REVIEW ARTICLE

# The Role of Vitamin D in Prevention, Treatment, and Health Recovery of COVID-19 Patients (Literature Review)

Demsa Simbolon

Nutrition Department, Poltekkes Kemenkes Bengkulu Indonesia

demsa_ui03@yahoo.com

## ABSTRACT

One non-pharmacological treatment for COVID-19 involves the consumption of vitamin D, which has been shown to positively impact the body's immune system. It can lower the risk of infection and contribute to both specific and non-specific immunity, including enhancing physical barriers, natural cellular immunity, and the adaptive immune system. However, further evidence is necessary to elucidate vitamin D's exact role in preventing, treating, and aiding recovery in individuals with COVID-19. This study aims to explore the role of vitamin D in preventing, treating severity, and promoting the recovery of individuals with COVID-19. Conducted through a literature review utilizing a summarized methodology, the study examines the findings regarding vitamin D's impact on the health outcomes of COVID-19 patients. The analysis of 11 relevant articles suggests that vitamin D does indeed play a crucial role in preventing, treating, and aiding recovery in individuals with COVID-19. It appears to reduce the severity of respiratory infections, strengthen the immune systems of COVID-19 patients, and potentially expedite recovery, as evidenced by shorter hospitalization periods among those supplemented with vitamin D.

Keywords: Covid-19, Prevention, Treatment, Recovery, Vitamin D.

## Introduction

Corona Virus Disease 2019 (COVID-19) is a disease that originated in Wuhan, China, and attacks the respiratory system in patients infected with the virus. The World Health Organization (WHO) announced SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) as a new coronavirus included in the β-coronavirus. COVID-19 is a large family of viruses that can cause infectious diseases in animals or humans. In humans, this virus can cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and severe acute Respiratory Syndrome (SARS). The COVID-19 virus can cause various symptoms in sufferers[1]. The main symptoms of COVID-19 disease are cough, fever, dry cough, and shortness of breath. Some COVID-19 sufferers experience flu-like symptoms, throat pain and diarrhea. Other symptoms that are not often found in patients are the production of sputum (28%), headache (8%), coughing up blood 5% and diarrhea. Clinical symptoms involving the digestive tract include abdominal pain, diarrhea, and experiencing nausea and vomiting[2]. The COVID-19 virus can be transmitted from an infected person to others around him through coughing or sneezing splashes. People who touch contaminated objects and then touch their eyes, nose, and mouth can contract the disease. The virus that causes COVID-19 can survive in the air for about an hour. On plastic and stainless steel surfaces, the virus can survive up to 72 hours[1].

On March 11, 2020, WHO called COVID-19 a global pandemic. COVID-19 cases have spread across different continents. In May 2020, 115 countries affected by the COVID-19 virus were confirmed with a total of 3.5 million cases with a total of 247,652 deaths[3]. The spread of the new SARS-CoV-2 virus and COVID-19 Disease continues to increase at a rapid rate. According to WHO data, 521,920,560 cases and 6,274,323 deaths have been confirmed[4]. As of November 24, 2021, the Government of the Republic of Indonesia has reported 4,254,443 people confirmed positive for COVID-19 and there have been 143,766 deaths (CFR: 3.4%) related to COVID-19 reported and 4,102,700 patients have recovered from the disease[5]. The death rate due to COVID-19 in Indonesia (7.2%) is higher than other countries in the Asian region such as Malaysia (1.7%), Thailand (1.8%), South Korea (2.3%), Singapore (0.09%), India (3.3%), Bangladesh (2.2%), and Sri Lanka (1.1%)[3].

Various efforts are made for the prevention, treatment, and recovery of people with COVID-19 disease, including by consuming Vitamin D. Vitamin D has been proven to have a good and positive effect on the immune system in the body. There are several proven mechanisms that vitamin D can reduce the risk of infection through the induction of cathelicidin and defensin which can reduce the rate of viral replication and reduce the concentration of proinflammatory cytokines. Vitamin D plays a role in both specific and non-specific immunity including playing a role in the physical barrier, natural cellular immunity, and adaptive immune system[6]. Consumption of vitamin D supplementation with higher levels than the symptoms of COVID-19 patients is classified as mild or moderate. Conversely, the lower the consumption of vitamin D, the symptoms of

COVID-19 patients are classified as severe[7]. Vitamin D deficiency occurs in people with COVID-19 caused by reduced frequency or duration of sun exposure and inadequate nutrient intake. COVID-19 patients with severe clinical manifestations due to vitamin D deficiency have a higher tendency to lead to death. Vitamin D deficiency can aggravate the clinical conditions experienced by COVID-19 patients[8].

Vitamin D has an important role as a non-pharmacological treatment for COVID-19 because it can affect immune function and is beneficial against other viral infections such as influenza virus (seasonal flu), rhinovirus (fluvial), and HIV[9]. Vitamin D plays a role in the recovery of COVID-19 patients, in a study conducted by Ling et al in 2020, some patients were given a Vitamin D3 booster of around 280,000 IU within 7 weeks, patients infected with the COVID-19 virus showed a reduced risk of death in COVID-19 patients[10]. Vitamin D deficiency is proven to potentially increase the risk of severe respiratory infections, some researchers suggest vitamin D supplements for the prevention and treatment of COVID-19 complications, especially acute respiratory diseases, but empirical evidence is still needed as an evidence base to prove this, it is necessary to conduct a literature review to know and explain how the role of Vitamin D in the prevention, treatment, and recovery of health of COVID-19 sufferers.

## Materials and methods

This study employs a literature review methodology to gather data and sources pertaining to a specific issue, sourced from various outlets such as journals, books, the internet, and other libraries. The process commences with topic selection and goal determination, followed by the design of literature search strategies, identification of relevant articles, critical appraisal of literature, data extraction, data synthesis, and the composition of literature review results. Employing a narrative approach, this literature review aims to explore research findings concerning the impact of Vitamin D on the prevention, treatment, and recovery of individuals with COVID-19. Literature search was conducted utilizing the Publish or Perish (POP) application, accessing the PUBMED, Google Scholar, and Scopus databases. The keywords employed in the search included "Vitamin D" and "COVID-19." Criteria for selecting literature candidates for review encompassed works published between 2019 and 2022, accessible in full-text PDF format, scholarly in nature (peer-reviewed journals), and available in both English and Indonesian languages (Table 1).

