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Immunological enhancement using Vitamin D supplements a treatment options for Covid-19 infection: A Review

By

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Abstract

In December 2019, Coronavirus menace was considered a pandemic which requires urgent attention of public health according to World health Organization, following its spontaneous outbreak worldwide from Human market of Seafood in Wuhan, South facet of republic of China. To combat the virus, various treatment approaches have been employed, including general and symptomatic care, antiviral medications, oxygen therapy, and immune system support. Notably, Vitamin D is involved in the maintenance of skin and bone health, alongside facilitating cell absorption of secondary messengers. Study has revealed that 1,25-hydroxycholecalciferol, a form of fat-soluble vitamin (Vitamin D), significantly regulates both the natural and adaptive immune responses. This study herein is aimed to investigate the potential of Vitamin D supplements in bolstering immunity and explore their efficacy as a treatment for the novel Coronavirus.

Keywords: *ARDS (acute respiratory distress syndrome; COVID-19), ACE2, Vitamin D, Immune system, SARS-CoV-2, COVID-19, and ACE2.*

Introduction

The World Health Organization changed the identity of nCoV virus that started in 2019 to COVID-19 on February 11, 2020. The Coronavirus pandemic (COVID-19) is a highly infectious and pathogenic anomaly caused by virus (SARS-CoV-2) virus, which has a diameter of 65-125 nanometers and a single-stranded RNA genome of approximately 26-32 kilobases in length (Muhammad *et al*., 2020). These viruses are members of the family Coronaviridae. Due to the spikes that resembled crowns on the virus's outer surface, it was given the name Coronavirus Corona. The most recent coronavirus (COVID-19) has been shown to cause infectious disease (WHO 2020). Coronaviruses are considered to establish a spectrum of infection of respiratory system, ranging from mild cases of the common flu to an intense and life-threatening challenge like Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). As of June 19, 2020, according to data from the World Health Organization (WHO), there were more than 8457305 confirmed cases of the Coronavirus in more than 200 nations, spanning all continents (Li *et al*., 2020). This causes a serious threat to world health. This fat-soluble vitamin has been linked to numerous cell types' ability to absorb secondary messengers, maintain healthy bones, and build healthy skin. Despite this, reports of vitamin D insufficiency exist worldwide. An indoor lifestyle, the development of diets high in processed foods, and avoiding the sun have all been linked. Therefore, a vitamin D supplement in accordance with current guidelines is essential for maintaining the body's equilibrium. One of the few available treatments for coronavirus sickness is the immune system, which acts as a

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barrier to the body's infiltration by foreign invaders. Fortunately, diverse immune cells contain the Vitamin D receptor (VDR), such as the T cells, B cells, and antigen-presenting cells, enabling the cells to produce and respond to Vitamin D. This allows Vitamin D to play a functional role in controlling both the natural and adaptive immune responses, thereby exerting control over the immune architecture of the body.

Replication process of SARS-CoV-2 within host cells

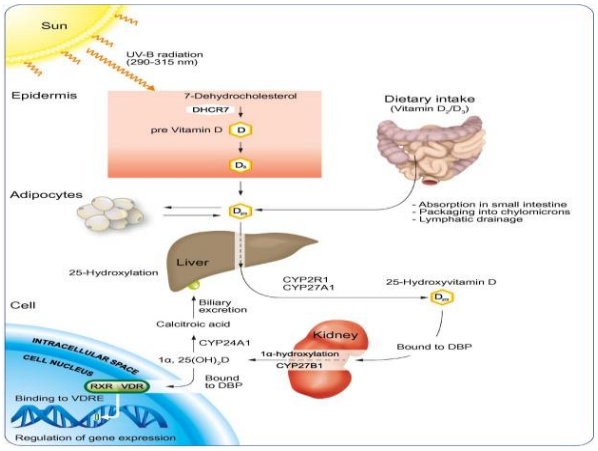
The living process of SARS-CoV-2 within their host cellular compartment begins with the attachment of the spike protein (S) to the receptor angiotensin-converting enzyme 2 (ACE2). This attachment triggers a conformational distortion in the S protein, leading to the fusion of the enclosure of the virus with the cell membrane through a pathway (endosomal route). Following this, the microbe (virus) releases its genetic material, RNA, into the host cell. The RNA of the genetic content is then changed into microbe replicase polyproteins, pp1a, and 1ab, which are subsequently disintegrated into minute compounds by proteinase enzyme, enabling the virus to replicate and propagate within the host cell. The polymerase enzyme produces a series of messenger RNA molecules through a process called discontinuous transcription, and then translated into the necessary protein present in the virus. These biomolecules (protein) and the genomic RNA are subsequently assembled into virions within the endoplasmic reticulum and Golgi apparatus, and then moved out of the cell using vesicular route. This process reveals the characteristic and biochemical mechanism by which Human Coronaviruses enter and infect host cells.

