Vitamin D and Infectious Diseases

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It is now 2 years since we have seen the impact of the CoronaVirus Disease-19 (COVID-19) caused by Syndrome-Coronavirus-2 worldwide, affecting millions of people and rates of mortality close to 6 million. Although we are beginning to see the real benefit of vaccines, in terms of reduced mortality rates, many individuals still remain to be vaccinated or do not respond to them leaving a large number of patients still experiencing severe respiratory symptoms associated with COVID-19. In recent months, we have seen another surge in individuals infected with COVID-19 and mortality rates are also increasing. In the absence of effective therapies or vaccines, the medical and scientific community have extensively explored a range of current available therapeutic agents, mainly focused on targeting viral replication as well as managing severe respiratory symptoms associated with COVID-19.

Vitamin D has emerged as one such candidate due to its recognized immunomodulatory effects. In this regard, the activation of the vitamin D receptor (VDR) signaling pathway may generate beneficial effects in acute respiratory distress syndrome by decreasing the cytokine/chemokine storm, thus having an important immunomodulatory and anti-inflammatory role.

Keywords: vitamin D ; immune-mediated disease ; Infectious diseases ; Rheumatic diseases ; cholecalciferol ; COVID-19

1. Introduction

Vitamin D is essential for the homeostatic regulation of calcium [1], and reduced vitamin D intake can result in vitamin D deficiency or inadequate levels, impacting bone metabolism and leading to an increase in the secretion of parathyroid hormone (PTH) and subsequent increase in bone resorption [2][3]. Vitamin D is synthesized (or introduced into the body with food), undergoes a first hydroxylation in the liver, and is transformed into 25-hydroxyvitamin D3 [25(OH)D_3] or calcidiol. Despite the fact that 25(OH)D is not the active form of vitamin D, it is measured in the clinical setting to establish vitamin D status due to its long half-life (2–3 weeks) [4][5][6]. Calcidiol is further hydroxylated to its active form, calcitriol; 1,25-dihydroxyvitamin D [1,25$(OH)_2D_3$], this second hydroxylation, mainly occurs in the kidney [7]. The activation process is regulated by the circulation of serum levels of PTH, calcium, and phosphorus. In turn, 1,25(OH)2D_3 controls PTH secretion through a negative feedback mechanism.

Vitamin D deficiency is a very common condition worldwide, particularly in elderly and osteoporotic subjects, in which the risk of bone fragility increases [2][8][9][10]. In addition to playing an essential role in maintaining bone health, vitamin D is also recognized for its immunomodulatory effects [11][12][13][14]. Both the vitamin D receptor (VDR) and metabolizing enzymes, such as 1-α-hydroxylase, are expressed by different types of immune cells including macrophages, T cells, dendritic cells, monocytes, and B cells [15][16][17][18][19], and evidence from pre-clinical studies has shown that vitamin D exerts biological effects on both the innate and adaptive immune systems [11][13][14]. Extra-renal 1-α-hydroxylase is not upregulated by PTH; therefore, 1,25$(OH)_2D_3$ production is dependent upon levels of the substrate 25$(OH)D_3$ and may be regulated by inflammatory signals, such as lipopolysaccharide (LPS) and cytokines [20][21]. In vivo studies have shown that the administration of vitamin D can lead to changes in or the development of a range of immune-related diseases [11][12][13][22]. This favors the idea that clinical and epidemiological data link vitamin D with the incidence and severity of many immune-mediated disorders such as rheumatoid arthritis [23], diabetes [24], and infectious diseases [25][26]. A summary of immune-mediated diseases commonly associated with vitamin D deficiency is presented in **Table 1**.

Table 1. Immune-mediated diseases commonly associated with vitamin D deficiency.

