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Review

Vitamin D and COVID-19: A Physiological Perspective

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ABSTRACT

Known for its ability to enhance the performance of the immune system, preclude microbial infections, and reduce susceptibility to influenza, Vitamin D (or 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) as the active form) has garnered a positive reputation in the management of COVID-19 for some time. Its deficiency is statistically correlated with infection of the disease, as well as disease severity and fatalities. There have been suggestions that Vitamin D supplements could either prevent the contraction of SARS-CoV-2, the coronavirus which causes the disease or alleviate the symptoms of the disease. Indeed, data have established a relationship between Vitamin D supplementation and the severity of respiratory illnesses, with some assays indicating optimistic results in COVID-19 patients who were supplemented with the vitamin. Accordingly, a great deal of research and efforts have been put into investigating the physiological mechanisms in the human body attributable to the vitamin's reputation against the coronavirus. Combined with what was already discovered before the advent of SARS-CoV-2, a great amount of knowledge has consequently now been unveiled. Via regulation of various pathways, $1,25(OH)_2D$ promotes the production of antimicrobial peptides, autophagy, as well as integrity and impermeability of cellular junctions against pathogens. Moreover, it mitigates the consequences of SARS-CoV-2 infection, such as cytokine storm (through immunomodulation of T cell differentiation pathways) and lung injury (through stimulation of the Angiotensin-Converting Enzyme 2 (ACE2) and manipulation of the Renin-Angiotensin System (RAS)). Nevertheless, Vitamin D deficiency still plagues the global population across all age groups, possibly contributing to the heightened global exposure to the coronavirus. With the COVID-19 pandemic inexorably raging on with no prospect of termination observable in the foreseeable future, this review article provides a concise yet thorough insight into the vast knowledge which could illuminate the significance of Vitamin D amidst the current predicament experienced by mankind, as well as instigate further curiosity and ignite further investigations into the role of vitamins, such as Vitamin D, as a safeguard against SARS-CoV-2.

Key words: 1.25-dihydroxyvitamin D, Angiotensin Converting Enzyme 2, COVID-19, Renin-Angiotensin System, SARS-CoV-2, T-cell Differentiation, Vitamin D

BACKGROUND

The outbreak of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes the Coronavirus Disease 2019 (COVID-19), has engendered a global pandemic placing a great toll upon humanity [1]. Consequently, there has been an astronomical amount of interest in any available means to alleviate such a toll on science and medical communities. One of those means happens to be the use of Vitamin D.

Known otherwise as Calcitriol or 1,25-dihydroxycholecalciferol, Vitamin D is a steroid hormone derived from dietary intake or endogenous synthesis, conditional upon exposure to sunlight ultraviolet radiation [2]. Past studies have established it as an integral agent in the functioning of the human immune system with the roles of immunomodulation and promotion of antimicrobial peptide expression [3–8]. Data have also indicated a link between its insufficiency or deficiency and vulnerability to infections, especially in the respiratory tract [9–11]. For this reason, intense research has been undertaken to shed light on the relevance of Vitamin D amidst the ongoing COVID-19 pandemic and to investigate the possible benefits of its supplementation. The results were promising; both statistical and clinical studies discovered a correlation between low vitamin D levels and increased COVID-19 risk, as well as infection severity and mortality [12–17]. In conjunction with knowledge from past research, a notion has been developed that the correlation is due to the vitamin's promotive role in the secretion of such antimicrobial peptides as β-defensin 2 (BD2) and cathelicidins, which not only act to eradicate microbes themselves but also help in the recruitment of cells in the human innate immune system, the autophagy of virus-borne cells, and the maintenance of cellular junctions, all of which are believed to help eradicate SARS-CoV-2

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from the bodies of the afflicted[2]. The vitamin's anti-inflammatory property is also accredited to suppressing the adaptive immune system's overaction that could entail a cytokine storm, which is accountable for symptoms, deterioration, and eventual fatality in multifarious cases[15].

Throughout this review article, the roles and mechanisms of Vitamin D are assiduously examined, using available data from apposite studies conducted hitherto that converged to provide a basis for the article's summarization. With vitamin D deficiency remaining a pre-eminent medical condition extensively affecting a sizeable portion of the global population[18], the ultimate purpose is to highlight the significance of the steroidal vitamin. The use of vitamin D has heightened in the wake of the Coronavirus outbreak and reminds the science and medical communities, as well as the general populace, of its potential efficacy in this grueling pandemic.

