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The Role of Vitamin D in Treatment and Prophylaxis of Viral Infections

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Abstract

Importance: Researchers and scientific expertise are in the marathon for reaching to effective therapeutics and powerful protective measures against viral infectious diseases generally and SARS-CoV2 infection (COVID-19) specially. Viral infections e.g. SARs-CoV2 causes immune activation and systemic hyper-inflammation which can lead to respiratory distress syndrome (ARDS). Vitamin D status may influence the severity of responses to viral infections and that the prevalence of vitamin D deficiency will be closely aligned to increase morbidity. In this paper we try to emphasize the role of vitamin D in the treatment and protection against viral infections.

Relevance: Vitamin D helps in decreasing the 'pro-inflammatory cytokines' in the lungs and acts in immuno-modulatory function, and also it will increase the anti-inflammatory, antiviral responses of the respiratory epithelial cells during infection. Recent research has indicated that vitamin D may have immune supporting properties through modulation of both the adaptive and innate immune system either by regulation of cytokines and cell signaling pathways. So, vitamin D acts as an important factor in decline cytokines storm in COID-19 infection.

Conclusion: The highly infectious nature of viruses and the increased morbidity and mortality without proper therapy and vaccine, many doctors in hospitals and other health care settings try to applicate good protocols of therapeutics to decrease the harmful effects of viral infection. Vitamin D is one of these supplements in the treatment protocol. Discontinuing vitamins could increase the mortality and morbidity of those affected, especially in deficient/ insufficient individuals. Obtaining serum 25 (OH) D levels in all patients with viral respiratory infections, especially COVID-19, could help in the detection and treatment of Vitamin D deficiency and potentially decrease recovery time and improve outcome. Even though evidence suggests that vitamin D has the anti-inflammatory, antiviral properties, so it will help in controlling trials to decrease morbidity and mortality of COVID-19 infection.

Keywords: Vitamin D; Anti-Inflammatory; SARS-Cov2; Immuno-Modulatory

Abbreviations: VDR; Vitamin D Receptor; TLRs: Toll-like Receptors; ALI: Acute Lung Infection; RAS: Renin-Angiotensin System; ARDS: Acute Respiratory Distress Syndrome; LPS: Lipopolysaccharide.

Introduction

Source and Physiological Role

Vitamin D is one of fat-soluble steroids with a physiological role in mineral homeostasis, primarily calcium, magnesium, and phosphate. As such, deficiencies in vitamin D have been detected in a number of metabolic bone diseases, such as osteoporosis, osteomalacia, and rickets [1]. Vitamin D in its natural form, cholecalciferol, is acquired through dietary sources, such as oily fish and egg yolks, but is also produced through de novo synthesis in the stratum basale and stratum spinosum of the epidermis using dehydrocholesterol in the presence of ultraviolet B (UVB) radiation. Cholecalciferol (D3) is thereafter hydroxylated into its biologically active forms 25-hydroxyvitamin D (calcifediol) and 1,25-dihydroxyvitamin D (calcitriol) [2] by the cytochrome P450 enzyme 25α hydroxylase (CYP27A1) in the liver. Mitochondrial 1α – hydroxylase enzyme (1α [OH] ase/CYP27B1) hydroxylates biologically inactive circulating metabolite 25-(OH) D intracellularly in the kidney, or extra- renal into active form 1,25 (OH)2 D. There is evidence that many cells that contribute to innate immunity, such as macrophages, monocytes, dendritic and epithelial cells can synthesize 1,25 (OH)2 D from 25 (OH) D by 1α – hydroxylation. Pulmonary epithelial cells can express 1α hydroxylase and produce Vitamin D locally, which increases Vitamin D regulated gene expression, through which it exhibits immuno-modulatory effects and host defense [3].