Infectious/Pulmonary Diseases	Skin Disease	Rheumatic Diseases	Metabolic	Other
Sepsis	Psoriasis	Rheumatoid arthritis	Type-1 diabetes	Multiple sclerosis

Infectious/Pulmonary Diseases	Skin Disease	Rheumatic Diseases	Metabolic	Other
Tuberculosis	Urticaria	Psoriatic arthritis		
COPD	Dermatitis	Ankylosing spondylitis		
Asthma		Systemic sclerosis		
		Lupus		

COPD = chronic pulmonary obstructive disease.

To date, evidence documenting the protective effects of vitamin D supplementation is derived from many observational studies and meta-analyses of clinical trials for the prevention of viral acute respiratory tract infection (ARTI) [27][28][29]. Low vitamin D status (i.e., <20 ng/mL [7], measured as plasma levels of vitamin D, 25(OH)D) is prevalent worldwide and frequently observed in regions of Northern latitudes, but also in Southern countries [9].

Indeed, the benefit of vitamin D supplementation in patients with COVID-19 only remains speculative and is partially supported by limited data from observational studies [30][31][32] and three clinical trials [33][34][35].

2. Vitamin D and the Immune System

The first indirect evidence of a potential role of vitamin D and its metabolites in immune regulation probably lies in an ancient paper published more than 150 years ago. The beneficial effects of pure, fresh cod liver oil in the treatment of 234 cases of tuberculosis were described [36]. The scientific community had to wait over 100 years to enter the era of the link between vitamin D and the immune system with the discovery of 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) specific high-affinity receptors in human leukocytes [37] and in human peripheral blood mononuclear cells [38]. The subsequent step was the demonstration that the expression of 1-α hydroxylase, the final enzyme for the activation of the terminal metabolite of the vitamin D biologic system, is not restricted to the kidney proximal tubule cells but is upregulated by immunologic stimuli also in the monocytic-macrophage lineage [38]. Since these historical discoveries, a large body of evidence has accumulated on the mechanistic role for vitamin D in the regulation of the immune response (either innate or adaptive) through its active metabolite, calcitriol [$1,25(OH)_2D_3$] [14][39][40]. A summary of the effects of vitamin D on innate and adaptive immunity is presented in **Table 2**. Two main observations support this hypothesis: The vitamin D receptor (VDR) is expressed in almost all immune cells, including B and T lymphocytes, monocytes, macrophages, and dendritic cells, and some immune cells are able to convert 25-hydroxy-vitamin D [25(OH)D] to $1,25(OH)_2D$ [14][39][40].

Table 2. Effects of vitamin D on innate and adaptive immunity.

Function/Cells	Effect	Reference
	Innate immunity	
Macrophage differentiation	Increased	Koeffler et al. 1984 [41]
Bacterial killing	Increased	Liu et al. 2006 [20]
Dendritic cells' maturation	Decreased	Penna et al. 2000 [42]
Antigen presentation	Decreased	Griffin et al. 2000 [43]
	Adaptive immunity	

Function/Cells	Effect	Reference
Th1 cytokines	Decreased	Boonstra et al. 2001 [44]
Th2 cytokines	Increased	Boonstra et al. 2001 [44]
Th17 differentiation	Decreased	Daniel et al. 2008 [45]
T-regs' differentiation	Increased	Chambers et al. 2014 [46]
B-cells	Decreased proliferation Induction of apoptosis Inhibition of plasma cell generation Inhibition of immunoglobulin secretion	Chen et al. 2007 [47]

