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Role of Vitamin D in Risk Reduction of COVID-19: A Narrative Review

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Abstract

The world is in the midst of the COVID-19 pandemic. In addition to quarantine, public health interventions which can reduce the risk of infection and death are urgently required. This article discusses the roles of vitamin D in reducing the risk of COVID-19, and how vitamin D supplementation may be a useful risk reduction measure. Vitamin D can reduce the risk of infections through a variety of mechanisms: induction of cathelicidins and defensins that can lower the rate of viral replication and decrease the concentrations of pro-inflammatory cytokines, which are responsible for induction of inflammation, injuring lining of lungs and contributing to developing pneumonia. Evidence supporting the role of vitamin D in reducing the incidence of COVID-19 includes a) winter outbreak; b) a timeframe when concentrations of 25-hydroxyvitamin D (25(OH)D) are lowest; c) a small number of cases in the southern hemisphere toward the end of summer; d) a vitamin D deficiency found to lead to acute respiratory distress syndrome (ARDS); e) and a rise in case-fatality rates with increasing age and comorbid chronic diseases, both of which are associated with lower concentrations of 25(OH)D. It is recommended that people at risk of COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly increase 25(OH)D concentrations, followed by 5,000 IU/d to reduce the risk of infection. Higher doses of vitamin D3 may be useful for treating people who are infected with COVID-19. To test these guidelines, randomized controlled trials and comprehensive population studies should be performed.

Keywords
- COVID-19
- acute respiratory tract infection
- vitamin D
- 25-hydroxyvitamin D
- SARS CoV-2

Introduction

The world is in the grasp of the novel coronavirus 2019 (COVID-19) pandemic. This infection began in late 2019 in Wuhan, China, which was originally called 2019-nCoV and renamed COVID-19 by the World Health Organization on February 11, 2020. Previous CoV epidemics include severe acute respiratory syndrome (SARS)-CoV, initiated in China in 2002, and Middle East respiratory syndrome (MERS)-CoV, first recorded in 2012. All these epidemics started with infection between animals and humans. The primary cause of death is usually due to extreme atypical pneumonia observed in patients.[1]

Vitamin D is a fat-soluble-vitamin which is distinct from others in that a main source comes from the conversion of its precursor under the skin by ultraviolet (UV)-light-induced action. Dietary sources include dietary supplements and

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fortified foods. Studies have demonstrated a high prevalence of the worldwide vitamin D deficiency. Deficiency of vitamin D may influence the immune system, as it plays a pivotal role in immunomodulation[2] and improves innate immunity by upregulating antimicrobial peptide expression and secretion, which enhances mucosal defences.[3] In addition, recent meta-analyses have documented a protective effect of supplementation with vitamin D on respiratory tract infections.[4-7]

25-hydroxyvitamin D (25(OH)D) promotes the production of antimicrobial peptides in response to both viral and bacterial stimuli and suggests a possible mechanism for the regulation of vitamin D-inducible defense against respiratory pathogens. Vitamin D metabolites have also been documented to induce other innate mechanisms for antimicrobial effectors, including autophagy induction and synthesis of reactive nitrogen intermediates and reactive oxygen intermediates. Such epidemiological and *in vitro* findings prompted multiple randomized controlled trials to determine whether supplementation with vitamin D could reduce the risk of COVID-19.[7] To date, we could identify five meta-analyses which have performed integrating data from up to 15 primary studies, of which only two studies indicate statistically significant protective effects[5,6] and three studies indicate no statistically significant effects.[8-10] All but one of those meta-analysis of data recorded statistically significant heterogeneity impact between primary trials.

We searched PubMed and Google scholar for publications regarding COVID-19 with respect to epidemiology, clinical symptoms, immune function, vitamin D and (25(OH)D), to conduct this narrative review.