Table 1. Research Inclusion and Inclusion Criteria

| Criterion | Inclusion | Exclusion |
|---|---|---|
| Period | The maximum journal publishing period is 3 years (2019-2022) | More than 3 years |
| Language | Indonesian and English | Not Indonesian and English |
| Subject | COVID-19 patients | Patients not with a diagnosis of Covid-19 |
| Types of Literature | Original research articles, literature reviews published in Journals, Proceedings, and research reports (full text, Open access) | Not open access/full text, only abstract and title |
| Keywords | Vitamin D, Covid-19 | Beyond Vitamin D, Covid-19 |

The results of data extraction are presented in tabular form. The literature search process is presented in the Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA) diagram. Through the stages of identification (1244 literature), screening (1077 literature), eligibility (60 literature), and those who meet the inclusion criteria as many as 11 literature (figure 1). Synthesis in the Literature Review study using the summarize method or summarizing eligible literature is then analyzed qualitatively.
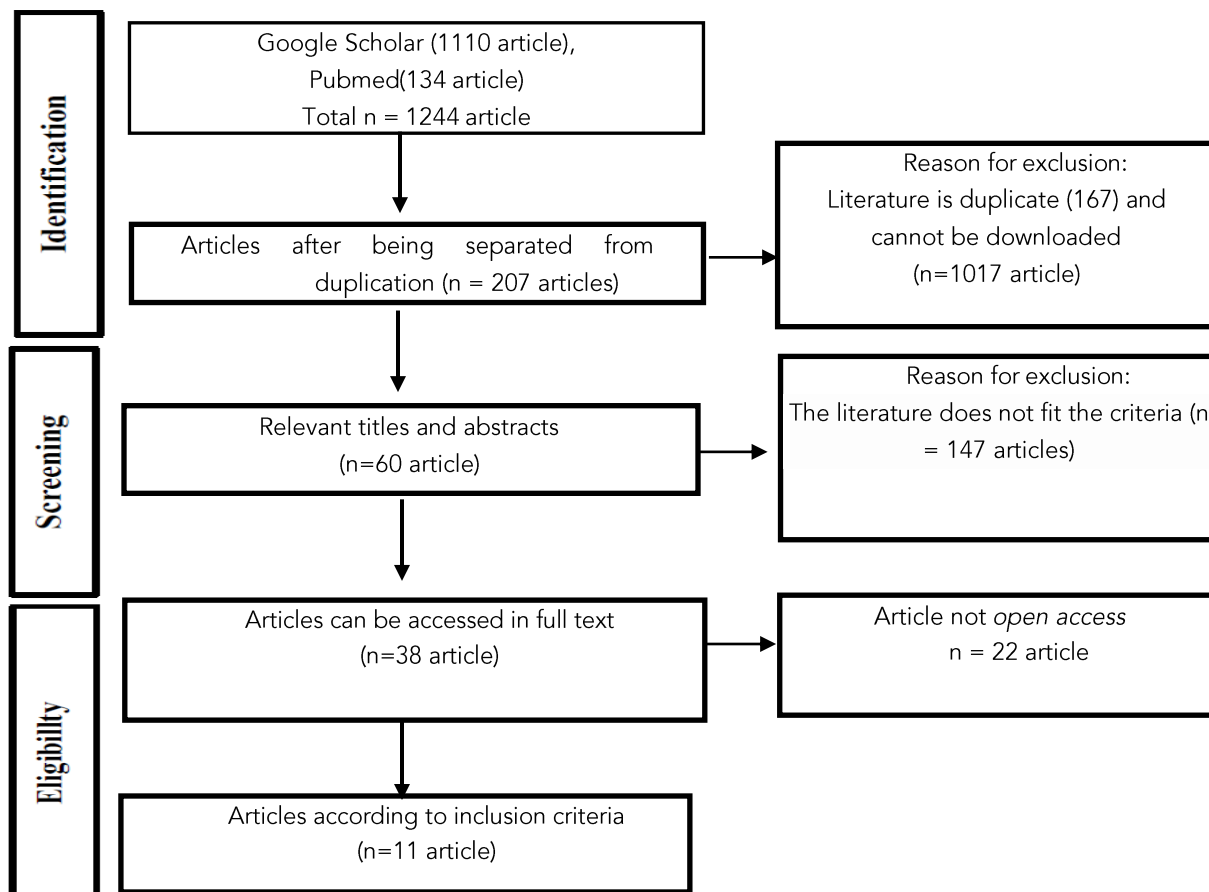


Figure 1: Preferred Reporting Item for Systematic Review and Meta-Analysis (PRISMA)

## Results

The results of the study found a significant negative association between average vitamin D levels and COVID-19 morbidity and mortality in 20 European countries. Vitamin D levels are particularly low in elderly populations in Spain, Italy, and Switzerland. It is also the most vulnerable population group to COVID-19. Vitamin D has been shown to protect against acute respiratory infections and is safe. It is recommended to conduct a special study on vitamin D levels in COVID-19 patients with different degrees of severity of the disease[11]. The results of the study reported a significant negative correlation between average vitamin D levels and COVID-19 cases per one million population in European countries. However, there was no correlation between vitamin D and COVID-19 mortality. Some retrospective studies show a correlation between vitamin D status and COVID-19 severity and mortality, while other studies have found no correlation by controlling for confounding variables. Some research suggests a role for vitamin D in reducing the risk of acute viral respiratory infections and pneumonia. These include direct inhibition by viral replication or by anti-inflammatory or immunomodulatory means. In meta-analyses, vitamin D supplementation is safe and effective against acute respiratory infections. Thus, people at higher risk of vitamin D deficiency during this global pandemic should take vitamin D supplements to maintain circulating 25(OH)D levels within optimal levels (75-125 nmol/L)[12].

The results of the study reported that the prevalence of vitamin D deficiency in this study was 90% and only 1 patient (10%) was deficient in vitamin D. There are many health benefits of vitamin D and very few side effects. A hypothetical review suggests that vitamin D supplementation may be beneficial for COVID-19. Other randomized controlled trials need to determine and evaluate these recommendations in preventing or treating COVID-19. Doctors should continue to care for people with vitamin D deficiency, especially in managing COVID-19 patients[13]. The findings of this review, which summarizes studies from 5 WHO regions (Europe Region, Americas Region, Southeast Asia Region, Eastern Mediterranean Region, and Western Pacific Region) except only the African region, show that low serum 25-OHD levels are associated with a higher risk of COVID-19 infection. Although the umbrella findings point to a potential role of vitamin D deficiency in COVID-19 severity in hospitalized patients and suggest an association between vitamin D supplementation and COVID-19 severity, however, stronger data from further randomized controlled trials are needed to confirm a possible association with mortality rates[14].