SARS-CoV-2 produces a range of proteins, including nucleoproteins, polyproteins, membranous proteins, such as RNA polymerase, proteases, glycoprotein, helicase, and accessory proteins, in addition to its characteristic spike protein (Wu *et al.*, 2020; Zhou *et al.*, 2003). The three-dimensional presentation of the spike protein in the receptor-binding component (RBD) is critical for maintaining van der Waals forces, which are essential for viral attachment and entry (Xu *et al.*, 2020). Specifically, key residues like lysine at position present in ACE2 receptor of human origin interact with specific groups in the receptor binding protein part of SARS-CoV-2, facilitating viral binding and infection (Wan *et al.*, 2020). The coronavirus RNA's methylated head and polyadenylated tail enable binding to host cell ribosomes, triggering translation and producing long polypeptide chains. Coronaviruses typically contain specific genes encoding nucleocapsid, spike generation, and viral replication proteins downstream of ORF1 (van Boheemen *et al.*, 2012). The glycoprotein spikes on the surface of the virus play a crucial role in facilitating attachment and entry into host cells, with the receptor-binding domain (RBD) exhibiting a flexible attachment among different viruses (Raj *et al.*, 2013; Perlman *et al.*, 2009). The infection process begins when the virus penetrates the host cell, sheds its protective outer layer, and the spike protein binds to the specific receptor on the host cell surface, initiating the infection cycle.

The proteolytic enzyme within the cell of the host activates the spike protein attached to the protein receptor upon attachment. Consequently, the viral envelope can fuse directly with the host membrane, facilitating cell entry via endocytosis. Specific proteases cleave the polyprotein into numerous nonstructural proteins, a vital step in the coronavirus entry process. Cellular enzymes called proteases, such as human airway trypsin-like protease (HAT), cathepsins, and transmembrane protease serine 2 (TMPRSS2), are essential for cleaving the spike protein and modifying it for penetration (Bertram *et al.*, 2001; Glowacka *et al.*, 2001). Different coronaviruses use distinct receptors to enter human cells: HCoV-NL63 and SARS coronaviruses bind to angiotensin-converting enzyme 2 (ACE2), while MERS coronavirus uses dipeptidyl peptidase 4 (DPP4) (Wang *et al.*, 2013; Raj *et al.*, 2013). Notably, SARS-CoV and MERS-CoV uniquely target exopeptidases, unlike other coronaviruses that primarily use aminopeptidases or carbohydrates as major receptors for cell entry (Wang *et al.*, 2013).

Vitamin D

Production and Activation



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Vitamin D occurs in two primary biologically relevant forms: D2 (ergocalciferol) and D3 (cholecalciferol), which is fat-soluble secco-sterols. These forms can be obtained through two main sources: production in the skin upon sunlight exposure, or ingestion from food sources (Feldman *et al.*, 1997). Notably, vitamin D is often referred to as both a vitamin and a hormone due to its unique ability to be produced by the body. Vitamin D can be ingested in two forms: vitamin D3 (cholecalciferol), which is the more common form, or vitamin D2 (ergocalciferol), which is formed when ergosterol from molds, yeast, and higher-order plants is exposed to UV light. The skin-synthesized form, cholecalciferol, results from the exposure of precursor 7-dehydrocholesterol to UV light with a wavelength of 290-315 nm. Several factors, including skin pigmentation, age, sun angle, air quality, and exposed skin surface area, influence the skin's ability to synthesize vitamin D."

