Abstract: Vitamin D is an important nutrient in the body that plays a vital role in immune system function. Several epidemiologic studies have shown that low vitamin D levels are found in a large percentage of COVID-19 patients with acute respiratory failure and that vitamin D levels may predict mortality in COVID-19 infection. Based on these findings, vitamin D supplementation may be an effective approach to preventing and/or treating COVID-19. Potential underlying mechanisms and clinical trial data evaluating the impact of supplementation in humans are described below.

Keywords: COVID-19; vitamin D; supplements; mechanism of action; immune function

Introduction

In recent years, COVID-19 has been the cause of serious illness and death. COVID-19 is caused by a virus known as severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2. Signs and symptoms of COVID-19 are far reaching and can impact a multitude of body systems. Most commonly, patients experience cough, fatigue, headache, fever, chest pain, and sore throat but complications such as shortness of breath, pneumonia, heart problems, acute kidney injury, organ failure, and progressive respiratory failure can also occur. Additionally, some individuals experience long-term effects following COVID-19 infection. This condition, termed long COVID, can include a wide range of ongoing health problems, which last weeks, months, or longer. Due to the broad range of symptoms, complications, and lack of treatment in the early phases of the pandemic, many individuals looked to supplements with hopes to prevent and/or treat COVID-19. Over the counter supplement use by Americans increased 29% during the pandemic. Of those who started supplements during this time, 65% reported a desire to enhance immunity or protect themselves from COVID-19. A number of supplements have been proposed for the prevention or treatment of COVID-19. Among the most popular are zinc, vitamin C, vitamin D, elderberry, echinacea, and melatonin. Vitamin D will be described here.

Vitamin D is an important nutrient in the body that helps maintain bone health and plays a vital role in immune system function, muscle function, and brain cell activity. Vitamin D is found naturally in some foods and added to others. It can also be produced endogenously in the skin upon exposure to ultraviolet (UV) radiation. The amount of Vitamin D produced or consumed can vary based on location and lifestyle; therefore, supplementation may be needed to ensure optimal

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health and prevent deficiency. Vitamin D deficiency, defined as a serum 25-hydroxyvitamin D (25(OH)D) concentration <30 ng/mL, occurs in approximately 1 billion people worldwide, and has been associated with a number of conditions, including an increased risk of respiratory infections. Populations at greatest risk of Vitamin D deficiency include older adults, patients with obesity, diabetes, and those with heart, liver, or kidney disease. Many individuals at greatest risk of vitamin D deficiency are also at increased risk of severe illness and death from COVID-19. Several epidemiologic studies have found that low vitamin D levels are found in a large percentage of COVID-19 patients with acute respiratory failure and that vitamin D levels may predict mortality in COVID-19 infection. Based on these findings, vitamin D supplementation presents a plausible approach to the prevention and treatment of COVID-19. Potential underlying mechanisms and clinical trial data evaluating the impact of supplementation in humans are described below.

**Potential Underlying Mechanisms**

Vitamin D is a fat-soluble vitamin synthesized in the skin via UV radiation or acquired through diet and/or supplementation. UV radiation converts 7-dehydrocholesterol in the epidermis to cholecalciferol. In the liver, cholecalciferol hydroxylates to form 25-hydroxyvitamin D₃, which is then converted into calcitriol, the active metabolite of vitamin D in the kidneys. Most of the physiological effects of vitamin D in the body are related to calcitriol, mediated through the vitamin D receptor (VDR). Vitamin D receptors are expressed by cells in the brain, heart, skin, gonads, prostate, and breast, as well as numerous types of immune cells including macrophages, monocytes, and dendritic cells. Studies show that vitamin D plays a role in the regulation of both the innate and adaptive immune system. In the innate immune system, vitamin D may function as an anti-inflammatory on macrophages, decreasing inflammatory stimuli. Vitamin D may also have an anti-inflammatory effect on monocytes, reducing oxygen radical formation, and minimizing damage by pathogens. In the adaptive immune system, vitamin D plays a role in decreasing antigen presentation, modulating T-lymphocyte response, or inducing cell death of activated B-lymphocytes.