VITAMIN D AND THE IMMUNE SYSTEM

Apart from its functions in calcium homeostasis and the maintenance of the skeletal system, vitamin D has played a critical role in the human immune system. Receptors for its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), have been found in cells of the immune system, including B cells, T cells, and such antigen-presenting cells (APCs) as macrophages and dendritic cells, which have the 1α-hydroxylase enzyme (CYP27B1) that synthesizes Vitamin D from its precursor, 25-hydroxyvitamin D (25-OHD)[3]. Strikingly, such a synthesis is entirely independent of regulation by the Parathyroid Hormone (PTH), inducible by cytokines, and ultimately regulated by the abundance of 25-OHD, which makes the CYP27B1 of immune cells exclusively dissimilar to its renal counterpart. The availability of the receptors (Vitamin D Receptors; VDR) and CYP27B1 in cells of the immune system allows them to generate active Vitamin D autonomously and to utilize it instantaneously. Such a provision suggests an autocrine activity of Vitamin D in the immunological sphere and its overall role in the body's defense mechanisms. Moreover, CYP27B1 has also been found in epithelial cells, which constitutes the first line of defense and plays a crucial role in mediating local immune responses, including instigating inflammation and recruiting immune cells via cytokine and chemokine molecules[19]. Accordingly, a conceptualization about the immunological functions of the steroidal hormones has taken root, which has helped to explicate the correlation between low serum 25-OHD levels and proneness to infections, as demonstrated by multiple studies in the past[20–25].

ROLE OF VITAMIN D IN ANTIVIRAL MECHANISMS

As mentioned previously, the coexistence of CYP27B1 and VDRs in cells of the immune system is part of an autocrine mechanism for defense against pathogens. One way such a mechanism acts is by promoting the secretion of antimicrobial peptides like β-defensin 2 (BD2) and cathelicidins[26]. For instance, the complex between $1,25(OH)_2D$ and VDR can bind with the promoter of the cathelicidin gene, expediting the transcription process and expanding the number of cathelicidins available for antimicrobial activities[27,28]. This capability of the vitamin was proven in a previous study which found a superior level of cathelicidin expression in individuals with high serum 25-OHD levels[29] and found to be emulated in lung epithelial cells[30].

When released, cathelicidins can either directly extinguish pathogens of sundry sorts or neutralize the toxins, thus performing an immeasurably vital task in innate immunity[31]. In viral infections, the antimicrobial peptide is efficacious at combating viruses and curtailing their replications[32–35]. This particular ability is also seen with BD-2, which could also stimulate the secretion and action of cytokines and chemokines responsible for the recruitment of immune cells to the site of infection[36–39]. Together, BD-2 and cathelicidins are potent tools of the body to thwart pathogens and preclude the dilapidation of illness.

Interestingly, the expression of both the CYP27B1 enzyme and VDRs, or more obliquely the amount of $1,25(OH)_2D$ endogenously synthesized by immune cells, is influenced by the availability of pathogens, or more accurately, the abundance of Pattern Recognition Receptors (PRRs) that bind with them[40,41]. Such an arrangement enables the immune cells to ratchet up their secretion of antimicrobial peptides upon detection of the pathogens they are meant to eliminate. However, it is not the only Vitamin D-related innate defense mechanism the human body employs when menaced by viruses.

One of the most rudimentary apparatuses in the body's defense against any pathogen is barriers, which are principally upheld by cellular junctions—especially those of the epithelia—where Vitamin D wields excellent relevance. The $1,25(OH)_2D$/VDR complex is capable of activating multiple signaling pathways responsible for the regulation of junction

proteins and conferring structural integrity and functionality (such as in transport) to tissues[42]. To elaborate, VDRs have been shown to bind with the promoter sequence for the genes of proteins in the Claudin family which are essential to tight junctions and regulate their production[43–45]. There have also been indications that they are involved in regulating Occludin and ZO-1 proteins, which are integral to the junctions[46,47]. For SARS-CoV-2, a virus that targets the respiratory system, it could be positively impacted by the modus operandi of Vitamin D, which has been shown to minimize lung permeability, strengthen pulmonary epithelial barriers against pathogenic invaders, and reduce the vulnerability to respiratory diseases[48,49].

