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Vitamin D as an Immunomodulatory Agent in the Prophylaxis and Management of COVID-19 Infection

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a new coronavirus that has quickly spread from a small incident to a worldwide epidemic, with the emergence of new variants adding to the complexity of the situation. COVID-19, the disease caused by SARS-CoV-2, can lead to multiorgan damage, and acquire a significant threat due to its highly contagious and sometimes fatal nature. In the pursuit of effective treatment strategies, the potential role of vitamin D in modifying various facets of the innate and adaptive immune systems has come under scrutiny. This review gives a summary of the current research on the relevance of vitamin D in both the prevention and treatment of COVID-19. While some conflicting findings have been reported, a consensus emerges regarding the numerous immunomodulatory effects of vitamin D, which could hold promise in the context of COVID-19. Furthermore, it is evident that low vitamin D levels may lead to impaired antimicrobial defenses, potentially contributing to unfavorable outcomes. Studies also suggest that supplementation can mitigate the effects of vitamin D deficiency, although the controversy surrounding the use of vitamin D supplements in the treatment of COVID-19 persists.

Keywords: SARS-CoV-2, immunity, molecular mechanism of action, brain, lung, kidney.

1. INTRODUCTION

The emergent SARS-CoV-2 virus, responsible for the COVID-19 pandemic, exhibits a remarkable affinity to induce a profound inflammatory response within the human host. This inflammatory response is of predominant significance in mounting an initial defense against the invading virus, but it carries the potential for both protective and detrimental consequences.[1] A comprehensive exploration of this response highlights the pivotal roles of many pro-inflammatory mediators, such as interferons (IFNs), interleukin-2,4,6,8,10,12,17 (IL-2,4,6,8,10,12,17), chemokines, interleukin-1β (IL-1β), transforming growth factor-β (TGF-β) & tumor necrosis factor-β (TNF-β), and in orchestrating the immune reaction against SARS-CoV-2 viruses.[2,3]

Vitamin D, a fat-soluble prohormone, is a critical nutrient with multifaceted roles in human physiology. It encompasses two main forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), each derived from distinct dietary sources. While vitamin D2 is primarily obtained from plant-based foods, such as mushrooms and fortified cereals, vitamin D3 is synthesized in the skin upon exposure to ultraviolet B (UVB) sunlight or can be consumed through animal-derived sources, like fatty fish and fortified dairy products.[4,5]

2. RESPONSE OF IMMUNE SYSTEM IN SARS-CoV-19 INFECTION

A controlled and effective immune response is necessary to contain the virus and provide protection against severe illness. However, when this response becomes imbalanced, as seen in the cytokine storm, it can exacerbate the inflammatory environment, lead to tissue damage, and worsen clinical outcomes.

2.1 Innate Immunity

The innate immune system acts as the initial line of

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defense against viruses (Figure 1).

2.1.1 Recognition Phase

In the case of SARS-CoV-2, recognition primarily hinges on the detection of viral elements by Pattern Recognition Receptors (PRRs). These receptors, located on the surface of immune cells or within cellular compartments, are responsible for identifying specific viral molecules known as Pathogen-Associated Molecular Patterns (PAMPs). In the context of coronaviruses, these PAMPs can include viral RNA and various components of the viral envelope.[6-8]

2.1.2 Pro-Inflammatory Cytokines

Once recognition occurs, macrophages and dendritic cells initiate the production and release of pro-inflammatory mediators, a reaction seen in response to SARS-CoV-2 and other coronaviruses. This includes prominent cytokines like tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β) and interleukin-1β (IL-1 β), which serve as crucial signaling molecules that help regulate the immune responses.[9,10] The presence of these cytokines is known to be associated with an inflammatory response, and their coordinated action triggers the recruitment of more immune cells to the site of infection during SARS-CoV-2 infection phase. They also contribute to establishing an inflammatory microenvironment that is unfavorable for viral replication.[11,12]

2.1.3 Complement System

The innate immune system's response to SARS-CoV-2 includes the activation of the complement system, a group of proteins designed to bolster the overall immune response. These proteins can coat viral particles through a process known as opsonization, making them more recognizable to immune cells and facilitating their engulfment. Additionally, they can assemble membrane attack complexes, creating perforations in viral envelopes that lead to viral inactivation.[13]

2.1.4 Interferons

In the presence of SARS-CoV-2, interferons, including interferon-alpha (IFN-α) and interferon-beta (IFN-β), are released as part of the innate immune response. These signaling proteins play a critical role in antiviral defense, inducing an antiviral state in neighboring cells. This state renders these neighboring cells less susceptible to viral replication and spread.[14]

Fig. 1: Immune responses to SARS-CoV-2 infection

2.2 Adaptive Immunity

2.2.1 T Cells

Cytotoxic T cells, often referred to as CD8+ T cells, are a subset of T lymphocytes with a crucial role in the immune response against SARS-CoV-2 and other viruses. When SARS-CoV-2 infects a host cell, it replicates within that cell, potentially leading to the production of thousands of viral particles. Cytotoxic T cells are specialized in recognizing and eliminating these infected cells. They are like the "assassins" of the immune system. They can recognize infected cells by identifying specific viral antigens presented on the surface of those cells.[15-17]