Vitamin D, whether obtained from skin production or dietary intake, has a short circulation half-life of around one to two days, as it is either stored in fat cells or metabolized in the

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liver (Mawer 1972). Initially, vitamin D is biologically inactive, but once synthesized; it must bind to albumin and vitamin D-binding protein (DBP) in the bloodstream to enable transportation to the liver. There, it undergoes hydroxylation by enzymes like CYP2R1 and CYP27A1, leading in the formation of 25-hydroxy vitamin D3 (25(OH)D3 or calcidiol), the primary metabolite. Further hydroxylation, primarily occurring at position 1, takes place in the kidney, facilitated by the enzyme 1-alpha-hydroxylase.

After its synthesis in the kidney, the active metabolite 1a,25(OH)2D enters the bloodstream and functions as a hormone, exerting its effects on distant organs and cells. As described by Wacker et al. (2013), vasculating 1a,25 (OH)2D has two primary effects: (1) enhancing the absorption of calcium and phosphorus in the intestines, and (2) promoting the maturation of preosteoclasts into mature osteoclasts. Additionally, it stimulates insulin secretion in pancreatic beta cells and inhibits renin synthesis in the kidney (Wacker et al., 2013). Notably, various organs and tissues, including muscles, colon, prostate, immune cells, and pancreas, which express the enzyme CYP27B1, can convert 25 (OH)D to 1a,25(OH)2D, thereby generating this active metabolite outside of the kidneys.

The production of 1,25(OH)2D within kidney and 25(OH)D in the liver is strictly controlled. Vitamin D and its metabolites regulate the enzyme vitamin D-25-hydroxylase in the liver, preventing excessive levels of 25 (OH) D in the bloodstream following supplementation with vitamin D or UV exposure. Parathyroid hormone (PTH) adjusts the synthesis of 1,25 (OH)2D in the kidney based on serum calcium and phosphorus levels (DeLuca 1988; Reichel 1989). 1,25 (OH)2D functions by entering target cells, similar to other steroid hormones, and binding to the vitamin D receptor in the nuclear compartment. As described by Jones *et al.* (1998), this binding triggers the formation of a complex that, along with transcription factors like the retinoid X receptor, regulates the expression of genes involved in calcium transport, cell cycle regulation, and bone matrix protein production.

Vitamin D receptors

The vitamin D receptor protein, which is has its origin from intestinal epithelial tissue of chick, was discovered to have a high affinity for calcitriol (Haussler 1995). As a member of the nuclear steroidal hormone receptor superfamily, VDR regulates gene transcription by binding to specific response elements in gene promoters. Initially identified in tissues involved in calcium and phosphate regulation, such as the intestine, bone, kidney, and parathyroid glands, VDR plays a vital role. The human VDR gene is located on chromosome 12q13-14, as reported by Faraco *et al.* (1989). Like other receptors in its class, VDR operates in the nucleus, functioning alongside receptors for androgen, thyroid hormone, glucocorticoids, estrogen, progesterone, retinoic acid, retinoid X, and over 150 orphan receptors (Evans 1988; Mangelsdorf et al., 1995)."

The assumed molecular mass of the VDR protein which is dependent on its amino acid sequence is 48.3 kD, but biochemical analysis reveals that mammalian VDR variants have a molecular weight ranging from 52 to 60 kD. Typically, VDR proteins consist of five active domains, including DNA-binding domain (DBD) which is greatly conserved, and several ligand-binding domains (LBDs), notably the C-terminal AF-2 domain. Structural and functional analysis of VDR has identified various domains involved in DNA ligation, binding of ligand, dimerization of receptors, and transactivation of gene. Moreover, a C-terminal stimulation active domain (AF-2) crucial for cofactor interaction has been identified. Studies using truncated receptors suggest that these domains function independently, but likely cooperate under normal physiological conditions. The VDR, T3Rs, and RARs produce a subfamily around the nuclear hormone receptor superfamily, characterized by homogeneity in the amino acid arrangement and mechanism of action. In contrast, "traditional" hormone receptors like GR, ER, and PR primarily acts as homodimers, distinguishing them from this subfamily.

