Relationship between COVID-19 and Vitamin D: Meta-analysis

[1]Dr.Thenmozhi.P, [2]M.Ashifa

[1]*Associate Professor, Medical Surgical Nursing Department, Saveetha College of Nursing, Saveetha Institute of Medical and Technical Sciences, Chennai, India*
[2]*B.Sc(N) IV Year, Saveetha College of Nursing, Saveetha College of Nursing, Saveetha Institute of Medical and Technical Sciences, Chennai, India*

ABSTRCT
Since the onset of the outbreak of COVID-19, many pharmaceutical agents that could have been proposed against corona virus. Several studies have evaluated the possible correlations that might exist between the agents and the SARS-CoV-2 infection pathway including potential role of vitamin D in its ability to prevent COVID-19 infection and/or fatalities.Hence, the aim of this meta-analysis is to summarize the evidence regarding the relationship between vitamin D and COVID-19. More than 20 articles reviewed from various sources of database such as google scholar, pub med, researchgate, medRxiv, web of science, science direct, medline and embase from January 2020 to March 2021.This analysis report reveal that Vitamin D is an essential for immunomodulation among people infected with COIVD 19 form the age group of childhood to old age. Vitamin D insufficient or deficient people more risk for getting covid infection and mortality rate also high if they infected with COVID 19. Vitamin D supplementation shows good progress in recovery from COVID 19 and improves the survival rate of the patients admitted in ICU. However more clinical trial or randomized control trail with large sample is required to calculate the exact dosage according to the age, comorbid conditions and severity of COVID 19 infection.

I. INTRODUCTION

The Corona virus disease 2019 (COVID-19) is a new type of infectious disease and its first transmission was identified in Wuhan, China in December 2019, consequently it spreads worldwide [1]. Every individual's immune defenses play a major role in mitigating the impact of Covid 19 such as morbidity and mortality [2]. The SARS-CoV-2 virus appears to infect individuals through an immune evasion process that can lead to the development of ARDS by a subsequent hyper reaction process and cytokine storm [3]. Vitamin D has diverse and extensive effects and plays a modulatory role on the immune system, as it increases the secretion of numerous antiviral peptides to support innate immunity and reducing the overactive adaptive immune response [4].

Naturally, Vitamin-D is a fat soluble vitamin and occurs in the form of Vitamin D2(Ergocalciferol) and VitaminD3(Cholecalciferol) which differ structurally. It is an endogenously produced steroid hormone that can be absorbed from exposure to sunlight, during which the protein 7-dehydrocholesterol (7-DHC) in the skin interacts with ultraviolet B rays and subsequently gets converted into the active form of vitamin D, which is vitamin D3. Once vitamin D enters the bloodstream, it can be used to assist the body in absorbing calcium, which helps to strengthen bones, allow for muscle movement, provide nerves with the ability to transmit messages between the brain and other parts of the body, as well as work with the immune system to fight off invading pathogens like bacteria and viruses [5]. Vitamin D reduces the production of inflammatory cytokines, such as interleukin-2 and interferon-gamma. Furthermore, in close connection, multiple pleiotropic effects have been demonstrated on the actions of vitamin D at the anti-inflammatory and immunomodulatory level with positive results in studies with influenza, coronavirus, and other respiratory infections[6]. Prior to the COVID-19 pandemic, several in vitro studies demonstrated that vitamin D plays an important role in local respiratory homeostasis through either its ability to promote the secretion of antimicrobial peptides or by directly interfering with the replication of respiratory viruses.