Viral antigens are fragments of the virus, often proteins, that are displayed on the infected cell's surface as a way of signaling to the immune system that it has been compromised. Once a cytotoxic T cell identifies an infected cell through its specific viral antigen, it binds to that cell and releases cytotoxic molecules, such as perforin and granzymes. These molecules create holes in the infected cell's membrane and trigger a process leading to cell death. This response limits viral replication by stopping the virus from using the host cell to reproduce.[18,19]

Helper T cells, or CD4+ T cells, play a different but equally vital role in the immune response to

SARS-CoV-2. These cells serve as conductors of the immune group. They don't directly attack infected cells or pathogens, but they provide essential guidance to other immune cells. When it comes to SARS-CoV-2, helper T cells coordinate the response.[20] They are instrumental in supporting B cells in producing antibodies that can neutralize the virus. Helper T cells interact with B cells by binding to them and providing signals to stimulate antibody production that binds to SARS-CoV-2, preventing the virus from infecting healthy cells. Helper T cells activate cytotoxic T cells, promoting their proliferation and effectiveness in identifying and eliminating infected cells.

In essence, cytotoxic T cells are like the "hitmen" that directly eliminate virus-infected cells, while helper T cells act as the "coordinators," facilitating the production of antibodies and assisting cytotoxic T cells in their function. This cooperative effort is fundamental in the adaptive immune response to SARS-CoV-2, ensuring that the virus is effectively targeted and controlled, ultimately leading to its clearance from the body.[20,21]

2.2.2 B Cells

B cells are active in the production of antibodies, immunoglobulins that can neutralize viruses like SARS-CoV-2.[22] These antibodies recognize viral antigens, inhibiting the virus's ability to infect host cells. When the body encounters a virus like SARS-CoV-2, B cells "sample" antigens presented by the virus and then use these antigens as templates to create antibodies that can recognize and bind to the viral antigens and block the virus's ability to enter and infect host cells. Essentially, they act as a shield that prevents the virus from binding to and entering healthy cells. Immune cells like macrophages and neutrophils recognize the antibodies attached to the virus and engulf the entire complex, effectively removing the virus from circulation. This process helps reduce the viral load and clears the infection.[23]

2.2.3 Cytokines

Cytokines constitute a varied array of signaling molecules generated by distinct immune cells, including T cells, B cells, and antigen-presenting cells. Interleukin-2 (IL-2) is a pivotal cytokine within the adaptive immune response, serving a dual function in the activation of T cells.[24] It promotes the proliferation and differentiation of 'conventional' T cells while also preserving and expanding the 'suppressive' Treg cell population. Among these 'conventional' T cells, naïve CD4+ and CD8+ T cells express the dimeric IL-2R, necessitating a high concentration of IL-2 to initiate their initial proliferation. Subsequently, once these T cells become activated, they express the high-affinity IL-2R, which guides the differentiation of the cells into either effector or memory cells. This dual role of IL-2 ensures the presence of an ample and highly responsive T cell population prepared to effectively combat viral threats.[25-27]

Interferon-gamma (IFN-γ) is another critical cytokine in the immune response to SARS-CoV-2, produced by various immune cells, including T cells and natural killer (NK) cells. Its primary role is to amplify the antiviral activities of macrophages, dendritic cells, and other immune cells. IFN-γ enhances the ability of these cells to recognize, engulf, and eliminate virus-infected cells and pathogens. This cytokine also plays a significant role in immune coordination, ensuring the various immune cells work together efficiently to combat the virus.[28-30]

When B cells encounter viral antigens, Interleukin-4 (IL-4) provides critical signals that stimulate B cell activation and differentiation into antibody-producing plasma cells. This process is pivotal in generating specific antibodies that can neutralize the virus.[31] Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that helps maintain immune tolerance and reduces inflammation, which is important for preventing an excessive immune response that can harm healthy tissues. TGF-β also plays a role in tissue repair after the immune system has cleared the virus. Interleukin-6 (IL-6) helps in the immune communication and coordination in SARS-CoV-2 infection.[32]

3. PATHOPHYSIOLOGY OF SARS-Co-V-2

SARS-CoV-2 primarily spreads through respiratory droplets, particularly when individuals cough or sneeze. The virus enters the host via the respiratory tract and specifically targets alveolar epithelial type 2 (AT2) cells. AT2 cells play a crucial role in

surfactant production, which, in turn, reduces surface tension within the alveoli, preventing their collapse. The spike proteins of SARS-CoV-2 interact with angiotensin-converting enzyme-2 (ACE2) receptors located on AT2 cells and are also present in other tissues such as the kidney, heart, enterocytes, pancreas, and endothelial cells. Once inside the host cell, the virus releases its positive-sense single-stranded RNA (ssRNA). Host cell ribosomes are utilized to generate polyproteins, and RNA-dependent RNA polymerases replicate viral RNA. The newly synthesized spike proteins are transported through the vesicle carriers, and the cytoplasmic proteinases cleave all polyproteins of SARS-CoV-2.[33,34]