The RXR acts as the main partner for VDR subfamily members to form heterodimers, although they can in the same time produce homodimers that probably not active in transcription. When bound to a ligand, the VDR functions primarily as a nucleophilic macromolecule. Research suggests (Sher et al., 1981; Walters et al., 1986) that a little portion of not loaded VDR may move to the inner cellular compartment. Alternatively, other studies propose that free VDR may be in equilibrium state between the cytosol and nuclear compartment, loosely associating with chromosomal DNA. Like other receptors in its class, VDR is activated when calcitriol, bound to the vitamin D binding protein (DBP), enters the cell. Calcitriol rapidly triggers non-genomic activities, including opening Ca2+ channels and activating second messenger pathways that interact with the nucleus. Ligand activation initiates nuclear transport and VDR phosphorylation."

VDR homodimerization or heterodimerization with RXR facilitates interaction with vitamin D response elements (VDREs) in gene promoters, initiating gene transcription. This interaction with the general transcription apparatus is necessary to commence gene transcription, thereby regulating protein expression and leading to various downstream effects. While the exact sequence of events remains unclear, ligand-attached VDR domicile to control sites on genetic makeup of the cell. It is improbable that VDR will function as a widespread gene expression repressor in the absence of molecule that binds to receptor, given the dependence of VDR/DNA binding on 1,25(OH)2D3 activation (Meyer *et al.*, 2002; Heikkinen *et al.*, 2011).

Vitamin D status and Supplementation

The body produces over 35 additional vitamin D3 metabolites, but they are partly active or dislodged spontaneously, suggesting they are intermediates products in the catabolism of the essential form, 1,25(OH)2D3. Therefore, maintaining the body's equilibrium requires adequate vitamin D intake according to modern standards. The amount of

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25(OH) D in the blood is used to define vitamin D status. According to Hanley *et al.* (2010), a 25(OH) D level below 25 nmol/L, which is usually barely enough to prevent rickets or *osteomalacia*, is considered deficient.

The Institute of Medicine (IOM) recommends a blood serum 25(OH)D level of 50 nmol/L, but the Endocrine Society, led by Holick *et al.*, argues that this may be insufficient for optimal calcium biochemical activity and bone functioning capacity. They presented a higher recommended value of 75 nmol/L, based on three key arguments. Firstly, at 80 nmol/L of 25(OH) D, calcium absorption is not hindered by vitamin D (Holick 2007; Hollis 2005; Rosen 2011). Secondly, this level minimizes parathyroid hormone (PTH) levels (Holick 2007). Thirdly, Priemel *et al.'s* study found that unmineralized osteoid levels only become pathological above 75 nmol/L of 25(OH)D (Holick 2007). Some experts suggest that achieving levels above 90-100 nmol/L is optimal for various health outcomes, including reduced-gap function, oral health, falls, and fracture risk (Haussler 1995). This implies that new autocrine activities and related disorders should be considered when defining the ideal 25(OH)D serum level. To consistently keep 25(OH)D levels above 75 nmol/L, the Endocrine Society recommends consuming at least 1,000 IU (Mangelsdorf *et al.*, 1995).

Presently only about 10% of the required vitamin D is obtained from food sources, and sunlight's UVB levels are often insufficient, many individuals in the UK need supplements to maintain adequate vitamin D intake (Davies *et al.*, 2012). In particular, high-risk groups should receive guidance on appropriate supplementation. These groups include pregnant women, breastfeeding mothers, individuals who spend minimal time outdoors (such as babies and teenagers), housebound individuals, those who cover their skin for cultural or religious reasons and receive little sunlight exposure, people of non-European descent living in northern climates or the UK, and the elderly.

Vitamin D and the immune architecture

The binding of vitamin D with VDR triggers a wide range of cellular processes. Research by Hossein-nezhad *et al.* (2013) and Wacker *et al.* (2013) has shown that VDR expression goes beyond bone-related tissues to include over 35 target tissues unrelated to bone metabolism, revealing the diverse effects of vitamin D. Once activated, VDR regulates the activity of over 100 genes, making up around 0.5-5% of the human genome, which control cellular growth, differentiation, death, and blood vessel formation. Notably, VDR is present in body protective cells, where it functions in converting 25(OH)D3 into its productive form through CYP27B1 production, influencing both adaptive and natural immune responses. Lack of vitamin D may increase the risk of uncontrollable immune challenge and infections. stimulation of VDR in immune cells results to the generation of proteins with potent immunomodulatory, pro-differentiative, and antiproliferative effects, as highlighted by Bao *et al.* (2010). Recent studies suggest combining vitamin D supplements with magnesium, as magnesium helps maintain calcium and phosphate balance (Grant *et al.*, 2020). Magnesium, essential for enzymatic processes, particularly in the kidney and liver, is crucial for enzymes involved in vitamin D biochemical role (Uwitonze *et al.*, 2018).

