DOI: https://doi.org/10.53555/nnmhs.v9i6.1733 Publication URL: https://nnpub.org/index.php/MHS/article/view/1733

THE RELATIONSHIP BETWEEN VITAMIN D DEFICIENCY AND THE SEVERITY OF COVID-19

Erick Persson Jeffry*

**Faculty of Medicine, Veterans National Development University, Indonesia, Email: erick.persson86@gmail.com*

Corresponding Author :
erick.persson86@gmail.com

Abstract

The global health issue known as the COVID-19 pandemic, resulting from the SARS-CoV-2 virus, has prompted extensive research into factors affecting the severity of the disease. Among these factors, the connection between vitamin D levels and the outcomes of COVID-19 has become an increasingly intriguing field of study.

Vitamin D is a fat-soluble vitamin renowned for its importance in bone health and immune system regulation. According to the latest studies, inadequate levels of vitamin D might be linked to a higher susceptibility to various respiratory infections. As a result, researchers are investigating the potential impact of vitamin D on the severity of COVID-19.

Multiple observational investigations have found a link among a lack of vitamin D and a higher vulnerability to respiratory infections such as COVID-19. Some studies have revealed that individuals with inadequate vitamin D levels had more severe COVID-19 symptoms, greater rates of admission to the hospital, and a greater mortality rate than those with adequate vitamin D levels. Vitamin D is thought to help regulate the immune response by influencing both the adaptive as well as the innate immune systems. Deficiency may affect immunological function, resulting in an altered antiviral response and increased inflammation, which may contribute to the development of COVID-19.

It is crucial to emphasize, however, that the existing research on the connection with insufficient vitamin D levels and the severity of COVID-19 are continuously evolving, with contradicting findings reported. There are significant constraints to the extant research, particularly differences in study methodologies, sample sizes, also populations investigated. Furthermore, it remains uncertain whether there is a cause-and-effect relationship between vitamin D deficiency and COVID-19 severity, as the observed relationships might be impacted by other confounding variables. Given vitamin D's possible involvement in immune function and the existing data linking it to COVID-19 severity, further well-designed research, particularly randomized controlled trials, are needed to demonstrate a causal relationship.

Keyword: *COVID-19; Inflammation; Vitamin D; Severity; Deficiency*

INTRODUCTION

The outbreak of the SARS-CoV-2 virus, which causes COVID-19, has had a devastating impact on global healthcare systems worldwide, presenting significantly public health crisis. From the initial cases in December 2019, as of September 22, 2022, there have been 613,793,706 confirmed instances of COVID-19 resulting in 6,532,674 fatalities.[1] Older individuals with pre-exiting contitions such as comorbidities such as hypertension, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and chronic renal deficiency are at a higher risk of developing a more severe form of COVID-19, which carries a greater mortality rate.[2]

The discovery of a possible beneficial effect of vitamin D on the prevalence also severity of acute respiratory tract infections implies that a deficiency in vitamin D may also be connected to the outcome of COVID-19 sickness.[3] Several observational studies have found a substantial link between COVID-19 infection and low levels of vitamin D in the bloodstream. An older research of 489 individuals, whose vitamin D levels were below 20 ng/mL or 1,25-dihydroxycholecalciferol levels were below 18 pg/mL within a year prior to a COVID-19 test, it was found that those with a deficiency in vitamin D (25-hydroxycholecalciferol below 20 ng/mL or 1,25-dihydroxycholecalciferol below 18 pg/mL) had a 77% higher likelihood of testing positive for COVID-19.[3,4]

According to certain research, the supplementation of 25OHD is associated with greater risk of higher mortality among COVID-19 patients during their hospital stay, and it does not significantly improve the length of hospitalization. Conversely, other research has showed that vitamin D supplements lessen the risk of death also the severity of illness. Notably, the administration of high-dose vitamin D supplements has been linked to milder cases of COVID-19 and higher survival rates in elderly.[5] Moreover, polymorphisms in the vitamin D binding protein gene, namely SNP in the rs7041 locus, have been observed to connect with COVID-19 prevalence and death rates, suggesting that genetic factors may possibly have a role to play.[6]

This paper examines the connection with vitamin D deficiency and the severity of COVID-19.