Epidemiology

COVID-19 is caused by a new beta-coronavirus, SARS CoV-2; its epicenter was located in Wuhan, China, and has spread worldwide. As of June30, 2020, there have been 10,185,374 confirmed cases of COVID-19, including 503,862 deaths.[11] This greatly exceeds average deaths caused by both SARS and MERS. People older than 60 years of age with hypertension, diabetes, chronic obstructive pulmonary disorder (COPD), and cardiovascular, cerebrovascular, liver, kidney and gastrointestinal (GI) disorders are more vulnerable to SARS-CoV-2 infection and experience higher mortality when COVID-19 develops. Because of limited number of patients, the involvement of malignant conditions is under debate. In general, 19 percent of patients with COVID-19 produce acute respiratory distress syndrome (ARDS) (PaO2/FiO2 < 300 mm Hg) within 24 to 48 hours after symptom onset.[12]

Pathology

COVID-19's pathogenic features mimic those of SARS and MERS. Puncture lung biopsies show the presence of pneumonia, edema, protein exudate with globules, focal hyperplasia of alveolar epithelial cells associated with patchy inflammatory infiltrates, and multinucleated giant cells in the early stages of the infection. Apart from hemorrhage and certain areas of interstitial fibrosis, diffuse alveolar damage (DAD) is found at the later stages. Fibrotic clots and gelatinous mucus in the small airways and disseminated intravascular coagulation are also present. The lungs are the most damaged organs according to clinical findings, followed by moderate heart, liver, kidneys and brain injury.[12]

Clinical Presentation

The most common symptoms that are observed in general population are fever (98%), cough (76%), dyspnea (55%), and myalgias or fatigue (up to 44%). These symptoms are also common in older adults; a study on 21 critically ill patients with SARS-CoV-2 infection, with a mean age of 70 years, found that the most common presenting symptoms were shortness of breath (76%), fever (52%), and cough (48%). Up to 86% of older adults had comorbidities and the most severe were chronic kidney disease (48%), congestive heart failure (43%), COPD (33%), and diabetes (33%). Most older adults have some type of organ damage caused by SARS-CoV-2, including ARDS (71%), acute kidney injury (20%), cardiac injury (33%), liver dysfunction (15%), and 67% of vasopressor support needed for care. Chest CT imaging of patients with SARS-CoV-2 in all age groups showed ground glass opacities (GGO) (87%), mixed GGO and consolidation (65%), vascular enlargement (72%), and traction bronchiectasis (53%). Among these were peripheral distribution (87.1%), bilateral lung involvement (82.2%), lower lung predominance (54.5%), and multifocality (54.5%). In contrast, chest X-ray results in older adults revealed bilateral reticular-nodular opacities (58%), GGO (48%), pleural effusions (~33%), peribronchial thickening (~25%), and focal consolidations (20%).[13]

Vitamin D and Immune Function

In older adults, vitamin D is necessary to help preserve bone and muscle strength, plays a key role in the prevention and treatment of falls and fractures, and helps absorb calcium from the gut. Recent research has also emphasized that vitamin D can play a major role within the immune system. With increasing age, the immune response shifts to a more proinflammatory state that can lead to chronic low-level inflammation and gradual accumulation of damage, with eventual progression to chronic illness. Proinflammatory condition associated with this age is referred to as "inflammation-aging." It may be especially relevant in times of metabolic stress such as infection wherein the body is already preset to a higher degree of inflammation and may compromise the requisite immune response to the infection. Research and experiments have shown that vitamin D can modify the response of the immune system by affecting the synthesis and distribution of the immune molecules known as cytokines. Vitamin D has been shown to help signal the increased anti-inflammatory molecules output and decrease proinflammatory molecules output. This change in immune response in theory may have some significant advantage in "cytokine storm" cases—a large release of proinflammation observed in those