The virus triggers an inflammatory response, stimulating macrophages to release cytokines (IL-1, IL-6, TNF-α) and chemokines into the bloodstream. Chemokines are small proteins that act as chemoattractant, guiding the movement of immune cells to the site of infection. C-X-C motif chemokine ligand 10 (CXCL10) and C-C motif chemokine ligand 2 (CCL2) recruiting T cells, monocytes, and other immune cells to the infected area. This results in vasodilation and increased capillary permeability, causing plasma to accumulate around the alveoli and leading to alveolar collapse and impaired gas exchange.[35,36]

Concurrently, there is an increase in the secretion of inflammatory cytokines, leading to a cytokine storm. These cytokines enhance the production and recruitment of neutrophils and macrophages through CD4+ T helper (Th1) cells. These processes can ultimately cause breathing difficulties, hypoxemia, and cough. The released cytokines, IL-1, IL-6, and TNF-α, affect the hypothalamus, leading to the release of prostaglandin, PGE2, and an increase in body temperature. Considering the hypoxic condition, sympathetic responses can induce tachycardia. Abnormal inflammatory responses can lead to septic shock and multi-organ failure.[37]

SARS-CoV-2 enters the respiratory tract through the interaction of its spike proteins with ACE2 receptors on type 2 alveoli cells, pivotal in surfactant production. This interaction initiates endocytosis and subsequent membrane fusion, facilitating the entry of the viral (+)ssRNA into the host cell's cytoplasm. Inside the host cell, the virus usurps the cellular translational machinery to synthesize proteins crucial for its replication. This interference disrupts the host cell's physiological surfactant production. The resultant reduction in surfactant levels leads to decreased oxygen saturation, triggering heightened respiration rates, ultimately culminating in respiratory failure. A comprehensive grasp of this pathophysiology is imperative for the development of effective COVID-19 treatments.[38,39]

4. VITAMIN D: MOLECULAR MECHANISM OF ACTION

Vitamin D's paramount importance is linked to its function as a precursor for the active hormonal form, calcitriol (1,25-dihydroxyvitamin D). This biologically active compound is synthesized through a series of enzymatic conversions in the liver and kidney. The initial step occurs in the skin, where UVB radiation converts 7-dehydrocholesterol into cholecalciferol (vitamin D3). Cholecalciferol is then transported to the liver, where it undergoes hydroxylation to form 25-hydroxyvitamin D (calcifediol), the major circulating form of vitamin D in the bloodstream.[40]

The pivotal transformation takes place in the kidneys, where calcifediol is further hydroxylated to generate calcitriol, which is a potent ligand for the vitamin D receptor (VDR). The VDR is present in a multitude of tissues, including immune cells, and its activation plays a fundamental role in regulating gene expression. The nuclear receptor-ligand complex governs the transcription of genes involved in calcium homeostasis, bone health, and numerous immune system functions.[41]

Calcifediol undergoes a complex cellular process pivotal for immune regulation. It initiates a cascade of events, including the activation of retinoid X receptors, which leads to the relocation of the vitamin D receptor element. This intricate process profoundly affects the expression of critical host genes, particularly those encoding vital antimicrobial peptides like β-defensin and cathelicidin (LL-37). Vitamin D also exerts its influence through Toll-like receptors, crucial for recognizing harmful proteins and initiating immune responses. It orchestrates the regulation of genes, including those encoding defensins, which directly

act on viral membranes.[42]

Upon activation, the VDR binds to the VDR element of the cathelicidin promoter region, thus initiating host defense against viral infections. Additionally, vitamin D enhances nitric oxide release, contributing to innate immunity by suppressing T-cell proliferation and shifting the balance from pro-inflammatory Th1 to anti-inflammatory Th2 cells. Vitamin D influences T-cell maturation, driving pro-inflammatory Th17 cells to differentiate into regulatory T cells with anti-inflammatory properties. Through these mechanisms, vitamin D effectively downregulates the production of IL-1, IL-6, IL-12, and TNF-α.[43,44]

Vitamin D's immunomodulatory effects extend to histone modification, encompassing both acetylation and methylation of core histones. Histone modification is facilitated by a multifaceted process involving the recruitment of coactivators and the formation of a multi-subunit complex, leading to chromatin modification and disruption of histone-DNA interaction.[45] Moreover, vitamin D interacts with basal transcription factors, ultimately establishing a stable preinitiation complex crucial for gene expression.

Mediator, a multi-protein complex, plays a pivotal role in this process, facilitating the recruitment of RNA polymerase II and promoting the formation of the preinitiation complex. The VDR and the enzyme CYP27B1 are identified as key targets for vitamin D in the endocrine system. Several studies suggested that vitamin D downregulates the expression of ACE2 receptors, potentially offering protection and maintaining immune balance and defending against infections, including viral diseases like COVID-19.[46]

5. ROLE OF VITAMIN D IN IMMUNITY

5.1 Effect on Innate Immunity

Vitamin D exerts a multifaceted influence on various aspects of innate immunity, further underscoring its pivotal role in the body's defense against infections, including those caused by viruses like SARS-CoV-2. Calcitriol plays a substantial role in boosting the phagocytic activity of macrophages, which are essential elements of the body's initial defense mechanism. Macrophages and monocytes employ Toll-Like Receptors (TLRs) to identify PAMPs on infectious agents.[47] This detection leads to the phagocytosis of these agents, constituting the primary defense line. Calcitriol has been shown to enhance the antimicrobial capabilities of these innate immune cells, reinforcing their capacity to engulf and eliminate pathogens.[48]