The study conducted in Jakarta, Indonesia, demonstrated a significant correlation between sun exposure and COVID-19 recovery among patients (p-value = 0.025). However, no significant correlation was found between sun exposure and the incidence or mortality of COVID-19. These findings suggest that sunlight exposure could play a crucial role in expediting recovery from COVID-19, not only in Jakarta but also in other countries, particularly those with high mortality rates from the pandemic. Furthermore, patients who received high-dose vitamin D supplementation exhibited normalization of vitamin D levels and

experienced improved clinical recovery. This improvement was evidenced by shorter treatment periods, reduced oxygen demand, and a decrease in inflammatory marker status. These results highlight the potential benefits of vitamin D supplementation in COVID-19 management and recovery[16].

Table 2. Data Extraction of Research Results on the Role of Vitamin D in Prevention, Treatment, and Health Recovery of COVID-19 Patients

| Title | Research Methods |
|---|---|
| The Role of Vitamin D in the Prevention of Coronavirus Disease 2019 Infection and Mortality[11]. | The study searched the literature for average vitamin D levels in each country, looking for the number of population COVID-19/1M cases in each country and deaths caused by COVID-19 disease. Statistical analysis using Pearson Correlation Coefficient Calculator. |
| Role of vitamin D in preventing COVID-19 infection, progression, and severity[12]. | This review discusses the role of vitamin D in reducing the risk of COVID-19 and other acute respiratory infections and severity. The study also analyzed the correlation of vitamin D levels with COVID-19 cases and deaths in 20 European countries as of May 20, 2020. |
| Vitamin D deficiency among patients with COVID-19: case series and recent literature review[13]. | Case series research for descriptive studies explaining vitamin D deficiency among COVID-19 patients. The test uses normal values from the results of vitamin D levels in the laboratory as an indicator of vitamin D status. We also analyzed vitamin D levels based on demographics and laboratory test data using Fisher's exact test. |
| The role of vitamin D in prevention of COVID-19 and its severity: an umbrella review[14]. | A systematic review and meta-analysis to assess whether low serum 25-OHD is associated with susceptibility to COVID-19, its severity, and mortality. The studies included in this review aimed to investigate the relationship between Vitamin D and COVID-19 under different social and clinical conditions. Only reviews published in English are included in this review. |
| Sunlight Exposure Increased COVID-19 Recovery Rates: A Study in the Central Pandemic Area of Indonesia[15]. | This cross-sectional study used the secondary data analysis came from COVID-19 surveillance data from government authorities, including the Ministry of Health, the Meteorology, Climatology, and Geophysics Agency, and the Jakarta regional government. |
| Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series[16]. | Centralized observational studies to determine the presence of influence Vitamin D Supplementation in COVID-19 Patients. |
| Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Symptoms in Patients with | This multi-center randomized clinical trial aimed to determine the effect of 5000 IU versus 1000 IU of daily oral vitamin D3 supplementation in symptomatic recovery and other clinical |

| Title | Research Methods |
|---|---|
| Mild to Moderate COVID-19: A Randomized Clinical Trial Shaun[17]. | parameters among mild to moderate COVID-19 patients with sub-optimal vitamin D status. |
| Evidence That Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths[18]. | This article reviews the role of vitamin D in reducing the risk of respiratory infections, knowledge of the epidemiology of influenza and COVID-19, and how vitamin D supplementation can be a useful measures to reduce the risk of COVID-19. |
| Increased risk for COVID-19 in patients with vitamin D deficiency[19]. | The study was exempted by the University of Florida (UF) Institutional Review Board as the study did not include personal health information. The UF i2b2 patient registry platform, which provides data aggregates from patient visits from various UF health centers, was used for the study |
| Vitamin D and Lung Outcomes in Elderly COVID-19 Patients[20]. | 65 COVID-19 patients (mean age 76 years) and 65 sex- and age-matched control subjects (CNTs) were analyzed. Statistical analysis using Mann–Whitney U, Kruskal-Wallis test, Spearman rank correlation, Simple and multiple linear regression test, and Chi-square tests are used to compare categorical variables. |
| Analysis of Vitamin D Level among Asymptomatic and Critically Ill COVID-19 Patients and Its Correlation with Inflammatory Markers[21]. | Continuous prospective observational study with a duration of 6 weeks. The sample was COVID-19 patients from the age group of 30-60 years who were admitted to a tertiary COVID-19 care center during the 6-week study span. Statistical test using Mann–Whitney U Test; unpaired 't' test and Chi-Square test |

Vitamin D supplementation for 2 weeks led to a significant increase in serum 25(OH)D levels in the 5000 IU group alone (p =0.003). Daily oral vitamin D3 supplementation of 5000 IU for 2 weeks reduced cough recovery time and gustatory sensory loss among patients with sub-optimal vitamin D status and mild to moderate COVID-19 symptoms. The use of 5000 IU of vitamin D3 as Adjuvant therapy for COVID-19 patients with suboptimal vitamin D status, even for a short duration, is recommended.[17] The results of the study reported that Vitamin D may reduce the risk of infection. Vitamin D induces cathelicidins and defensins that can decrease the rate of viral replication and reduce the concentration of pro-inflammatory cytokines that produce

inflammation that injures the lining of the lungs, causing pneumonia, as well as increasing the concentration of anti-inflammatory cytokines. Several observational studies and clinical trials report that vitamin D supplementation reduces the risk of influenza. Vitamin D deficiency contributes to acute respiratory distress syndrome; and that case fatality rates increase with age and with chronic comorbidities of the disease[18].

Patients with vitamin D deficiency are 4.6 times more likely positive for COVID-19 compared to patients with no vitamin D deficiency (P <0.001). The study showed that vitamin D deficiency was strongly associated with COVID-19 infection after controlling for

sex, malabsorption, dental disease, race, diabetes, and obesity. Vitamin D deficiency increases the risk of getting COVID-19[19]. There is a significant positive correlation between serum vitamin D levels and severity. This study confirms that serum deficiency of 25OH-vitamin D is associated with more severe lung involvement, longer duration of illness, and risk of death, in elderly COVID-19 patients. Detection of low vitamin D levels also in younger COVID-19 patients with fewer comorbidities further points to vitamin D deficiency as an important risk factor at any age[20]. Vitamin D deficiency significantly increases the chances of having severe disease after SARS-CoV-2 infection. The intensity of the inflammatory response is also higher in vitamin D-deficient COVID-19 patients. In vitamin D-deficient COVID-19 patients It is necessary to increase Vitamin D intake to reduce morbidity and mortality. It is necessary to provide vitamin D supplements to populations at risk of COVID-19[21].

