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Covid-19 Pandemic: Viral Infections and Vitamin D

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Introduction

Vitamin D is a steroid hormone, produced endogenously with the effect of ultraviolet radiation on the skin or available from exogenous food sources or dietary supplements. Vitamin D insufficiency is a public health problem affecting over a billion people across all life stages worldwide. In the past decade, several studies demonstrated a potential link between vitamin D deficiency and various diseases, including systemic infection. Vitamin D insufficiency affects the immune functions as vitamin D exerts an immunomodulation role, increasing innate immunity by secretion of antiviral peptides, which improves mucosal defenses [1]. 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. A 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 [2]. 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. The 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 2020 (most countries after peak). This review also discussed the possible preventing role of vitamin D in acute respiratory tract infections [3]. 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 Papainlike 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 poorer clinical outcome in Covid-19 infection, such as interleukin 6 elevation, delayed interferon-gamma response, and, a negative prognostic marker in subjects with acutely-ill pneumonia, including those having Covid-19.

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Epidemiological and clinical observations regarding COVID-19

Some clinical and epidemiological studies support to outline the hypothesis regarding COVID-19 and its relationship with vitamin D status. Recent studies indicated that COVID-19 is associated with the increased generation of pro-inflammatory cytokines, C-reactive protein (CRP), ARDS, pneumonia, and heart failure. In China, chronic fatality rates were 6-10% for people with chronic respiratory tract disease, cardiovascular disease, hypertension, and diabetes [7]. In other studies, serum concentrations of 25(OH) D were inversely associated with pro-inflammatory cytokines, IL-6, increased CRP, and increased risk of pneumonia, ARDS, diabetes and heart failure. In randomized control trials, vitamin D supplementation has been shown to reduce the risk of respiratory diseases. A placebo-controlled trial with 5660 subjects showed that vitamin D supplementation significantly reduces the risk of respiratory tract infections. A review included five clinical studies reported that respiratory tract infections were significantly lower in the vitamin D supplementation group than the control group [8]. Another study included 25 randomized controlled trials, with 10,933 participants in total from 14 different countries indicated the beneficial effects of vitamin D supplementation in reducing the risk of at least one acute respiratory tract infection.

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