Moreover, immune signaling pathways, including those involving interferon-gamma (IFN-γ), STAT-1α, lipopolysaccharide (LPS), and Toll-like receptors (TLRs), play a significant role in the regulation of vitamin D-related processes in immune cells. These signaling pathways increase the expression of 1α hydroxylase in monocytes, which is responsible for catalyzing the formation of vitamin D, the active form of vitamin D. Notably, exposure to vitamin D has been shown to stimulate monocyte differentiation, causing these cells to adopt a macrophage-like phenotype. In macrophages, stimulation with vitamin D has an anti-inflammatory effect, characterized by increased production of the anti-inflammatory cytokine IL-10 and a reduction in pro-inflammatory markers such as TNF-α, IL-1β, IL-6, and cyclooxygenase-2 (COX-2). These effects are mediated through the mitogen-activated protein kinase (MAPK) phosphatase pathway.[49]

Moreover, the activation of Toll-like receptors has the potential to elevate the expression of the VDR. In contrast, vitamin D can decrease the expression of miRNA155, a molecule known to hinder the expression of anti-inflammatory genes. Research has also shed light on how the VDR, when bound to its ligand, can impact the epigenetic regulation of immune cells, with a particular focus on monocytes.[48]

Within dendritic cells, the binding of vitamin D initiates a transformation towards a more tolerogenic phenotype. This alteration is reflected in both cell morphology and the expression of surface proteins. Notably, there is a reduction in the levels of major Histocompatibility Complex (MHC) class II receptors, along with the CD80 and CD86 co-stimulatory molecules, which are crucial for orchestrating an immune response. Concomitantly, there is an increase in the presence of CCR-5 and CD40 receptors, fostering an environment with anti-inflammatory characteristics. Moreover, vitamin D elevates the expression of programmed death-ligand 1 (PD-L1) and TNF, which, in turn, promotes the

activity of regulatory T cells, resulting in an overall anti-inflammatory effect.[49,50]

VDRs are also expressed in natural killer (NK) cells and neutrophils, two other crucial players in innate immunity. VDR signaling has been shown to optimize neutrophil response by enhancing their ability to kill naive cells while reducing the production of pro-inflammatory cytokines by infected neutrophils. Essentially, vitamin D fine-tunes the neutrophil response, preventing it from becoming excessive. Furthermore, vitamin D modulates NK cell response by decreasing the expression of IFN-γ and reducing cytotoxic activity, demonstrating its role in maintaining immune balance and preventing excessive immune reactions.[51,52]

5.2 Effect on Adaptive Immunity

The influence of vitamin D extends to various immune cells, including dendritic cells, macrophages, T cells, and B cells, within the realm of adaptive immunity. Its anti-inflammatory effects on dendritic cells and macrophages are particularly noteworthy, as they involve downregulating the expression of major Histocompatibility Complex II (MHC II) and co-stimulatory molecules, ultimately reducing pro-inflammatory signaling. This modulation of dendritic cells and macrophages, in turn, has significant repercussions on the response of T lymphocytes.[53]

The anti-inflammatory environment induced by vitamin D signaling plays a role in decreasing the proliferation of autoreactive T cells, which have the potential to initiate autoimmune responses. In some instances, it may enhance the proliferation of regulatory T cells (Tregs), which are critical in maintaining immune balance. Furthermore, this anti-inflammatory milieu tends to favor the development of a T-helper 2 (Th2) phenotype as opposed to Th1 or Th17 phenotypes, contributing to immune regulation.[54]

Directly within T cells, the impact of vitamin D signaling varies based on the T cell phenotype and differentiation state. Upon activation, T lymphocytes upregulate the expression of VDR. Stimulation with vitamin D leads to reduced signaling of pro-inflammatory cytokines like interleukin-2 (IL-2) and interferon-gamma (IFN-γ), particularly associated with Th1 responses, and interleukin-17 (IL-17) and interleukin-21 (IL-21), linked to Th17 responses. However, it acts synergistically with IL-2 to promote and sustain a Th2 phenotype, further contributing to immune balance.[54,55]

In B cells, VDR expression has been shown to induce apoptosis in activated B cells and reduce the generation of plasma cells. Additionally, vitamin D signaling affects B cells by altering the composition of cell surface markers, reducing T cell activation by B cells. It also enhances the production of the anti-inflammatory cytokine interleukin-10 (IL-10) in B cells, further promoting an anti-inflammatory milieu.[56]

Recent evidence indicates that vitamin D and its hydroxyderivatives can bind and activate the liver X receptor (LXR). The LXR has been implicated in regulating the differentiation of T cell phenotypes and, consequently, the functioning of the adaptive immune system. This complex interplay of vitamin D within adaptive immunity underscores its role in maintaining immune homeostasis and preventing excessive inflammation or immune dysregulation.[57]

