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Association of Innate Immunity and Nutritional Immunomodulation under Coronavirus Infection

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ABSTRACT

The appearance of coronaviruses, particularly SARS-CoV-2, had highlighted the significant role of the innate immune system in determining the severity and outcome of viral infections. As the first line of defence, the immune response relies on pattern recognition receptors, such as Toll-like receptors and the NLRP3 inflammasome, to initiate pro-inflammatory responses aimed at combating viral threats. However, an excessive or dysregulated immune response, including hypercytokinemia, can lead to tissue damage and exacerbate disease severity. Recent studies suggest that nutritional immunomodulation can influence the effectiveness of the immune system and potentially mitigate the impact of coronavirus infections. Nutrients like vitamins D, C, and zinc have been shown to modulate immune functions by enhancing immune activity, promoting anti-inflammatory responses, and improving viral clearance. These nutritional interventions may improve the body's response towards viral infections, reduce inflammation, and prevent excessive immune activation. This review explores the intricate relationship between coronaviruses, innate immunity, and nutritional immunomodulation, emphasizing the potential of targeted nutritional strategies to support immune function and manage the impact of coronavirus infections. Understanding the molecular mechanisms behind these interactions may provide new insights for therapeutic interventions in viral diseases like COVID-19.

Keywords: COVID-19, Vitamin D, Vitamin C, Zinc, Immunity

1. INTRODUCTION

The virus that brought COVID first time was recently originated and identified in Wuhan, China in December 2019. The International Health Regulations Emergency Committee of WHO had announced this virus exposure

as a serious health concern worldwide. After observing a huge increase in the cases globally WHO became a COVID-19 as a pandemic situation. Human coronavirus 229E (HCV-229E), SARS-CoV, HCV-OC43, SARS-CoV-2, HCoV-NL63, and HCoV-HKU1 are the seven human contagious coronaviruses which were recognized [1,2]. SARS-CoV-2 is the most known human coronavirus, causing the pandemic COVID-19, the human respiratory disease. Virus genome has RNA, viral membrane, and nucleocapsid (N) protein forming helical capsid. CoV's membrane proteins are constituted of viral proteins spike (S), and membrane (M) and envelope (E), respectively [3] **(Figure 1)**. SARS-CoV, SARS-CoV-2, and other CoVs, type infection of the host cell results from the interaction of lipids and proteins with receptors in the host cells, such as dipeptidyl peptidase 4, aminopeptidase N, and the S protein for angiotensin-converting enzyme 2, murine carcinoembryonic antigen-related adhesion molecule 1, and other cellular receptors. In the present study we explored the relationship between coronaviruses, innate immunity, and nutritional immunomodulation, and how it affects individual immunity, emphasizing specially with coronavirus infections.

