative ways have been described, but the effects of the different hydroxyl metabolites on the immune system are currently unknown. Monocytes/macrophages and dendritic cells express the vitamin D–activating enzyme CYP27B1 and the vitamin D receptor (VDR). Thus, these cells are able to directly use 25(OH)VitD for intracrine responses and local conversion to active 1α,25(OH)$_2D_3$. In monocytes/macrophages, intracrine synthesis of 1α,25 (OH)$_2D_3$ promotes antibacterial responses to pathogens; in dendritic cells, this action inhibits dendritic cell maturation and thereby modulates CD4+ T-cell functions. Similarly, epithelial cells are able to respond in an intracrine fashion to 25(OH)VitD as well as to 1α,25(OH)$_2$VitD to promote antibacterial responses. UV = ultraviolet; VitD = vitamin D. (Adapted from Lang and Aspinall.[2])

[OH]$_2$VitD) is able to interact with the cognate nuclear vitamin D receptor (VDR) at the target organ levels, which generates appropriate biological responses.[2]

The classic actions of vitamin D are control of bone remodeling and skeletal homeostasis.[1] However, the VDR gene is expressed in ~400 tissues and cell types, suggesting that vitamin D has a far wider physiologic function beyond the exclusive control of calcium metabolism. Upon activation, the VDR binds to hormone response elements on DNA sequences, resulting in expression or transrepression of specific gene products.[3] Downstream targets of this nuclear receptor are involved in mineral metabolism but also in a variety of other metabolic pathways. Activated VDR modulates the transcription of many genes, and their downstream products regulate potent cell growth and differentiation effects.[4]

Parallel to the classic activation pathway, alternate routes have recently been described. They are initiated by

CYP11A1 leading to different hydroxy metabolites, among which are 20(OH)VitD and 22(OH)VitD. They also exert pleiotropic effects.[5] Furthermore, the well-established mechanism of activation by binding of 1α,25 $(OH)_2$VitD to the genomic site of VDR coexists with nongenomic membrane-associated sites. In addition to the classic activation pathway, the VDR contains an alternative form binding-A-pocket, the occupation of which leads to rapid nongenomic responses at membrane level. There is also a membrane-associated rapid steroid-binding protein (also known as protein disulfide-isomerase A3) that has been identify also as an alternative membrane-bound receptor.[6] Other nuclear receptor targets comprise the retinoic acid–related orphan receptors (ROR)α and RORγ, which also regulate some phenotype functions (particularly in skin cancer). Recently, 1β,25$(OH)_2$VitD has also been measured in human serum, which is a poor genomic agonist but a potent nongenomic antagonist of 1α,25$(OH)_2$VitD.[7] Its exact role in health requires further exploration.

The potential role of vitamin D in modulating the host defense to foreign antigens and pathogens has been investigated and some VDR transcription-dependent actions identified as having a role in regulating the immune system.[8,9] However, the exact roles played by the different bioactive forms via VDR and non-VDR receptors remains to be identified.[5] More recently, the VDR network has been extended outside the immune system,[10] with studies showing that intestinal VDR was associated with maintaining the gut intestinal barrier and regulating intestinal inflammation, autophagy, and susceptibility to infection.[11,12] Moreover, intestinal VDR was shown to be regulated by vitamin D and also by the gut microbiota and other hormonal compounds.[10]

The goal of the present comprehensive review was to highlight the current body of evidence on ways by which vitamin D status interferes with the normal responsiveness in the immune system. How serum vitamin D status acts on the host defense against infections, both positively and negatively, and the clinical perspectives in terms of vitamin D supplementation for the treatment and prevention of infectious diseases are also discussed.

VITAMIN D–MEDIATED THERAPIES FOR INFECTIONS: MORE THAN A CENTURY OF EVIDENCE

Vitamin D–mediated remedies for infectious disorders have been suggested for more than a century. In 1903, the Nobel Prize of medicine was awarded to Niels Ryberg Finsen, who demonstrated that ultraviolet (UV) light was beneficial in treating lupus vulgaris, a skin disorder associated with *Mycobacterium tuberculosis*.[13] Subsequently, the use of cod liver oil was widely practiced in the late 19th and 20th centuries and resulted in a steady decline in death rates from tuberculosis in the United Kingdom. It was however only many decades after that the potential role of vitamin D in host resistance to infection was confirmed with the successive discovery of that: (1) immune cells were able to produce CYP27B1 and convert 25(OH)VitD into 1α,25$(OH)_2$VitD; (2) the majority of immune system cells expressed VDR; (3) the production of 1α,25$(OH)_2$VitD in the immune system induced antibacterial products (ie, cathelicidin, β-defensin); and (4) impaired vitamin D status contributes to the burden of infectious diseases across the world.[13–17]

HOW DOES THE IMMUNE SYSTEM WORK?

