Archives of Razi Institute, Vol. 76, No. 5 (2021) 1545-1549

DOI: 10.22092/ari.2021.356070.1769

Short Communication

Importance of Vitamin D3 in COVID-19 Patients

Nasser, F. A[1 *], Younis, L. A[1], Abidreda, K. H[1], Alyasiri, I[1]

1. College of Pharmacy, Jabir Ibn Hayyan Medical University, Najaf, Iraq

Received 2 September 2021; Accepted 2 October 2021
Corresponding Author: fadhil.abass@jmu.edu.iq

Abstract

Outbreaks of a respiratory ailment in Wuhan, China, known as the Corona virus Disease-2019 (COVID-19), began in late December 2019. Since then, several pieces of advice have been made to boost the immune system to fight more efficiently with this infection. Previously published studies showed that vitamin D3 (Vit D3) level was low in COVID-19 patients. One of the most important factors in COVID-19 severity would be the inflammatory response. It is well documented that the inflammatory cytokine storm increases the severity of COVID-19. Cytokine storm results from dysregulation of the innate immune system with an outpouring of proinflammatory cytokines and chemokines, leading to abnormal activation of the adaptive immune pathway. It has been approved that Vit D3 has immunomodulatory functions and plays an anti-inflammatory role, particularly in viral infections. Therefore, the current study was designed to investigate the possible role of Vit D3 deficiency in the COVID-19 patients' innate immunity. This study included 180 participants who were divided into group (A) consisted of 60 COVID-19 positive patients with normal level of Vit D3, group (B) consisted of 60 COVID-19 positive patients with Vit D3 deficiency, and group (C) consisted of 60 COVID-19 positive patients that had received Vit D3 therapy. The results showed that the rate of hospitalization in the group (B) (41.3%) was significantly increased, compared to group (A) (12.5%). In this regard, Vit D3 therapy led to a significant increase in the level of Vit D3, and the patients who received Vit D3 were recovered from hospital 5 days on average sooner than those in the group (B). Therefore, the consumption of Vit D3 as a daily supplement would be a reasonable suggestion for these days of the COVID-19 pandemic to increase the power of immunity of the body.

Keywords: Coronavirus (COVID-19), Health, Risks, Vitamin D3

1. Introduction

In December 2019, the World Health Organization cataloged Corona virus Disease 2019 (COVID-19) as "a novel corona virus-induced pneumonia" after the virus spread swiftly following its first appearance in Wuhan, China. The International Viral Classification Commission designated the new corona virus as the cause of severe acute respiratory syndrome on the same day (SARS-CoV-2). Recent history has observed the occurrence of severe respiratory sickness associated with a corona virus, such as COVID-19, multiple times. COVID-19, SARS, and Middle East Respiratory Syndrome (MERS) are all corona virus-based respiratory illnesses that have been discovered in the last two decades. It is known that corona viruses are viruses that are surrounded by a capsid and have a single-stranded RNA genome (26e32 kb) (1). It has also been shown that patients with COVID-19 infection have normal or decreased leukocyte counts, radiographic signs, and symptoms, such as pneumonia, as well as clinical signs and symptoms, including fever, nonproductive cough, dyspnea, myalgia, and fatigue (2). This resembles the signs and symptoms associated with SARS-CoV and MERS-CoV infections. Although there is no exact knowledge on how the pathophysiology of COVID-19 works, useful insights

can still be obtained from SARS-CoV-2 infections by looking at how similar MERS-CoV is to SARS-CoV; accordingly, this information can be used to better detect COVID-19. A previously published study conducted by De Wit, Van Doremalen (2) has shown that corona virus S protein, a critical factor in virus entrance, infects host cells. SARS-envelope CoV's spike glycoprotein has a strong cellular receptor, which is ACE2, and it is the reason why the virus is able to spread. SARS-CoV and MERS-CoV infection stop the IFN-I pathway in infected mice, which protects them against viral infection; however, infection prevents IFN-I (IFN-a and IFN-b) from activating (3). Human health studies have established that human body levels of Vit D3, calcium levels, and bone metabolism are connected to the immune system (4). Vit D3levels affect how the adaptive immune system, such as T-cell activation and dendritic cell maturation, works. Vit D3 is also responsible for the skin's natural antibacterial defense and helps in various other ways as well (5). It has already been mentioned that how the interaction among Vit D3, calcium levels, and bone metabolism are linked. Experts are currently trying to understand the association between Vit D3 levels and the immune system's ability to fight off illness.

A study found that Vit D3 insufficiency was linked to higher rates of illness and death and was particularly evident in older people (6).Cytokine storm results from dysregulation of the innate immune system with an outpouring of proinflammatory cytokines and chemokines, leading to some degree of abnormal activation of the adaptive immune system. It has been approved that Vit D3 has immunomodulatory functions and plays an anti-inflammatory role, particularly in viral infections.