Additionally, Vitamin D can also induce the procedures of autophagy, which is undertaken in cells infected with the pathogen and in cancerous cells[50]. This could be done through the upregulation of Beclin1, which can account for autophagy upon binding with class III phosphatidylinositol 3-kinase, or the downregulation of mammalian target of rapamycin (mTOR), which acts at various steps of the autophagy pathway to inhibit the process of cellular self-devouring[51]. As autophagy proceeds in a virus-borne cell, viral particles are bound for lysosomal degradation and antigen presentation, which would kickstart the type I Interferon (INF) antiviral pathway, thereby repressing viral replication and pathogenesis[52,53]. The entirety of these factors above contributes to achieving the purpose of subjugating viral invaders in the human body.

VITAMIN D'S IMMUNOMODULATORY ROLE AGAINST CYTOKINE STORM

While the SARS-CoV-2 virus itself can adversely affect the afflicted body in various ways, perhaps more concerning and threatening are the body's own mechanisms in tackling it. Importantly, an extravagance in inflammatory responses embodied by the "cytokine storm" has been associated with the severity of COVID-19 and its associated mortality[54–57]. It has also been reported as a chief cause of fatality for the Middle East Respiratory Syndrome (MERS), the early 2000s Severe Acute Respiratory Syndrome (SARS), and influenza, in general[58].

Conventionally, a cytokine storm, or even a proportionate release of cytokines, starts with antigen presentation, which leads to the activation of cells in both the immunological domain and the surrounding tissues. This triggers the secretion of such pro-inflammatory signal molecules as Interleukin 1 (IL-1), Interleukin 6 (IL-6), Interleukin 8 (IL-8), Interleukin 10 (IL-10), Interferon Gamma (IFNγ), and Tumor Necrosis Factor Alpha (TNF-α)[59]. The secretions of these molecules proceed in a positive feedback loop[60], and the higher their serum levels are, the more lung inflammation and damage they are accountable for[61,62]. This can be explicated as the cytokines attract and activate immune cells like macrophages and neutrophils, which are then prompted to release leukotrienes and reactive oxygen species (ROS) in an attempt to destroy pathogens that unfortunately entail collateral damage upon surrounding tissues[63]. In the case of SARS-CoV-2 in the respiratory tract, such tissues are those of the alveoli and the encompassing capillaries, the destruction of which could result in acute lung injury (ALI) or, worse, the deadly acute respiratory distress syndrome (ARDS)[64,65]. Moreover, activated neutrophils can also deploy their intracellular genetic material to set up neutrophil extracellular traps (NETs) designed to ensnare pathogenic intruders in an exorbitant amount in the occurrence of a cytokine storm, leading to the occlusion of blood vessels called "immunothrombosis"[66].

The entirety of this constitutes the pathogenesis of COVID-19 and presents a distinct case as to the disease's lethal quality. Intriguingly, it is also subject to the influence of Vitamin D, whose manifold functions include being an immunomodulator, among other functions[7].

Understanding the immunomodulatory role of steroidal vitamin, one can experience insight into adaptive immunity and the inflammatory pathway. Typically, adaptive immunological processes pertaining to this context begin with antigen presentation by APCs to naïve helper T cells, a process that activates them via the interaction between a T-cell receptor (TCR), a CD4 glycoprotein, and an antigen-MHC II complex (Class II Major Histocompatibility Complex)[67]. Activated helpers T cells can then differentiate into either type I helper T cells (Th1), majorly involving Interleukin 12 (IL-12)[68], or type II helper T cells (Th2), notedly with the signaling of Interleukin 4 (IL-4)[69], which promote cellular and humoral immune responses, respectively. For the former, IFNγ is secreted to promote inflammatory responses that incorporate the release of pro-inflammatory cytokines, whereas, for the latter, IL-4 and Interleukin 5 (IL-5) are secreted to activate antibody production by B lymphocytes[70–73]. A homeostatic mechanism has been found to exist between the two; a comparative increase in the Th1 pathway can suppress the Th2 pathway, and vice versa[74,75].

As previously mentioned, the cytokine storm, an excessive release of pro-inflammatory cytokines, is harmful and often contributes to deterioration and death. Therefore, one would surmise that a disproportionate Th1 inflammatory response and an accompanying skewness in the Th1/Th2 ratio could potentially entail a lethal or, at least, devastating cytokine storm[54,76]; this is where Vitamin D's immunomodulatory role becomes highly relevant.