The immune system comprises 2 distinct but interacting types of immunity: innate and adaptive. In the frame of infectious diseases, the purpose of the immune system is to recognize invading pathogens, prevent their spread, and eliminate them from the body.[1] This extraordinarily complex system relies on billions of cells patrolling the body and a dynamic complex network of soluble mediators. The innate immunity is our body's first line of defense that responds to foreign antigens in a generic way without conferring long-lasting and specific immunity. It is very fast and effective in clearing the vast majority of common pathogens at an early stage of invasion. As soon as pathogens breach the epidermal and/or mucosal barriers, innate cells, such as macrophages, and natural killer and dendritic cells rapidly detect them. Identification is mediated in part by toll-like receptors (TLRs), which are pattern-recognition receptors inserted at the surface of the membrane cell. Once activated, cells are able to express various types of soluble mediators (ie, cytokines, chemokines) and antibacterial peptides to eliminate pathogens from organs, tissues, and blood and/or lymph circulation. Furthermore, innate cells activate and modulate the adaptive immunity according to the timing, type, and amount of soluble mediators produced.[13]

Compared with innate immunity, adaptive immunity is slower to start but powerful enough to finalize the clearance of infections that elude innate immunity. Adaptive immunity is characterized by its specificity to

foreign antigens and its ability to generate long-lasting immune memory. Activation of B cells and T cells results in humoral (ie, antibody) and cell-mediated responses, respectively. Although the antibody-mediated immunity is dedicated to protection against extracellular infections and toxins, cell-mediated immunity contributes to the control of intracellular pathogens. The activation of the adaptive immune system often starts with the antigen presentation by innate cells to CD4+ T cell (ie, helper T cells), which leads to their interaction with naive B cells and assists their activation and differentiation into memory and antibody-secreting B cells (ie, long-lived plasma cells). The activation of naive CD4+ T cells generates different helper T-cell classes, which differ according to the type of immune *response and cytokine profiles* they produce. Thus, the type 1 response (Th1) supports cell-mediated immunity, whereas type 2 helper T-cell response (Th2) mediates the humoral response, and type 17 helper T-cell response (Th17) plays a role in autoimmunity. Long-term immune memory is supported by memory B cells and T cells in the blood as well as the primary and secondary lymphoid organs. Memory responses differ quantitatively and qualitatively from primary responses. These responses are more rapid and produce a wider variety of antibody classes; as such, generating long-lasting memory response is the objective of vaccination.[2]

VITAMIN D AND THE IMMUNE SYSTEM

The immunomodulatory role of vitamin D mediated via 25(OH)VitD and 1α,25$(OH)_2$VitD has been extensively reviewed previously.[13] Much of the current knowledge has arisen from studies using animal models and ex vivo human cells and exposure to exogenous 1α,25$(OH)_2$VitD at amounts usually much higher than physiologic levels.[13] The results showed that the activity of both innate (ie, monocytes, macrophages, dendritic cells) and B and T cells can be regulated by vitamin D (Figure 1) not only via the classic endocrine signaling pathway but also via intracrine and paracrine ways. Almost all the innate and adaptive cells possess CYP27B1 and VDR[1,4] and thus are able to convert 25(OH)VitD into 1α,25$(OH)_2$VitD and induce a signaling pathway, mediating either intra-cell activity (ie, intracrine) or a cell-to-cell communication (ie, paracrine) to induce changes in nearby cells. The active forms of vitamin D exert multidirectional effects within the immune system, including: stimulating the function of macrophage, T cells, and activated B cells; maturation of dendritic cells; modulation of tumor necrosis factor expression; production of neutral antibacterial proteins and peptides (eg, cathelicidins, β-defensin) and reactive oxygen species; and the expression of inducible nitric oxide synthase[13] (Figure 1, Table). Neutrophils, natural killer cells, antigen-presenting cells, and numerous epithelial cells such as airway, gingiva, urinary bladder, and gastrointestinal system cells produce antibacterial proteins and peptides. All these cells are in direct contact with pathogens. In natural killer cells, vitamin D also downregulates the production of interferon-γ and upregulates the expression of the natural killer toxicity receptors NKp30 and NKp44.

Stimulation with the active form of vitamin D at the antigen-presenting cell level activates the innate immune system by increasing macrophage phagocytosis and upregulating CD14 expression. On the other hand, the production of interleukin (IL)-10 and pro-inflammatory cytokines is inhibited, together with the expression of CD40 (required for B-cell activation) and CD80/86 (required for T-cell activation). The expression of major histocompatibility complex class II is also downregulated.[18] At the epithelial cell level, 1α,25$(OH)_2$VitD upregulates the gene expression for gap junction, adherence, and tight junction proteins to strengthen barrier function.[19] The cathelicidin-encoding gene expression is regulated by vitamin D, but it is also stimulated by bacterial infections and potent pro-inflammatory cytokines (particularly tumor necrosis factor-α, IL-1, IL-6, and interferon-γ). Cathelicidins also play a pivotal role by recruiting leukocytes, inducing chemotaxis of immunocompetent cells to the infection site, and being involved in the inhibition of lipopolysaccharide-dependent activation of the endothelium and vasodilation.[20]

Finally, it has been shown that vitamin D regulates the inflammatory response, altering the pro-inflammatory/anti-inflammatory balance toward an anti-inflammatory phenotype to control the inflammatory burst once triggered.[21] To some extent, this scenario has been supported by the analysis of VDR and CYP27B1 knockout mice.[2] These animals present an increased number of mature dendritic cells and aberrant dendritic cell trafficking. In humans, 1α,25$(OH)_2$VitD is an important regulator of the inflammatory response,[21] which is mediated by the

Table. Summary of the effects of 1α,25$(OH)_2$VitD on cells of the adaptive immune system.[13,27] These findings result from studies using animal models and ex vivo human cells exposed to exogenous 1α,25$(OH)_2$VitD at amounts usually much higher than physiologic levels.

