AARDS
COVID-19 LONG HAULER CLINIC

Preventing and Treating Long-Haul COVID-19 and Other Types of Inflammation

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Vitamin D

The Role of Vitamin D in the Age of COVID-19: A Systematic Review and Meta Analysis:

Evidence recommends that vitamin D might be a crucial supportive agent for the immune system, mainly in cytokine response regulation against COVID-19. Hence, we carried out a systematic review and meta-analysis in order to maximize the use of everything that exists about the role of vitamin D in the COVID-19.

Twenty-three studies containing 11901participants entered into the meta-analysis. The meta-analysis indicated that 41% of COVID-19 patients were suffering from vitamin D deficiency (95% CI, 29%-55%), and in 42% of patients, levels of vitamin D were insufficient (95% CI, 24%-63%). The serum 25-hydroxyvitamin D concentration was 20.3 ng/mL among all COVID-19 patients (95% CI, 12.1-19.8). The odds of getting infected with SARS-CoV-2 is 3.3 times higher among individuals with vitamin D deficiency (95% CI, 2.5-4.3). The chance of developing severe COVID-19 is about five times higher in patients with vitamin D deficiency (OR: 5.1, 95% CI, 2.6-10.3). There is no significant association between vitamin D status and higher mortality rates (OR: 1.6, 95% CI, 0.5-4.4).

This study found that most of the COVID-19 patients were suffering from vitamin D deficiency/insufficiency. Also, there is about three times higher chance of getting infected with SARS CoV-2 among vitamin D deficient individuals and about 5 times higher probability of developing the severe disease in vitamin D deficient patients. Vitamin D deficiency showed no significant association with mortality rates in this population.

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Vitamin D in infectious complications in critically ill patients with or without COVID-19:

Vitamin D was primarily recognized for its role in calcium homeostasis, whose deficiency caused rickets [1]. In the recent years, vitamin D has been found to play an important role in modulating immune cells, and inhibiting the inflammatory response [2]. Vitamin D is implicated in the regulation of over 2000 genes, is known to respond to infection, plays a role in antimicrobial peptide production, and triggers innate immunity. The overall result of vitamin D deficiency is the alteration of key immune response biological processes, such as gene expression, cytokine production, metabolism and cell function [3,4].

Studies have revealed a high prevalence of vitamin D deficiency in critically ill patients, and that vitamin D deficiency might be associated with worse outcomes in patients with coronavirus disease 2019 (COVID-19), such as more severe disease and higher mortality rates. Many risk factors have been recognized for decreased vitamin D levels, including age, latitude, the use of sunscreen, limited sun exposure, non-White ethnicity, obesity, low dietary intake of vitamin D, and malabsorption syndromes. However, the low vitamin D levels seen in critically ill patients may be a result of many factors, including drug interactions, irregular gastrointestinal function and the result of fluid resuscitation [5].

Vitamin D3 (cholecalciferol) is made in the skin from 7-dehydrocholesterol when exposed to UVB light. Vitamin D2 (ergocalciferol) is derived from the plant sterol ergosterol. Vitamin D is metabolized first to 25-hydroxyvitamin D (25(OH)D), then to the active metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). The liver has been established as the major source of 25(OH)D production from vitamin D, while the kidney is the major source of circulating levels of $1,25(OH)_2D$ [7]. All genomic actions of $1,25(OH)_2D$ are mediated by the vitamin D receptor (VDR). VDR is a transcription factor that exists in nearly every tissue, and member of the steroid hormone nuclear receptor family. VDR binds to DNA sites termed vitamin D response elements (VDREs). There are thousands of these binding sites throughout the genome regulating hundreds of genes in a cell-specific fashion. Fig. 1 illustrates vitamin D metabolism and signaling. Serum total 25(OH)D, the sum of 25(OH)D2 and 25(OH)D3, is the best reflection of vitamin D status.

Vitamin D deficiency has been shown to be associated with worse outcomes of infectious complications, especially in patients admitted to the ICU [8]. The most recognized extra-skeletal action of vitamin D is the regulation of immune function [9]. Vitamin D is an important link between toll-like receptor (TLR) activation, leukocyte accumulation, local inflammation, and antibacterial responses in innate immunity [10], [11], [12]. TLRs are essential in innate and adaptive immune responses. Macrophages recognize lipopolysaccharide through TLRs, leading to a series of events, which result in the production of peptides with potent bactericidal activity, namely cathelicidin and β-defensin. These peptides co-localize with ingested microbes, within phagosomes, disrupting their cell membranes [13]. Besides antimicrobial activity, these peptides have antiviral activity, and can also inactivate the influenza virus [14]. Vitamin D deficiency has been shown to be associated with reduced TLR expression levels; therefore vitamin D ultimately modulates the expression of cathelicidin and β-defensin, which may

enhance endothelial barrier function [15].