METHODS

The study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project guidelines for data collection, analyzing, and reporting. These considerations guided development of the accepted standards. Aims of this study to investigate connection among vitamin D deficiency with the COVID-19 degree of severity.

These constitute the main difficulties presented by the present research. 1) Publications must constantly be published in English and emphasize connection with vitamin D deficiency and severity of COVID-19 in order to be accepted for publication. 2) The evaluation specifically focused on publications released between 2019 and the timeframe of this review, excluding those published afterwards. Editorial, non-DOI contributions, and critiques of previously published papers, or article whose contents are almost identical with those published in study will not be included in the compilation.

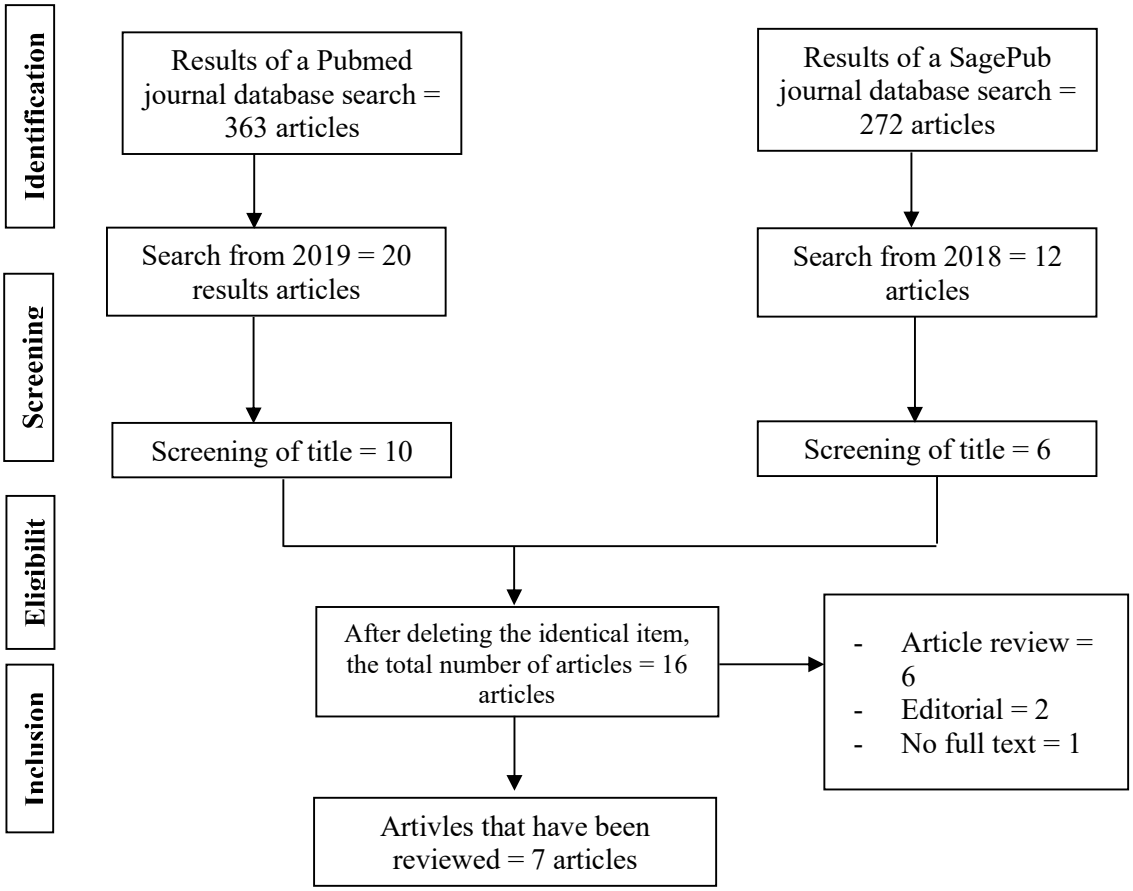

Figure 1. Article search flowchart

The quest for articles that would be reviewed in the systematic review began on March, 16th 2023 by entering the phrases "Vitamin D deficiency" and "COVID-19 severity" into the PubMed and SagePub databases. *("vitamin d deficiency"[MeSH Terms] OR "vitamin d deficiency"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("sever"[All Fields] OR "severe"[All Fields] OR "severed"[All Fields] OR "severely"[All Fields] OR "severer"[All Fields] OR "severes"[All Fields] OR "severing"[All Fields] OR "severities"[All Fields] OR "severity"[All Fields] OR "severs"[All Fields])* is used as search terms.