2.1. Innate Immunity

The discovery of a physiological role of vitamin D in the regulation of the innate immune response began with the finding that activated macrophages and dendritic cells express CYP27B1 (the gene encoding for 1-α hydroxylase) and the VDR gene [21][48]. In 2006, a pivotal study demonstrated that toll-like receptor (TLR) activation of human monocytes and macrophages with a synthetic *M. Tuberculosis*-derived lipopeptide led to a shift in the gene expression profile of these cells enhancing the expression of VDR and CYP27B1, with an increase in the endogenous production of $1,25(OH)_2D$ from circulating 25(OH)D [20]. In the same study, $25(OH)D_3$ (calcifediol) supplementation on TLR-stimulated human monocytes in culture strongly enhanced the expression of cathelicidin, a natural antibacterial peptide, thus supporting the idea that $1,25(OH)_2D$ through binding to VDR could regulate the innate immune response. These observations, together with an IL-15-dependent, CYP27B1-induced stimulation of macrophage development and differentiation and the well-known excessive $1,25(OH)_2D_3$ production by macrophages in several granulomatous diseases, led to the assumption that vitamin D can act as a potent stimulator of mechanisms associated with pathogen elimination. Furthermore, $1,25(OH)_2D$ in monocytes and hepatocytes inhibit the expression of hepcidin, another natural antibacterial protein directed to suppress the transmembrane protein, ferroportin, thus inhibiting iron export from cells and limiting iron supply to microorganisms to sustain their growth [49].

Dendritic antigen-presenting cells express VDR and are modulated by $1,25(OH)_2D$ towards a more tolerogenic phenotype through a delay in their maturation, thus limiting the ability to present antigen to T cells. In mature dendritic cells, VDR expression is reduced [50] with a decrease in sensitivity to $1,25(OH)_2D$, allowing an initial presentation of antigen to T cells. The inhibition of cell maturation acts as a barrier to the overstimulation of T cells. Neutrophils express VDR but lack CYP27B1 [51], indicating that these cells may preferentially function as a hormonal target for $1,25(OH)_2D$. Existing data indicate that vitamin D can induce the formation of neutrophil extracellular traps (NETs) and acts on primary human neutrophils as a modulator of the inflammatory response by lowering inflammatory neutrophil-derived cytokine production [52]. Collectively, these data indicate that vitamin D reinforces bacterial killing by these cells, while restricting a neutrophil-induced inflammatory response [53]. Furthermore, $1,25(OH)_2D$ is also able to influence eosinophil function through the downregulation of interleukin (IL)-15, the pivotal cytokine involved in the recruitment of these cells [54], and lowers immunoglobulin-E (IgE)-dependent mast cell activation [55]. Natural killer (NK) cells play an intermediate role between innate and adaptive immunity [56]. Several studies confirm that vitamin D also exerts a regulatory role on this family of T lymphocytes by modulating their cytotoxicity, cytokine secretion, and degranulation [57].

Other evidence suggests that $1,25(OH)_2D$ may directly modulate the expression of several cytokines implicated in innate immunity. In co-cultures of infected macrophages, vitamin D induces the expression of IL-1-beta and IL-8 [58] and, in infected human peripheral blood mononuclear cells, downregulates the expression of other proinflammatory cytokines such as IL-6, tumor necrosis factor-(TNF)-α, and interferon (IFN)-γ [59]. These data confirm an important role of $1,25(OH)_2D$ in enhancing a prompt response to infection together with a modulating effect on the acute inflammatory response.

2.2. Adaptive Immunity

Besides the indirect consequences on T-cell differentiation and function derived from the effects of vitamin D on innate immune cells, $1,25(OH)_2D$ acts as a regulator of mature T cells by altering the balance between T helper (Th)1 and Th2 cell differentiation. Specifically, $1,25(OH)_2D$ enhances the expression of IL-4 and strongly inhibits IFN-γ production from naïve CD4+ T cells in culture, thus showing the capacity to inhibit Th1 and reciprocally promote Th2 cell differentiation [44]. This effect may suggest a possible preventive or therapeutic role of $1,25(OH)_2D$ in several Th1 cell-driven diseases, such as multiple sclerosis, type 1 diabetes mellitus (T1D), inflammatory bowel diseases, and rheumatoid arthritis (RA). Another study performed in a mouse model of human Crohn disease confirmed that calcitriol with or without dexamethasone upregulates Th2 markers and is able to reduce not only Th1 differentiation but also the Th17-driven response, indicating that vitamin D may exert some of its effects on inflammation and autoimmunity through the regulation of IL-17 expression in T cells [45]. A reduction of Th17 cells is usually counterbalanced by an increase in T-regulatory cells' (T-regs) reciprocal axis. The $1,25(OH)_2D_3$ together with transforming growth factor beta (TGF-β) is able to induce forkhead box P3 expression in naïve CD4+ T cells, promoting T-regs' differentiation [46], and to increase the production of the anti-inflammatory cytokine IL-10 from CD4+/CD25+ T-regs [60] with potential beneficial effects in several autoimmune diseases. With the aim to better understand the molecular mechanisms involved in the orderly shutdown and retraction of CD4+ type Th1 cell response, Chauss et al. recently analyzed the bronchoalveolar lavage fluid CD4+ T cells of patients with COVID-19 and identified an autocrine/paracrine vitamin D loop that allows Th1 cells to activate and respond to vitamin D as part of a complex shutdown program repressing IFN-γ and enhancing IL-10 [61]. Indeed, the molecular pathways identified in this work may yield important information to aid in the development of novel therapeutic approaches to accelerate the shutdown program of hyper-inflammatory cells in COVID-19 patients.