Serum levels are considered a more accurate indicator of Vitamin D status. 25 (OH)D level equal to or greater than 30 ng/ml (75 nmol/L) is considered sufficient. The Vitamin D levels between 20–29 ng/ml (50-–nmol/l) are deemed insufficient, and the levels less than 20 ng/ml (50 nmol/L) as deficient [4]. Extracellular 25 hydroxyvitamin D binds to serum Vitamin D binding protein, which then is internalized, and synthesized intracellularly 1, 25 dihydroxy Vitamin D tends to act on the nuclear Vitamin D receptor (VDR) [5].

Vitamin D-24-hydroxylase (24 [OH] ase/CYP24A1) catabolizes 1, 25 (OH) 2 D, and its precursor 25 (OH) D [6]. 1, 25 (OH) 2 D activates target gene expression by binding to the nuclear VDR. Moreover, based on co-regulatory proteins and the nature of the stimulus, there can be up and down-regulation of target genes. 1,25(OH)2 D by exerting negative feedback on the Vitamin D signaling system through decreasing CYP27B1 expression/1α (OH) ase transcription and also increasing CYP24A1 by increasing 24 (OH) ase catabolic function can limit its synthesis. It is observed that human respiratory epithelial cells in vitro showed increased levels of 1α-hydroxylase and decreased levels of inactivating 24-hydroxylase, hence enhancing the activation of Vitamin D [3].

Role of Vitamin D in Fighting Viral Infection

Vitamin D shows its effect on both adaptive and innate immune responses. Various in vitro studies showed that 1, 25 (OH) D affected the development of Th1 mediated immunity by inhibiting it, which is essential for cellular response induction. Cytokines that are dependent on the activity of nuclear factor κB (NF-κB) in multiple cells, including macrophages, by blocking the activation of NF-κB p65 through upregulation of the NF-kB inhibitory protein 1κBα are also directly modulated by 1, 25 (OH) 2 D. Toll-like receptors (TLRs) are trans-membrane proteins that recognize molecular motifs of viral and bacterial origin and initiate innate immune responses. TLR3, which is mainly involved in defense against viruses, recognizes viral double-stranded RNA. The treatment with Vitamin D has shown to reduce double-stranded RNA-TLR3–induced expression of IL-8 in respiratory epithelial cells [3]. Both 25 (OH) D and 1, 25 (OH) 2 D were shown to modulate T-cell adaptive immunity. The mechanism is by decreasing the pro-inflammatory type 1 cytokines such as IL-6, IL-8, IL-12, IFN-γ, as well as IL-17 and increasing anti- inflammatory type 2 cytokines (such as, IL-4, IL-5, and IL-10) [7].

More specifically, 1, 25 (OH) 2D inhibits proliferation of plasma cell and immunoglobulin secretion, and it induces B cell apoptosis [8].

It has been hypothesized that vitamin D exerts its antimicrobial effects in three main ways: Through augmenting natural protective barriers, enhancing innate cellular immunity, and boosting adaptive immunity [9]. With regard to reinforcing natural barriers, vitamin D has been implicated in the preservation of tight junctions, gap junctions, and adherent junctions between epithelial cell the disruption of which is a pathogenic mechanism of upper respiratory tract viruses, such as respiratory syncytial virus [10,11].

Specifically, with regard to COVID-19, correction of vitamin D deficiency is thought to suppress CD26/DDP4, one of the adhesion molecules through which the closely related COVID-MERS virus and indeed the COVID-19 virus is believed to acquire access to host cells [12-14]. The virus successfully invade the host, the next immunological barrier is the innate immune system will do its role. Vitamin D has been shown to enhance innate immunity through promoting the release of defensins and cathelicidins, the latter of which have

demonstrated direct antimicrobial effects against enveloped and non-enveloped viruses [15,16]. Vitamin D also has been shown, in both animal data and clinical data, to be linked to reduced viral replication [17].

Further significance is the role of vitamin D in mediating the inflammation that underlies ALI and ARDS. Vitamin D deficiency in particular has been recognized as a direct contributor to ARDS in the bacterial sepsis, major surgery, and non-cardiogenic respiratory failure [18-20].