## Discussion

DEFINITION AND SOURCE OF VITAMIN D

Vitamin D is a secosteroid (chemical compound) formed in the skin through the process of photosynthesis by sun exposure. The structure of vitamin D compounds is derived from steroid compounds that have four rings of cyclo-pentano-perhydrophenanthrene compounds, namely the A, B, C, and D rings. Biologically, vitamin D is inert, that is, the state of not doing something at all, has a very small effect, and undergoes two consecutive hydroxylation processes in the liver and the kidneys so that active metabolism is formed[22]. Vitamin D is a fat-soluble vitamin with two main physiological forms: ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3). The two forms have different side chain structures. Vitamin D2 comes from plants and plants as well as fungi while vitamin D3 is made by animals including humans and vitamin D3 comes from sun exposure to the skin (UVB radiation) from 7-dehydro-cholesterol[23]. Vitamin D is a steroid that belongs to the secosteroid group (open ring) which undergoes carbon breakdown in the cylo-pentano-perhydro-phenanthrene ring[24].

Vitamin D possesses a unique quality as it can be synthesized through the skin when exposed to sunlight. It exists in two forms: vitamin D2 and vitamin D3. Vitamin D2, also known as ergosterol, originates from viosterol and undergoes conversion to ergosterol through UV light exposure. Since ergosterol is a component of fungal cell membranes, D2 can naturally occur in fungi exposed to sunlight. On the other hand, vitamin D3, or cholecalciferol, is synthesized in the skin and is abundant in oil-rich fish like salmon, mackerel, and herring. Vitamin D synthesized in the skin remains in the bloodstream twice as long as vitamin D obtained from food. Adequate sun exposure for vitamin D synthesis typically involves spending 5-30 minutes outdoors, between 10:00 a.m. and 3:00 p.m., at least twice a week. Exposed areas such as the face, arms, back, or legs (without sunscreen) facilitate this process. Sunlight initiates the synthesis by breaking down the B ring of pro-vitamin D3 (7-dehydrocholesterol or 7-DHC) via UV light, forming pre-D3, which then undergoes isomerization into D3 through a temperature-sensitive process. Prolonged UVB exposure locally inactivates vitamin D3 without causing

toxicity from sun exposure. Melanin, clothing, and sunscreen can impede UVB from reaching 7-DHC, thus reducing D3 synthesis. In individuals over 65 years old, 7-DHC levels in the skin decrease by 70% compared to younger adults, necessitating longer sun exposure for vitamin D3 synthesis. Sunscreens with SPF 30 or higher can significantly diminish skin vitamin D synthesis by over 95%[25.]

There are two primary sources of vitamin D: endogenous and exogenous. Endogenous sources, mainly synthesized within the body, occur when ultraviolet B (UVB) rays from sunlight penetrate the epidermis and dermis layers of the skin. This UVB exposure triggers the conversion of a precursor molecule, 7-dehydrocholesterol, into vitamin D, which then circulates in its active form throughout the body. Vitamin D synthesized in the body lasts longer in the skin's capillaries compared to that obtained from food or supplements. To ensure sufficient vitamin D levels, approximately 530 minutes of sun exposure per week, spread across two to three sessions, is recommended. Sun exposure should ideally occur between 11:00 a.m. and 2:00 p.m., when UVB light is at its peak and relatively stable, typically around 12 MED/hour. However, the duration of sun exposure may need adjustment during peak UVB periods to prevent overexposure. It's essential to expose at least 20% of the skin's surface directly to sunlight without clothing or sunscreen to maintain adequate vitamin D levels. Exogenous sources of vitamin D primarily come from dietary supplements and vitamin D supplements, as food sources alone may not sufficiently meet the body's vitamin D requirements. Vitamin D is essential among various vitamins required by the body,

contributing to the regulation of calcium and phosphate levels crucial for maintaining healthy bones, teeth, and muscles. Several food sources contain varying amounts of vitamin D. For instance, salmon provides 526 IU of vitamin D per 100 grams, fulfilling up to 200% of daily vitamin D needs. Canned tuna offers 268 IU per serving, while Patin fillet contains 795 IU. Sardines can provide 193 IU per day, and oysters offer 320 IU per 100 grams. Shrimp can meet 25% of daily vitamin D requirements per serving. Oatmeal provides approximately 136 IU of vitamin D per cup, while cereals (about 78 grams per cup) can offer 54-136 IU, covering up to 17% of daily needs. Other sources include egg yolks, mushrooms, cow's milk, soy milk, cod liver oil, orange juice, tofu, and tempeh[26].

THE ROLE OF VITAMIN D IN THE PREVENTION OF COVID-19

Vitamin D has potential in the immune system and has an important role as an anti-virus. Vitamin D3 is called calcitriol which serves as a humoral and cellular defense mechanism. Vitamin D metabolites regulate the production of specific antimicrobial proteins directly killing pathogens and helping reduce infections, including in the lungs. The role of vitamin D in responding to COVID-19 infection could be two-fold. Vitamin D supports the production of antimicrobial peptides in the respiratory epithelium, making infection with the virus and the development of COVID-19 symptoms less likely. Vitamin D can help reduce the inflammatory response and can regulate the immune system to fight infection from SARS-CoV-2[27]. Vitamin D affects several immune pathways, namely by increasing mucosal defenses and simultaneously reducing excessive inflammation. Vitamin D

supplementation can reduce the risk of COVID-19 infection. The recommended dose of vitamin D is 10,000 IU per day for several weeks to increase vitamin D concentrations rapidly followed by a dose of 5,000 IU per day. The target concentration of Vitamin D is 40-60 ng/mL Vitamin D supplementation is expected to reduce the risk of infection, including COVID-19 infection, because Vitamin D can increase body immunity. The recommended dose is 600–800 IU per day for adults aged ≤70 years, and 800–1000 IU per day for >70 years of age[7].

The results of the literature review found that Vitamin D plays a role in preventing COVID-19 infection or has the potential to protect against respiratory infections in more severe COVID-19 patients. Vitamin D intake that is less than 25 nmol/L can cause a more severe COVID-19 infection. For COVID-19 patients who experience Vitamin D deficiency, they are required to consume vitamin D to increase serum 25(OH)D to reduce infection in COVID-19 patients. The results of the study of Margarucci et al., (2021) showed that there was a statistically significant reduction found from vitamin D supplementation in the risk of developing acute respiratory infections. In a subgroup analysis, they found a protective effect in daily or weekly supplementation. Vitamin D exerts a strong protective effect on those with levels of 25(OH)D > 10 ng/mL. There is an inverse relationship between serum Vitamin D levels and the risk of acute respiratory infections[14].

