Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 7 Issue 10 October 2023

Review Article

Relationship between Vitamin D Deficiency and Covid-19

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DOI: 10.31080/ASMS.2023.07.1680

Received: July 17, 2023

Published: September 29, 2023

Abstract

As we all know, a new coronavirus was detected in Wuhan, China in December 2019. Patients infected with 2019-nCoV, later named SARS-Cov-2, were reported to have fever, cough, fatigue, and shortness of breath. The novel coronavirus severe acute respiratory syndrome (SARS-CoV-2) has rapidly progressed from an epidemic to a global pandemic, with new variants rapidly emerging. Because of the highly contagious and deadly nature of the virus, finding effective treatments was a top priority and a global pandemic was declared by the World Health Organization (WHO) on 11 March.

Vitamin D is an immunomodulatory hormone with proven efficacy against various upper respiratory tract infections. Vitamin D may be protective against acute respiratory infections as it modulates the inflammatory cytokine response of respiratory epithelial cells and macrophages, suppressing CS and other manifestations seen in SARS-Cov-2. Therefore, it is recommended as one of the treatment options in SARS-CoV-2 infection. In 20 European countries, low vitamin D levels were observed in cases of COVID-19 with a higher incidence of mortality, increased risk of death during disease severity, need for intensive care and even Covid-19 infection contributing to ARDS or fulminant myocarditis.

In this review, it was aimed to investigate the role of vitamin D in the prevention and treatment of the severe course of COVID-19. While there have been some conflicting results reported, the consensus is that vitamin D has a number of immunomodulatory effects that may be beneficial in the context of COVID-19, and that low levels of vitamin D can cause and potentially contribute to dysfunction of significant antimicrobial effects.

In addition, some studies show that the effects of vitamin D deficiency can be alleviated by supplementation, and vitamin D supplementation is recommended in Covid-19 infection because it is inexpensive, easy to use and safe.

Keywords: Coronavirus; SARS-Co-V-19; Vitamin D; Immune System; COVID-19; Infection; Review

Introduction

Vitamin D is known as a steroid hormone and is produced endogenously in human skin from 7-dehydrocholesterol due to exposure to ultraviolet B (UVB) from sunlight or available from exogenous food sources or dietary supplements [1,2]. Vitamin D insufficiency is a public health problem affecting over a billion people across all life stages worldwide [3]. Several studies demonstrated a potential link between vitamin D deficiency and various diseases, including systemic infection [3-6].

During the covid 19 pandemic, the play of vitamin D in infection prevention and treatment has become very controversial. This is because sufficient blood vitamin D levels play an effective role in immune system functioning, which can help in a satisfactory cellular response and in protecting against the severity of infections caused by microorganisms [3,7]. Vitamin D deficiency (25 (OH)D below 50 nmol/l) has been associated with severe COVID-19 [8], raising discussions about the benefitsof supplementation of this vitamin when treating the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [7]. Some recent reviews hypothesized that vitamin D insufficiency may compromise respiratory immune function, increasing the risk of COVID-19 severity and mortality [9]. There are also some retrospective studies that determined the correlation of vitamin D levels with COVID-19 severity and mortality [10-18].

The SARS-CoV-2 infects pulmonary epithelial cells using the angiotensin converting enzyme-2 (ACE-2) receptor. Besides pulmonary epithelial damage, SARS-CoV-2 also infects macrophages through ACE-2 receptors and activates them. Macrophages, neutrophils, and T cells get activated through sustained elevation of cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) alpha, resulting in type 2 pneumocyte apoptosis, and in some patients a path that leads to acute respiratory distress syndrome (ARDS). The host responses are sometimes amplified by an overwhelming expression of pro-inflammatory cytokines. This 'cytokine storm' is responsible for some of the serious manifestations of COVID-19 such as ARDS. Hypoxemia and bilateral lung infiltration are features reminiscent of severe viral pneumonia that result from endothelial injury, excessive cytokines, and immune overkill [19].

Other factors are also related to the severity of the COVID-19 disease, such as respiratory disorders, heart conditions, obesity, and hypertension [20]. Some of these factors are also intim-ately linked with vitamin D deficiency [20,21]. Thus, the association between COVID-19 and vitamin D may be confounded with chronic diseases [7]. 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. It is that 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 [3].

The aim of this review is to evaluate the association between vitamin D deficiency and COVID-19 infection with literature.