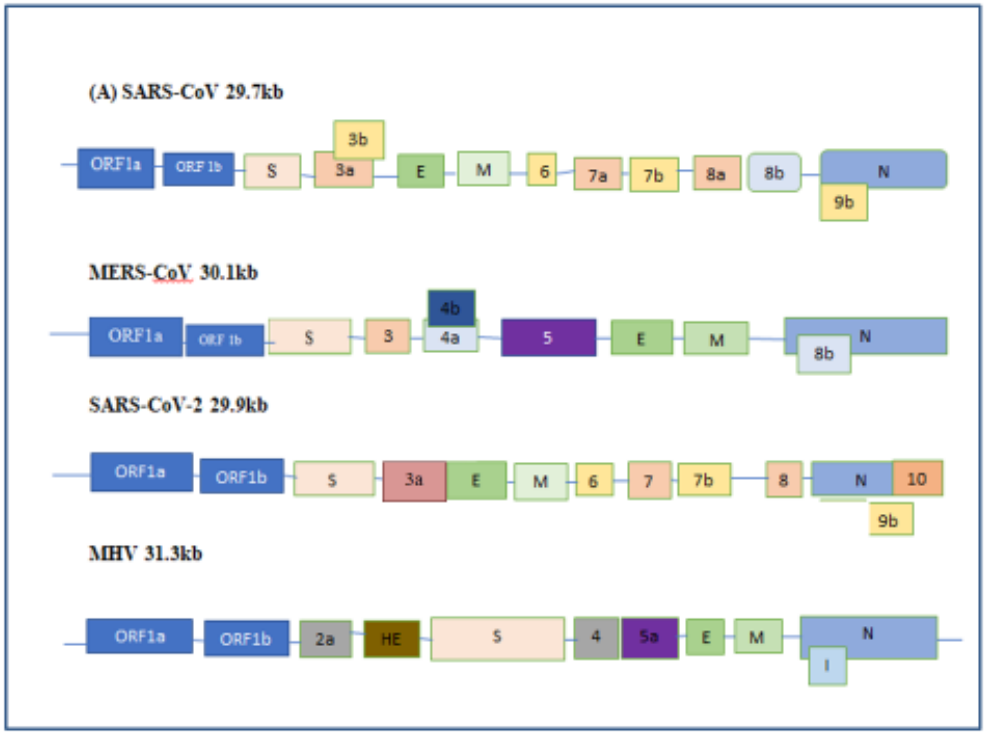

Figure 1: Diagram representing positive-sense RNA genomes of the severe acute respiratory syndrome (SARS)-CoV, Middle East respiratory disease (MERS)-CoV, SARS-CoV-2, and Murine hepatitis virus (MHV). Hemagglutin-esterase (HE), internal protein (I), four structural proteins (spike (S), membrane (M), envelope (E), and nucleocapsid (N)). S, M, E, and N proteins are unique to each virus [4,5].

The immune system plays a critical role in the defence against SARS-CoV-2. The response to the virus involves two major branches: innate immunity**,** which provides the first line of rapid, nonspecific defence, and acquired immunity**,** which offers a highly specific and long-lasting response. Both Innate and acquired immunity, can eliminate virus, and protect from various health concerns. In the case of COVID-19, the immune responses play

a very important both protective roles. Innate immunity serves as the initial defence, using pattern recognition receptors (PRRs), cytokine production, and immune cell recruitment to reduce the virus transmission. SARS-CoV2 has developed some changes to decrease these immune responses, reducing the initiation of effective defence. However, acquired immunity, which includes B and T cells, and the generation of neutralizing antibodies, develops more slowly but is necessary for protection and immunity over the long term. Immunity become enhanced by the vaccinations, which are able to reduce the spread of SARS CoV infection [6,7]. Immuno modulation has been a crucial treatment method to reduce the impact of COVID-19 [8]. Approaches to reduce harmful hyper inflammatory reactions or strengthen protective immunity may greatly improve outcomes. In this review, we analyzed the dynamic relationship between coronaviruses, the innate immune response, and the role of nutritional immunomodulation in influencing disease outcomes.

1.1. Response of type 1 IFN during CoV infection

Various approaches have implicated the role of the IFN response during CoV infection. Type 1 IFN is preferred to limit MERS-CoV infection, and SARS-CoV [9]. Decreased type 1 IFN and high values of proinflammatory cytokines result in extremity of disease in certain mice which are lacking crucial factors of type 1 IFN secretion in comparison to normal mice. When SARS-CoV and MA15 viruses infect wild type mice, the virus replicates and delays type 1 IFN signaling. However, it also produces a strong proinflammatory cytokine that activates TNF and IL-6, leading to respiratory immunopathology with minimal host activation [10].

Recent study that looked at peripheral blood from people with varying levels of infection revealed that IFN-1 reactions are extremely affected in person with high infection even after upregulation of tumor necrosis factor, IL-6, and NF-κB controlled inflammation which is also supported by reduced concentration of IFN-1 and ISGs [11]. Recent reports demonstrated that *in vivo* mice study, IFN-1 reactions are required for macrophages and pro-inflammatory monocytes for affected lungs [12].

2. Coronaviruses and Inborn immunity

The innate immune system is important in identifying and destroying infected cells during viral infections and coordinating an adaptive immune response [13]. The research of CoVs is not restricted to a single animal model because of the species-specific binding of S protein with its cellular receptors [14]. Mouse-adapted strain of SARS-CoV MA15 functions as a model mouse for SARS-CoV because of its mimicking characteristics [15].