In vitro data have shown that, in addition to modulating innate immune cells, vitamin D also induces immune tolerance. Data from animal and human studies with vitamin D supplementation, have demonstrated the beneficial effects of vitamin D on immune function *in vivo*, especially on autoimmunity [35, 36, 37].

Due to the above, clinical trials with vitamin D supplementation are underway in COVID-19 patients in an effort to improve outcomes (Table 2). In the frail elderly with less severe COVID-19, a single oral
bolus vitamin D3 dose of 50,000 IU per month, or 80,000–100,000 IU every 2–3 months, during, or just before COVID-19 infection, was associated with a better survival rate [105,106]. Very recently, a cross sectional multicenter observational study showed that a high dose cholecalciferol booster therapy (approximately ≥ 280,000 IU in a time period of up to 7 weeks) was associated with a reduced risk of COVID-19 mortality [107]. A retrospective study suggested a potential benefit of cholecalciferol (400,000 IU bolus oral cholecalciferol, 200,000 IU administered in two consecutive days) in comorbid COVID-19 patients [108]. In outpatients, 10,000 IU of vitamin D3 for 14 days resulted in fewer symptoms, compared to the control group [109]. On the other hand, administration of 200,000 IU vitamin D3 as a loading dose, and 10,000 IU daily thereafter via enteral feeding, did not impact the biologically active metabolite $1,25(OH)_2D$, prompting the authors to suggest that both forms should be included in monitoring vitamin D status, and future interventional studies should target the usefulness of calcitriol administration in COVID-19 patients [104]. A systematic review and meta-analysis on vitamin D supplementation and clinical outcomes in COVID-19, including 10 observational studies and 3 RCTs, concluded that vitamin D supplementation might be associated with improved clinical outcomes, especially when administered after the diagnosis of COVID-19 [110].

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Role of vitamin D in preventing of COVID-19 infection, progression and severity:

Some recent reviews demonstrated some pathways by which vitamin D decreases the risk of microbial infections [28, 29, 30, 31]. Vitamin D follows different mechanisms in reducing the risk of viral infection and mortality. To reduce the risk of common cold, vitamin D uses three pathways: physical barrier, cellular natural immunity, and adaptive immunity [32]. A recent review also supported the possible role of vitamin D in decreasing the risk of COVID-19 infections and mortality [12]. These comprise maintaining of cell junctions, and gap junctions, increasing cellular immunity by decreasing the cytokine storm with influence on interferon γ and tumor necrosis factor α [12]and regulating adaptive immunity through inhibiting T helper cell type 1 responses and stimulating of T cells induction [33]. Vitamin D supplementation was also found to enhance CD4+ T cell count in HIV infection [34].

One of the major manifestations of severe SARS-CoV-2 infection is lymphopenia [35]. In both the mouse models and in human cell lines, vitamin D exerted activity in lung tissue and played protective effects on experimental interstitial pneumonitis [36]. Several *in vitro* studies demonstrated that vitamin D plays a significant role in local "respiratory homeostasis" either by stimulating the exhibition of antimicrobial peptides or by directly interfering with the replication of respiratory viruses [37]. Vitamin D insufficiency can, therefore, be involved in ARDS and heart failure [12]and these are the manifestations of severely ill COVID-19 subjects. Therefore, vitamin D deficiency promotes the renin-angiotensin system (RAS), which may lead to chronic cardiovascular disease (CVD) and reduced lung function [38]. People with such comorbidities account for a higher percentage of severe ill cases in COVID-19 [35].

Yet, it is important to fully elucidate the virulence mechanisms of COVID-19, several cellular mechanisms including Papain-like protease (PLpro)-mediated replication, dipeptidyl peptidase-4 receptor (DPP 4/CD26) binding, disruption of M-protein mediated type-1 IFN induction and MDA5 and RIG-I host recognition evasion have been recognized in the closely-related COVID-MERS virus [39], [40]. Of the above processal, human DPP-4/CD26 has been exhibited to connect with the S1 domain of the COVID-19 spike glycoprotein, suggesting that it could also be a salient virulence factor in Covid-19 infection [41]. The expression of the DPP-4/CD26 receptor is reduced significantly in vivo upon the correctness of vitamin D insufficiency [42]. There is also an indication that maintaining of vitamin D may reduce some of the unfavorable downstream immunological sequelae thought to extract poorer clinical outcome in Covid 19 infection, such as interleukin 6 elevation, delayed interferon-gamma response[37], and, a negative prognostic marker in subjects with acutely-ill pneumonia [43], including those having Covid-19.