The results of research in European countries by Ilie (2020) identified a potential relationship between vitamin D levels and COVID-19 cases and deaths. In European countries in nursing homes, the average vitamin D level is 23 nmol/L and in Italy, 76% of women over 70 years are found to have circulating levels below 30 nmol/L[11]. People in European countries have lower levels of Vitamin D due to lack of exposure to day eye light and also because skin pigmentation lowers the Vitamin D system. From these findings, it can be explained that Vitamin D plays a role in the prevention of COVID-19 infection or more potentially in the protection of Vitamin Itamine D from more severe consequences of infection. in a meta-analysis study that vitamin D supplements are safe and affect preventing acute respiratory infections[28]. There is a significant association between vitamin D levels shown to protect against acute respiratory infections. Suggests that there is a relationship between vitamin D levels and acute respiratory infections. There are many health benefits of Vitamin D and very few side effects. The results of a literature review show that Vitamin D supplementation is beneficial for the prevention of COVID-19 infection. Other research results recommend that Vitamin D plays a role in preventing or treating COVID-19.

## THE ROLE OF VITAMIN D IN THE TREATMENT OF COVID-19 DISEASE

The severity of COVID-19 disease is due to the presence of an infection that induces an immune response. The immune response obtained at the incubation stage aims to destroy the virus and prevent its development in a progressive direction. Disruption of the immune response will allow the virus to proliferate and cause extensive damage to infected tissues, especially organs with high expression of angiotensin 2 (ACE2) (intestines and kidneys). Cytokine storms such as interleukin-1 (IL-1) and tumor necrosis factor

(TNF), will be secreted in severe COVID-19 infection. The discharge of this cytokine storm is mediated primarily by leukocyte and T cells that induce hyaluronan-synthase 2 (HAS2). Hyaluronan (HA) can cause acute respiratory distress syndrome. Inhibition of HA can be done directly by administration of hyaluronidase and hymecromone or indirectly through vitamin D which reduces the response to T cells[29]. During infection, people with COVID-19 show an uncontrolled immune response, caused by hyperactivation of macrophages and monocytes. This response increases in neutrophils, IL-6, and reactive protein C (PCR) and a decrease in the total number of lymphocytes. Activation of Th1/Th17 by Helper T lymphocytes may contribute to exacerbations of the inflammatory response, while B lymphocytes provide specific antibodies to SARS-CoV-2 aimed at neutralizing the virus[30].

Vitamin D deficiency in COVID-19 patients affects and aggravates the decline in immune system function, causing cytokine storms, which is a process that can worsen the condition of COVID-19 patients due to dysregulation of the body's immune system, including in elderly patients, causing severe clinical manifestations that can cause organ failure and lead to death in COVID-19 patients. Patients with COVID-19 with severe symptoms require longer hospital treatment due to vitamin D deficiency[7]. The results of Gita's study (2022), showed that vitamin D deficiency correlated with higher mortality rates in COVID-19 patients. Vitamin D deficiency occurs in people with COVID-19 caused by reduced frequency or duration of sun exposure and inadequate nutrient intake. Vitamin D deficiency conditions are very influential on the immune system and aggravate the patient's clinical condition. COVID-19 patients who experience vitamin D deficiency must get intensive care in the Intensive Care Unit (ICU) and generally have pneumonia[8].

The results of Piumika's (2021) research show a positive relationship between the rate of vitamin D deficiency and COVID-19 infection and mortality rates in Europe and Asia. There is a relationship between vitamin D deficiency and COVID-19 severity. In COVID-19 cases with severe clinical symptoms, 65% with vitamin D deficiency is higher than in COVID-19 cases with mild clinical symptoms. About 18% of the mortality rate of COVID-19 cases is due to severe clinical experience and is related to vitamin D deficiency[31]. The results of Khoiroh's research (2021) suggest that vitamin D deficiency is most commonly found in COVID-19 patients with severe symptoms who are treated in the ICU room. Some COVID-19 patients with mild symptoms did not feel fever and found serum levels of 25(OH)D >20 ng/ml. Giving vitamin D-based drugs such as vitamin D supplementation and calcification therapy (25-hydroxyvitamin D) can reduce clinical impact or mild or severe symptoms. This medical therapy aims to increase serum vitamin D levels in COVID-19 patients[32].

The risk of infection and death due to confirmed cases of COVID-19 can be lowered with Vitamin D. Vitamin D is recommended by the Centers for Disease Control and Prevention (CDC) to treat COVID-19. Reduced mortality is known to be associated with vitamin D supplementation[29]. Vitamin D levels were found to be significantly lower in patients with severe clinical symptoms than in those with mild symptoms. For patients who

experience death, levels of vitamin D are lower than patients who survive. The results of the study with multivariate logistic regression analysis showed a relationship between serum vitamin D levels and increased mortality in COVID-19 patients. Low levels of vitamin D in the body cause a decrease in immune function thereby increasing susceptibility to infections. Vitamin D has an important role in the immune regulation of both the innate and adaptive immune systems. Vitamin D can increase the phagocytosis ability of macrophages and increase the recognition of pathogens through toll-like receptors[7].

In patients already infected with Covid-19, higher doses of vitamin D supplementation may be beneficial. Vitamin D levels in clinical COVID-19 patients, which means that the higher the vitamin D levels, the more clinical COVID-19 patients are classified as mild or moderate, and vice versa, the lower the consumption of vitamin D, the patient's clinical symptoms are classified as severe[7]. COVID-19 patients with normal serum vitamin D or 25(OH)D levels showed clinical rehabilitation reflected in shorter hospitalizations, lower oxygen demand, and reductions in inflammatory markers. Some COVID-19 patients with mild symptoms do not have fever. Normal vitamin D levels in the body or the higher the vitamin D levels, the clinical COVID-19 patients are relatively mild[33]. In patients with COVID-19, vitamin D can prevent the development of infection, reduce severity, and relieve the effects of cytokine storms in severe infections by preventing viral invasion, suppressing viral replication, and increasing the process of autophagy. Vitamin D supplementation recommended for mild-moderate COVID-19

patients is 1000 – 2000 IU per day[34]. It is recommended to take vitamin D at 10,000 IU / day for several weeks and continue at 5000 IU / day[29]. Giving vitamin D at a dose of 10000 IU per day for the first 1 week to increase serum levels of 25-OHD to 40 – 60 ng / mL, followed by 5000 IU per day to maintain serum vitamin D levels in patients at risk of COVID-19 infection, while in COVID-19 patients it is recommended to take vitamin D 50 000 IU 2 times per week in the first week, followed by 50 000 IU 1 time per week in the second and third weeks to achieve serum 25-OHD levels above 40 ng/mL[34].