2.1. CoV infection-induced activation of the NLRP3 inflammasome

Various issues, such as related to weight, gastritis, autoinflammatory disorders, and pathogen-related diseases, are linked to the pyrin domain NLRP3. *In vitro* studies demonstrated that the SARS-CoV open reading frame (ORF) 3 mediates the activation of the NLRP3 inflammasome and promotes interleukin-1β release in LPS-primed murine bone marrow-derived macrophages [16]. In THP-1 macrophages, the SARS-CoV ORF8b protein interacts with the LRR region of NLRP3, activating the NLRP3 inflammasome and produced IL-1β [17]. BALB/c mice's bronchoalveolar lavage fluid produces IL-1β because of ion channel activation stimulated by the SARS-CoV E protein. The host's ability to fight against viruses often depends on the NLRP3 inflammatory complex. Many RNA viruses, such as West Nile virus (WNV), activate the NLRP3 inflammasome in mouse models, which enhance the release of proinflammatory cytokines. Consequently, these cytokines cause pyroptotic cell

death [18]. Excessive NLRP3 inflammasome stimulation may cause serious pathological harm. Proinflammatory cytokines like inflammasome-derivative IL-1β, TNF and IL-6 cause lung injury and acute respiration syndrome (ARDS) in a SARS-CoV infection scenario in mice [20]. More research is needed to examine the factors necessary for SARS-CoV-2-derived NLRP3 inflammasome gathering completely and NLRP3 inflammasome-controlled ARDS, given that IL-1β remained linked with COVID-19 severity [21]. Three different mechanisms of cell death are pyroptosis, necroptosis, and apoptosis.

2.2. Pyroptosis during CoV infection

Pyroptosis, a type of inflammatory cell death, membrane pore synthesis, and proinflammatory cytokine processing are all caused by the multiprotein molecule known as an inflammasome. Innate immune signaling and inflammasome stimulation are common and essential obstacles during viral illness [22]. SARS-CoV-2 infection can trigger pyroptosis in infected cells, particularly in dendritic and macrophages cells. Inflammasome assembly activates inflammatory caspases, which cleave and remove the N-terminal portion of gasdermin D (GSDMD). The released N-terminal fragment creates pores in the plasma membrane, ultimately leading to pyroptosis [23]. Caspase-1-dependent GSDMD cleavage provides a route for the IL-1β and IL-18 secretion, NLRP3 inflammasome stimulation and IL-1β production in THP-1 macrophages [24].

2.3. Necroptosis during CoV infection

Necroptosis previously appeared to play a minor role in CoV infection, however recent study has revealed a mechanism for necroptosis cell death during CoV infection [25]. In COVID-19, SARS-CoV 2 infection, cause necroptosis, especially in immune cells like macrophages, which causes tissue damage and inflammation in the lungs. Following SARS-CoV-2 infection, a study using Calu-3 cells was investigated utilizing immunofluorescence and western blot to evaluate MLKL phosphorylation. The staining patterns showed that the infected cell plasma membrane contained the protein pMLKL in higher amounts. This indicates that the virus activates the necroptotic pathways by suppressing MLKL phosphorylation and virus proliferation [26]. The production of membrane channels during necroptosis, a form of inflammatory cell death that relies on the receptor-interacting serine/threonine protein kinase 1 (RIPK1) and RIPK3 complex, is initiated by the protein mixed lineage kinase domain-like pseudokinase (MLKL) [27]. Furthermore, in infected cells, the RIPK3 reduced the pMLKL, indicating that SARS-CoV-2 alters RIPK3 directly to cause necroptosis [28,29]. Necroptosis, thus can increase viral propagation by rupturing cells and inhibiting viral replication by killing cells. According to these findings, RIPK3 signaling pathways may be involved in the onset of acute lung injury and the length of sickness in individuals with COVID-19 pneumonia [30].