One of the first studies to correlate vitamin D and SARS-CoV-2 was a genetic study looking to identify repressors and activators of the ACE2 and FURIN genes, both of which have been found to be necessary for the entry of this virus into human cells. In addition to its non-enzymatic

synthesis, vitamin D is enzymatically converted into its active form—1,25-dihydroxyvitamin D [1,25(OH)2D]—in the kidneys and liver mainly, although it is also produced in other organs, tissues, and cells, such as prostate, placenta, lungs, brain, and immune cells [3]. Since the onset of the outbreak, many agents that could have efficacy against COVID-19 have been proposed. Several studies have evaluated the possible correlations that might exist between this nutrient and the SARS-CoV-2 infection pathway including potential role of vitamin D in its ability to prevent COVID-19 infection and/or fatalities. However as of this time, there is no known effective pharmaceutical treatment, although it is much needed for patient contracting the severe form of the disease. Hence, the aim of this meta-analysis is to summarize the evidence regarding the relationship between vitamin D and COVID-19.

II. MATERIALS AND METHODS

A quantitative approach with meta-analysis was adopted to link the relationship between the vitamin D and COVID 19. More than 20 articles reviewed from various sources of database such as google scholar, pub med, researchgate, medRxiv, web of science, science direct, medline and embase from January 2020 to March 2021. Included the findings from the meta-anaylsis, systemic review, cohort study, retrospective observational study and randomized control trials.

III. RESULTS:

The meta-analysis included more than 15 studies from various sources and the findings are discussed below. This analysis report reveal that Vitamin D is an essential for immunomodulation among people infected with COIVD 19 form the age group of childhood to old age. Moreover Vitamin D supplementation has been shown as an effective and safe against acute respiratory tract infections. Vitamin D insufficient or deficient people more risk for gettingcovid infection and mortality rate also high if they infected with COVID 19. Vitamin D supplementation shows good progress in recovery from COVID 19 and improves the survival rate of the patients admitted in ICU.

IV. DISCUSSION:

D. De Smet, K. De Smet, K et al had conducted the retrospective observational study at Central network hospital to investigate the level of vitamin D deficiency in West Flanders, Belgium and its correlation to severity of COVID-19 as staged by CT with 186 SARS-CoV-2-infected patients hospitalized from March 1, 2020 to April 7, 2020 and concluded that vitamin D deficiency is a prevalent risk factor for severe COVID-19. Vitamin D supplementation might be an inexpensive and safe mitigation for the SARS-CoV-2 pandemic. Main outcome measure was analysis of 25(OH)D in COVID-19 patients versus season/age/sex-matched diseased controls [7].RoyaGhasemian, Amir Shamshirian et al had rapid systematic review and meta-analysis along with an ecological investigation in order to maximize the use of everything that exists about the role of vitamin D in the COVID-19. A systematic search was performed in PubMed, Scopus, Embase, Cochrane Library, Web of Science and Google Scholar (intitle) as well as preprint database of medRxiv, bioRxiv, Research Square, preprints.org, search engine of ScienceDirect and a rapid search through famous journals up to August 4, 2020. The study found that a high percentage of COVID-19 patients who suffer from vitamin D deficiency or insufficiency as well as a significant increased risk of COVID-19 infection in patients with low levels of vitamin D [8].Anshul Jain et al, had conducted a continuous prospective observational study to analyze the vitamin D level in COVID-19 patients and its impact on the disease severity at M.L.B Medical College and reported that the fatality rate was high in vitamin D deficient (21% vs 3.1%). Vitamin D level is markedly low in severe COVID-19 patients. Inflammatory response is high in vitamin D deficient COVID-19 patients. This all translates into increased mortality in vitamin D deficient COVID-19 patients [9].Nurshad Ali had conducted a systemic review to discuss the possible roles of vitamin D in reducing the risk of COVID-19 and other acute respiratory tract infections and severity.Several studies demonstrated the role of vitamin D in reducing the risk of acute viral respiratory tract infections and pneumonia due to direct inhibition with viral replication or with anti-inflammatory or immunomodulatory ways. In the meta-analysis, vitamin D supplementation has been shown as safe and effective against acute respiratory tract infections. However, concluded that there is not enough evidence on the association between vitamin D levels and COVID-19 severity and mortality. Therefore, randomized control trials and cohort studies are necessary to test this hypothesis [10].VadirBaktash et al had conducted a