Mild manifestations of COVID-19 in high-risk patients with sufficient plasma levels of 25-OH-Vitamin D3. Some studies are convincing with the link between vitamin D deficiency and more severe clinical manifestations of Covid-19. The prevalence of vitamin D deficiency among patients with severe manifestations of COVID-19 admitted to intensive care units reached 96.82% in contrast to 32.96% in asymptomatic patients. In addition, serum IL-6 and TNFα levels were negatively correlated with 25-OH-vitamin D3 levels with an overall mortality rate nearly sevenfold higher in patients with vitamin D deficiency[35]. A retrospective, multicentric study found that COVID-19 patients who were deficient in vitamin D generally had poor outcomes whereas patients who had high vitamin D levels fared better[36].

The results of Ali's (2020) study found a significant relationship between vitamin D status and clinical outcomes. There was a significant difference in the severity of COVID-19 infection based on the average mild (78 nmol/L), ordinary (68.5 nmol/L), severe (53 nmol/L), and critical vitamin D. COVID-19

sufferers with old age and low vitamin D levels have a risk of COVID-19 infection that is more severe and can cause death. Vitamin D intake of less than 25 nmol / L has a more severe infectious effect, it is recommended that patients infected with COVID-19 take Vitamin D to increase serum 25(OH)D to reduce the effects of infection caused by COVID-19[12]. The results of a study by Pinzon, et, al (2020) on 10 patients infected with COVID-19 with an average age of 49.6 years and a BMI of less than 25 kg / m2, found that elderly women tend to have lower vitamin D levels. All patients had positive serological or real-time PCR tests for COVID-19. All patients had mild to moderate severity. Based on laboratory examination, 9 patients had vitamin D deficiency status (vitamin D levels < 20 ng / mL) including 3 patients with vitamin D levels <8.1 ng / mL[13].

## THE ROLE OF VITAMIN D IN THE HEALTH RECOVERY OF COVID-19 PATIENTS

The results of the literature review found that Vitamin D plays a role in the recovery of the health of COVID-19 patients through Vitamin D supplements and sun exposure. The duration of sun exposure can accelerate the health recovery of COVID-19 storytellers. Sunlight affects the recovery of COVID-19 patients who experience mild infections. Supplements given to patients with vitamin D deficiency of 5000 UI can increase serum levels experienced by COVID-19 patients with vitamin D deficiency[7]. Patients who received vitamin D supplements had clinical recovery as evidenced by shorter hospitalizations, less need for oxygen aids, and accelerated recovery from coughing, and loss of taste experienced by COVID-19 patients.

The results of Asyary's (2020) study show that the duration of sun exposure for COVID-19 patients in Jakarta fluctuates every day. The shortest duration of daily sun exposure was 0 minutes, while the longest duration was 480 minutes, with average daily sun exposure being 217.95 minutes or 3.6 hours. Sun exposure correlates significantly with the recovery of COVID-19 cases.[15] The results of Ohaegbulam's study (2020) on 4 COVID-19 patients who were given vitamin D supplements, namely the first, 2 patients were given claciferol supplements of 1000 UI with standard doses, and 2 other patients were given ergocalciferol with high doses (50,000 UI every day). The results found that on day 6, patients who received higher doses of supplements had longer hospitalizations lower oxygen requirements, and increased concentrations of vitamin D in the blood. While patients who get standard doses experience vitamin D deficiency which causes a longer length of hospitalization. In this case, the patient studied has a history of hypertension and diabetes. It can be concluded that patients given higher vitamin D supplements experience low hospitalization and oxygen demand and have increased concentrations of vitamin D in the blood but patients given standard supplements experience vitamin D deficiency[16].

In line with the results of Sabico's study (2021) on 69 COVID-19 patients with an average BMI of 30.7kg/m2 given vitamin D, consisting of 33 COVID-19 patients given vitamin D supplements of 1000 IU and 36 COVID-19 patients given 5000 IU for two weeks while being treated. Patients who received Vitamin D3 doses of 5000 IU daily for two weeks were able to substantially reduce the length of hospitalization and speed recovery from cough and loss of taste experienced by

COVID-19 patients and this was very clinically significant compared to patients who received Vitamin D doses of 1000 IU had a longer period of hospitalization and recovery of cough and loss of taste. The beneficial effects of a Vitamin D supplementation dose of 5000 IU, in this case, apply only to COVID-19 cases suffering from mild and moderate viral infections with mild to insufficient Vitamin D deficiency status[17].

The results of research by Grant et al (2020) stated that Vitamin D can increase cellular immunity, in part by reducing cytokine storms caused by the innate immune system. The innate immune system produces pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients. Vitamin D can reduce the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor and interferon. Administration of vitamin D reduces the expression of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages and references in them). Vitamin D suppresses the response mediated by type 1 (Th1) helper T cells, by suppressing the production of inflammatory cytokines IL-2 and interferon-gamma (INFγ). Vitamin D promotes cytokine production by type 2 (Th2) helper T cells, which help increase indirect suppression of Th1 cells by actions mediated by many cell types. Vitamin D also promotes the induction of T-regulatory cells, thereby inhibiting the inflammatory process[18].

The results of the study by Katz et al (2020) on 87 adult patients infected with COVID-19 were diagnosed with Vitamin D deficiency. Patients with Vitamin D deficiency were five times more likely to be infected with COVID-19 compared to patients without deficiency. Vitamin D triggers the production of antimicrobial proteins cathelicidins and defensin that can inhibit viral replication rates and reduce levels of inflammation-producing cytokines responsible for damage to the lining of the lungs, leading to acute respiratory diseases. Vitamin D also promotes the gene responsible for ACE2 expression, which is regulated downward by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[19].