Method of Literature Review

We planned a literature search on PubMed, Google Scholar and Up to Date using the following MeSH terms: Search 1: (''COVİD-19'' or ''novel coronavirus''or ''SARS-CoV-2'' or ''severe acute respiratory syndrome coronavirus 2'') AND (''vitamin D''); Search 2: (''Covid-19'' or ''novel coronavirus'' or ''SARS-CoV-2'' or ''severe acute respiratory syndrome coronavirus 2'') AND (''vitamin D'') AND (''immun system'' or ''immune response'' or ''adaptive immunity'' or ''innate immunity''); Search 3: (''Covid-19'' or ''novel coronavirus'' or ''SARS-CoV-2'' or ''severe acute respiratory syndrome coronavirus 2'') AND (''vitamin D'') AND ''pathogenesis''); Search 4: (''Covid-19'' or ''novel coronavirus'' or ''SARS-CoV-2'' or ''severe acute respiratory syndrome coronavirus 2'') AND (''vitamin D'') AND''Europe''); Search 5: (''Covid-19'' or ''novel coronavirus'' or ''SARS-CoV-2'' or ''severe acute respiratory syndrome coronavirus 2'') AND (''vitamin D treatment'') or (''vitamin D supplementation''); Search 6: (''vitamin D deficiency or insufficiency'') AND (''viral infection''). The MeSH terms were checked and accepted by co-authors.These articles were listed according to the subheadings related to the subject.And then reviewed and eliminated based on titles and abstracts. Later shared amongst the co-authors for full text review.

Finally, the relationship between vitamin D deficiency and Covid-19 infection was discussed and some common recommendations were made.

COVİD-19 and the immune system

As we mentioned above, at the end of December 2019, the COVID-19 epidemic started in Wuhan, China. COVID-19 has affected different people with a wide range of clinical manifestations, from asymptomatic and hospitalization-free recovery to severe acute respiratory syndrome (SARS). Innate and acquired immunity seem to be responsible for defense against the virus and recovery from disease. The innate immune system is necessary as the first

line of defense to detect the virus and then activate the acquired immunity. The innate immune response is mediated by sentinel cells such as monocytes/macrophages and dendritic cells, and receptors known as pattern recognition receptors (PRR). These receptors can recognize various components of the virus leading to intracellular signaling and subsequent synthesis of various cytokines. These cytokines then recruit other immune cells, activate adaptive immune responses and inhibit viral spread. The most common receptors include Toll-like receptors, C-type lectin receptors, and RIG-I-like receptors [22].The response of the immune system is very important in the Covid-19 process. A patient who is positive for Covid-19 may have suppression and decrease in both the general sense and the immune system together with the clinical symptoms. There are cytokine storm, acute respiratory distress syndrome, changes in acute phase reactants and serum biochemistry in Covid-19. Most patients develop a typically 1-week self-limiting viral respiratory illness, culminating in the development of neutralizing antiviral T cell and antibody immunity. IgM-, IgA-, and IgG-type virus-specific antibody levels are important measures to predict population immunity to this disease and whether cross-reactivity with other coronaviruses occurs. Especially in healthcare workers, high viral load during the initial infection and recurrent virus exposure may be an important factor for the severity of the disease. It should also be noted that many aspects of severe patients are unique to COVID-19 and are rarely observed in other respiratory viral infections such as severe lymphopenia and eosinopenia, diffuse pneumonia and lung tissue damage, a cytokine storm leading to acute respiratory distress syndrome. Lymphopenia causes a defect in antiviral and immunomodulatory immunity. At the same time, a cytokine storm begins with the extensive activation of cytokine-secreting cells with mechanisms of innate and adaptive immunity, both of which contribute to a poor prognosis [23]. Innate immunity, our immune system's first line of defense, plays a central role in combating this new virus. We review the evidence that variability in innate immune system components between humans greatly contributes to heterogeneity. A better understanding of the pathophysiological mechanisms observed for cells and soluble mediators involved in innate immunity is a prerequisite for the development of diagnostic markers and therapeutic strategies targeting COVID-19. However, this will also require additional studies addressing the causality of events so far [24].The innate immune system is the first line of defense against pathogens and is significantly involved in the activation of effector adaptive immune responses as well as antigen detection and restriction of pathogens [25].

