Vitamin D's Association with COVID-19 Prevention and Treatment

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Abstract

The SARS-CoV-2 has created havoc worldwide for more than 3 years and remains problematic. Currently, more than 275 million people have been infected and 2.2 million killed. With the well-established and high coverage of COVID-19 vaccines, severe symptoms are becoming less common, yet mild symptoms still trouble many. Therefore, a short-term cheap relief treatment that civilians worldwide can use for such mild symptoms is a necessity. Vitamin D has become a possible option as statistics and research have shown a strong correlation between vitamin D level and infection rate and severity of COVID-19. This paper will discuss the relationship between vitamin D and COVID-19 through 1) Function of vitamin D, 2) Population affected by vitamin D deficiency, 3) Vitamin D deficiency aggravating symptoms of COVID-19, 4) A statistical analysis of 4131 patients on their COVID-19 test results and vitamin D level, and finally 5) A discussion on vitamin D deficiency leading to an increase in COVID-19 infection and severity rate.

Introduction

The first case of the COVID-19 disease appeared in Wuhan, China in December 2019, while the virus that causes this disease, the *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), was first identified in January of the following year. This disease led to a massive outbreak, first in China, then around the world, and was declared by the World Health Organization as a global pandemic in March 2020. Up to this date, the COVID-19 disease has caused the death of 1.73 million people while infecting over 78.6 million people worldwide, making SARS-CoV-2 one of the most dangerous and harmful coronaviruses (World). Fortunately, with the recent widespread coverage of SARS-Cov-2 vaccines, the pandemic is under control and the number of severe symptom patients has significantly decreased. However, many are still troubled by the milder symptoms of COVID-19. Despite its nature in society becoming like the flu, there is a lack of drugs to treat COVID-19 like how oseltamivir is treating seasonal flu. Paxlovoid and Remdesivir drugs are also possible solutions, but they are costly and mainly meant for patients with severe

COVID-19 symptoms. Therefore, it is crucial to develop a treatment method that is affordable and accessible to the public for mild COVID-19 symptoms (FDA, 2020).

Pathology of COVID-19

COVID-19 is caused by a coronavirus named SARS-CoV-2 and causes a variety of respiratory tract infections. This virus is composed of four main structural proteins, which are the nucleocapsid, the membrane, the envelope, and the spikes. The nucleocapsid is where the genetic material of the virus is enclosed, which is a 30-kilobase (kb) RNA. The outer envelope of the virus is made of envelope proteins which are important for replication and maturing of the virus, and membrane proteins which are important for the integrity of the virus. The last structural protein, spike protein, is responsible for passage into the cell. In addition, 16 nonstructural proteins are responsible for the replication of the virus RNA inside the host cell. SARS-CoV-2 can invade host cells through the spike proteins lining its envelope. These spike proteins are first activated by the TMPRSS2 and then attach to the angiotensin-converting enzyme 2 (ACE2) which most cells have on their surface. After the spike protein is attached to the ACE2, the SARS-CoV-2 is allowed into the host cell for further invasion and replication. SARS-CoV-2 can spread to anyone in all age groups and genders in the form of airborne particles. Of all these patients, older adults with age over sixty-five, people with chronic disease, people with a weakened immune system, and obese individuals with a BMI (Body Mass Index) of 40 or higher are at high risk of developing severe symptoms. Most of these people are prone to vitamin D deficiency as their exposure to the sun is less than an average adult. This shows a strong connection between vitamin D deficiency and developing severe symptoms after being infected with SARS-CoV-2 (Government of Canada, 2020). This review research paper reviews the function of vitamin D and vitamin D's role in COVID-19 treatment.

Vitamin D And Its Functions

Currently, there are two main types of Vitamin D that humans consume. First, vitamin D3, also known as cholecalciferol, is produced by the UVB radiation hitting the 7-dehydrocholesterol in the skin, while the second Vitamin, vitamin D2, also known as ergocalciferol, is largely artificial. These two types of vitamin D are very similar to each other as they can both be added to food and consumed in the diet, and they serve the exact purpose. However, the structures of ergocalciferol and cholecalciferol are different from each other.