The anti-viral immunity could be induced by Vit D3. It is of prime importance nowadays considering the global COVID-19 pandemic. The anti-bacterial responses, such as the stimulation of cathelicidin and β-defensin 2 are also observed during an immune response to the viral attack, thereby preventing the virus entry into host cells and its subsequent multiplication (7). Vitamin D3 is also responsible for inducing autophagy as a result of both anti-bacterial and anti-viral activity. This is also one of the ways for host cells of getting rid of viral load. Autophagy leads to the encapsulation of viral particles, degradation in lysosomes, and creating a hostile anti-viral schematic event via antigen presentation and adaptive anti-viral responses (8-10).In the past, antimicrobial peptides (AMPs) were used as natural antibiotics to eliminate bacteria; however, today they have further applications. AMPs build chemical barriers on the skin's surface. It is believed that AMPs activate and coordinate the innate and adaptive immune systems, which are responsible for providing our bodies with immunity (8-10).

There are two classes of powerful antimicrobial proteins in the body, including cathelicidins, which are produced in the skin tissue, and beta-defensins. When the subject is human cathelicidin, it is often referred to as one of its peptide variants (LL-37) or the name attributed to its precursor protein (hCAP18) (8-10). Cathelicidin, an antimicrobial peptide and endogenous inflammatory mediator, might be working together to produce certain proinflammatory effectors via various routes. Cathelicidin peptides are cell motility-inducing chemokine secretory peptides. They also play a role in stimulating innate immune responses alongside their direct antibacterial activity (8-10).

Neutrophils and neutrophil-like cells are the cells of the immune system which can generate cathelicidins, as well as skin cells. Several published studies have revealed that Vit D3 directly interacts with cathelicidin in keratinocytes (11, 12). The results of the previously published studies showed that oral Vit D3 supplementation boosts cathelicidin production and antimicrobial activity in keratinocytes when conductedin vitro, which confirms earlier findings of the same experiment performed in the laboratory (11, 12).

Therefore, the current study aimed to investigate the possible role of Vit D3 deficiency in the COVID-19 patients' innate immunity.

2. Materials and Methods

2.1. Study Design

This study included 180 participants who were divided into three groups of (A) (control) consisted of 60 COVID-19 positive patients with the normal level of Vit D3, (B) consisted of 60 patients with Vit D3 deficiency (Vit D3 deficiency was defined as a 25(OH) D level of <12 ng/mL [30 nmol/L]), and (C) (Vit D3) consisted of 60 patients that had received Vit D3 therapy at a dose of 5000 IU of Vit D3 (Devit-3 ampoule, Deva Company). It was found that patients had been infected with COVID-19 using computed tomography scans and Polymerase Chain Reaction(PCR) estimations.

2.2. Sample Preparation

Samples were gathered following the agreed-upon timeline between April 2019 and April 2020. The tests were performed in the Najaf Health Department's Public Health Laboratory, Najaf, Iraq. At the beginning of the experiment, blood samples were taken, and Vit D3 level was measured. The Cobas 6000 analyzer (Roche Diagnostics, Germany) was used to measure 25 (OH) D levels. The technique behind the Cobas 600 analyzer was chemiluminescent immunoassay. After the initiation of the experiment, the blood samples were taken at 24-h intervals.

2.3. Exclusion Criteria

Diabetes mellitus (chronic), renal problems, and liver abnormalities are all examples of medical conditions that prevent someone from participating in the study.

2.4. Statistical Analyses

The statistical analysis was performed in SPSS software, and the findings were calculated using the mean and standard deviation (Mean±SD). To determine statistical significance, the Student's t-test was employed, and a p-value less than 0.05 was considered statistically significant.

3. Results

The results of the primary screening in the current study showed no significant differences between groups A andB regarding age and body mass index. However, there was a significantly lower level of Vit D3 levels in patients with COVID-19 ($P<0.05$) as shown in table 1. In group B, the level of Vit D3 was 15.92±9.83, compared to the healthy group (30.61±11.15). Group A consisted of people with the normal level of Vit D3 and infected with COVID-19, while group B showed severe deficiency in case of Vit D3 level. Results showed that the rate of hospitalization in group B (41.3%) was significantly increased, compared togroup A (12.5%).

Table 1. Parameters in subjects in groups A (control) and B

Parameters	Group A (control) (n=60)	Group B (n=60)	P-value
Age	35.48±14.34	39.24±17.1	0.3
Body mass index (kg/m^2)	24.5±1.49	24.3±2.34	0.67
25OH Vit D3 Total (ng/mL)	30.61±11.15	15.92±9.83	0.000

In addition, there was a significantly higher level of Vit D3 levels in patients with COVID-19($P<0.05$) after treatment with Vit D3 supplement (5000 i.u) for four weeks, compared to group B (without treatment with Vit D3 supplement) as shown in table 2. In this regard, Vit D3 therapy led to a significant increase in the level of Vit D3, and the patients who received Vit D3 were recovered from hospital 5 days on average sooner than those in group B.