T Lymphocytes	T-Reg Lymphocytes	B Lymphocytes
Augmentation of VDR expression	Induction of T-reg cell development	Augmentation of VDR expression
Regulation of T-cell development and migratory function	Influences T-reg cells differentiation and functions	Upregulation of CYP24A1
Regulation of TCR signaling	Augmentation of the suppressive activity and expansion of antigen-specific T-reg cells	Inhibition of B-cell proliferation by upregulating p27
Activation of PLC-γ1		Diminution of CDK4, CDK6, and cycling D expression
Alteration of cytokine secretion patterns	Negative regulation of the expansion of CCR6 on the Th17 cells	Mediation of death of proliferating B cells
Suppression of effector T-cell activation	Cooperation with IL-6 and TGF-β to mediate IL-10 production	Inhibition of the differentiation of B-cell precursors into plasma cells
Induction of regulatory T cells	Augmentation of IL-27–mediated IL-10– producing CD4+ T cells	Inhibition of Ig production
Regulation of T-cell trafficking and homing	Induction of Foxp3+ T-reg cell expansion	Inhibition of NF-κB
Induction of CCR10 expression	Diminution of IL-2 levels	Inhibition of XBP1 and ERN1
Suppression of Th1 response	Stimulation of the generation of IL-10 producing CD41/CD25 and TLR9 expression	
Induction of Th2 response	Active regulation of proliferation and cytokine production of CD81 cells	
Promotion of epidermal T-cell homing		
Inhibition of chemokines and chemokine receptors		
Promotion of T-cell shift from Th1 to Th2 in CD41 cells		
Inhibition of production of pro-inflammatory cytokines (IL-2, IFN-γ, TNF-α, and IL-5) by Th1 cells		
Enhancement of TGF-β and IL-4 transcripts		
Augmentation of IL-4 production by Th2 cells		
Augmentation of Th2 cell function		
Inhibition of T-cell surface expression of CLA		
TGF-β–mediated Foxp3+ on CD4+ T cells		
Negative regulation of CCR6 expression on Th17 cells		
Diminution of IL-2 secretion in CD4+ T cells		
Suppression of development of Th17 cells and decreases IL-17 expression		

(continued)

Table. (continued).

T Lymphocytes	T-Reg Lymphocytes	B Lymphocytes
Upregulation of PLC-γ1 expression leading to increased antigen-specific T-cell activation and proliferation		
Modulation of the expression of HLA-DR and CD8		

CCR = chemokine receptor; CD = cluster of differentiation; CDK = cycling-dependent kinase; CYP = cytochrome P450; ERN1 = endoplasmic reticulum-to-nucleus signaling 1; IFN = interferon; IL = interleukin; Foxp3+ = Fork head box p3; = $1,25(OH)_2D_3$ 24-hydroxylase; p27 = cycling dependent kinase inhibitor; HLA = human leukocyte antigen; Ig = immunoglobulin; NF-κB = nuclear factor kappa-B; PLC-γ1 = phospholipase C gamma 1; TCR = T-cell receptor; TGF = transforming growth factor; Th = T-helper cell (CD4+); TLR = toll-like receptor; TNF = tumor necrosis factor; T-reg = regulatory T-cell; VDR = vitamin D receptor; XBP1 = X box–binding protein 1.

modulating expression of TLR[22] and co-receptor CD14.[21] Similarly, it has been shown that in a paracrine manner, vitamin D dampens inflammatory responses with human epithelial cells by upregulating IL-1β secretion in *M tuberculosis*–infected macrophages.[23]

All these findings center the immunomodulatory roles of vitamin D on innate immunity, but the regulation of inflammation does not infer that vitamin D negatively affects our protective immunity (Table). Individuals with high plasma 25(OH)VitD levels exhibit a normal or enhanced response to common bacterial and viral vaccines.[2,24]

BEYOND BUILDING BONE, WHAT IS THE OPTIMAL SERUM VITAMIN D STATUS FOR IMMUNITY HEALTH?

The circulating 25(OH)VitD concentration is often taken as the common correlate of vitamin D status and a true reflection of the vitamin D produced by the skin and obtained from food and/or supplements. This stable metabolite has a concentration that is 1000-fold higher than the active form and a circulating half-life of ~2 weeks. In contrast, circulating $1\alpha,25(OH)_2$VitD has a shorter half-life (~15 hours), and its serum concentrations are closely regulated by using parathyroid hormone, calcium, and phosphate levels. Its concentration does not typically decrease until the vitamin D deficit is extensive.[25] Low vitamin D levels are a public health concern, but the precise definition of deficiency and the method of supplementation to obtain optimal serum 25(OH)VitD levels are still open to debate.[26] For example, common advice is to reach and maintain a serum level ≥75 nmol/L (≥30 ng/mL), which is the serum concentration associated with good bone health, optimal fracture reduction, and reduced likelihood of secondary hyperparathyroidism. Consequently, a serum concentration <50 nmol/L (<20 ng/L) is usually considered deficient and between 50 and 75 nmol/L insufficient. However, it has become apparent that tissue concentrations of vitamin D that effectively control the mediated effects are dissociated from the 25(OH)VitD levels. With respect to the immune system, for example, the serum concentration associated with optimal tissue saturation that elicits an effective response and protection is currently unknown.[27] Similarly, the doses that induce differentiation, regulate proliferations of various normal cells and cancer cells, or regulate gene expressions in multiple signaling pathways have to be determined.[1]