Major components of innate immunity are physical barriers such as skin and mucosal surfaces; innate immune cells including monocytes, macrophages, dendritic cells, natural killer cells and neutrophils; and several molecules in plasma and cells to fight against invading pathogens. In this system, innate responses to pathogens are nonspecific without memory, but they are immediate and occur within hours of exposure to the microbe. This system recognizes conserved molecular substances produced by microbial pathogens. These microbial structures, often essential for microbial survival, are called pathogen-associated molecular models (PAMPs) [26]. The most important PAMPs are viral PAMPs, and infections derived from these microbes and the resulting symptoms are major concerns of the World Health Organization (WHO) today. In viral infections, the innate immune system uses several types of receptors to recognize viral PAMPs, such as pattern recognition receptors (PRRs) located at different locations in cells and cellular components in blood and tissues [27]. According to recent research, some PRRs play an important role in SARS-CoV-2 detection and restriction [22].

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is an ongoing global health crisis. Immediately after inhalation of SARS-CoV-2 viral particles, alveolar type II epithelial cells harbor and initiate local innate immunity. These particles can infect circulating acrophages, which then present the coronavirus antigens to T cells. Subsequently, the activation and differentiation of various T cells, as well as the uncontrollable release of cytokines (also known as cytokine storms), cause tissue destruction and enhanced immune response [28].

The SARS-CoV-2 virus causes conditions ranging from asymptomatic infection to the deadly coronavirus disease 2019 (COVID-19). An intact immune system can overcome SARS-CoV-2 and other viral infections. Defective innate, mainly interferon I- and III-dependent responses can lead to multi-organ spread of the virus. Adaptive B and T cell responses, including memory, greatly influence the severity and outcome of COVID-19. Regarding B-cell immunity, germinal center formation is delayed or even

absent in the most severe cases. Extrafollicular low-affinity anti-SARS-CoV-2 antibody production will occur instead of specific, high-affinity antibodies. Helper and CD8+ cytotoxic T-cells become hyperactivated and subsequently depleted, giving rise to ineffective viral cells. clarity from the body. Dysregulation of neutrophils and monocytes/macrophages as well as lymphocyte hyperreactivity can lead to potent production of inflammatory mediators, also known as cytokine storm. Eventually, disruption of this complex network of immune cells and mediators leads to a serious, sometimes fatal, COVID-19 or other viral illness [29].

Upon SARS-CoV-2 infection, certain elements of the defense system are either not activated at all or only moderately activated with a significant delay. This causes the orchestration of the immune response to the virus to be disrupted. Also, other components of the immune system become hyperactive, leading to cytokine storm and multiple system inflammatory syndrome (MIS). These events lead to injury to various organs, especially the lungs [30-32].

Covid-19 and Vitamin D

Tom D.Thacher, Family Physician at the Mayo Clinic, writes to the editor of the Mayo Clinic Proceeding: Severe coronavirus disease 2019 (COVID-19) responds to high viral loads of severe acute respiratory syndrome coronavirus-2 (SARSCoV-2). It is the result of an excessive and dysregulated immune response. Severe COVID-19 most commonly results in a clinical resistance and pathophysiology similar to acute respiratory distress syndrome (ARDS). Severe COVID-19 such as ARDS may have multisystemic effects related to the release of proinflammatory cytokines, he noted.

Vitamin D is primarily involved in calcium metabolism, but is also an important immune and inflammatory modulator and can theoretically reduce the severity of COVID-19 infection by reducing the expression of genes involved in the inflammatory pathway. Experimental evidence has shown that cytokine production, macrophage response, airway epithelial repair and permeability, supports the potentially beneficial effects of vitamin D on the renin-angiotensin system and infection risk [33]. Thus, within this contextual framework, it forms the basis for the investigation of the therapeutic effect of vitamin D in COVID-19.