Some clinical and epidemiological studies support to outline the hypothesis regarding COVID-19 and its relationship with vitamin D status. Recent studies indicated that COVID-19 is associated with the increased generation of pro-inflammatory cytokines, C-reactive protein (CRP), ARDS, pneumonia, and heart failure [44], [45], [46], [47]. In China, chronic fatality rates were 6-10% for people with chronic respiratory tract disease, cardiovascular disease, hypertension, and diabetes [12], [48]. In other studies, serum concentrations of 25(OH)D were inversely associated with pro-inflammatory cytokines, IL-6, increased CRP, and increased risk of pneumonia, ARDS, diabetes and heart failure [11], [49], [50], [51], [52], [53], [54]. In randomized control trials, vitamin D supplementation has been shown to reduce the risk of respiratory diseases [55], [56]. A placebo-controlled trial with 5660 subjects showed that vitamin D supplementation significantly reduces the risk of respiratory tract infections [57]. A review included five clinical studies reported that respiratory tract infections were significantly lower in the vitamin D supplementation group than the control group [58]. Another study included 25 randomized controlled trials, with 10,933 participants in total from 14 different countries indicated the beneficial effects of vitamin D supplementation in reducing the risk of at least one acute respiratory tract infection [59].

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Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections:

(1) VDR is highly expressed in the cuboidal alveolar type II cells (ACII) of the lung [7] [37]. Overexpression of VDR exerts anti-inflammatory effects in the lung [41]. VDR-knockout mice experienced more severe acute lung injury (ALI) than wild-type mice, following LPS treatment. The endocrine system of vitamin D has been shown, in various in vitro models, to inhibit the production and release of cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10 involving ARDS [7,42, 43, 44, 45, 46]. The calcitriol/VDR signaling may also protect against ALI by inhibiting the angiopoietin-2-TEK receptor tyrosine kinase-myosin light-chain kinase pathway [39]. Thus, 1α,25(OH)2D is important in maintaining the structure and function of epithelial barriers in multiple tissues [47] mediated by alveolar epithelial tight junctions and gene regulation of occludin and zonula occludens-1 (ZO-1) expression [38]. 1α,25(OH)2D also inhibits neutrophil recruitment in an animal model of acute lung injury, due to its inhibitory effect on cytokines [48].

(2) There is ample evidence that 1α,25(OH)2D/VDR is a powerful negative regulator of renin angiotensin system (RAS). Indeed, renin is increased in VDR null mice [49]. Similarly, 1α hydroxylase-deficient mice exhibit increased activity of the intrarenal RAS that is downregulated with the administration of 1α,25(OH)2D [38]. Chronic vitamin D deficiency may induce RAS activation [50]. 1α,25(OH)2D inhibits renin, ACE and Ang II expression, and induces ACE2 levels in LPS-induced ALI. In addition, dysregulation of local and circulating RAS, with enhanced ACE/Ang II expression levels and reduced ACE2/Ang-(1–7) expression levels, was reported to contribute to ischemia-reperfusion-induced ALI in mice [51]. Therefore, vitamin D may attenuate LPS Induced ALI by, at least partially, inducing ACE2/Ang-(1–7) axis activity and inhibiting renin and the ACE/Ang II/AT1R cascade (Fig. 2) [37]. VDR activation is also able to inhibit the protein Skp2 [52,53] which plays a central role in the mechanism of viral replication of the COVID-19. Indeed, COVID-19 uses blockade of autophagy for accelerated replication and infectivity [54]. To achieve this, the virus induces Skp2, which, in turn, inactivates Beclin 1, an essential component of the autophagic process. 1α,25(OH)2D also stimulate the production of Klotho, known to attenuate multiorgan aging and increase longevity also promotes autophagy through the maintenance of adequate cellular levels of Beclin [55].

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Vitamin D increases the antiviral activity of bronchial epithelial cells in vitro:

Background

By modulating the antiviral immune response via vitamin D receptor, the active form of vitamin D (1,25-dihydroxyvitamin D, calcitriol) could play a central role in protection against respiratory virus infections. This in vitro study tested the hypothesis that respiratory viruses modulate vitamin D receptor expression in human bronchial epithelial cells and this modulation affects the antiviral response to exogenous vitamin D.

Methods

Human primary bronchial epithelial cells were infected with rhinoviruses and respiratory syncytial virus in the presence or absence of vitamin D. Expression of vitamin D receptor, 1α-hydroxylase (1α(OH)ase), 24-hydroxylase (24(OH)ase), innate interferons, interferon stimulated genes and cathelicidin were measured by quantitative polymerase chain reaction. The antiviral effect of vitamin D on rhinovirus replication was determined by measurement of virus load. A direct inactivation assay was used to determine the antiviral activity of cathelicidin.

Results

Both RV and RSV decreased vitamin D receptor and 24(OH)ase and, in addition, RSV increased 1α(OH)ase expression in epithelial cells. Vitamin D decreased rhinovirus replication and release, and increased rhinovirus-induced interferon stimulated genes and cathelicidin. Furthermore, cathelicidin had direct anti-rhinovirus activity.

Conclusions

Despite lower vitamin D receptor levels in rhinovirus-infected epithelial cells, exogenous vitamin D increased antiviral defences most likely via cathelicidin and innate interferon pathways.

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