Table 2. Levels of 25OH Vit D3 Total (ng/mL) in subjects in groups B (without Vit D3 supplement) and C (treated with Vit D3 supplement)

Parameters	Group B (n=60)	Group C (n=60)	P-value
25OH Vit D3 Total (ng/mL)	15.92±9.83	32.3±3.5	0.000

In several studies previously published by different research teams, 25 (OH) D concentrations in the blood samples of COVID-19 patients were found to be low. This low level of 25(OH) D was associated with the severity of the COVID-19 (11, 12). The results of a

study conducted by Meltzer, Best (12) showed that 489 patients, who had PCR tests with documented 25 (OH) D levels measured in the last one year and were positive for COVID-19, were 12.2% in the group with sufficient Vit D3 levels and 21.6% in the group with Vit D3 deficiency. In another study conducted by Kaufman, Niles (11) involving 191,779 patients with COVID-19, people with 30-34 ng/mL of VitD3 level had a 54% lower risk of COVID-19, compared to people with 25(OH) D<20 ng/mL. Similar to the mentioned results, the 25(OH) D levels of COVID-19 hospitalized patients were found to be low in our study.

A single oral dose of 200,000 IU VitD3 was given to 240 hospitalized patients with COVID-19 who were moderate to severely ill. There was no difference between the vitamin D3 group (n=120) and the placebo group (n=120) regarding the length of stay and in-hospital mortality rate (11). In another study conducted by Han, Jones (13), mechanically ventilated adult ICU patients showed that administering high doses of oral VitD3 did not differ between ICU length of stay and hospital mortality. These findings are not consistent with the findings of the current study.

Adequate intake of Vit D3through diet or sun exposure can compensate for the daily need for Vit D3. The COVID-19 patients in group C in the current study were patients with malnutrition without adequate exposure to sunlight. The proper function of the immune system depends on good nutrition status, and optimal nutrition is important in establishing an appropriate immune response. Therefore, nutritional deficiencies and insufficient sunlight exposure can weaken the immune system, leading to susceptibility to all infections. Therefore, as a sign of malnutrition, it can be said that patients with malnutrition may have a more severe infection as Vit D3 levels reflect the nutritional level of the person rather than the direct effect of low Vit D3 on the severe course of COVID-19 infection and high mortality rate. Patients who received more Vit D3 during treatment experienced recovery faster than those who did not get additional Vit D3.Vit D3 ingestion increases glutathione reductase synthesis, which is a strong antioxidant (14). It is well approved that any prescriptions which can increase antioxidant capacity in the living organisms subsequently lead to a significant increase in the capacity of the immune system.

Authors' Contribution

Study concept and design: F. A. N.
Acquisition of data: F. A. N.
Analysis and interpretation of data: L. A. Y.
Drafting of the manuscript: K. H. A.
Critical revision of the manuscript for important intellectual content: F. A. N. and L. A. Y.
Statistical analysis: I. A.
Administrative, technical, and material support: F. A. N. and L. A. Y.

Ethics

The study protocol was approved by the Local Ethics Committee at the Najaf Health Department's Public Health Laboratory, Najaf, Iraq. Written informed consent was obtained from patients (when possible) or from their authorized representatives.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016;24(6):490-502.
2. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523-34.
3. Channappanavar R, Fehr AR, Zheng J, Wohlford-Lenane C, Abrahante JE, Mack M, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J Clin Investig. 2019;129(9):3625-39.
4. Bikle DD. What is new in vitamin D: 2006–2007. Curr Opin Rheumatol. 2007;19(4):383-8.

5. Yim S, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1, 25-dihydroxyvitamin D3. J Cyst Fibros. 2007;6(6):403-10.
6. Moan J, Porojnicu AC, Dahlback A, Setlow RB. Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure. PNA S. 2008;105(2):668-73.
7. Reichrath J. Vitamin D and the skin: an ancient friend, revisited. Experimental dermatology. 2007;16(7):618-25.
8. Maghbooli Z, Sahraian MA, Ebrahimi M, Pazoki M, Kafan S, Tabriz HM, et al. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PloS One. 2020;15(9):e0239799.
9. Merzon E, Tworowski D, Gorohovski A, Vinker S, Golan Cohen A, Green I, et al. Low plasma 25 (OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS J. 2020;287(17):3693-702.
10. Munshi R, Hussein MH, Toraih EA, Elshazli RM, Jardak C, Sultana N, et al. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. J Med Virol. 2021;93(2):733-40.
11. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PloS One. 2020;15(9):e0239252.
12. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open. 2020;3(9):e2019722-e.
13. Han JE, Jones JL, Tangpricha V, Brown MA, Hao L, Hebbar G, et al. High dose vitamin D administration in ventilated intensive care unit patients: A pilot double blind randomized controlled trial. J Clin Transl Endocrinol. 2016;4:59-65.
14. Lei G-S, Zhang C, Cheng B-H, Lee C-H. Mechanisms of action of vitamin D as supplemental therapy for Pneumocystis pneumonia. Antimicrob Agents Chemother. 2017;61(10):e01226-17.