According to pulmonary physiology, it has been demonstrated in animal models that vitamin D attenuates microbial acute lung infection(ALI) and acute respiratory distress syndrome(ARDS) through modulating the expression of the renin-angiotensin system (RAS), including ACE 1 and 2 [21]. One of the key pathogenic mediators of microbial-induced ALI is the increase in alveolar capillary membrane permeability, which evokes pulmonary oedema, hypoxemia, and pulmonary hypertension. The respiratory epithelium is able to convert vitamin D to its active form as part of local paracrine and autocrine signaling pathways implicated in host defense [22].

ACE2 enzyme inactivates angiotensin II, and as such acts as a negative regulator of the RAS. As such, ACE2 has been deemed protective against the development of ARDS, with animal models suggesting a key role in regulating vascular permeability, lung oedema, and Oxygenation [23]. In a rat model of ARDS, calcitriol was demonstrated to upregulate pulmonary ACE2 and downregulate renin and angiotensin II, indicating there may be a key mechanistic role for vitamin D in hindering the progression of infection-induced ARDS [21].

Results from a meta-analysis of vitamin D supplementation and risk of acute (bacterial and viral) respiratory tract infection show a 12% overall protective effect of vitamin D supplementation. This increased to 19% with a daily or weekly regimen compared to a monthly bolus regimen. Furthermore, a 70% protective effect was observed when deficiency was corrected [24].

Significance in COVID-19

In the case of COVID-19, which acquires entry to cells through binding to ACE2 [25]. However, the binding of the viral S1 spike protein to ACE2 causes both the virus and the enzyme to be trans-located into the cell through endocytosis, effectively reducing the surface expression of ACE2 and possibly contributing to the progression of pulmonary disease [26]. There is appearance to be associations between high levels of ACE2 and survival benefit, implicating the attenuation of the RAS system as a means of protection against ARDS [27]. Ethnic variations in the expression of ACE2 receptors have also been noted, with the highest expression seen in East Asian males [28].

The ethnic differences in ACE2 expression and polymorphisms may be a contributor to disease severity either independently or in conjunction with vitamin D status, and permits further investigation. Additionally, the higher superiority of male: female sex-specific COVID- 19 mortality may in part be related to hormonal dependency of expression and/or activity of ACE2 seen in animal studies [29]. The effects of severe vitamin D deficiency have been explored in humans: Following the inhalation of bacterial cell wall constituent, lipopolysaccharide (LPS), a marked increase in alveolar inflammation (IL-1B) was noted in vitamin D-deficient individuals compared to those with mild deficiency [30].

Specifically, there has been increasing speculation that vitamin D deficiency may support the likelihood of mortality and disease severity in COVID-19 [31]. Observed differences in COVID-19 mortality between the northern and southern hemispheres also add to the case for vitamin D having a role in the pathogenesis of COVID-19 [32].

These associations, along with the physiological and immunological roles of vitamin D have prompted clinical trials in vitamin D supplementation in COVID-19 patients and permit further mechanical investigation [33].

Conclusion

According to the emerging relationship between vitamin D status and alleged Covid-19 infection, vitamin D supplementation has already been proposed elsewhere [34]. At this time, clinical trial has been proposed for vitamin D supplementations (a single dose of 25,000 UI of vitamin D) in preventing and treating mild forms of suspected Covid-19 [35]. In a recent paper, it is assumed that vitamin D prophylaxis (without overdosing) could reduce, especially in patients with hypovitaminosis D, the severity of illness caused by SARS–CoV-2 [36]. The importance of treating the hypovitaminosis D along with an early nutritional supplementation has been highlighted for the potential preventing role of malnutrition sequelae in these patients. On the basis of the possible direct and indirect effect of vitamin D on immune system and cytokines production, we speculate a possible influence of this vitamin on the immunologic response to the virus and/or a modulating effect on the drugs being administered, namely hydroxyl-chloroquine and anti-IL 6 and anti-IL 1 agents [37].

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