In this issue of Mayo Clinic Proceedings, Angelidi and colleagues report the association between vitamin D status and hospital outcomes in 144 COVID-19 patients in New York and Boston early in the year (February - May 2020) [34]. Using a retrospective cohort design, they found that mortality and the need for invasive mechanical ventilation were increased in patients with lower serum 25 (OH) D values in the 6 months before or during hospital admission for COVID-19. While the study by Angelidi., *et al*. is encouraging, the limitations of the early and available evidence need to be acknowledged before it can be concluded that vitamin D supplementation improves outcomes in COVID-19. To summarize them briefly: First, Low vitamin D status may be a cause or consequence of more severe COVID-19; Second, low serum 25 (OH) D levels may be a marker of disease severity or inflammation and not an indicator of the therapeutic benefit of supplemental vitamin D; Third, in a randomized controlled trial evaluating vitamin D supplementation in critically ill (unrelated to COVID-19) patients, there was no benefit in patients with baseline 25 (OH) D levels below 20 ng/mL [35].Fourth, as observed in monoclonal antibody studies for COVID-19, vitamin D status may have differential implications in the prevention and treatment of severe COVID-19 [36].There are many hypotheses about what might affect the replication of the virus; Vitamin D is thought to have an important role in maintaining immune homeostasis by stimulating the display of antimicrobial peptides or by directly interfering with viral replication [37]. It is known that vitamin D deficiency may lead to elevation of the renin-angiotensin system, leading to ARDS and chronic cardiovascular disease [38]. This may explain why susceptibility to COVID-19 has increased. There has been a decrease in vitamin D levels due to increased working hours, a more sedentary lifestyle, an unbalanced diet, and changes in our lifestyle [39]. Vitamin D deficiency is widely linked to skeletal disorders such as rickets or osteoporosis. It can also be linked to autoimmune diseases and infections, as well as other health conditions such as certain cancers, cardiovascular diseases, inflammatory bowel diseases, psychological disorders.

Previous studies have found that vitamin D has an immunomodulatory role by enhancing innate immunity by secreting antiviral peptides that improve mucosal defenses [3]. Some studies have also linked vitamin D deficiency to respiratory infections, including epidemic flu, and a meta-analysis found low

serum vitamin D levels were associated with a 64% greater risk of contracting community-acquired infections [40]. Amru Ainine., *et al*., aiming to better understand the relationship between vitamin D deficiency and COVID-19 outcomes, to answer the hypotheses whether vitamin D levels are correlated with the outcome or severity of COVID-19 infection, length of stay, mortality, and clinical frailty score and levels, conducted a prospective cohort study of patients who presented with positive viral swabs for comparison (using the Rockwood score). In addition, 40.2% of the patients had a vitamin D level below 25 nmol/L and these values were deficient [41]. According to the National Diet and Nutrition Survey; 24% of men 19-64 years old and 21.7% of women had vitamin D concentrations below 25 nmol/L, which is also 16.9% of men aged 65 and over and 24.1% of women It was also valid for. This suggests that patients presenting with COVID-19 actually have significantly lower levels of vitamin D than the general population [42].

Vitamin D and immune system

Vitamin D (Cholecalciferol) is the active steroid hormone by produced on the skin response to ultraviolet radiation and also taken from exogenous food sources or dietary supplements. Receptors for this hormone are widely distributed in most human tissues. Its primary effect is to support active calcium absorption in the gut [33].

Because of to changes in our lifestyle with increased working hours, more sedentary life and imbalanced diet, there has been a reduction in vitamnin D levels. Vitamin D deficiency is widely linked to skeletal disorders, such as rickets or osteoporosis. It can also be attributed to other health conditions such as certain cancers, cardiovascular disease, inflammatory bowel diseases, psychological disorders as well as autoimmune diseases and infections [42]. Previous studies have found that Vitamin D has an immunomodulatory role, increasing innate immunity by secretion of antiviral peptides, which improves mucosal defences [3].