Vitamin D and natural (innate) immune system

The innate defense system against microbes is the swift and nonspecific response of the innate immune system. As explained by Lang *et al.* (2013), all innate immune cells can detect and eliminate unneeded materials in organs, such as blood, and the lymphatic system. They interact with pathogens and other immune cells, regulating the adaptive immune response by controlling the time function, type, and number of pro-inflammatory molecules produced. Early observations on the effectiveness of cod liver oil in treating tuberculosis highlighted vitamin D's crucial role in stimulating innate immunity. Low levels of calcitriol have been connected to higher mortality rates from severe infections in end-stage renal disease patients (Gombart *et al.*, 2009), while low serum levels of 25(OH)D have been associated with upper respiratory tract infections (URTI) (Laaksi *et al.*, 2007; Cannell *et al.*, 2008), including influenza (Cannell *et al.*, 2006), and chronic obstructive pulmonary disease (Black *et al.*, 2005).

The human protein cathelicidin (hCAP18), that is derived from the active peptide LL-37, increases in response to disease and fights against viruses, bacteria, and fungi by disrupting their membranes (Ramanathan *et al.*, 2002). Vitamin D is essential for producing cathelicidin (LL-37) and certain defensins (like hBD-2), which have potent antiendotoxin and antimicrobial effects (Chun *et al.*, 2008; Schwalfenberg *et al.*, 2011). This innate immunity activity uses antimicrobial peptides to eliminate invasive microorganisms. When TLR2/1 and TLR4 are activated, individuals exhibit increased expression of 1-hydroxylase and VDR. The vitamin D-VDR-RXR complex then moves to the nuclear enclosure, binds to specific gene regions, and promotes the transcription of genes responsible for cathelicidin and beta-defensin, facilitating active vitamin D synthesis (Adams *et al.*, 2008; Cynthia, 2011). Additionally, active vitamin D significantly influences the expression of TLR4 and CD14 co-receptors. Human studies have linked LPS induction to CYP27B1 expression through TLR4/CD14 receptor complexes (Stoels *et al.*, 2006; Adams *et al.*, 2013).

Vitamin D's active form triggers the release of prostaglandin E2 and IL-10, while reducing the expression of MMPs 7 and 10, suppressing MMP-7 secretion, and inhibiting both MMP-9 secretion and activity in mononuclear cells (PBMCs) infected with tuberculosis (Coussens *et al.*, 2009). Moreover, it enhances oxidative burst and increases hydrogen peroxide secretion in monocytes (Cohen *et al.*, 1986). Monocytes, which have high levels of vitamin D receptors (VDR), are highly responsive to the differentiating effects of active vitamin D. By recruiting other immune cells and activating antigen-specific T-cells, vitamin D promotes wound healing and fights infection.

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Activated vitamin D can reduce inflammation by suppressing the production of pro-inflammatory cytokines like TNF and IL-12, and chemokines, by downregulating GM-CSF expression, modulating macrophage responses, and stimulating immunosuppressive prostaglandin E2 production from macrophages (Di Rosa *et al.*, 2011). Macrophages, which have the necessary enzymes to produce active vitamin D, experience both intracrine and paracrine effects. As a result, vitamin D deficiency impairs macrophages' ability to produce specific surface antigens, lysosomal enzymes, and H2O2, compromising their ability to fight microbes (Abu-Amer *et al.*, 1993; Xu *et al.*, 1999).

Vitamin D and Adaptive Immune Architecture

When pathogens are present, the adaptive immune system springs into action, using its immunological memory to mount a more targeted and effective response, unlike the natural immune system's rapid and general reaction to threats. The adaptive response is slower and relies on specialized cells like B-cells and T-cells to carry out its functions. Although these cells have low levels of vitamin D receptors (VDR) when they're inactive, they significantly increase VDR expression when they're activated and start proliferating.