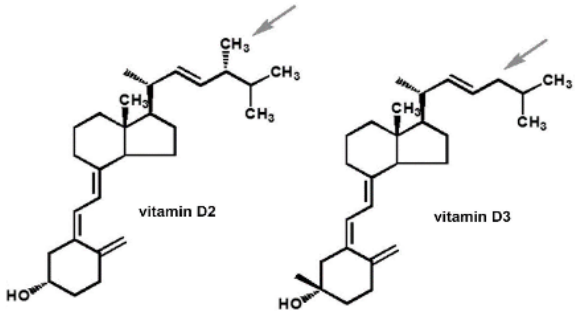

FIGURE 1. Diagram of a molecule of vitamin D2 and a molecule of vitamin D3 This diagram shows the molecule of vitamin D2 and vitamin D3, respectively. As seen on the diagram, the difference between the two molecules is that vitamin D2 has an additional methyl group (CH3) located at the site of the arrow (Jorge et al, 2018).

Vitamin D2 and vitamin D3 have to be biologically activated by going through two hydroxylation reactions in the liver before they can be used by the body. The first reaction is arbitrated by 25-hydroxylase (CYP2R1) and produces 25-hydroxyvitamin D (25 OH-D) which is only used to diagnose. The 25OH-D then goes into the second hydroxylation reaction in the kidney and produces the final functional calcitriol (1,25-dihydroxyvitamin D). The level of vitamin D in an individual's body can be easily found by measuring the concentration of 25 OH-D concentration in the blood plasma (Harvard Medical Publishing, 2021). Calcitriol is used in the human body to regulate calcium and phosphate levels, but they have also been found to take up a role in the immunologic function. Vitamin D has been found to inhibit the production and differentiation of B cells; it inhibits the production of T helper cells that produce inflammatory cytokines and promotes the production of T regulatory cells which serve the role of suppressing and regulating other immune cells in the body; Vitamin D also suppress monocytes from producing proinflammatory cytokines such as IL-1, IL-6, IL-8, and IL-12. All these discoveries suggest that vitamin D can reduce the production of inflammatory cytokines and increase the production of anti-inflammatory cytokines like IL-10, which would decrease the chance of a cytokine storm (Aranow, 2011). Vitamin D has been found to provide antiviral and antibacterial protection against many diseases that cause respiratory tract infections, such as tuberculosis, Epstein-Barr virus, and influenza, through physical barriers and improving immune systems. Severe respiratory tract infections will increase the level of CYP27B1 in the respiratory epithelial cells, which would convert into calcitriol through the hydroxylation reaction. This increase in calcitriol will induce the secretion of cathelicidin. Cathelicidin is a family of polypeptides in the lysosomes of macrophages and polymorphonuclear leukocytes; it serves a crucial role in the fight against bacteria and viruses. The reason is that cathelicidin has

been found to engage and enhance white blood cells (Neutrophils, T cells, and monocytes) in the infected area. As stated in the previous paragraph, both vitamin D2 and D3 can produce calcitriol through the two hydroxylation reactions in the liver and in the kidney, which means that the amount of cathelicidin will also increase as the level of vitamin D in the body increases. This discovery suggests that vitamin D may be involved in the fight against ARDS (Acute respiratory disease syndrome) and heart failure (Xu et al, 2020).

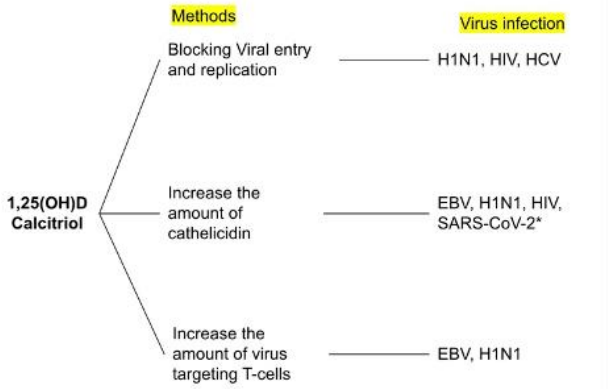

FIGURE 2. 1, 25(OH)2D3 flowchart. This diagram shows the different methods of protection that the 1, 25(OH)2D3 offers to the body when encountering different viral infections (EBV, H1N1, HIV, HCV). Some of the antiviral measures include blocking viral entry and replication, Increasing the amount of cathelicidin, and increasing the amount of virus-targeting T-Cells.