6. VITAMIN D AND SARS-CoV-2

The emergence of the SARS-CoV-2 pandemic has brought about significant shifts in people's daily lives, impacting various factors, from lifestyle choices to dietary habits. The role of food and the micronutrients it provides in regulating the human immune system is of paramount importance. Among these micronutrients, vitamin D holds a special place as a potent immunomodulator.[58] Research has shown that individuals with vitamin D deficiency are at a higher risk of developing severe complications associated with lower respiratory tract infections.[59] They have a 117% increased likelihood of requiring oxygen therapy and a 217% elevated risk of needing mechanical ventilation compared to individuals with adequate levels of calcifediol. Moreover, vitamin D's influence on reducing the severity and incidence of respiratory infections is well-documented. There exists a linear correlation between vitamin D concentrations and the cumulative incidence of infections, with the frequency of infections significantly rising when calcifediol values fall below 30 ng/ml.[60]

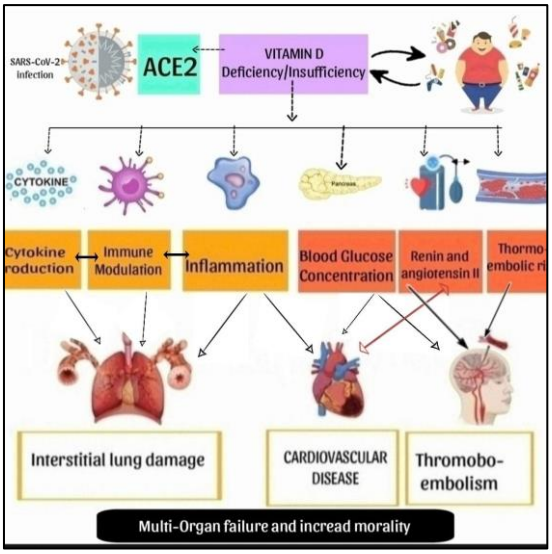

Fig. 2: The relation between Vitamin D deficiency and SARS-CoV-2 infection

Given the well-established role of vitamin D in various respiratory infections and responses to the immune system, it is reasonable to assume that it may also play a crucial role in SARS-CoV-2 infections.[61] The mechanisms through which vitamin D affects immune responses are significant, especially during the viral infections and emerging diseases like COVID-19 (Figure 2). This knowledge can guide strategies for harnessing the potential of vitamin D in optimizing immune function and supporting overall health. The collective evidence strongly suggests that vitamin D should be considered as a potential factor in preventing, alleviating symptoms, or treating SARS-CoV-2 infections.[62]

6.1 Role of Vitamin D in Brain Disorders

The emergence of SARS-CoV-2 challenges our immune system, which lacks prior exposure to this new pathogen. Consequently, our first line of defense relies on innate immunity, which can sometimes trigger an exaggerated immune response termed a "cytokine storm." This overactive response has severe consequences in the brain, leading to conditions like acute necrotizing hemorrhagic encephalopathy.[63]

Research shows that antibodies generated within this neuroinflammatory environment can sometimes react against elements of the immune system, possibly contributing to brain autoimmune disorders.[64] However, it's unclear whether this can occur in uninfected individuals. Studies on healthy individuals reveal the presence of autoantibodies targeting type-1 interferon, more prevalent with age, which may explain worse outcomes in older COVID-19 patients. SARS-CoV-2 infections often involve a robust innate immune response and prolonged systemic cytokine elevation, linked to cognitive impairment and neurodegenerative diseases. Survivors might be at risk of neurodegeneration in the years to come.[65,66]

Brain cells may serve as latent SARS-CoV-2 reservoirs, potentially linked to delayed cell death and oxidative stress pathways, contributing to neurodegenerative diseases. This viral latency could accelerate pre-existing neurocognitive disorders or lead to new ones. SARS-CoV-2 has been reported to increase the synthesis of alpha-synuclein, which is associated with Parkinson's disease.[67] The "cytokine storm" in COVID-19 could exacerbate or induce neurocognitive diseases. The virus may influence neurotransmission systems, impacting dopamine, GABA, and the neuromuscular junction, potentially contributing to neurodegenerative consequences. Antibodies generated against SARS-CoV-2 epitopes could hasten the development of neurodegenerative conditions, including myasthenia gravis, associated with COVID-19.[37,63,68]

Vitamin D significantly impacts the central nervous system (CNS) development and function.[69,70] Neurons and microglia express VDR and may metabolize calcifediol directly through 1-hydroxylase. Notably, calcitriol can regulate the expression of neurotrophic factors like glial cell line-derived neurotrophic factor and nerve growth

factor, indicating its potential neuroprotective role. Recent research demonstrates calcitriol's ability to reduce reactive oxygen species-induced cell death while increasing antioxidant species in glial cells.[71]

Research conducted with animal models of neuroinflammation emphasizes the neuroprotective role of vitamin D in combatting inflammation. This suggests that sufficient exposure to sunlight can yield beneficial immunomodulatory effects, particularly in conditions like multiple sclerosis.[72] Furthermore, the combination of omega-3 fatty acids and vitamin D has demonstrated the capacity to regulate neuroinflammatory processes in models of traumatic brain injury, underscoring the potential of vitamin D-based treatments for encephalopathies associated with SARS-CoV-2. Notably, vitamin D signaling in neurons can stimulate the synthesis of IL-34, a substance crucial for microglia survival and Central Nervous System (CNS) homeostasis. This process may serve as a protective measure for the CNS against autoimmune reactions by preventing excessive activation of microglia during early-life inflammation.[73]