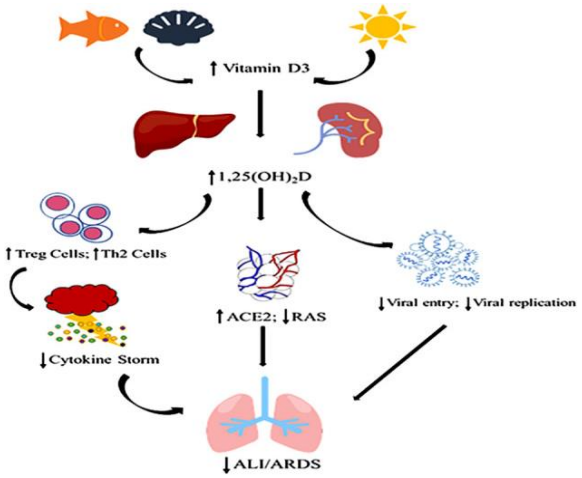
Vitamin D's active form influences the transformation and proliferation rates of B cellular entity, leading to reduced proliferation (Chen *et al.*, 2007; Mahon *et al.*, 2003). Despite their low initial VDR levels, active vitamin D regulates VDR expression in B cells. For example, it increases VDR levels in primary human B cells, tonsil B cells, and B-cell lymphoma cell lines SUDHL4 and SUDHL5, and boosts CYP27B1 mRNA levels. Additionally, vitamin D directly affects B cell homeostasis by preventing the cycle of B cells from gaining entrance into the cell cycle, modifying B cell proliferation by regulating CDK4, CDK6, and cyclin D levels, increasing p27 mRNA levels, inhibiting memory and plasma cell generation, and promoting apoptosis of immunoglobulin-producing B cells (Chen *et al.*, 2007).

The existence of VDR-present B immune cells has been a topic of debate, but it is now clear that B cellular structure can respond to active vitamin D through self-regulating (automatic or intracrine) mechanisms. The role of functional vitamin D depend on an individual's blood levels and the conditions of their B cells (whether functional or dormant). Once activated, VDR in primed T cells moves to the nucleus within 48 hours and triggers the activation of the phospholipase C-1/PLC-1 gene when bound to active vitamin D. As a result, PLC-1/PLC-1 protein accumulates in the cytoplasm (Von Essen *et al.*, 2010).

Although VDR is absent in dormant T lymphocytes, its expression increases significantly, up to five-fold, when T cells are activated (Topilski *et al.*, 2004). Active vitamin D directly impacts Th1 and Th2 cells, altering the T cell phenotype by suppressing Th1 responses, which in turn facilitates the migration and/or retention of T cells in the skin (Lemire *et al.*, 1995). Furthermore, treating T cells with calcitriol or its analogs leads to increased production of anti-cytokines Th2 cytokines (IL3, IL4, IL5, IL10) and decreased secretion of pro-inflammatory Th1 and Th22 (IL22) cytokines, and (IL2, interferon-, tumor necrosis factor) (Cantorna 2011).

Most research on fat-soluble vitamin (B) and T cell roles has explored how T cells respond to active calcitriol or its analogs (Jeffery *et al.*, 2009). However, few studies have examined how supplementing with natural vitamin D (ergo-/cholecalciferol) affects different T cell subsets. Vitamin D may influence T functional cells through various mechanisms, including: direct conversion of 25(OH)D to calcitriol by T cells, direct systemic role on T cells, nondirectional effects on antigen manifestation mediated by localized antigen-presenting cells, and systemic effects on T cells (Prietl *et al.*, 2013). Activation of the VDR by active vitamin D leads to changes in production of cytokines, suppression of effector T-cell activation, and induction of Tregs (T regulatory or suppressor T cells) (Abraham *et al.*,2004; Topilski *et al.*, 2004). Tregs, a subset of CD4 T cells, inhibit excessive or autoimmune responses by regulating proinflammatory responses in other immune cells (Rudensky 2011). Vitamin D can stimulate and activate Tregs directly and indirectly through intracrine conversion or systemic effects, leading to enhanced suppressive activity (Wu *et al.*, 2020).

Cross-talk between Vitamin D supplementation and coronavirus.



