Covid-19 Pandemic: Viral Infections and Vitamin D

Nurshad Ali*

increasing innate immunity by secretion of antiviral peptides, which improves mucosal defenses. In clinical studies, low levels of serum vitamin D were associated with acute respiratory tract infections including epidemic influenza.

The outbreak and fast spreading of SARS-CoV-2 are a global health threat with an unstable outcome worldwide. Recent data reported the antiviral effects of vitamin D, which can hinder viral replication directly, and also be effective in an anti-inflammatory and immunomodulatory way. It seems that SARS-CoV-2 primarily uses the immune evasion process during infection, which is followed by hyper reaction and cytokine storm in some patients, as a known pathogenic process of acute respiratory disease syndrome (ARDS) development. SARS-CoV-2 uses angiotensin-converting enzyme 2 as the host receptor to enter into alveolar and intestinal epithelial cells. Subsequent dysregulation of the renin-angiotensin system may lead to excess cytokine production resulting in prospective fatal ARDS.

*Considering the differences in the severity and fatality of COVID-19 in the globe, it is important to understand the reasons behind it. Improvement of immunity through better nutrition might be a considerable factor. Each nutrient such as vitamin D shows significant roles in immune function. However, little is known about the role of vitamin D in preventing COVID-19 infection and fatality. This study evaluated the correlation of vitamin D concentrations with COVID-19 cases and deaths per one million of the population in 20 European countries using data from the COVID-19 pandemic data portal for 20 May 20 (most countries after peak). This review also discussed the possible preventing role of vitamin D in acute respiratory tract infections. Furthermore, the available studies that determined the role of vitamin D in COVID-19 severity and mortality have been discussed. PubMed, Google Scholar, Web of Science, Scopus, **Cochrane Central Register** of Controlled Trials, and medRXiv were searched for relevant literature about the role of vitamin D in COVID-19 infections, severity, and mortality.

Vitamin D and mechanisms to decrease viral infections

Some recent reviews demonstrated some pathways by which vitamin D decreases the risk of microbial infections. Vitamin D follows different mechanisms in reducing the risk of viral infection and mortality. To reduce the risk of common cold, vitamin D uses three pathways: physical barrier, cellular natural immunity, and adaptive immunity [4]. A recent review also supported the possible role of vitamin D in decreasing the risk of COVID-19 infections and mortality.

These comprise maintaining of cell junctions, and gap junctions, increasing cellular immunity by decreasing the cytokine storm with influence on interferon γ and tumor necrosis factor α and regulating adaptive immunity through inhibiting T helper cell type 1 responses and stimulating of T cells induction. Vitamin D supplementation was also found to enhance CD4+ T cell count in HIV infection.

One of the major manifestations of severe SARS-CoV-2 infection is lymphopenia. In both the mouse models and in human cell lines, vitamin D exerted activity in lung tissue and played protective effects on experimental interstitial pneumonitis . Several **in vitro** studies demonstrated that vitamin D plays a significant role in local "respiratory homeostasis" either by stimulating the exhibition of antimicrobial peptides or by directly interfering with the replication of respiratory viruses. Vitamin D insufficiency can, therefore, be involved in ARDS and heart failure and these are the manifestations of severely ill COVID-19 subjects [5]. Therefore, vitamin D deficiency promotes the renin-angiotensin system (RAS), which may lead to chronic cardiovascular disease (CVD) and reduced lung function. Although, many studies supported the immunomodulatory characteristics of vitamin D and its significant role in the maintenance of immune homeostasis; well-designed randomized controlled trials are required to elucidate the plausible role of vitamin D in protective immune responses against respiratory microbes and in preventing various types of acute respiratory tract infections.

The relevance of vitamin D to COVID-19

Yet, it is important to fully elucidate the virulence mechanisms of COVID-19, several cellular mechanisms including Papain-like protease (PLpro)-mediated replication, dipeptidyl peptidase-4 receptor (DPP-4/CD26) binding, disruption of M-protein mediated type-1 IFN induction and MDA5 and RIG-I host-recognition evasion have been recognized in the closely-related COVID-MERS virus. Of the above processal, human DPP-4/CD26 has been exhibited to connect with the S1 domain of the COVID-19 spike glycoprotein, suggesting that it could also be a salient virulence factor in Covid-19 infection.

The expression of the DPP-4/CD26 receptor is reduced significantly in vivo upon the correctness of vitamin D insufficiency [6]. There is also an indication that maintaining of vitamin D may reduce some of the unfavorable downstream immunological sequelae thought to extract

***Corresponding author:** Nurshad Ali, Department of Biochemistry and Molecular Biology, Shahjalal University of Science and Technology, Sylhet , Bangladesh, E-mail: nali-bmb@sust.edu

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