Vitamin D deficiency is linked to various neurological disorders such as Parkinson's disease, schizophrenia, depression, and cognitive decline.[74] This underscores its crucial role in maintaining normal CNS function. In an animal model of oxidative stress and neurodegeneration, vitamin D was found to impact memory and cognition. Its deficiency could accelerate cognitive impairment, but supplementation with vitamin D showed immunomodulatory and antioxidant effects, reducing pro-inflammatory interleukins, and increasing anti-inflammatory mediators. These effects were observed alongside a decrease in the formation of amyloid β-protein and an enhancement in memory performance. Collectively, these discoveries imply that vitamin D supplementation could be a viable strategy to deter the onset and advancement of post-COVID-19 neurodegenerative conditions, such as Parkinson's and Alzheimer's disease.[75-77]

Nevertheless, it's vital to acknowledge that research in this area is ongoing, and more studies are required to establish clear links and mechanisms. Additionally, individual factors like vitamin D status, genetics, and the severity of SARS-CoV-2 infection can all influence outcomes related to neuron recovery. Therefore, patients with neurological symptoms associated with SARS-CoV-2 should seek guidance from healthcare professionals regarding the role of vitamin D and other potential interventions in their specific cases.

6.2 Role of Vitamin D in Lungs Infection

Vitamin D's potential to prevent and manage lung symptoms associated with SARS-CoV-2 infection extends to its influence on conditions like Acute Respiratory Distress Syndrome (ARDS), pulmonary edema, lung failure, and complications affecting other organs.[79] These severe outcomes are often linked to a cytokine storm, characterized by elevated levels of proinflammatory cytokines and chemokines. Studies have highlighted vitamin D's significant impact on primary human alveolar type II cells, with more than 600 genes being activated or inhibited by vitamin D in these cells.[79,80] Moreover, during viral infections, inactive vitamin D can be converted to its active form by alveolar epithelial cells, resulting in the upregulation of defense genes like cathelicidin and beta-defensin. This implies a potential organ-specific protective effect of vitamin D in the lungs.[81]

Vitamin D's role extends to inhibiting airway smooth muscle proliferation and increasing surfactant synthesis, which is critical for lung function. *In vitro* studies have demonstrated that physiologically relevant doses of vitamin D directly protect alveolar epithelium by promoting cellular proliferation, wound repair, and reducing cell death.[82] High doses of vitamin D treatments have shown promise in reducing inflammation and mortality in respiratory conditions. For instance, a single high-dose vitamin D treatment significantly decreased IL-6 levels and reduced mortality in patients with ventilator-associated pneumonia. Similarly, vitamin D3 supplementation reduced the production of proinflammatory cytokines and increased the production of antimicrobial peptide cathelicidin while enhancing antioxidation and autophagy in mice with pneumonia.[82]

Notably, high-dose preoperative vitamin D oral administration was linked to preventing acute respiratory distress syndrome following

esophagectomy. Vitamin D's protective role is reminiscent of historical data that correlated UVB exposure with pneumonia outcomes and fatality rates. Increases in UVB doses were associated with reductions in pneumonia and mortality rates for conditions like influenza. It's well-established that vitamin D levels rise with increased ultraviolet exposure, reinforcing the link between UVB, vitamin D, and reduced pneumonia and mortality rates.[83,84]

Physiologically, vitamin D supports lung health by regulating surfactant production, a substance crucial for preventing the collapse of alveoli and ensuring efficient oxygen exchange. By promoting surfactant synthesis and maintaining lung structural integrity, vitamin D contributes to overall respiratory well-being. Recent research has suggested that vitamin D also modulates the epigenome of immune cells, influencing their function and responsiveness. This further underscores its multifaceted role in shaping immune responses, particularly in the respiratory infections.[85,86]

6.3 Role of Vitamin D in Vascular Disorders

Vitamin D has gained attention in the field of cardiovascular health, particularly concerning COVID-19 patients. Emerging evidence indicates that a significant percentage of COVID-19 patients, up to 8.0%, experience acute heart damage. This condition has a strong association with mortality, making it a critical concern. In some cases, inflammation has been suggested as a potential cause of myocardial damage.[87]

The role of cytokines in cardiovascular complications cannot be overlooked. Cytokine accumulation directly affects vascular endothelial function and myocardial contractility. IL-6 and TNF-α can decrease myocyte contractility by reducing systolic calcium levels.[88] Research involving myocardial ischemia-reperfusion models in rats demonstrated that vitamin D significantly reduced myocardial injury and inflammatory cytokine levels.[89]

In another animal study, vitamin D played a protective role by reducing TNF-α and IL-6 levels in cases of isoprenaline-induced myocardial infarction.[90] Similarly, studies involving vitamin D treatments showed reduced myocardial damage in various cardiotoxicity models, underlining its potential in cardiovascular protection.[91] Meta-analyses and studies on patients with heart failure have shown that vitamin D supplementation can reduce proinflammatory cytokine concentrations, such as TNF-α and IL-6, and increase anti-inflammatory IL-10 levels.[92] These effects were observed in both adult and infant patients with congestive heart failure. Moreover, in older patients with chronic heart failure, vitamin D supplementation was found to have beneficial effects on left ventricular structure and function.[93]