SERUM VITAMIN D CONCENTRATION AND DEGREE OF SUSCEPTIBILITY TO INFECTIONS

Epidemiologic studies have reinforced the hypothesis that vitamin D deficiency can profoundly mitigate our susceptibility to diverse pathogens. This action was first suspected when it was reported that the incidence of viral infections typically peaked during winter months when epidermal vitamin D synthesis was lower and serum 25(OH)VitD levels reached a

nadir.[14] It was then shown that children with inadequate serum levels experienced infections of viral origin, particularly influenza virus and respiratory syncytial virus infections.[28] The current body of evidence for the association between poor vitamin D status and susceptibility to infections is still insufficient to determine the exact 25(OH)VitD concentration protection level, or if there is any.

In the field of tuberculosis, in which this relationship has probably best been studied, a significant association was clearly measured between vitamin D deficiency and the prevalence of *M tuberculosis* infection, as well as the susceptibility to develop active infections.[13,29] This theory was confirmed by a recent meta-analysis of 25 studies totalling 3599 case subjects and 3063 control subjects.[15] In this particular context, it was shown that vitamin D deficiency was more likely a risk factor than a consequence of *M tuberculosis* infection. Second, the findings legitimized the translation of the vitamin D–mediated activation mechanisms of macrophages to attempt clinical trials of supplementation as treatment and prevention of tuberculosis in specific populations.

For upper respiratory tract infections, in the National Health and Nutrition Examination Survey, Ginde et al[30] reported in a cohort study of 18,883 participants aged ≥12 years that serum levels were independently and inversely associated with recent infections. After adjusting for confounding, those subjects with circulating vitamin D concentrations <25 nmol/L (10 ng/L) were 1.4 times more likely to report a recent episode compared with those with 25(OH)VitD levels ≥75 nmol/L (30 ng/L) after adjustments. The proportion was also significantly different according to vitamin D status (24% in those with levels <25 nmol/L vs 20% with levels 25–75 nmol/L vs 17% with levels ≥75 nmol/L). Interestingly, this association was stronger in patients with asthma and chronic obstructive pulmonary disease (odds ratio [OR], 5.67 and 2.26, respectively), disorders in which vitamin D deficiency is suspected to accelerate decline in lung function, increase inflammation, and further reduce mucosal immunity.[31] In a cohort study (198 healthy adults with a 3.5-month follow-up), 45% in those with 25(OH)VitD levels <95 nmol/L reported acute viral respiratory tract infections compared with 17% in those with circulating 25(OH)VitD levels ≥95 nmol/L.[32] Circulating 25(OH)VitD levels >95 nmol/L were also associated with a significant 2-fold reduction. All infections were confirmed by determination of pathogens in swabs collected from participants who exhibited symptoms of respiratory tract infection. In 6789 middle-aged adults in Great Britain, 12% of those with circulating 25(OH)VitD levels <25 nmol/L reported a respiratory infection in the month before blood sampling compared with 6% in those with 25 (OH)VitD levels >100 nmol/L.[33] Similar trends were measured in North American children with mild to moderate persistent asthma, a population in whom vitamin D insufficiency was common and associated with higher ORs of any hospitalization or emergency department visit for severe exacerbation over a 4-year period (OR, 1.5 [95% CI, 1.1–1.9]).[34]

In the hospital setting, for influenza virus infections, a lower concentration of 25(OH)VitD was a risk factor of infection or more severe course.[20] Among infants hospitalized for respiratory syncytial virus bronchiolitis, vitamin D status at the time of infection was otherwise not associated with indicators of bronchiolitis severity.[35] Similarly, in a 1-year study assessing the incidence of acute exacerbations of chronic obstructive pulmonary disease in adults, the baseline vitamin D status was not predictive of subsequent acute exacerbations.[36] However, in this population with severe pulmonary disease, multiple confounding risk factors for infection have contributed to the lack of significance (eg, deficiencies in other micronutrients, decreases in the epithelial ciliary clearance and cough reflex).[37]

There are also many reports focusing on other pathogens such as HIV[14] and hepatitis B virus (HBV.)[19,38] In HIV-positive patients, the prevalence of moderate (≤50 nmol/L [20 ng/mL]) and severe (≤25 nmol/L [10 ng/mL]) deficiency was 36.8% and 10.5%, respectively,[39] and poorer status has reportedly been linked with shorter survival times and an increased incidence of AIDS events.[40,41] Similarly, in HBV-positive patients, the prevalence of vitamin D deficiency was high (84.3%) and associated with adverse clinical outcomes.[38] Thus, vitamin D deficiency (<50 nmol/L [20 ng/mL]) or severe deficiency (<25 nmol/L [10 ng/mL]) was observed significantly more frequently among patients with HBV (52 %) and subgroups (chronic HBV infection, 47.8%; HBV-associated liver cirrhosis, 54.4%; HBV-associated hepatocellular carcinoma, 55.3%) compared with the control group (32.5%). The status and HBV-DNA load were strongly and inversely

correlated, and lower concentrations were associated with significant clinical progression of liver cirrhosis. Thus, vitamin D status seems to play a role in the immunologic function adjustment and tolerance in the natural course of chronic HBV infection, with higher levels enabling individuals to achieve a sustained virologic response.[19]