infected with COVID, which can ARDS. Importantly, in a large cross-sectional clinical trial (n = 18,883), the risk of respiratory infection increased with lower blood vitamin D levels, and the effect was even stronger in those with underlying lung conditions.[14] Many case-control studies have also documented associations between low vitamin D and increased risk of infection, while in a trial that supplemented patients at risk of respiratory infection with 1,000 IU of vitamin D a day for a year, the use of supplements decreased both symptoms and antibiotic use.[15,16] Recently, a large meta-analysis (data analysis of a large collection of previous studies) of 10,933 people from 25 trials conducted in 15 countries investigated whether taking a vitamin D supplement helped to prevent colds, flu, and chest infections (acute respiratory tract infections).[7] Vitamin D had a significant protective effect when it was given daily or weekly to people with lowest vitamin D levels: the risk of having at least one acute respiratory tract infection was reduced from 60% to 32% in these people. Overall, the chance of developing at least one acute respiratory tract infection decreased with vitamin D supplements. The authors of the study have concluded that taking a vitamin D supplement is safe and can help protect against acute respiratory tract infections, particularly when baseline levels are low. A recent study (2019) conducted on 21,000 participants from eight trials found that people with low levels of blood vitamin D had a 64% increased risk of pneumonia acquired by the population. Maintaining an appropriate vitamin D level in adults is also beneficial in the prevention of acute respiratory tract infections and thus could be helpful in the COVID-19 pandemic.[17] The relative association between the incidence of COVID-19 infection, acute respiratory tract infection and vitamin D supplementation also needs to be evaluated.

Vitamin D and Mechanisms to Reduce Microbial Infections

The general metabolism of vitamin D and its behaviour is well-known. In the skin, vitamin D3 is formed by the action of UVB radiation hitting 7-dehydrocholesterol in the skin, accompanied by a thermal response. The general metabolism of vitamin D and its activity is well-known. In the skin, vitamin D3 is formed by the action of UVB radiation hitting 7-dehydrocholesterol in the skin, accompanied by a thermal reaction. The vitamin D3 or oral vitamin D is transformed into 25(OH)D in the liver and then into 1,25(OH)2D (calcitriol) hormonal metabolite in the kidneys or other organs as needed. Most of the impact of vitamin D results from the entry of calcitriol into the nuclear vitamin D receptor, a DNA-binding protein that interacts directly with regulatory sequences near target genes and recruits active chromatin complexes that are genetically and epigenetically involved in modifying transcription performance. A well-known function of calcitriol is to help in managing the serum calcium concentrations, which it does in a parathyroid hormone (PTH) feedback loop that has many important roles in the body itself. Various studies have analyzed that how vitamin D decreases the risk of viral infection. Vitamin D has several pathways by which risk of microbial infection and death is reduced. A recent review of the role of vitamin D in reducing the common cold risk divided these mechanisms into three categories: physical barrier, natural cellular immunity, and adaptive immunity. Vitamin D helps preserve close junctions, junctions of openings and junctions of adherents (e.g., by e-cadherin). Some articles addressed how viruses damage the integrity of the junction through virus contamination and other microorganisms. Vitamin D improves cellular innate immunity, in part by inducing 1,25-dihdroxyvitamin D and defensins into antimicrobial peptides, like human cathelicidin, LL-37. Cathelicidins exhibit strong antimicrobial activity against a variety of microbes including Gram-positive and Gram-negative bacteria, enveloped and nonenveloped viruses, and fungi. Those host-derived peptides destroy the invading pathogens by destroying their cell membranes and neutralize the endotoxin's biological activity. Partially, vitamin D also improves cellular immunity by raising the innate immune system-induced cytokine storm. The innate immune system generates both proinflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients.

Concentrations of serum 25(OH)D continue to decrease with age, which may be a possible reason behind COVID-19, because case-fatality levels increased with age.[1] A cross-sectional study has reported significant crude relationship between vitamin D levels and the number COVID-19 cases, especially the mortality caused by the infection. Also, authors have reported that the ageing population is most vulnerable to COVID-19, and they are the ones who had the most deficit Vitamin D levels.[18] Reasons for lower vitamin D levels include less time spent in the sun, and reduced production of vitamin D due to lower levels of 7-dehydrocholesterol in the skin. Additionally, certain prescription medications by stimulating the pregnane-X receptor decrease serum 25(OH)D concentrations. These include antiepileptics, antineoplastics, antibiotics, anti-inflammatory agents, antihypertensives, antiretrovirals, endocrine medicines, and certain herbal medicines. Pharmaceutical drug use typically increases with age.[1]