In individuals with any cardiovascular disease, it has been established that proinflammatory cytokines play a significant role in pathogenesis. Vitamin D supplementation, particularly in higher doses, has demonstrated efficacy in reducing the release of proinflammatory cytokines. Given the higher mortality rates among cardiovascular patients who contract COVID-19, the role of vitamin D supplementation in reducing inflammation is particularly promising. It holds the potential to decrease the mortality rate in COVID-19-infected cardiovascular patients.[94]

6.4 Role of Vitamin D in Kidney Damage

Kidney damage during the COVID-19 is a concerning issue, and there's emerging evidence that vitamin D might play a protective role in this regard. Numerous studies have highlighted an increased incidence of acute renal injury in patients with COVID-19, and such injury is associated with higher mortality rates. It has also been suggested that severe COVID-19 infections are linked to chronic kidney disease (CKD), underscoring the need for caution among CKD patients.[95] In individuals with CKD, active vitamin D levels have been associated with decreased mortality, and 1-hydroxylated vitamin D analogs have shown effectiveness in treating secondary hyperparathyroidism. Vitamin D supplementation has safely increased serum calcifediol concentrations, with significant improvements observed in lipid profiles with higher doses.[96]

Additionally, vitamin D has been found to improve immune function by regulating pro-inflammatory and anti-inflammatory factors. It protects against inflammation and lowers fasting blood sugar, insulin, TNF-α, and IL-6 levels. Vitamin D supplementation

has also demonstrated protective effects against drug-induced kidney and liver injury. Therefore, it's suggested that vitamin D supplementation could potentially mitigate the cytokine storm seen in COVID-19 and reduce mortality in patients with renal disease.[97]

Moreover, the abundant expression of ACE2 protein in various cell types has been linked to kidney damage. Increased ACE2 expression is observed in kidney damage and experimental diabetes models. Vitamin D treatment has been shown to inhibit ACE2 expression, which could potentially lower the entry of SARS-CoV-2 into the kidneys and protect against kidney damage.[98-100]

Further these findings suggest a potential role for vitamin D in kidney protection during COVID-19, further research is essential to establish the precise mechanisms and the most effective vitamin D supplementation strategies for patients with kidney disease in the context of SARS-CoV-2. Patients with kidney issues should consult healthcare professionals for personalized recommendations.

6.5 Role of Vitamin D in Diabetes

During SARS-CoV-2 infection and its impact on individuals with diabetes mellitus (DM), several crucial factors come into play, especially in older adults. Age-related factors like hypertension, obesity, and DM are often associated with metabolic syndrome, significantly increasing both morbidity and mortality among SARS-CoV-2 patients.[101] Furthermore, it's common for patients with one comorbidity to have multiple others, further complicating the clinical picture. While the direct contribution of coronary vascular disease (CVD), severe obesity, and hypertension to the progression of SARS-CoV-2 infection remains unclear, elevated plasma glucose levels and the presence of DM are known predictive factors for adverse outcomes in SARS-CoV-2 infections.[102]

Patients with DM who also have comorbid conditions such as CVD, hypertension, and severe obesity face an elevated risk of morbidity and mortality. One possible reason for this increased risk is the higher viral load facilitated by the presence of ACE2 receptors in key organs, including the pancreas, heart, and kidneys. This may lead to altered endosomal pH, reduced viral clearance, T-cell immune dysfunction, and hyperactivation of inflammatory signaling pathways.[103] Rodent models of DM have demonstrated a heightened expression of ACE2, potentially amplifying SARS-CoV-2's ability to enter cells. The expression of furin, a protein that facilitates the entry of SARS-CoV-2 by cleaving spike proteins, was found to be augmented in DM patients in 2018. This furin-related discovery sheds light on a growing association between DM and SARS-CoV-2, highlighting the need for further investigation into the underlying molecular and cellular mechanisms.[104-106]

Maintaining adequate vitamin D levels is essential for DM patients, given its impact on metabolic health and insulin sensitivity. Additionally, vitamin D appears to influence the expression of ACE2 receptors, which are key entry points for SARS-CoV-2.[107] While ongoing research is exploring this interaction, vitamin D's potential to regulate ACE2 receptors may be particularly significant for DM patients at risk of severe COVID-19 outcomes. Vitamin D's immunomodulatory properties have the potential to mitigate the dysregulated immune responses observed in DM patients infected with SARS-CoV-2. Vitamin D, by modulating the immune response and reducing excessive inflammation, could offer protection to DM patients against severe disease progression.[108]

6.6 Role of Vitamin D in Coagulation

Coagulation abnormalities have been associated with various thrombotic complications in COVID-19 infectious phase, although bleeding is not commonly reported in COVID-19 patients. This condition has led to a spectrum of coagulation-related issues, including Deep Vein Thrombosis (DVT), venous thromboembolism, Pulmonary Embolism (PE), cor pulmonale, and arterial thrombosis and embolism, such as ischemic stroke and Myocardial Infarction (MI). Among these, DVT and PE are particularly prevalent among patients who have succumbed to the disease.[109]