A meta-analysis of 9715 subjects whose serum 25 (OH)VitD concentration was confirmed found that vitamin D deficiency increased susceptibility for severe infections, sepsis, and 30-day and in-hospital mortality in critically ill patients.[42] Similar results were reported by a later meta-analysis.[43] The results of the pooled analysis showed that the OR associated with sepsis occurrence in participants with vitamin D deficiency was 1.78 (95% CI, 1.55 to 2.03) compared with control subjects in studies that reported participant numbers. The pooled OR was 1.45 (95% CI, 1.26 to 1.66) in studies that reported an adjusted OR of vitamin D deficiency for developing sepsis. The standardized mean difference of 25(OH)VitD concentrations was –0.24 (95% CI, –0.49 to 0.00) and was lower in the sepsis group compared with nonsepsis or control subjects.

Finally, taken together, these findings offer a rationale for exploring the use of vitamin D as a therapeutic aid against different pathogens.[13,44] In addition, they support the suggested optimal circulating 25(OH)VitD concentration of $\geq$75 nmol/L (30 ng/mL) to prevent upper respiratory tract infections and enhance innate and mucosal immunity and bring about anti-inflammatory actions, possibly by the induction of regulatory T cells and the inhibition of pro-inflammatory cytokine production.[27] Levels $>$100 nmol/L (40 ng/mL) do not, however, seem to provide additional benefits,[13,30,37,45] whereas serum values $\leq$40 nmol/L (16 ng/mL) seem to be associated with an increased risk of sepsis.[46] Much beyond the identification of a possible threshold of vulnerability/protection, it is very complex and a real challenge to understand how to best model the serum 25 (OH)VitD concentration–immune response relationship (hypothesized in Figure 2).

DOES THE EVIDENCE SUPPORT WIDESPREAD VITAMIN D SUPPLEMENTATION?

The Most Recent Data Tends Toward "Yes"…

A recent systematic review, whose aim was to consolidate data regarding the use of vitamin D as a treatment or preventive strategy against infections, considered 38 trials from 60 eligible articles and 1284 identified manuscripts.[44] Studies that considered analogue, topical, or micronutrient formulations of vitamin D, and assessed only serum status or lacked a comparison group, were excluded. Kearns et al concluded that although some prospective studies yield positive results, several robust studies were negative. These studies used a variety of dosing strategies, and there was high variability between the studies. The difference in individual responsiveness to supplementation and study designs that do not primarily investigate infectious outcomes also probably masked the benefits on infection incidence.

Specifically for respiratory tract infections, Kearns et al[44] noted that only a few studies suggested that supplementation had some benefits in reducing the risk in young and healthy adults; in patients with chronic lung disease, the effectiveness was not very clear. These results are in contrast with those from a recent systematic review and meta-analysis.[47] This meta-analysis assessed the overall effect of vitamin D supplementation on risk of acute respiratory tract infections. With the pooled analysis of 25 randomized controlled trials (11,321 participants; age range, 0–95 years), the authors concluded that supplementation was safe and effective against acute respiratory tract infection overall (adjusted OR, 0.88 [95% CI, 0.81–0.96]). Interestingly, they also determined that patients who experienced the greater benefit were those with baseline serum levels $<$25 nmol/L (adjusted OR, 0.30 [95% CI, 0.17–0.53]) compared with those with 25(OH)VitD levels $\geq$25 nmol/L (adjusted OR, 0.75 [95% CI, 0.60–0.95]). Moreover, a similar benefit was measured in people receiving daily or weekly doses without additional bolus doses (adjusted OR, 0.81 [95% CI, 0.72–0.91]) compared with those receiving $\geq$1 bolus dose (adjusted OR, 0.97 [95% CI, 0.86–1.10]). Although these results provided arguments for the reduction of acute respiratory infection with vitamin D, this meta-analysis has further intensified the debate around the recommendation of widespread supplementation. Indeed, 3 months earlier in the same journal, Bolland et al[48] discussed the current state of evidence to finally and reasonably conclude that vitamin D supplements should not be taken by adults to prevent nonmusculoskeletal disease. Since 2012, eight systematic reviews and/or meta-analyses have dissected this topic, with conflicting results