Vitamin D Deficiency in Relation with COVID-19

Vitamin D deficiency is very common in current society, covering almost half of the American population (41.6% of the vitamin D prevalence rate in the US). A study from Meltzer et al. shows that persons living in higher latitudes in the winter, nursing home residents, health care workers, and people with darker skin are more prone to vitamin D deficiency (Meltzer et al, 2020). Another epidemiological research done on the level of 25OH-D has shown that a significant number of healthy adults are found to be vitamin D deficient at the end of winter (Panagiotou et al, 2020). This study result shows that even healthy adults are at large risk of vitamin D deficiency, let alone the four types of patients mentioned in the last paragraph of the introduction. Most of these survey populations have one thing in common: The lack of exposure to sunlight.

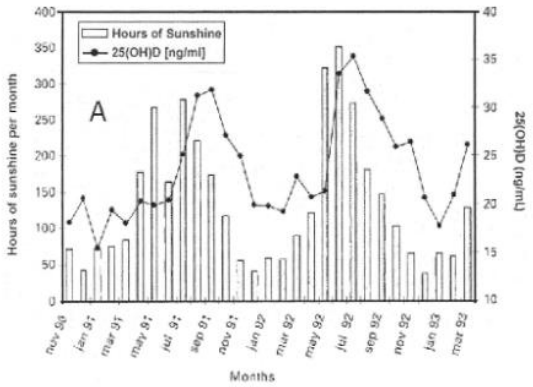

FIGURE 3. Hours of Sunlight Versus 25OH-D level. The relationship between the concentration of 25OH-D and hours of sunlight over two years and three months (Holick et al, 2008).

Clinical data and research have shown that vitamin D can defend against respiratory tissue inflammation. SARS-CoV-2 has been found to target the patient's immune system during infection, which will lead to hyperinflammation (Cytokine storm). The cytokine storm occurrence in the lung will often lead to acute respiratory disease syndrome and other complications due to its ability to cripple the body's immune system. On the other hand, vitamin D can increase the secretion of cathelicidin, which can enhance and encourage the immune system. A recent study was done by doctors from Tyne Hospitals in Newcastle, Northeast London on the concentration of 25 OH-D in 134 patients (mainly of Caucasian origin) who are infected by the SARS-CoV-2. The results showed that 81% percent of the patients in the ICU (Intensive Care Unit) have vitamin D deficiency (patient is considered vitamin D deficient if their 25 OH-D concentration is smaller than 50 nmol/L), while only 60.9 percent of patients from the general ward have vitamin D deficiency. This data shows that vitamin D deficiency will worsen the symptoms of COVID-19. Therefore, it can be assumed that vitamin D, an antiviral and antibacterial substance to H1N1, Mycobacterium tuberculosis, HIV, etc. can reduce the severity of SARS-CoV-2 infection by limiting the ARDS and heart failures-the two main severe symptoms of COVID-19 (Xu et al, 2020). A study has been conducted by Meltzer et al. on the relationship between COVID-19 test results and vitamin D levels. The researchers have retrieved the data of 4314 patients from the University of Chicago Medicine (UCM) electronic health record during the period of March 3rd to April 10, 2020. A patient is considered vitamin D deficient if his most recent 25(OH)D3 level within one year was lower than 20ng/mL; A patient is considered vitamin D sufficient if his most recent 25(OH)D3 level within one year was higher than 20ng/mL. Other characteristics are also considered in the study, including age, gender, sex, race, ethnicity, employment status, median date since last vitamin D check, comorbidity,