The eligibility of each study was assessed by the writers by reviewing its abstract and title. Consequently, they primarily relied on historical literature as their main source of reference. Unpublished English contributions were considered only after evaluating numerous studies with similar conclusions. To ensure the systematic review included only papers that met the inclusion criteria, the search results were narrowed down to those that aligned with the specified parameters. Subsequently, the research will undergo evaluation. The examination of the study involved noting the names, authors, publication dates, location, study activities, and parameters. Duplicate articles were eliminated from the database after saving the search results in an EndNote file. Two reviewers evaluated the relevance of each paper's title and abstract to this particular study.

Prior to determining the articles to be further analyzed, each writer thoroughly examined the research presented in the titles and abstracts of the publications. Subsequently, studies that met inclusion criteria and are deemed suitable for inclusion in the review will be evaluated. Once our study is concluded, writer will carefully select relevant publications for reviewing, adhering to the established guidelines for selecting reviewable papers. This process aims to ensure a straightforward and efficient approach to choosing objects for further examination. The selection of previous studies and the rationale for their inclusion in the review, if applicable, will be clearly justified.

RESULT

AlSafar et al (2021) conducted a research with 522 participants, everyone of them confirmed for SARS-CoV-2, were included. The researchers discovered a significant connection with the concentrations of 25(OH)D below 12 ng/mL and a higher probability of severe COVID-19 infection, as well as a higher risk of mortality. Age remained the only additional substantial element associated with risk, however comorbidities and cigarettes had no effect on the results once they were controlled for. The only other independent risk factor was age.[7]

D'Avolio, et al (2020)[8] proposed that vitamin D supplementation could potentially lower infection's possibility; hence, writers evaluated level of 25-hydroxyvitamin D (25(OH)D) concentrations in patient serum. PCR-positive for those with SARS-CoV-2 had substantially reduced concentrations of 25(OH)D ($p = 0.004$) in comparison among patient with PCR-negative (24.6 ng/mL); this was further corroborated by dividing patients based on age >70 years. Based on this initial discovery, vitamin D supplementation may may serve as an effective approach to minimizing infection's risk.

Table 1. Litelature used in this study

Author	Origin	Method	Sample	Conclusion
Alsafar, 2021[7]	United Arab Emirates	Cross sectional study	522 people tested positive for SARS-CoV-2	Values of 25(OH)D below 12 ng/mL significantly correlated among higher probability of severe COVID-19 infection in addition to mortality. Age was the only additional independent factor associated with risk, however comorbidity and smoking had no effect on the results once they were controlled for.
D'Avolio, 2020[8]	Switzerland	Cohort prospective study	27 patients PCR+ for SARS-CoV-2; 80 patients PCR– 1377 controls with 25(OH)D measured	Those who screened confirmed by PCR had substantially reduced concentrations of 25(OH)D ($p = 0.004$) compared to individuals who reported negative (24.6 ng/mL) in this group of patients. This was verified when patients over the age of 70 were grouped together.
Panagiotou, 2020[9]	United Kingdom	Cohort prospective study	134 people tested positive for SARS-CoV-2	It is likely graded supplementation with vitamin D was responsible for the lack of connection between death and baseline 25(OH)D.