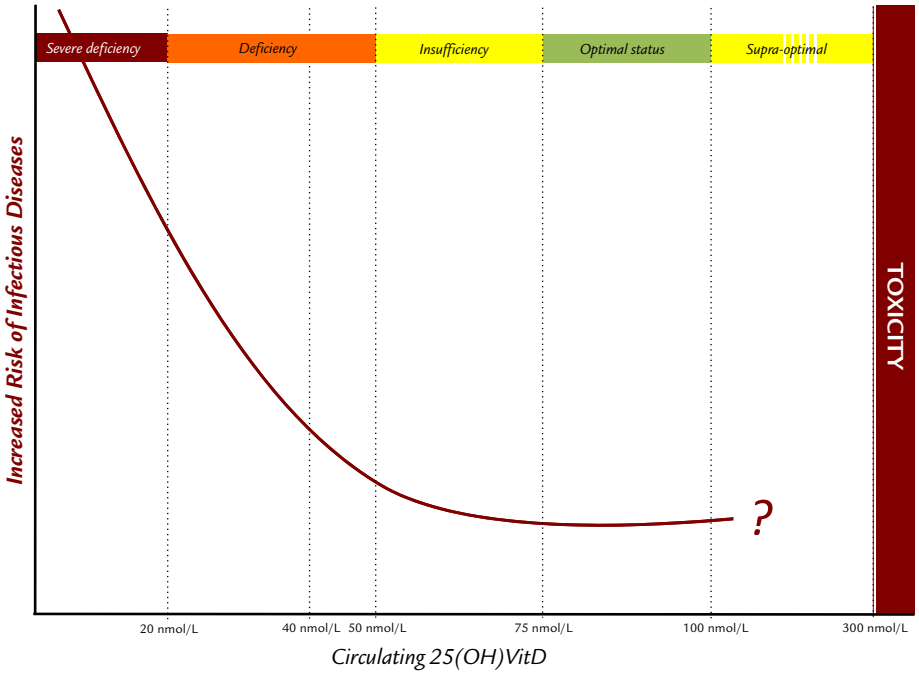

Figure 2. The graphic proposes a 25-hydroxy vitamin D (25[OH]VitD) status–risk of infection relationship. The presented model is mainly based on data obtained from epidemiologic studies, and the different vitamin D statuses are those commonly considered for bone health. "Toxicity" (also called hypervitaminosis D) usually results from megadoses of supplements but not by diet or sun exposure and is associated with hypercalcemia. We hypothesized a continuous relationship (bold red line) between serum values and the risk of infection rather than by stages according to vitamin D status. This theory is based on results from studies at cell levels providing a continuous relationship between 25(OH)VitD concentration and antibacterial products.[13] On either side, the dashed lines represent the heterogeneity between individuals according to their immunologic response to circulating 25(OH)VitD but also some variability in the interactions between the pathogen and the host.

(3 reported benefits[49–51] and 5 did not[52–56]). Thus, the recent meta-analysis by Martineau et al[47] should not really change the landscape of vitamin D supplementation, which finally stays in the line with previous conclusions formulated by Kearns et al and Bolland et al.

...Although the Controversy Remains Active

In a recent editorial, Bolland et al[57] analyzed why the conclusions of Martineau et al[47] were so different from previous reports. First, in absolute terms, the primary result from the meta-analysis[47] was a reduction from 42% to 40% in the proportion of participants experiencing at least 1 episode of infection. A reduction of 2% may not seem sufficient to justify widespread supplementation. Second, the definition of acute respiratory tract infection varied widely between studies. It consists of a mixture of diverse conditions such as acute otitis media, laboratory-confirmed influenza, self-reported common colds, parent-reported colds or chest infections, or radiograph-confirmed pneumonia. Third, some methodologic limitations were highlighted, such as unclear selection of trials (eg, prospective data collection was an inclusion criterion, 2 studies that collected data retrospectively were included). Fourth, when the authors aimed to analyze potentially important factors modifying the response to supplementation, vitamin D status was only available for 40% of trial participants. The conclusion of the editorial was that results of the

meta-analysis should be viewed more as hypothesis-generating only, requiring confirmation in well-designed, adequately powered, randomized controlled trials.[57]

One important comment was also to consider individuals with very poor vitamin D status in clinical trials because they were never targeted by the controlled trials of supplementation in the frame of respiratory infections. These comments were also formulated (ie, low dosages or short duration of supplementation), as well as underpowered numbers, to explain why many randomized clinical studies found no benefits for severe infections or sepsis after serum vitamin D optimization in deficient patients.[43] In the most recent clinical trial of 475 patients with vitamin D deficiency,[58] the administration of high doses of vitamin D compared with placebo did not reduce hospital length of stay, hospital mortality, or 6-month mortality. However, hospital mortality and mortality rates in this study were significantly lower in the severe vitamin D deficiency subgroup (25[OH] VitD <30 nmol/L [12 ng/mL]).

As mentioned previously, vitamin D has been extensively studied in the prevention and treatment of tuberculosis.[13] Globally, vitamin D as an adjunctive therapy has demonstrated little impact on the clearance of *M tuberculosis*,[44,59–61] but with patients with different polymorphisms of VDR, severely poor vitamin D status, or infection with different strains of *Mycobacterium*, more significant results have been reported.[60,62–64] Additional benefits may be expected on the clearance of *M tuberculosis* such as dampening the inflammatory response[65] or gains in body weight, which may help patients recover.[59,62,63,66]

Finally, the current body of evidence supports the view that vitamin D supplementation holds promises as a risk-modifying intervention in tuberculosis and upper respiratory tract infections. In addition, in terms of adverse events, most of the studies reported no difference between groups or observed events deemed related to vitamin D directly.[44]

VITAMIN D AND VACCINE RESPONSE

In terms of prevention of infectious diseases, vaccines are the most powerful of public health tools. They provide tremendous benefits in protecting vulnerable populations against life-threatening and disabling pathogens worldwide.[67] In response to vaccines, the potential role played by vitamin D may be mediated via its direct interaction with antigen-presenting cells and more particularly with dendritic cells as specifically reviewed recently.[2] These roles may include dendritic cell activation, via TLRs by vaccine antigen (with or without adjuvant), and intra-cell upregulation of CYP27B1 with the induction of cytokine production and T-cell proliferation.[27] The cytokine production results in the inhibition of the Th1 response-like cytokines (IL-2 and IFN-γ), the increase of the Th2 response-like (IL4, IL5, IL10, and IL13), and the production of Th17 response-like cytokine (IL-17) secretion.[68] There are also indirect effects on B-cell homeostasis, proliferation, and immunoglobulin production.[69] Although $1\alpha,25(OH)_2$VitD may directly blunt B-cell functions, it would, paradoxically, stimulate immune response to vaccine through its effects on innate immunity.[2]