The inflammatory cells up-regulate Vitamin d receptors (VDR) and promote conversion of vitamin D metabolites to Calci triol. Its role in immunity can be explained in three ways: 'physical barrier, innate immunity, and adaptive immunity'. Vitamin D is required to maintain connections between epithelial cells via E-cadherin. Thus, the first physical barrier encountered by viral or other pathogens is strengthened. Innate immunity includes the production of both proinflammatory and anti-inflammatory cytokines. Vitamin D affects several of the toll-like receptors, which are activated upon recognition of pathogens, release cytokines and make reactive oxygen species (ROS) and antimicrobial peptides. These peptides, such as cathelicidin, work against the pathogens by disturbing their cell membranes and neutralizing endotoxins and hence help reduce the viral load and its virulence. Vitamin D affects T cell maturation with a skewing away from the inflammatory Th17 phenotype. This way it reduces the production of pro-inflammatory cytokines (IL-17, IL-21) and up regulation of IL 10 mediated responses that cause inflammation which injures the lining of the lungs, eventually causing pneumonia. These cytokines also include tumor necrosis factor α (TNF- α) and interferon γ (INF- γ) which are released by the type 1 T- Helper (Th1) cells. Vitamin D modulates adaptive immunity by promoting type 2 T helper (Th2) cells to produce cytokines. These cytokines then suppress Th1 cells. Vitamin D promotes induction of the T regulatory cells which help to inhibit inflammatory processes. Vitamin D also plays a role in regulation of immune responses mediated by macrophages and dendritic cells (DC) that are the first line of host defence. Vitamin D modulates the macrophages' response, preventing them from releasing too many inflammatory cytokine and chemokine such as IL-1, IL-6, IL-8, IL-12 and TNFα by monocytes and increases the expression of anti-inflammatory cytokines. Therefore antiviral effects of vitamin D include direct interfering with viral replication, and acting as an immune-modulatory and anti-inflammatory agent. The immune-modulatory role of vitamin D in respiratory infections is due to expression of the enzyme 1α-hydroxylase by the airway epithelium, DC and lymphocytes which is essential for the activation of vitamin D within the lungs [43]. Several studies suggested that vitamin D plays a significant role in local ''respiratory homeostasis'' by stimulating the exhibition of antimicrobial peptides and by directly interfering with the replication of respiratory viruses [3,37]. Despite all the literature information, little is known about the effect of vitamin D deficiency on the severity of Covid-19 infection or mortality [48].

Vitamin D dose recommendations in Covid-19 infection are not clear.The daily or weekly doses were highly variable, depending on the age of the patient and the severity of the infection.

Effect of vitamin D supplementation on Covid-19 infection

Covid-19 has been accepted a global pandemic by the World Health Organization (WHO). But recommendation is limited about the potential protective factors of this infection yet. There is no clear evidence that vitamin D supplementation prevents the severity and mortality of Covid-19.There are some randomized trials in evaluating the role of vitamin D in Covid-19 infections and severities [3] and there are many studies that vitamin D supplementation is beneficial in viral diseases.It is reported that very good results are obtained both on disease severity and on earlier recovery [43,44]. Vitamin D supplementation has been shown as safe and effective in preventing acute respiratory tract infections [3,45]. They also added that subjects who had severe vitamin D deficiency experienced the maximum benefits from the supplementation. The authors also noticed that the protective role of vitamin D was high in subjects with a baseline serum 25 (OH)D levels <25 nmol/L compared to those with serum 25 (OH)D concentrations >25 nmol/L. D supplementation also found to increase gene expression related to antioxidation (glutathione reductase modifier subunit) [3]. The increased production of glutathione spares the use of vitamin C, which has potential antimicrobial activities [46,47], and has been suggested to prevent and treat COVID-19 infection [48]. Recommended daily dose is 600-4000 IU in most guidelines and a serum concentration of above 20 ng/mL is considered as sufficient [43,49].

Vitamin D supplementation has been shown to have protective effects against respiratory tract infections in the randomized trials and meta-analysis ; therefore, people who are at higher risk of vitamin D deficiency during this global pandemic should consider taking vitamin D supplements to maintain the circulating 25 (OH) D in the optimal levels (75-125 nmol/L)[3].

Conclusions

It is seen in our review that vitamin D plays a role not only in controlling skeletal homeostasis, but also in many non-skeletal tissues and organs, and its role in modifying and reducing the inflammatory cytokine response of respiratory epithelial cells and macrophages to various pathogens. It is emerging that vitamin D, which can directly reduce viral replication, may be a supportive factor on antiviral effects, immunomodulation and anti-inflammation, and these effects can be used as an aid in combating immune evade mechanisms caused by SARS-CoV-2.

At the same time, vitamin D has a protective role. Specifically, it has been shown in pneumonia, cytokine hyperproduction, and ARDS, and we therefore have evidence that vitamin D may act as a potential immune modulator in COVID-19 infection due to its immunomodulatory function supported by substantial clinical evidence. Vitamin D3 supplements are inexpensive and readily available.

Finally, given the wide variability in vitamin D requirements as a function of disease state, our results support the concept that it may be useful to develop specific guidelines for desired vitamin D levels and doses for each of the conditions known to affect vitamin D metabolism and in what conditions.

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