Carpagnano, 2021[10]	Italy	Retrospective, observational study	COVID-19 caused acute respiratory failure in 42 individuals	Vitamin D deficiency affected 81% of these patients. The population was divided into four groups based on their vitamin D levels: those with sufficient levels, those with insufficient levels, those with moderately low levels, and those with severely low levels. No variations were detected between demographic and clinical variables. After a duration of 10 days in the hospital, individuals who suffered from severe vitamin D deficiency exhibited a 50% probability of death, while those with vitamin D levels measuring 10 ng/mL had a 5% chance of mortality (p = 0.019).
Murai, 2021[11]	Brazil	Randomized Clinical Trial	240 randomized patients	There was no notable variance in the duration of hospitalization among individuals with COVID-19 spent in the hospital were given either a placebo or a single high dose of vitamin D3. Based on these results, it is not advisable to administer a high dose of vitamin D3 as a treatment for individuals with moderate to severe cases of COVID-19..
Sabico, 2021[12]	Saudi Arabia	Randomized Clinical Trial	A total of 69 adults who tested positive for SARS-CoV-2 using RT-PCR	The administration of 5000 IU of vitamin D3 orally on a daily basis for a duration of two weeks resulted in a reduction in recovery time for cough and loss of gustatory sensation in individuals experiencing mild to severe COVID-19 symptoms and with insufficient vitamin D levels. Patients with inadequate vitamin D levels who have been diagnosed with COVID-19 should consider receiving 5000 IU of vitamin D3 as an adjunctive treatment, even if only for a brief period.
Saponaro, 2022[13]	Italy	Cross sectional	Ninety-three successive COVID-19-related pneumonia patients	Considering the association among 25OHD concentrations and inflammatory indicator levels, it is plausible to assume that these people' levels of vitamin D should be included in the treatment strategy. More research is needed to determine whether vitamin D levels are a predictor of poor prognosis or a risk factor that may be addressed by supplementation.

A research was carried out by Carpagnano, et al (2021)[10]. The participants in the study were separated into four distinct vitamin D categories: none, insufficient, moderately deficient, and severely deficient. There were no variations in demographic nor clinical characteristics. After a period of ten days in the hospital, individuals with severe vitamin D deficiency had a 50% rate of mortality, whereas individuals with vitamin D levels of 10 ng/mL had a 5% mortality rate (p = 0.019). Hypovitaminosis D was frequent among COVID-19 patients in the respiratory distress syndrome ward. Severe lack of vitamin D was connected with a mortality upsurg. Individuals in severe vitamin D deficiency may benefit from adjunctive therapy.

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Murai, et al (2021)[11] found that the distinction in outcomes within the vitamin D3 category among control category that received a placebo did not prove significantly different in regards to mortality in hospitals (7.6% vs 5.1%; difference = 2.5% [95% CI = -4.1-9.2%]; P = 0.43), intensive care unit hospitalization (16.0% vs 21.2%; difference = -5.2% [95% CI = -15.1-4.7%]; P = 0.30), or needed for The sole adverse event associated with the therapy was one case of vomiting.
However the 5000 IU category exhibited a substantial increase in blood concentrations of 25(OH)D during 14 days of therapy (adjusted p = 0.003), according to another research. Within-group compared found that BMI and concentrations of IL-6 decreased significantly as time went on all categories (p-values 0.05), while between-category evaluations have no statistically significant. After djusting for age, gender, baseline BMI, and D-dimer, Kaplan-Meier survival analysis demonstrated that the category receiving 5000 IU cleared cough (6.2 ± 0.8 versus 9.1 ± 0.8; p = 0.039) and ageusia (11.4 ± 1.0 versus 16.9 ± 1.7; p = 0.035) at a significantly faster than the 1000 IU category.

Saponaro, et al (2021)[13] revealed 65% of individuals provided hypovitaminosis D (25OHD ≤20 ng/ml) and indicated significantly higher levels of IL-6 [20.8 (10.9-45.6) vs. 12.9 (8.7-21.1) pg/ml, p = 0.02], CRP [10.7 (4.2-19.2) vs. 5.9 (1.6-8.1) mg/dl, p = 0.003], TNF-α [8.9 (6.0-14.8) vs. 4.4 (1.5-10.6) pg/ml, p = 0.01], D-dimer [0.53 (0.25-0.72) vs. 0.22 (0.17-0.35) mg/l, p = 0.002], and IL-10 [3.7 (1.8-6.9) vs. 2.3 (0.5-5.8) pg/ml, p = 0.03]. Even after accounting for age and gender, a substantial inverse relationship was observed in 25OHD among all of these indicators. Hypovitaminosis D was more common in peoples with severe ARDS than to others (75% vs. 68% vs. 55%, p 0.001), and non-surviving patients had lower levels of 25OHD.