The results of research by Sulli et al., (2021) explained that serum Vitamin D levels were found to be significantly lower in COVID-19 patients. A negative association was found between serum vitamin D levels and radiological lung severity. Vitamin D levels were found to be significantly lower in COVID-19 patients with diffuse (severe) interstitial lung consolidation compared to those with mild interstitial lung involvement. Vitamin D deficiency (<20 ng/mL) is more common in people with COVID-19[20]. Serum Vitamin D levels with comorbidities in COVID-19 patients can affect those serum levels, as well as disease severity and age. 61% Levels of hospitalized patients average age 76 years with serum vitamin D <50 nmol/L (<20 ng/mL). 57% of COVID-19 patients showed a more severe deficiency with a value of <10 ng/mL. Vitamin D levels were significantly lower in COVID-19 patients with severe conditions with an average serum vitamin D level of 7.9 ng/mL[37].

The results of a study by Jain et (2020) on 154 patients found that 91 patients were asymptomatic (group A), 63 patients were seriously ill and required treatment in the ICU (group B). In this study, it was found that patients had Vitamin D deficiency in critical

patients and without symptoms. Of the 154 patients treated, 21 of them died. Vitamin D deficiency markedly increases the chances of developing severe disease after being infected with SARSCov-2. The intensity of the inflammatory response increased in Vitamin D deficient COVID-19 patients and also increased morbidity and mortality in Vitamin D deficient COVID-19 patients[21].

The results of Alipio's research (2020) explain that vitamin D can help fight COVID-19 because it has various antiviral, immunomodulatory, and cardiometabolic effects that have been recognized. Vitamin D has different mechanisms for reducing the risk of viral infection and death. This mechanism is carried out with the physical barrier, increases cellular immunity, and modulates adaptive immunity. Vitamin D can also reduce cytokine storms caused by the innate immune system thereby boosting cellular immunity. Symptoms of COVID-19 patients are said to be mild if the serum level of 25(OH)D is 31.2 ng/mL and in COVID-19 patients with severe symptoms the serum level of 25(OH)D is 21.2 ng/mL[38]. Vitamin D has the potential to prevent the virus from binding to it and reduce complications associated with COVID-19. Vitamin D can also play a protective role and support the healing of damaged tissues, especially in the lungs. Meeting the needs of vitamin D apart from supplementation can also be done by consuming vitamin D and sun exposure. Foods that contain vitamin D include fish, egg yolks, butter, cow's milk, mushrooms, and cereals. Other sources of vitamin D can also be found in vegetables and fruits such as spinach, broccoli, orange juice, kiwi, bananas, and mangoes[32].

Relying solely on food sources is insufficient to meet the body's vitamin D requirements.

Sun exposure is crucial for adequate vitamin D production. Basking in the sun aids in the synthesis of vitamin D, particularly vitamin D3, which enhances immunity and boosts the white blood cells' ability to combat harmful microorganisms like the COVID-19 virus. The optimal frequency for sun exposure to increase vitamin D levels for COVID-19 prevention is recommended between 9:00-10:00 AM (WIB) for a maximum of 7-15 minutes, or until the skin begins to turn slightly reddish. This routine should ideally be repeated 2-3 times per week to maintain adequate vitamin D levels[29]. For COVID-19 patients with mild to moderate conditions, the recommended vitamin D supplementation is 1000-2000 IU per day. However, there is an alternative recommendation to administer vitamin D at a higher dose of 10,000 IU per day for the initial week to elevate serum levels of 25-OHD to a range of 40-60 ng/mL. Following this, a maintenance dose of 5000 IU per day is advised to sustain adequate serum vitamin D levels in patients at risk of COVID-19 infection. In cases of COVID-19 patients experiencing severe symptoms, a different supplementation regimen is suggested. Initially, it is recommended to administer 50,000 IU of vitamin D twice per week during the first week. Subsequently, the dosage should be adjusted to 50,000 IU once per week during the second and third weeks. This regimen aims to achieve serum 25-OHD levels above 40 ng/mL[34].

## Conclusion

Vitamin D may help prevent COVID-19 infection by bolstering the body's immune response. It's worth noting that many COVID-19 patients exhibit vitamin D deficiency.

Normal vitamin D levels in COVID-19 patients typically range from 30-35 ng/mL. Mild symptoms in COVID-19 patients are often associated with vitamin D levels exceeding 20 ng/mL, whereas severe symptoms correlate with levels below 12 ng/mL. Additionally, severe symptoms in COVID-19 patients can be exacerbated by underlying degenerative conditions like hypertension, heart disease, type 2 diabetes, osteoporosis, and factors such as limited sun exposure. Supplementing with vitamin D is recommended for COVID-19 patients as it can help prevent infection, mitigate respiratory symptoms, alleviate cytokine storms in severe cases, and enhance overall immunity. Vitamin D also plays a crucial role in the recovery process by facilitating shorter hospitalization periods, accelerating relief from symptoms like coughing and loss of taste, and attenuating cytokine storms associated with the disease. The recommended daily dosage of vitamin D for adults aged ≤70 years is 600-800 IU, while those over 70 years old should aim for 800-1000 IU daily. For COVID-19 patients with mild to moderate symptoms, supplementation with 1000-2000 IU per day is advised, whereas those with severe symptoms may require higher doses, such as 50,000 IU twice per week.

## References:

1. Sukur  moch H, Kurniadi B, Harus, Faradillahisari R. Penanganan Pelayanan Kesehatan Di Masa Pandemi Covid-19 Dalam Perspektif Hukum Kesehatan. Inicio Legis. 2020;1(1):1-17. doi:10.21107/il.v1i1.8822

2. Fitriani NI. Tinjauan Pustaka Covid-19: Virologi, Patogenesis, dan Manifestasi Klinis. Sustain. 2020;14(2):1-4.

3. Sumarni S. Kerja harmoni zat gizi dalam meningkatkan imunitas tubuh terhadap Covid-19: Mini Review. Amerta Nutr. 2020;4(3):250-256.

4. World Health Organization (WHO). WHO Coronavirus Disease (COVID-19) Dashboard.; 2022. https://covid19.who.int/.%0A(accessed May 20, 2022).