According to research data, $1,25(OH)_2D$ promotes the differentiation of naïve T cells into Th1 cells via increases in the amounts of GATA-3 and STAT6, which are transcription factors integral to the differentiation pathway[77]. Furthermore, the active steroid also inhibits IFNγ release while increasing IL-4 secretion[78]. Both of these effects contribute to the shift in the direction of T cells differentiation towards Th2, decreasing the amount of both Th1 cells and the potentially problematic pro-inflammatory cytokines they produce[79]. Moreover, $1,25(OH)_2D$ can also induce the differentiation of naïve T cells into regulatory T cells (Treg) responsible for the restraint of Th1 cells either by upregulating Foxp3, a crucial protein in the differentiation process or by manipulating with a cluster of differentiation (CD) molecules on the surface of dendritic cells, one of whose functions is to foster the development of Tregs[80,81]. The totality of this helps to modulate the inflammatory pathway and safeguard the body against disease pathologies[82].

VITAMIN D AND THE RENIN-ANGIOTENSIN AXIS

One of the most critical reasons why the Renin-Angiotensin System (RAS) bears so much relevance in the topic of vitamin D is that COVID-19 pivots around the SARS-CoV-2's infection mechanism.

Typically, the RAS acts to maintain the homeostasis of blood pressure, as well as blood electrolytes[83]. Its ultimate and most bioactive effector, the octapeptide Angiotensin II (Ang-II), usually binds with type I angiotensin receptors (AT1Rs) to attain the goal of increasing BP through vasoconstriction and the secretion of Aldosterone (which stimulates renal Na^+ absorption and thus more water retention). However, the binding can also have adverse effects as it promotes inflammation, platelet aggregation, production of mitotic agents, and ROS synthesis (which diminishes the availability of nitric oxide, upon which the functionality of endothelial cells is dependent)[84]. These effects can morph into deleterious conditions, such as thrombosis, fibrosis, oxidative stress, and endothelial dysfunction[84,85].

Alternatively, Ang-II can also interact with Angiotensin-converting Enzyme 2 (ACE2), which cleaves away the phenylalanine at its carboxy terminus, turning it into Angiotensin–(1-7), which can also be produced from the sequential cleavages of Ang-II's precursor, the decapeptide Angiotensin I (Ang-I), by Angiotensin-converting Enzyme (ACE) and ACE2, respectively[83]. Angiotensin-(1-7) then binds with the G protein-coupled receptor (GPCR) Mas, leading to effects opposite to those stemming from the interaction between Ang-II and AT1R—vasodilation, anti-fibrosis, anti-inflammation, and vascular protection, just to name a few[86].

Unfortunately, SARS-CoV-2's mechanism of entry into human cells happens to hinge upon ACE2. After the human serine-protease TMPRSS2 enzyme primes its spike proteins, they bind with ACE2 on the human cell membrane, beginning entry by receptor-mediated endocytosis[87]. As the virus proliferates, the binding of ACE2 becomes more extensive, and the availability of ACE2 plunges in the short term, ensured by the enzyme's downregulation in the long term, decreasing Ang-II's conversion into Angiotensin-(1-7)[88]. This shifts the balance of the RAS greatly in that less binding between Angiotensin-(1-7) and Mas would be incurred, whereas the binding between Ang-II and AT1R would be elevated[89]. These interactions prove to be of great detriment for COVID-19 patients. The former has been described to protect the body against pulmonary fibrosis, acute lung injury, and fibrosis[90,91]. The latter is where Vitamin D has profound effects upon alleviating the consequences of SARS-CoV-2 infection.

The steroidal hormone has been indicated to increase the expression of ACE2 and ergo, the activity of the ACE2/Angiotensin-(1-7)/Mas axis[92,93]. This consequently suppresses the potentially pernicious ACE/Ang-II/AT1R axis and moderates the body's inflammatory response, palliating acute lung injury and precluding multiple organ damage that could be precipitated by COVID-19[94,95].

VITAMIN D SUPPLEMENTATION AGAINST COVID-19?

While the aforementioned association between Vitamin D deficiency and either risk of COVID-19 contraction or severe outcomes, corroborated by all the germane mechanisms detailed above, might tantalize one to believe that Vitamin D supplementation can translate into protection against SARS-CoV-2, the reality is yet too complex for such a straightforward notion.