DISCUSSION

Vitamin D is a fat soluble vitamin that synthesized from 7-dehydrocholesterol by UVB light. It is then transformed in the liver to 25(OH)D, and subsequently in kidneys or other organs to the active form (calcitriol 1, 25(OH)D). Vitamin D is necessary for the maintenance of healthy bones and teeth. According to in vitro study, vitamin D, in addition In addition to assisting the body's absorption of calcium and phosphorus through the gastrointestinal tract, it also plays an important function in the body's immune system.[14,15]

Vitamin D deficiency nors inadequacy are widespread illnesses affecting both adults as well as kids worldwide. Its link to metabolic, autoimmune, and viral pathologies has received much attention.[16] This study indicates a correlation between serum 25(OH)D levels and the severity of COVID-19 infection. The preventive benefit of vitamin D supplementation in viral respiratory infections are well-established, also comparable effects for COVID-19 are beginning to appear.[13,17,18]

Principles behind vitamin D's capacity is reducing possibility inflammation caused by bacteria were studied. This is accomplished by generating antimicrobial peptides such as cathelicidins, IL-37, and defensins, which are subsequently released to circulation, enhancing cellular immunity that is inherent. Furthermore, it reduces the cytokine storm by lowering synthesis of inflammatory cytokines as a prime instance IFN and TNF. It also modulates the adaptive immune response by suppress response of Th1 also increasing Th2 cell cytokine production.[18]

The link amongst hypovitaminosis D, inflammation of the airway, and a higher probability of respiratory tract infections started at onset of COVID-19, when a slew of investigations looked at the vitamin D efficacy administration as an adjunctive treatment for respiratory conditions. In addition, there were no disparities in the average time for the initial exacerbation, exacerbation rate, FEV1, admission to the hospital, quality of life, or fatalities in the vitamin D and placebo categories. Analysis of post-hoc in people with vitamin D lack is severe (10 ng/mL) found that the vitamin D category had a significantly lower exacerbation rate.[19,20]

Numerous investigations have shown that vitamin D encourages immune cells to produce antimicrobial peptides such as cathelicidins and defensins. AMPs possess a wide range activities, involving antibacterial and antiviral characteristics, also can inactivate the influenza virus. AMPs' antiviral properties are due, among other things, to cathelicidin's destruction of envelope proteins. Cathelicidins are a specific type of innate immune proteins present in mammals, with LL-37 being the most prevalent form found in humans. LL-37 functions similarly to other antimicrobial peptides by preventing viral entry into cells.[21,22]

Elderly and vulnerable individuals with COVID-19, along with those who had previously received high-dose vitamin D3 supplements before infection, showed improved outcomes in terms of infection survival and severity of illness. However, administering a single dose of 200,000 IU of vitamin D3 did not yield any significant clinical benefits for hospitalized patients with moderate to severe COVID-19, raising doubts about the overall effectiveness of this treatment.[10] On the other hand, another study suggested that vitamin D3 supplementation with a higher dose of 500,000 IU might contribute to early recovery.[12]

Grant et al. recommend a prophylactic approach for individuals at risk of contracting influenza or COVID-19, suggesting a daily intake of 10,000 international units (IU) of vitamin D3. For pregnant women who are part of a quarantine system and have limited sun exposure, it is possible to provide them with lower doses of vitamin D or maintain lower vitamin D levels. However, it remains crucial for these women to supplement their diet with vitamin D and consume nutritious meals.[23]

CONCLUSION

Vitamin D levels less than 12 are a reliable predictor of COVID-19 severity, based on the majority of research. As a result, vitamin D substances are thought to be advantageous for COVID-19 patients.

REFERENCE

[1]. Argano, C., Mallaci Bocchio, R., Natoli, G., Scibetta, S., Lo Monaco, M. and Corrao, S., 2023. Protective Effect of Vitamin D Supplementation on COVID-19-Related Intensive Care Hospitalization and Mortality: Definitive Evidence from Meta-Analysis and Trial Sequential Analysis. Pharmaceuticals, 16(1), p.130.
[2]. Gallo G., Calvez V., Savoia C. Hypertension and COVID-19: Current Evidence and Perspectives. High Blood Press. Cardiovasc. Prev. 2022;29:115–123. doi: 10.1007/s40292-022-00506-9
[3]. Nielsen, N.M., Junker, T.G., Boelt, S.G., Cohen, A.S., Munger, K.L., Stenager, E., Ascherio, A., Boding, L. and