The development of these thrombotic complications is multifactorial. COVID-19 induces a hypercoagulable state characterized by platelet activation, inflammation, endothelial dysfunction, blood vessel constriction, muscle immobilization, stasis, and Disseminated Intravascular Coagulation

(DIC). Fever and inflammation contribute to hypercoagulability, which impairs fibrinolysis. Elevated levels of the cytokine IL-6 correlate with hypercoagulability and the severity of the disease, while increased antiphospholipid antibodies are linked with thrombosis.[110]

Moreover, the liver increases the production of procoagulant substances, leading to moderately prolonged prothrombin time and activated partial thromboplastin time. COVID-19 patients may also experience moderate thrombocytopenia, elevated C-reactive protein levels, lymphocytopenia, and increased levels of D-dimer and Fibrin Degradation Products (FDPs), all of which are indicators of excessive systemic inflammation and the potential development of DIC.[111]

Guidelines recommend thromboprophylaxis to manage these coagulation issues. This prophylaxis can involve the use of low-molecular-weight heparin, or direct oral anticoagulants such as apixaban or rivaroxaban.[112] It's worth noting that heparins exhibit additional benefits beyond their anticoagulant properties. They bind tightly to the spike proteins of COVID-19, hindering the virus's entry into cells. Heparins also downregulate IL-6 and reduce immune activation. There is some evidence suggesting that systemic anticoagulation may be associated with reduced mortality without increasing major bleeding, especially among patients requiring mechanical ventilation.[113]

The fact that systemic anticoagulation has not been shown to be helpful in treating acute respiratory distress syndrome (ARDS) caused by reasons other than COVID-19 must be acknowledged. Therefore, its efficacy can be circumstances specific. It's crucial to consider extended prophylaxis after hospital discharge to mitigate the risk of post-discharge thrombotic events.[114] Overall, addressing coagulation abnormalities in COVID-19 is a multifaceted challenge, and interventions should be tailored to the individual patient's condition and risk factors.

6.7 Role of Vitamin D in Eye Infections

COVID-19 primarily affects the respiratory system, but it can also have various impacts on other organs and systems in the body, including the eyes. The relationship between COVID-19 and ocular symptoms is an area of ongoing research. One of the more common eye symptoms reported in COVID-19 patients is conjunctivitis or "pink eye." This can cause redness, itching, tearing, and a gritty feeling in the eyes. It is thought to result from viral particles encountering the eye's mucous membranes. COVID-19 may lead to episcleritis and scleritis that involve inflammation of the episclera or sclera, retinal abnormalities, blood clots, ischemic events, and tear film abnormalities.[115]

The eye's susceptibility to SARS-CoV-2 infection is noteworthy due to the presence of ACE2 receptors and TMPRSS2 proteases on ocular surface cells. These are the same cellular components that the virus exploits to enter the body. In the eye, these receptors are found in various locations, including the cornea, inside the eyelids, and the conjunctiva, which is the white part of the eye. This presence of entry points for the virus on ocular surface cells is a key factor in understanding how SARS-CoV-2 can affect the eyes.[116,117]

While vitamin D is primarily recognized for its importance in maintaining overall health and its immunomodulatory effects, its specific impact on preventing eye-related conditions or disorders is still being studied. Some eye disorders and symptoms related to COVID-19, such as conjunctivitis and retinal abnormalities, are believed to be influenced by the virus's impact on the eyes. It's possible that vitamin D's immunomodulatory properties could play a role in mitigating the severity of such ocular manifestations. However, more research is required to establish the direct connection and recommended strategies for using vitamin D to prevent or manage eye disorders.[118]

7. FUTURE DIRECTIONS

The ever-changing nature of SARS-CoV-2 and its complex impact on the immune system present challenges in understanding the role of vitamin D. Variants of the virus can lead to severe outcomes, even in younger individuals, prompting a reassessment of our knowledge. The root cause of vitamin D deficiency and the immune issues in COVID-19 patients is still debated, with some suggesting that conditions like diabetes and obesity may be more influential.[119] The diverse clinical trials have substantial variations, necessitating well-

designed, powerful studies. Observational studies have their limitations, and results may not be universally applicable. The mode of vitamin D intake remains uncertain, whether through sunlight or supplementation. However, seasonal variations in vitamin D synthesis should be considered when supplementing. Studies recommend restoring normal levels and possibly preemptively addressing low levels, but the optimal approach is still being discussed. Further research is essential to understand the effects of mutant SARS-CoV-2 strains and the mechanisms of vitamin D during the COVID-19 infection.

8. CONCLUSION

In summary, the existing body of evidence indicates a significant association between vitamin D and COVID-19, suggesting potential benefits from vitamin D supplementation in managing and treating the disease. A substantial portion of the literature points to improved COVID-19 prognosis and outcomes with adequate vitamin D levels, whether achieved through supplementation or not, although some studies report no significant differences based on vitamin D levels or no clear benefits from supplementation. Some even indicate a reduced risk of infection with prior supplementation. Future research should prioritize unraveling the precise mechanisms behind this relationship and optimizing treatment dosages to maximize patient benefits upon infection. Meanwhile, addressing vitamin D deficiency is advisable, given the safety of supplementation and the potential advantages it offers in protecting against COVID-19, outweighing any risk of toxicity.

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