Supplementation with vitamin D also improves the expression of antioxidation-related genes (glutathione reductase and subunit controller glutamate—cysteine ligase). The increased production of glutathione spares the use of ascorbic acid (vitamin C), which has antimicrobial activities, and COVID-19 has been proposed for prevention and treatment.[1] There are articles that have suggested that the use of vitamin D supplements can improve the clinical status and prognosis in COVID-19 patients.[1,18,19]

Vitamin D Deficiency and Chronic Illnesses

Chronic disease patients are at a higher risk of pandemic danger, because COVID-19 is best combated by a powerful immune system. But chronic diseases such as cardiovascular diseases, HIV, diabetes, kidney disease, etc. are immunosuppressive, making patients more vulnerable to infections with difficulties in management.[20] A cross-sectional study

Table 1 Details of ongoing trials

Sr.no.	Study title	Trial registration no.
1.	COVID-19 and vitamin D supplementation: a multicenter randomized controlled trial of high dose versus standard dose vitamin D3 in high-risk COVID-19 patients (CoVitTrial)	NCT04344041
2.	COVID-19 prophylaxis with hydroxychloroquine, vitamin D, and zinc supplementation in Danish nursing home residents–a randomized controlled trial	2020-001363-85
3.	Prevention and treatment with calcifediol of Coronavirus COVID-19-induced acute respiratory syndrome (SARS)	2020-001717-20
4.	Vitamin D on prevention and treatment of COVID-19	NCT04334005
5.	The LEAD COVID-19 Trial: low-risk, early aspirin and vitamin D to reduce COVID-19 hospitalizations	NCT04363840
6.	Impact of zinc and vitamin D3 supplementation on the survival of aged patients infected with COVID-19	NCT04351490
7.	A study of hydroxychloroquine, vitamin C, vitamin D, and zinc for the prevention of COVID-19 infection	NCT04335084
8.	Vitamin D and COVID-19 management	NCT04385940
9.	Vitamin D testing and treatment for COVID 19	NCT04407286

done on 520 participants to study the association between vitamin D deficiency and hypertension showed the higher prevalence of vitamin D deficiency in people with hypertension than in people without hypertension.[21] Similarly, a cross-sectional study done on 2953 patients of hypertension, among which 362 were having resistant hypertension found a statistically significant association between vitamin D deficiency and resistant hypertension.[22] Another study conducted on type-2 diabetes mellitus patients showed positive association between vitamin D deficiency and type-2 diabetes patients.[23] A retrospective study, demonstrated significant associations between small vessel disease (SVD) and 25(OH)D deficiency. The authors also found combined presence of hypertension and vitamin D deficiency increased the probability of developing SVD.[24] A cross-sectional study on 57 patients diagnosed with coronary artery disease and 62 age- and sex-matched controls elucidated that low levels of 25 (OH) D are associated with prevalent coronary artery disease independent of cardiovascular risk factors.[25] Previous studies have shown the link between vitamin D deficiency and chronic illnesses like diabetes, hypertension, cardiovascular disease, cancer, immune system diseases, etc. This may be one of the reasons why people suffering from chronic illnesses are more vulnerable to COVID-19 infection.[26-29]

Related Ongoing Research

Many clinical trials are going on to explore the impact of vitamin D on COVID-19 (►**Table 1**).

Conclusion

It seems possible that vitamin D supplementation (without overdosing) may contribute to reducing the seriousness of illness induced by COVID-19, particularly in settings where hypovitaminosis D is prevalent. This may become even more important with the lack of exposure to sunlight as a result of lockdown measures to track the spread of COVID-19. To enforce this effectively would require recommendations from government around the world, and further clinical research is urgently required to explore potential impacts of vitamin D deficiency on COVID-19 outcomes.

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Conflict of Interest
None declared.

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