Hviid, A., 2022. Vitamin D status and severity of COVID-19. Scientific Reports, 12(1), p.19823.
[4]. Meltzer, D. O. et al. Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw. Open. 3(9), e2019722. https://doi.org/10.1001/jamanetworkopen.2020.19722 (2020)
[5]. Murai I.H., Fernandes A.L., Sales L.P., Pinto A.J., Goessler K.F., Duran C.S.C., Silva C.B.R., Franco A.S., Macedo M.B., Dalmolin H.H.H., et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19: A Randomized Clinical Trial. JAMA. 2021;325:1053–1060. doi: 10.1001/jama.2020.26848.
[6]. Karcioglu Batur, L. & Hekim, N. Te role of DBP gene polymorphisms in the prevalence of new coronavirus disease 2019 infection and mortality rate. J. Med. Virol. 93(3), 1409–1413 (2021).
[7]. AlSafar H, Grant WB, Hijazi R, Uddin M, Alkaabi N, Tay G, et al. COVID-19 Disease Severity and Death in Relation to Vitamin D Status among SARS-CoV-2-Positive UAE Residents. Nutrients. 2021 May;13(5).
[8]. D'Avolio A, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, et al. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. Nutrients. 2020;12(5):1359.
[9]. Panagiotou G, Tee SA, Ihsan Y, Athar W, Marchitelli G, Kelly D, et al. Low serum 25-hydroxyvitamin D (25 [OH] D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. Clin Endocrinol (Oxf). 2020;93(4):508.
[10]. Carpagnano GE, Di Lecce V, Quaranta VN, Zito A, Buonamico E, Capozza E, et al. Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. J Endocrinol Invest. 2021;44(4):765–71.
[11]. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. JAMA. 2021 Mar;325(11):1053–60.
[12]. Sabico S, Enani MA, Sheshah E, Aljohani NJ, Aldisi DA, Alotaibi NH, et al. Effects of a 2-Week 5000 IU versus 1000 IU Vitamin D3 Supplementation on Recovery of Symptoms in Patients with Mild to Moderate Covid-19: A Randomized Clinical Trial. Nutrients. 2021 Jun;13(7).
[13]. Saponaro F, Franzini M, Okoye C, Antognoli R, Campi B, Scalese M, et al. Is There a Crucial Link Between Vitamin D Status and Inflammatory Response in Patients With COVID-19? Front Immunol. 2021;12:745713.
[14]. Chen Y, Zhang J, Ge X, Du J, Deb DK, Li YC. Vitamin D receptor inhibits nuclear factor κB activation by interacting with IκB kinase β protein. J Biol Chem. 2013;288(27):19450–8.
[15]. Wang T-T, Nestel FP, Bourdeau V, Nagai Y, Wang Q, Liao J, et al. Cutting edge: 1, 25-dihydroxyvitamin D3 is a direct inducer of antimicrobial peptide gene expression. J Immunol. 2004;173(5):2909–12.
[16]. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017;18:153–65.
[17]. Lanham New SA, Webb AR, Cashman KD, et al. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ Nutr Prev Heal. 2020;1–5.
[18]. Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020;12:1–19.
[19]. Jolliffe DA, Greenberg L, Hooper RL, Mathyssen C, Rafiq R, de Jongh RT, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. Thorax. 2019 Apr;74(4):337–45.
[20]. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, Van Eldere J, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2012;156(2):105–14.
[21]. Leikina E, Delanoe-Ayari H, Melikov K, Cho M-S, Chen A, Waring AJ, et al. Carbohydrate-binding molecules inhibit viral fusion and entry by crosslinking membrane glycoproteins. Nat Immunol. 2005;6(10):995–1001.
[22]. Dürr UHN, Sudheendra US, Ramamoorthy A. LL-37, the only human member of the cathelicidin family of antimicrobial peptides. Biochim Biophys Acta (BBA)-Biomembranes. 2006;1758(9):1408–25.
[23]. Mirzadeh M; Khedmat L. Pregnant women in the exposure to COVID-19 infection outbreak: the unseen risk factors and preventive healthcare patterns. J Matern Neonatal Med. 2020;