However, data from some research studies seem to substantiate the notion. For example, a meta-analysis[96] found lower intensive care unit (ICU) admissions in COVID-19 patients supplemented with Vitamin D. One study[97] also observed a decrease in disease severity, mortality rate, and serum level of markers of inflammation in Vitamin D-supplemented patients. Moreover, another study[98] reported that high-dose Vitamin D supplementation aided the body's clearance of SARS-CoV-2 and helped mildly symptomatic and asymptomatic individuals infected with COVID-19 to become COVID-19-negative. These findings are in line with that of a preceding study[99] which reported that Vitamin D supplementation helped protect against acute respiratory infections.

Nevertheless, the current evidence is insufficient to conclude that Vitamin D supplements are substantively helpful against COVID-19 or for suggesting Vitamin D supplementation as a hedge against the disease. Furthermore, some studies would digress from such a conclusion. One[100], for instance, found no significant difference in the length of hospitalization between patients given Vitamin D supplements and those given placebo. Another study[101], albeit not precisely concerning COVID-19, also reported no reduction in pneumonia risk and an even elevated risk of pneumonia recurrence from taking oral Vitamin D supplements. Due to this reason, there remains more investigations to be executed and queries to be answered.

CONCLUSIONS

Multiple clinical studies and circumstantial observations have correlated Vitamin D levels and COVID-19 infection, severity, and mortality. This correlation could be rationalized by an insight into the multifaceted roles of Vitamin D in the physiology of the human immune and endocrine systems.

On the immunological side, the steroidal hormone's active form, $1,25(OH)_2D$, can promote the secretion of antimicrobial peptides like Cathelicidins and BD-2, responsible for thwarting viral replication and achieving viral clearance. Vitamin D can also stimulate autophagy by upregulating Beclin1 and downregulating mTOR, leading to antigen presentation and subsequent activation of the type I INF antiviral pathway. It can also maintain cellular junctions, especially those in the respiratory epithelia, via regulation of Claudins, Occludin, and ZO-1, among a host of junction proteins, thus preserving the integrity of the body's barriers and reducing their permeability against pathogens. Moreover, it is responsible for fostering naïve T cells into Th2 cells functioning in humoral immunity and inhibiting the inflammatory Th1 pathway, an immunomodulatory role that helps avert the calamitous cytokine storm. Meanwhile, on the endocrinological side, the vitamin can promote the activity of ACE2 and, thus, the binding between Angiotensin-(1-7) and Mas receptors, repressing that between Ang-II and AT1R could result in fibrosis and acute lung injury.

This whole prospective may appear promising and generate an incentive for Vitamin D supplementation as a protective measure against COVID-19. Yet, the current information pool is inadequate for one to suggest such a supplementation regimen. There remains a great deal of unclarity, and hence, a considerable necessity for even more thorough research in the future.

ABBREVIATIONS

1,25(OH)2D: 1,25-dihydroxyvitamin D
25-OHD: 25-hydroxyvitamin D
ACE2: Angiotensin-converting Enzyme 2
ACE: Angiotensin-converting Enzyme
ALI: Acute Lung Injury
Ang-II: Angiotensin II
APC: Antigen-presenting Cell
ARDS: Acute Respiratory Distress Syndrome
AT1R: Type I Angiotensin Receptor
BD-2: β-defensin 2
CD: Cluster of Differentiation
COVID-19: Coronavirus Disease 2019
CYP27B1: 1α-hydroxylase
GPCR: G protein-coupled receptor
IL-1: Interleukin 1
IL-4: Interleukin 4
IL-5: Interleukin 5
IL-6: Interleukin 6
IL-8: Interleukin 8
IL-10: Interleukin 10
IL-12: Interleukin 12
INF: Interferon
INF-γ: Interferon Gamma
MERS: Middle East Respiratory Syndrome
MHC II: Class II Major Histocompatibility Complex
mTOR: mammalian target of Rapamycin
NET: Neutrophil Extracellular Trap
PRR: Pattern Recognition Receptor
PTH: Parathyroid Hormone
RAS: Renin-Angiotensin System
ROS: Reactive Oxygen Species
SARS: Severe Acute Respiratory Syndrome
SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

TCR: T-cell Receptor
Th1: Type I Helper T cells
Th2: Type II Helper T cells
TNF-α: Tumor Necrosis Factor Alpha
Treg: Regulatory T cells
VDR: Vitamin D Receptor

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