5. Kemenkes. Situasi Terkini Perkembangan Coronavirus Disease (COVID-19) 25 November 2021.; 2021.

6. Ardiaria M. Peran Vitamin D Dalam Pencegahan Influenza Dan Covid-19. JNH (Journal Nutr Heal. 2020;8(2):79-85. doi:10.14710/JNH.8.2.2020.79-85

7. Berhandus C, Ongkowijaya JA, Pandelaki K. Hubungan Kadar Vitamin D dan Kadar C-Reactive Protein dengan Klinis Pasien Coronavirus Disease 2019. e-CliniC. 2021;9(2):370-378. doi:10.35790/ecl.v9i2.33043

8. Puspitasari G, Puspita D. Defisiensi Vitamin D dengan Tingkat Mortalitas Pasien COVID-19 yang Dirawat di Rumah Sakit. Higeia J Public Heal Res Dev. 2022;6(1):20-30. doi : https://doi.org/10.15294/higeia/v6i1.49618

9. Deluccia R, Clegg D, Sukumar D. The implications of vitamin D deficiency on COVID-19 for at-risk populations. Nutr Rev. 2021;79(2):227-234. doi:10.1093/nutrit/nuaa092

10. Farhan A. Pengaruh Vitamin D Terhadap Tingkat Keparahan Covid-9. J Holist Tradit Med. 2021;6(2):588-594.

11. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020;32(7):1195-1198. doi:10.1007/s40520-020-01570-8

12. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public Health. 2020;13(10):1373-1380. doi:10.1016/j.jiph.2020.06.021

13. Pinzon RT, Angela, Pradana AW. Vitamin D deficiency among patients with COVID-19: case series and recent literature review. Trop Med Health. 2020;48(102):1-7. doi:10.1186/s41182-020-00277-w

14. Margarucci LM, Montanari E, Gianfranceschi G, et al. The role of vitamin D in prevention of COVID-19 and its severity: An umbrella review. Acta Biomed. 2021;92(6):1-16. doi:10.23750/abm.v92iS6.12216

15. Asyary A, Veruswati M. Sunlight exposure increased Covid-19 recovery rates: A study in the central pandemic area of Indonesia. Sci Total Environ jour. 2020;729(139016):1-5.

16. Ohaegbulam KC, Swalih M, Patel P, Smith MA, Perrin R. Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series. Am J Ther. 2020;27(5):485-490. doi:10.1097/MJT.0000000000001222

17. Sabico S, Enani MA, Shshah E, et al. Probiotic improves symptomatic and viral clearance in COVID-19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial. Nutrients. 2021;13(2170):2-14. doi:10.1080/19490976.2021.2018899

18. Grant WB, Lahore H, McDonnell SL, et al.

Evidence that vitamin D supplementation could reduce the risk of influenza and COVID-19 infections and deaths. Nutrients. 2020;12(4):1-19. doi:10.3390/nu12040988

19. Katz J, Yue S, Xue W. Increased risk for COVID-19 in patients with vitamin D deficiency. Nutrition. 2020;84(111106):1-5.

20. Sulli A, Gotelli E, Casabella A, et al. Vitamin D and lung outcomes in elderly COVID-19 patients. Nutrients. 2021;13(3):1-13. doi:10.3390/nu13030717

21. Jain A, Chaurasia R, Sengar NS, Singh M, Mahor S, Narain S. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Sci Rep. 2020;10(1):1-8. doi:10.1038/s41598-020-77093-z

22. Mexitalia M, Susilawati M, Pratiwi R, Susanto J. Vitamin D dan paparan sinar matahari untuk mencegah COVID-19. Fakta atau mitos? Medica Hosp J Clin Med. 2020;7(1):320-328. doi:10.36408/mhjcm.v7i1a.474

23. Astuti Y. Vitamin D Dalam Kehamilan (Literature Review). J Ilm Pannmed (Pharmacyst, Nurse, Nutr Midwivery, Environ Dent Hyg. 2020;15(3):1-5.

24. Handono K, Nurdiana, Susianti N, et al. Vitamin D Dan Autoimunitas. UB Press; 2018.

25. Paramita, Louisa M. Berbagai Manfaat Vitamin D. CDK. 2017;44(10):736-740. https://media.neliti.com/media/publications/399703-berbagai-manfaat-vitamin-d-12d38cfd.pdf

26. Fiannisa R. Vitamin D sebagai Pencegahan Penyakit Degeneratif hingga Keganasan. MEDULA Med Prof J Univ Lampung. 2019;9(4):385-392.

27. Istyanto F, Maghfiroh A. Peran Mikronutrisi Sebagai Upaya Dalam Pencegahan Covid-19. J Ilm Permas J Ilm STIKES Kendal. 2021;11(1):1-8.

28. Martineau AR, Forouhi NG. Vitamin D for COVID-19: a case to answer? Lancet Diabetes Endocrinol. 2020;8(9):735-736. doi:10.1016/S2213-8587(20)30268-0

29. Joewono M. Waktu Berjemur Terbaik Guna Meningkatkan Vitamin D Dalam Pencegahan Coronavirus Disease 2019 (Covid-19). J Media Kesehat. 2021;14(1):66-74. doi:10.33088/jmk.v14i1.622

30. Handayani RT. Pandemi Covid-19, Respon Imun Tubuh, Dan Herd Immunity. J Ilm Permas J Ilm Stikes Kendal. 2020;10(3):373-380.

31. Sooriyaarachchi P, Francis T V, King N, Jayawardena R. Increased physical inactivity and weight gain during the COVID-19 pandemic in Sri Lanka: An online cross-sectional survey. Diabetes Metab Syndr Clin Res Rev. 2021;15:1-8.

32. Khoiroh M, Atmaka DR, Ayuningtyas PR. Effectiveness of vitamin D-based therapy in reducing clinical impact of Covid-19 patients: A systematic review. Rom J Diabetes, Nutr Metab Dis. 2021;28(3):331-336. doi:10.46389/rjd-2021-1050

33. Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D status is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. Int J Infect Dis. 2021;104:58-64. doi:10.1016/j.ijid.2020.12.077

34. Saraswati NAS, Amanda DA, Wijaya H. Vitamin D dan COVID-19: Tinjauan Literatur. Cermin Dunia Kedokt. 2022;49(2):98-101. doi:10.55175/cdk.v49i2.199

35. Kralj M, Jakovac H. Vitamin D, and COVID-19 in an immunocompromised patient with multiple comorbidities—A Case Report. Clin Case Reports. 2021;9(4):2269-2275. doi: 10.1002/ccr3.4010

36. Mohan M, Cherian JJ, Sharma A. Exploring links between Vitamin D deficiency and COVID-19. PLoS Pathog. 2020;16(9):1-6. doi:10.1371/journal.ppat.1008874

37. Panagiotou G, Tee SA, Ihsan Y, et al. Low Serum 25-Hydroxyvitamin D (25D) Levels in Patients Hospitalised with COVID-19 Are Associated with Greater Disease Severity: Results of a Local Audit of Practice.; 2020. pesquisa.bvsalud.org

38. Alipio M. Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-2019). SSRN Electron J. 2020;(82):1-6. doi:10.2139/ssrn.3571484