These potent vitamin D–associated effects on cytokine production and in regulating innate and adaptive immune functions have been confirmed in murine studies.[70,71] Thus, $1\alpha,25(OH)_2$VitD locally produced induced the migration of dendritic cells from the site of vaccination to nondraining lymphoid organs, where T cells and B cells were stimulated to mount an antibody response to diphtheria vaccine.[72] Complementary studies, in animal models and ex vivo human cells, highlighted the negative impacts of vitamin D deficiency and the benefits of its supplementation on vaccine response (eg, HBV, measles, rubella, bacille Calmette-Guerin vaccinations).[73–76]

With respect to vaccine effectiveness in the context of vitamin D deficiency and supplementation, results of epidemiologic and clinical trials are conflicting and, similar to studies of infections, revealed some methodologic weaknesses and limiting and confounding factors. Thus, although some prospective studies reported positive results,[2,24,77] the lack of standardization has led to a variety of dosing and timing strategies, and the difference in individual responsiveness to vitamin D may contribute to the blunting of some of vitamin D's effects.[2,17] Moreover, when vaccine effectiveness is investigated, it is important to take into account the vaccine type, its antigenic contents, the pathogen (epidemiology and ways of infectivity), and/or the immune component(s) that effectively induce the protection. Furthermore, the link between immunogenicity and protection is not direct,[78,79] and in addition to the quantitative

response, the quality of the antibodies (ie, avidity and affinity) is important. Subsequently, vaccine immunogenicity can be highly influenced by previous contacts (via infection, vaccination, or both). For example, with influenza vaccine, a clear inverse relationship exists between pre-immunization serum hemagglutination inhibition titers and postvaccination antibody response.[2]

HOW TO OPTIMIZE VITAMIN D STATUS EFFICIENTLY AND SAFELY

Production of vitamin D in the skin requires exposure to UVB-containing wavelengths ($\lambda = 280–320$ nm), and this action is expected to naturally supply the body's requirement for this pro-hormone. Interestingly, vitamin D produced in the skin may last at least twice as long in the blood compared with ingested forms. The same spectrum of solar radiation, UVB, also represents a major risk factor for all forms of skin damage and cancers, including malignant melanoma.[80] During the photochemical transformation to vitamin D, alternative hydroxy metabolites and, depending on the UVB dose, luminesterol and tachysterol are also produced, which contribute to protection from UV-induced DNA damage.[5] These anti-carcinogenic and anti-melanoma effects are mediated via their interaction and expression of the VDR and RORα and RORγ. Uncontrolled and intensive sun exposure is not advisable; this practice remains dangerous to skin health, and an optimum balance between exposure/protection seems to be insufficient to reach and maintain optimal status year-round. Indeed, the ability of sunlight to raise vitamin D status is also highly modulated by factors such as the timing of exposure, skin surface area exposed, and skin type, including pigmentation level.[81] Further consideration must also be given to clothing and sunscreen and the impact of variation of UVB according to season and latitude.[80] Thus, the farther one lives from the equator, the less time of the year one can rely on solar exposure to produce vitamin D.

To compensate this endogenous production, it is not reasonable to rely on ingestion of natural vitamin D–rich food. The result is that vitamin D insufficiency affects ~50% of the population worldwide.[1,13] Thus, reasonable vitamin D supplementation remains necessary for the most at-risk groups,[26] including, among others, adults aged ≥65 years (and not only institutionalized and home-bound persons),[17] those with heavily pigmented skin,[1] or those with osteoporosis.[82]

Both types of vitamin D (D_2 and D_3) supplements are available, and vitamin D_3 is the type that most experts believe should be used in practice.[1,83] Vitamin D_3 is more effective at raising and maintaining 25 (OH)VitD levels, and vitamin D_2 does not bind as well to the VDR in human tissues.[2,26] Thus, in most individuals (ie, those not at-risk for vitamin D deficiency), a safe sunlight exposure (ie, short regular exposure, avoiding sunburn, applying sunscreen after 15 minutes of exposure) during the summer period and daily 1000-IU vitamin D_3 supplementation in the winter may be suggested for the maintenance of target values year-round.[27]

IS THE SERUM VALUE THE RIGHT TARGET?

In addition to the methodologic weaknesses previously emphasized to explain why clinical trials have failed to take advantage of vitamin D, the ways in which we chose to exert these immunomodulatory roles also plays a part in this acknowledgement of failure. Indeed, it is becoming increasingly clear that the dynamic response to vitamin D (ie, the individual responsiveness to vitamin D) does not correlate with the static assessment of the serum status. Some arguments to this statement are obtained from pharmacologic, genomic, and, more recently, epigenetic studies.