BMI (body mass index), and most recent vitamin D treatment (Meltzer et al, 2020). Of the 4314 patients studied over thirty-eight days, 3815 did not have their vitamin D level measured in the past year and 10 did not have a complete set of data to all the characteristics. Of the 489 patients included in the results, 124 patients (25%) had vitamin D deficiency during the past year before the study was conducted, 78 patients (15%) had uncertain deficiency, and 287 patients (59%) were sufficient. 71 patients (15%) of the 489 total tested positive for COVID-19. Of the 71 patients, 32 are vitamin D deficient, while 39 are vitamin D sufficient. Since fewer people are vitamin D deficient than sufficient, patients who have vitamin D deficiency have a 21.6% chance of contracting the SARS-CoV-2, while this number is much lower at 12.2% for patients who are vitamin D sufficient. In conclusion, vitamin D-deficient patients have 1.77 times more risk of testing positive for COVID-19 than those who are sufficient (Meltzer et al, 2020).

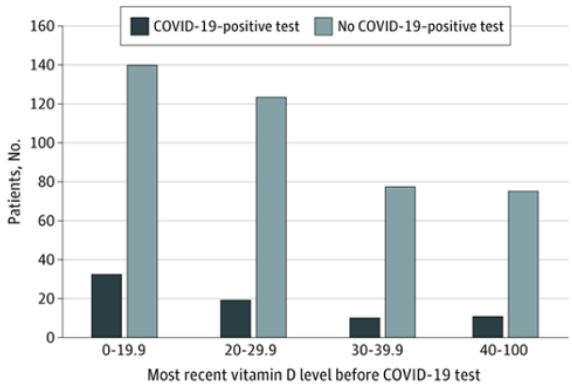

FIGURE 4: COVID-19 test versus vitamin D level. A double bar graph showing the number of COVID-19 positive tests on the level of vitamin D between one year and 14 days of the COVID-19 test. The result shows that people with low vitamin D concentrations or with vitamin D deficiency are much more likely to contract SARS-CoV-2 (Meltzer et al, 2020).

Discussion and Conclusion

From the study conducted above, the multivariable analysis shows that people are more likely to contract SARS-CoV-2 if they are vitamin deficient. However, it is crucial to identify that other variables could be affecting the result in the multivariable analysis, which means that Vitamin D deficiency is not the sole factor in increasing the probability of contracting SARS-CoV-2. It is only a statistical correlation. Studies have shown that vitamin D has a statistically significant connection with COVID-19 disease. Vitamin D deficiency can worsen the symptoms of COVID-19 and the probability of contracting the disease. The final product of vitamin D2 and D3, calcitriol, has been found to have the ability to increase the secretion of cathelicidin, a polypeptide that can

strengthen the immune system. There is a correlation that suggests vitamin D deficiency will increase the chance of contracting SARS-CoV-2. However, this correlation is based on an analysis of statistics and data on COVID-19 infections. Detailed clinical research has to be hosted in order to confirm the correlation (Meltzer et al, 2020). Though SARS-Cov-2 vaccines have prevented 95% of hospitalizations and 91% of severe infections, the percentage of symptomatic and asymptomatic infection prevention remained at 76% and 44% respectively. Such results demonstrated that people with vaccines are still partially vulnerable to milder symptoms (Yang et al, 2023). Therefore, I recommend that each individual should be taking a considerable amount of vitamin D through food, vitamin D supplements[1] , and increasing exposure to sunlight to reduce the effect of the virus on the body. However, one crucial aspect to take into consideration is that intake of vitamin D supplements of vitamin D replete individuals does not result in improved health; in fact, an overtake (>4,000 IU) could result in kidney damage, irregular heart rhythms, vomiting, constipation, and other health implications (Bouillon et al., 2021; Mayo Clinic, 2023). Therefore, please seek professional medical care before taking vitamin D supplements to avoid overtake. Regardless of method, it is crucial to be vitamin D sufficient to decrease the chance of infecting SARS-CoV-2 or improve/minimize the symptoms of SARS-CoV-2. Most importantly, increasing the daily vitamin D intake is a cheap, easy method that people across various nations and classes can use in the fight against COVID-19. To conclude, it is recommended that Vitamin D is used as a supplement to reduce symptomatic infection, limit SARS-Cov-2 severity, and speed up mild symptoms' recovery.

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