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The level of blood of 25(OH)D continue to reduce as a function of age increment, which may be relevant to COVID-19 since number of death increases with age (Novel 2020; Vasarhelyi *et al.*, 2011). miminum vitamin D levels have been found in severe COVID-19 cases and patients with pre-existing conditions (Glicio 2020; Lau *et al.*, 2020). The functional form of vitamin D, calcitriol, also decreases with age, leading to reduced vitamin D production and less sun exposure (MacLaughlin 1985). Notably, the COVID-MERS virus, which shares similar mechanisms with COVID-19, employs strategies like PLpro-mediated replication, binding to DPP-4/CD26, disrupting type-1 IFN induction, and evading host recognition by MDA5 and RIG-I, highlighting potential targets for intervention.

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Research has shown that DPP-4/CD26 in human binds with the S1 active domain of the COVID-19 spike glycoprotein, suggesting a actives role in the severity of COVID-19 infections (Mousavi 2019). Correcting deficiency of vitamin D has been connected to a vital lowering in DPP-4/CD26 receptor expression in living organisms (Colunga 2020). COVID-19 saga is connected with a high generation of cytokines that are pro-inflammatrory, leading to a higher risk of pneumonia, sepsis, acute respiratory distress syndrome, and heart failure, according to studies (Wei *et al.,* 2015; Zhou *et al.,* 2020). Vitamin D may reduce the effect of COVID-19 infection and death rate by improving cell junctions and gap junctions, enhancing cellular protection, and regulating adaptive immunity. This includes moderating the cytokine storm triggered by pro-inflammatory and anti-inflammatory cytokines that responds to infection both of viral and bacterial origin, as seen in COVID-19 sufferers, and influencing interferon and tumor necrosis factor. Additionally, vitamin D modulates adaptive immunity by suppressing T helper cell type 1 responses and promoting T cells (Wei *et al.,* 2015).

Regular vitamin D supplementation, whether daily or weekly, can help prevent acute respiratory organ infections, especially in individuals with vitamin D reduced amounts. This addition of supplement has also been linked to increased presentation of antioxidant genes, such as glutathione reductase modifier subunit, which may offer benefits in preventing and treating COVID-19 infections. Vitamin D supplementation may reduce the need for vitamin C, which has antimicrobial properties, by increasing glutathione production. Additionally, vitamin D and defensins stimulate the generation of nonpathogenic peptides like human cathelicidin LL-37, which enhance innate cellular immunity. These peptides exhibit direct antibacterial activity against various microorganisms, disrupting their cell membranes and inhibiting endotoxin effects. Notably, vitamin D deficiency may exacerbate the renin-angiotensin system (RAS), potentially contributing to chronic cardiovascular disease (CVD) and diminished lung function. Dysregulation of RAS could lead to excessive cytokine production, potentially resulting in severe acute respiratory distress syndrome (ARDS). Research suggests that individuals with pre-existing conditions, including deficiency of vitamin D, constitute a larger proportion of seriously ill COVID-19 patients, implicating vitamin D deficiency in the development of ARDS and heart failure, common symptoms among severely affected COVID-19 patients (Jeffrey *et al.*, 2009).

This vitamin helps in keeping the respiratory state by promoting antimicrobial peptides and inhibiting respiratory virus replication. It has presented protective effects against interstitial pneumonitis both in experimental animal works and cell lines of human origin. Additionally, adequate vitamin D levels may mitigate adverse immune responses associated with COVID-19, which include high il-6(interleukin 6) levels and retarded interferon-gamma response, leading to better clinical outcomes.

Conclusion

Fat-soluble vitamin especially vitamin D performs a crucial function in modulating both the natural and adaptive immune systems. As there is no approved medication for COVID-19, strengthening the immune network is vital to enhance the body's natural defense against infections and pathogens. Deficiency of vitamin D or insufficiency has been linked to heightened autoimmunity and susceptibility to infections. In contrary, the role of vitamin D on human immunity varies depending on individual vitamin D levels. Considering its established benefits on various health outcomes, supplementation of vitamin D could be a cheap and dominant strategy to possibly obliterates millions of COVID-19 cases and high incidence of related deaths, while also reducing the burden on healthcare systems**.**

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