Pharmacologic Arguments

With a target serum value of 75 nmol/L (30 ng/mL), the common dosage recommendations for daily vitamin D uptake can vary according to age from 400 to 600 UI in children to 600 to 1000 UI/d[3,26] in adults (and even more for some). In addition, the picture becomes still less precise and more complex when vitamin D–deficient individuals are considered. For these individuals, loading doses followed by a maintenance dose may be necessary to achieve and maintain target values year-round/life-long.[83] Furthermore, if the question of target value and dosage is to be solved around its application in bone health, the precise requirements eliciting in vivo immunomodulatory beneficial effects are still to be defined.[13] Thus, practical modalities to achieve and maintain serum values have yet to be formally determined.[26]

The body's response to supplementation varies according to vitamin D status at baseline and the dose and frequency of administration. Estimates suggest that for every 100 IU of vitamin D ingested, the serum level increases by 2.5 nmol/L (1 ng/mL). Thus, to achieve a blood level >75 nmol/L would require the ingestion of 3000 IU/d, but when serum levels are <30 nmol/L (15 ng/mL), the body seems to be able to use vitamin D more efficiently to rapidly raise the concentration to ~50 nmol/L (20 ng/mL).[13] The daily, weekly, and monthly administration of the daily equivalent of 1000 IU provided equal efficacy and safety profiles in some trials,[84] whereas others found a slightly lower efficacy with monthly doses compared with daily or weekly doses.[85] How this finding is reflected in beneficial health outcomes must be specifically studied.[26] High-dose, intermittent therapy (once every 6–12 months) results in either transient hypercalcemia[86] or transient increased risks of falls or fractures.[82,87]

Beyond Genetic Polymorphisms

Recent research has led to a better understanding of the inter-individual variability of vitamin D status and immune response before and after supplementation.[26] Genetic, metabolic, or environmental mechanisms have thus been identified from the analysis of *VitDmet*[88] and *VitDbol*[89,90] trials. For the authors, a personal response index should be assigned to each individual (highest index for best responders), which represents the (epi)genetic properties of an individual.[3] The mechanistic core of vitamin D signaling is the VDR, and although the human genome includes at least 23,000 different VDR-binding sites, just a small subset is accessible to VDR. This scenario occurs because the DNA is packaged with heterochromatin, which can limit the access of most transcription factors. Recent research suggests that nearly 9000 chromatin regions were changed in their accessibility after supplementation with $1\alpha,25(OH)_2$VitD.[91] This is just one example, with some other examples more specifically measured in immune cells,[92] which demonstrate that supplementation with the parent compound vitamin D leads to an increase in chromatin accessibility and gene transcription but also a modulation of the human epigenome and transcriptome.[3]

Variability of the immune response to vitamin D may result from different single nucleotide polymorphisms (SNPs). These have been found to correlate with various serum levels,[1,3] and studies of VDR polymorphisms in humans support the hypothesis that variability in host genes encoding vitamin D–responsive elements affects the baseline immune response after supplementation.[13] Among SNPs, for example, being homozygous for the presence of the *Fok1* site "*f*" yields a VDR less active than the "*F*" form, and individuals with the *ff* genotype are suspected to be more prone to developing acute lower respiratory tract infections or tuberculosis. This finding was confirmed by a recent meta-analysis in which homozygosity for the *FokI* polymorphism was, for example, associated with an increased risk of tuberculosis.[93] In a randomized controlled trial, no effect on sputum conversion time was observed when the *Fok1* genotypes were considered in patients with tuberculosis who received vitamin D supplementation.[60] In addition to vitamin D status, *FokI*, *TaqI*, and *BsmI* polymorphisms of the VDR are also predictive of the treatment response of patients with chronic hepatitis C.[94,95] In patients with HBV, genetic variations of CYP2R1 and CYP27B1 also influenced host immune response in chronic infection.[96,97] Polymorphisms in the VDR gene also affect the immune activation and the clinical outcome of *Bordetella pertussis* infection,[98] as well as the immune response to measles[74] and rubella vaccine.[75]

The influence of SNPs is also extended to genes coding vitamin D–binding protein.[3,27] Differences in serum concentrations of vitamin D–binding protein and affinity influence the capacity of 25(OH)VitD to target monocytes[99] and induce antibacterial responses.[100,101] There are 3 allelic forms with varying affinity to the circulating and active forms of vitamin D (Gc1F > GC1S > Gc2), the highest effect being measured with higher abundance/affinity Gc1F. However, in monocytes, the response to 25(OH)VitD was more pronounced in terms of induction of antibacterial response in the presence of the Gc1S or Gc2 form than Gc1F. In the context of tuberculosis, the Gc2/2 phenotype was significantly associated with *M tuberculosis* infection, but only when the baseline serum concentration was <20 nmol/L.[101]

CONCLUSIONS

The overall body of evidence suggests that vitamin D plays an important role in modulating the immune

response to infection. Although the association between vitamin D deficiency and the susceptibility to various pathogens is becoming clearer, this review demonstrates that the achievement of an accurate assessment of the health benefits of optimized vitamin D status is still fraught with methodologic and epidemiologic challenges. Moreover, it becomes particularly clear that the dynamic responsiveness to supplementation does not correlate with the static assessment of the serum status, and this because it is driven at the individual level by the epigenome (ie, in response to environmental changes and individual's lifestyle or health condition) as well as by SNPs at different levels of the vitamin D cascade. Finally, the debate regarding the recommendation for widespread vitamin D supplementation to prevent diseases remains active, except for those at high risk of osteomalacia and osteoporosis.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article

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