2.4. Role of apoptosis in CoV infection

Necroptosis, a regulated form of cell death, is triggered by specific signals like viral infection. In COVID-19, necroptosis can occur in response to SARS-CoV-2 infection, especially in immune cells such as macrophages. It may contribute to tissue damage and inflammation, particularly in the lungs. Apoptosis may cause membrane blebbing to destroy cells rather than directly releasing their contents [31]. Along with SARS-CoV and SARS-CoV ORF6, it was discovered that activation of caspase-3 contributed to apoptosis in Vero E6 cells.

Additionally, MHV infection causes Vero E6 and HEK293T cells to undergo apoptosis. In an o*in vitro* study, humanoid airway epithelial cells infected with SARS-CoV-2 exhibited a rise in apoptotic cytopathic factors.

3. Immunomodulatory function of Vitamin D

Vitamin D works in two ways, one as a nutrient and the other as a hormone (fat-soluble); its formation takes place when UVB radiation encounters the epidermis of the skin, leading to changes of 7-DHC into circulating precursor cholecalciferol. In liver, after hydroxylation to produce 25-hydroxyvitamin D, cholecalciferol changed in the kidney region into active form 1, 25-hydroxyvitamin D (1, 25(OH) 2D). Inborn and acquired immunity, both are supported by Vit D functions along with many physiological systems **(Figure 2)**. Defensins and cathelicidin are antimicrobial peptides whose expression is stimulated by support of Vit. D as it improves the inborn immunity [32]. Certain viruses are well-known to disrupt the integrity of epithelial tight junctions, result in vulnerability to infections and the development of pulmonary edema [33]. Formation of proinflammatory cytokines like interleukin-2 and IFN-Γ are two further ways that vitamin D might affect the acquired immune response [34]. Death rate was found to be higher in northern hemisphere in comparison to southern regions which stated that COVID-19 death rates are not similar in each region [35]. The observation also stated that regions with an increase prevalence of vitamin D insufficiency faced a greater burden of Covid-19 death rate and morbidity [36]. Vitamin D insufficiency can be linked with the increased expression of C-reactive protein (CRP) which is a signature marker for inflammation in sufferers with extreme COVID-19 infection. Vitamin D deficiency is connected to various health problems, like obesity, hypertension, coagulopathy, and living in northern regions with limited sunlight exposure and decreased 7-DHC synthesis, leading to insufficient vitamin D levels [37]. Another reason to clarify the fact that elderly individuals are facing a greater death rate due to COVID-19 is low sunlight contact and low formation of 7-DHC in the skin.