Human active B-lymphocytes carry VDR as well as 1-α-hydroxylase, suggesting that vitamin D may strongly also influence this family of immune cells [47]. B-cell response is influenced by vitamin D via an inhibition of the ongoing proliferation of activated B-cells, induction of B-cell apoptosis, and inhibition of the generation of plasma cells. As a net result of these effects, vitamin D acts as an inhibitor of immunoglobulin secretion, also suggesting a possible role of vitamin D in B-cells-related disorders.

Experimental data accumulated in the past three decades provide convincing evidence for an immunomodulatory effect of vitamin D either on innate or on adaptive immunity [14][62]. To mention a paradigmatic example, in RA, vitamin D exerts effects against the intrinsic disease mechanisms, which include Th1 polarization, lower expression of Th2 cytokines, higher immunoglobulin production, enhanced Th17 differentiation, and lower T-regs' activation and function. Based on these anti-inflammatory properties of vitamin D, a protective effect on several inflammatory and autoimmune diseases has been hypothesized by numerous reports demonstrating (mainly retrospective studies) low circulating levels of 25(OH)D in a high proportion of patients with chronic inflammatory conditions. In this respect, it is important to address two critical points. First of all, a mechanism of reverse causality induced by chronic diseases cannot be ruled out. Secondly, data derived from several recent studies support the hypothesis that systemic inflammation lowers 25(OH)D concentrations, thus contributing to the low circulating levels observed in patients suffering from chronic inflammatory diseases. In this context, in a recent experimental study based on a human endotoxemia model reproducing systemic inflammation in vivo, circulating levels of 25(OH)D significantly decreased shortly after initiation of a bolus of *E. coli*-derived lipopolysaccharide [63].

3. Vitamin D and Infectious Diseases

As we have previously alluded to, $1,25(OH)_2D$ exerts several direct and indirect effects on innate immunity by directly affecting antimicrobial activity and by influencing gut microbiota composition. Compelling evidence suggests that $1,25(OH)_2D$ is capable of enhancing the production of defensin β2 and cathelicidin antimicrobial peptide (CAMP) by macrophages/monocytes; of up-regulating CAMP in keratinocytes, epithelial, intestinal, lung and corneal cells, and placenta trophoblasts; of increasing the chemotaxis, autophagy, and phagolysosomal fusion of innate immune cells; and of enhancing corneal, intestinal, and epithelial barrier function (e.g., maintaining tight and gap junctions) [19][64]. Moreover, macrophages formed after IL-15 stimulation have been shown to respond to vitamin D by increasing their antimicrobial activity (in contrast to those obtained after IL-10 stimulation that are weakly influenced by vitamin D) [19].

The effects of vitamin D on the adaptive immunity are relevant mainly, but not only, to autoimmune and rheumatic diseases [14][19][40][65]. As we have already mentioned, $1,25(OH)_2D$ has been shown to down-regulate the immune response mediated by Th1 cells, to up-regulate Th2 cells' activity, to suppress Th 17 formation and activity, to increase Tregs' function, to modulate differentiation and antibody production of B cells, and to induce apoptosis and cell cycle arrest of proliferating B cells [14][19][40][65].