As mentioned previously, adequate levels of vitamin D have been linked to a decrease in respiratory tract infections as well as a decrease in severe COVID-19 cases. This association is thought to be mediated, in part, by a vitamin D-induced increase in cathelicidin. Cathelicidin is a peptide produced by neutrophils and mucosal cells in the respiratory tract with direct antimicrobial effects on bacteria, viruses, and fungi. It also plays a protective role in epithelial/alveolar permeability. In cases of severe COVID-19, high levels of circulating cytokines and chemokines released from the infected lungs (cytokine storm), may be responsible for acute respiratory distress, multiple organ failure, and death. Vitamin D is thought to suppress this immune system overactivity, thereby reducing the risk of damage to vital organs.

**Clinical Trial Data**

The number of interventional studies evaluating the impact of vitamin D on COVID-19 is growing rapidly. As of October 28, 2022, 41 clinical trials have been completed and 23 are underway, according to ClinicalTrials.gov. The most recent systematic review and meta-analysis of interventional trials was published in May 2022. The study included nine randomized controlled trials (RCTs) and fourteen non-randomized studies of intervention (NRISs) with 5,870,189 total subjects. Studies were divided into three categories based on the outcomes assessed: primary, secondary, and tertiary prevention. The primary prevention analysis evaluated the association between vitamin D supplementation and risk of incident COVID-19. Vitamin D supplementation did not significantly reduce the risk of testing positive for COVID-19, regardless of regimen (bolus vs non-bolus). Only two of the studies included provided baseline 25(OH)D levels; thus, no subgroup analysis evaluating in impact of baseline vitamin D status was performed. The secondary prevention analysis, which assessed the association between vitamin D supplementation and COVID-19 related outcomes in mild (ambulatory) COVID-19 cases, was unable to aggregate data. Only one study evaluated the risk of hospitalization and while two studies reported on severity of symptoms, the methods used to measure symptoms differed, and therefore, the data could not be pooled. The tertiary prevention analysis, which assessed the impact of vitamin D supplementation in patients hospitalized with COVID-19, found a significant reduction in ICU admission, need for mechanical ventilation, and COVID-19 mortality in those patients supplemented with vitamin D. Protective effects of vitamin D appear stronger when non-bolus regimens were used and in patients with baseline vitamin D status ≥25 nmol/L.

Since the completion of the aforementioned meta-analysis, a number of interventional studies evaluating the impact of vitamin D supplementation on COVID-19 outcomes have been published.
All but two of the studies\textsuperscript{23,24} found benefits to vitamin D supplementation in patients hospitalized with COVID-19. Of note, bolus dosing was used in both studies that found no benefit, and in the Mariani et al study, baseline 25(OH)\textsubscript{Vit}D levels >30 ng/mL. Varying doses and dosing regimens were explored in those studies with favorable effects of vitamin D supplementation. Two studies compared high- vs low-dose vitamin D supplementation in hospitalized patients.\textsuperscript{18,21} The first compared alfalcaldiol 1mcg/day orally, to cholecalciferol 200 000 IU intramuscularly once.\textsuperscript{18} The second study compared oral cholecalciferol 2000 iu/day to cholecalciferol 10000 iu/day.\textsuperscript{21} Both studies found significant improvements in outcomes with the higher dose.

\textbf{Conclusion}

Clinical trial data suggests that vitamin D supplementation, when used in addition to best care available, is associated with reduced ICU admission, need for mechanical ventilation, and death in patients hospitalized with COVID-19. Further investigation is needed to determine the best dose and regimen, as well as underlying mechanisms of action in the acute setting.

Insufficient evidence exists to determine whether vitamin D supplementation reduces the risk of acquiring COVID-19, particularly in patients with vitamin D deficiency. Likewise, additional studies are needed to determine whether vitamin D supplementation improves outcomes in ambulatory patients with mild-moderate COVID-19. Based on the prevalence of vitamin D deficiency, the low risk of adverse effects associated with supplementation, and the stronger protective benefits observed from supplementation in hospitalized patients with baseline vitamin D levels ≥25 nmol/L, it may be worthwhile for patients desiring protection from severe COVID-19 to consider a daily vitamin D supplement. Appropriate dosing depends on the baseline vitamin D status. For patients with vitamin D deficiency, eight weekly doses of oral ergocalciferol 50 000 IU, or 5000 IU of oral cholecalciferol daily have been recommended.\textsuperscript{7,25} Once a target vitamin D level is reached, 800–3000 IU of cholecalciferol per day have been recommended to maintain adequate levels.\textsuperscript{7,25}

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