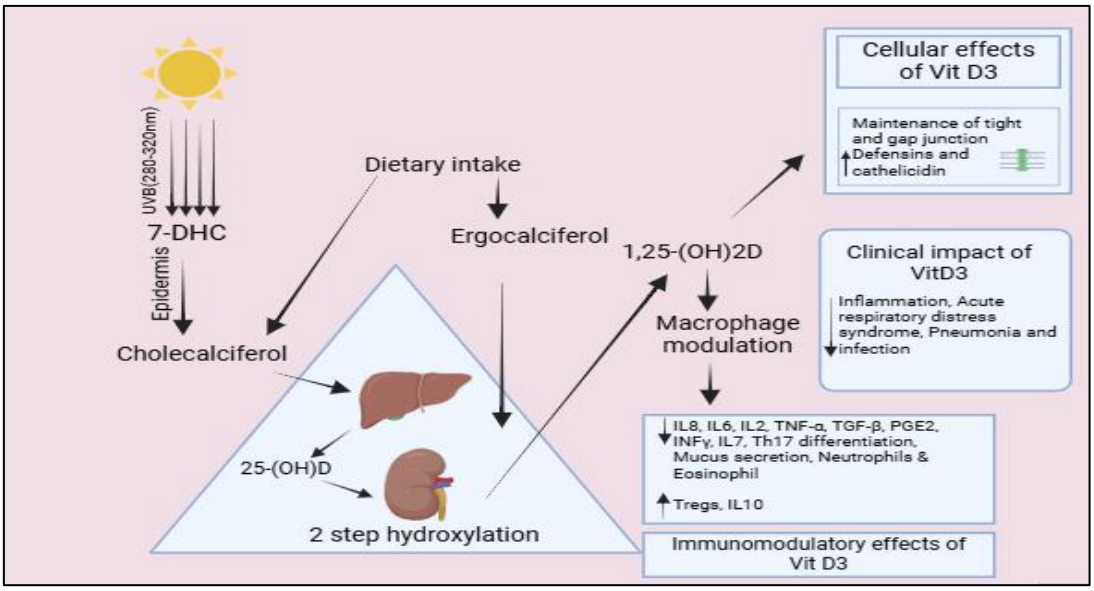

Figure 2: Immunomodulation by Vitamin D**.** 7-DHC- 7-dehydrocholestrol, IFN-Interferon, TNF-Tumor necrosis factor, IL-interleukin, Th- T-helper, PGE2-Prostaglandin E2.

4. Immunomodulation and vitamin C function

Vitamin C, an antioxidant has a role in protecting the biomolecules from oxidation damage by reducing the ROS level [38]. During infection, the body utilizes its mechanism to neutralize the oxidative stress and rapidly utilizes Vitamin C and its concentration is 50-100 times more than of plasma, in normal cases. Elevated levels of oxidants stimulate NF-κB, triggering a signaling cascade that enhances the generation of oxidative molecules and inflammatory intermediates. NF-κB plays a critical role in various inflammatory responses and the pathogenesis of diseases. Therefore, its inhibition may serve as a potential therapeutic strategy against viral infections [39]. In older adults, vitamin C supplementation has been linked to decrease in incidence and severity of pneumonia) [40]. Lower vitamin C was observed in the plasma of patients having acute respiratory infections. It will be interesting, if TNF-α is involved during the entry of SARS-CoV-2 into host cells [41]. Vitamin C intake of 1 g/day can increase peripheral blood mononuclear cells' production of IL-10 [42]. IL-10 and IL-6 work together as a negative feedback mechanism to regulate inflammation. However, more extensive investigation are needed to confirm the mechanism, though vitamin supplements can be helpful for people who are susceptible to COVID-19 infection due to micronutrient deficiencies.

5. Zinc as immunomodulatory nutrient

In both innate and adaptive responses to viral disease, zinc plays an essential role. According to [43], taking zinc supplements can help partially counteract the remodeling of lung tissue and the rise in pro-inflammatory cytokines that occur when zinc levels are low. Zinc deficiency also causes *in vitro* mortality and changes the way the cell barrier functions in lung epithelial tissues by up regulating TNF-α, IFN-Γ, and Fas receptor signaling. During COVID-19, zinc is considered to be significant due to its combination immunomodulatory and antiviral characteristics. Positive effects on NK cells, oxidative burst, CD4+ and $CD8^+$ T, and phagocytosis were observed due to the modulation activity of Zn, and it also serves a vital role in chemotactic functioning and employment of neutrophil granulocytes. The Count of NK and T cells along with the creation of soluble IL-2, and IL-2 receptors were found to increase when supplemented by an additional source of Zn [44]. The therapeutic antiviral effect of Zn was due to its capacity for inference with viral multiplication and protein synthesis [45,46]. Zinc supplementation has been demonstrated to reduce lower respiratory tract infections and other symptoms associated with COVID-19 [47].

CONCLUSIONS

Inborn immune machinery can recognize various coronavirus strains and stimulate different cell death pathways in response to COVID-19 infection. Unregulated activity of inflammatory reactions and cell death can induce severe complications like lung injury, tissue damage, and higher death rates in COVID-19. SARS-CoV-2 exhibits functioning to various protective elements of the host's body like IFN production along with it also enhanced proinflammatory cytokines and chemokines expression. To establish a suitable environment for the growth of healthy cells, cell death mechanisms should be regulated. A great influence comes from interferon expression in support with proinflammatory reactions to infectious viruses. Immunomodulatory properties of some micronutrients, vitamins like C, D, E and zinc are found to be effective in reducing complications of this

disease. Further clinical examinations are necessary to support the ideas of supplementation in protection from this and other viral strains.

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