Historically, as we have alluded to previously in this work, the antimicrobial properties of vitamin D have been recognized for their protective effects on *M. Tuberculosis* disease. The 25(OH)D levels have been shown to influence the incidence of tuberculosis disease and its clinical course as well [66][67][68]. More recently, the potential beneficial effects of vitamin D in several other infectious diseases have been observed, including hospital-acquired *Clostridium Difficile* infection (CDI), influenza, ARTIs, COVID-19 infection, and sepsis (including mortality due to sepsis) [29][64][69][70][71][72].

Upala et al. investigated the association between vitamin D deficiency and sepsis in hospitalized patients in a systematic review and meta-analysis of observational studies [70]. The authors observed a higher risk of sepsis in patients with serum levels of 25(OH)D <20 ng/mL measured before or during hospitalization compared to those without vitamin D deficiency. Another meta-analysis also revealed an independent association between severe vitamin D deficiency (below 10 ng/mL) and increased mortality in adult patients with sepsis [71].

Several studies investigated the potential relationship between CDI and vitamin D. Particularly interesting are the results of a meta-analysis of epidemiological studies examining the association between serum 25(OH)D concentrations and CDI severity or recurrence. The study demonstrated a higher odds of severe CDI in subjects with lower 25(OH)D compared to those with higher 25(OH)D [72]. On the other hand, there was no significant association between 25(OH)D status and CDI recurrence.

Both epidemiological studies and RCTs demonstrated that, by raising 25(OH)D concentrations in winter, the risk of developing influenza can be reduced, particularly in school children and infants [64]. A recent review of the literature, including five RCTs, concluded that the beneficial effect of vitamin D supplementation on the risk of developing influenza was seen for doses of cholecalciferol of around 1200 IU per day [64]. According to these results, an observational study examining the relationship between serum 25(OH)D concentration and incidence of ARTIs (mainly influenza) demonstrated a protective effect of vitamin D for concentrations above 38 ng/mL [73].

The most compelling data on the antimicrobial effects of vitamin D are those related to ARTIs [29]. In this area, the results of a systemic review and meta-analysis of individual patients' data, investigating the effects of vitamin D supplementation on the risk of ARTI, are particularly relevant. Vitamin D deficiency was demonstrated to significantly reduce the incidence of ARTI (outcome: proportion of participants with a least one ARTI and rate of ARTI). In subgroup analysis of patients receiving daily or weekly vitamin D, the protective effect was stronger in those subjects with baseline serum 25(OH)D concentrations below 10 ng/mL. Interestingly, the beneficial effects of vitamin D were seen in subjects receiving daily or weekly vitamin D without additional bolus doses, but not in those receiving one or more bolus doses. All these findings were, in general, also confirmed by considering potential confounders [29]. Recently, these findings were confirmed in another meta-analysis that showed that the protective effect of vitamin D was associated with daily doses of 400–1000 IU given for up to 12 months [74].

Nitric oxide (NO) functions as a pro-inflammatory mediator and plays a recognized role in a range of inflammatory [75] diseases including respiratory diseases [76]. The association between NO and vitamin D is also recognized. Vitamin D has been shown to act as a transcription factor for the regulation of endothelial NOS in mice [77] and improve NO-dependent vasodilation in adipose tissue arterioles from bariatric surgery patients [78]. Vitamin D has also been shown to increase the expression of inducible nitric oxide synthase (iNOS) in patients with COVID-19 [79].

Overall, the results of basic and clinical studies strongly support the role of vitamin D in preventing and reducing the severity, and possibly the complications, of several infectious diseases. In general, and considering potential confounding variables, data derived from these studies point towards beneficial effects in subjects with varying degrees of vitamin D deficiency at baseline who receive appropriate doses/dosing regimens of vitamin D.

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