prospective cohort study to assess the importance of vitamin D deficiency in older patients with COVID-19 and reported that older adults with vitamin D deficiency and COVID-19 may demonstrate worse morbidity outcomes. Vitamin D status may be a useful prognosticator [11].William B Grant et al discussed with several observational studies and clinical trials and reported that vitamin D supplementation reduced the risk of influenza, whereas others did not. Evidence supporting the role of vitamin D in reducing risk of COVID-19 includes that the outbreak occurred in winter, a time when 25-hydroxyvitamin D (25(OH)D) concentrations are lowest; that vitamin D deficiency has been found to contribute to acute respiratory distress syndrome; and that case-fatality rates increase with age and with chronic disease comorbidity, both of which are associated with lower 25(OH)D concentration. To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d. The goal should be to raise 25(OH)D concentrations above 40-60 ng/mL (100-150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D3 doses might be useful. Randomized controlled trials and large population studies should be conducted to evaluate these recommendations [12].PetreCristianIlie et al,stated that Vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland. This is also the most vulnerable group of population for COVID-19 [13].F. M. Panfili et al.,had reviewed the literature about the immunomodulatory role of Vitamin D collecting data from the databases Medline and Embase. Vitamin D proved to interact both with the innate immune system, by activating Toll-like receptors (TLRs) or increasing the levels of cathelicidins and β-defensins, and adaptive immune system, by reducing immunoglobulin secretion by plasma cells and pro-inflammatory cytokines production, thus modulating T cells function. Promising results have been extensively described as regards the supplementation of vitamin D in respiratory tract infections, autoimmune diseases and even pulmonary fibrosis. In this review, suggested that vitamin D supplementation might play a role in the prevention and/or treatment to SARS-CoV-2 infection disease, by modulating the immune response to the virus both in the adult and pediatric population [14].

Marcos Pereira et al,had conducted a systematic review and meta-analysis to analyze the association between vitamin D deficiency and COVID-19 severity, via an analysis of the prevalence of vitamin D deficiency and insufficiency in people with the disease. Five online databases-Embase, PubMed, Scopus, Web of Science, ScienceDirect and pre-print Medrevixwere searched. Vitamin D deficiency was not associated with a higher chance of infection by COVID-19, but identified that severe cases of COVID-19 present 64% more vitamin D deficiency compared with mild cases. A vitamin D concentration insufficiency increased hospitalization and mortality from COVID-19 and also observed a positive association between vitamin D deficiency and the severity of the disease [15].RuhulMunshi, et al.,systematically explore the association of vitamin D serum levels with COVID-19 severity and prognosis. Serum vitamin D levels could be implicated in the COVID-19 prognosis. Diagnosis of vitamin D deficiency could be a helpful adjunct in assessing patients' potential of developing severe COVID-19. Appropriate preventative and/or therapeutic intervention may improve COVID-19 outcomes [16].PetreCristianIlie et al,had conducted a study to propose an hypothesis that there is a potential association between mean levels of vitamin D in various countries with cases and mortality caused by COVID-19. Vitamin D levels are severely low in the aging population especially in Spain, Italy and Switzerland. This is also the most vulnerable group of the population in relation to COVID-19. It should be advisable to perform dedicated studies about vitamin D levels in COVID-19 patients with different degrees of disease severity [17].Frank H et al, had determined the prevalence of vitamin D insufficiency among COVID-19 intensive care unit (ICU) patients.Vitamin D insufficiency is highly prevalent in severe COVID-19 patients. Vitamin D insufficiency and severe COVID-19 share numerous associations including hypertension, obesity, male sex, advanced age, concentration in northern climates, coagulopathy, and immune dysfunction. Thus, suggest that prospective, randomized controlled studies of Vitamin D insufficiency in COVID-19 patients are warranted [18].D M McCartney et al reviewed that Vitamin D supplementation has also been shown to reduce the risk of respiratory infection. Vitamin D deficiency is common and may contribute to increased risk of respiratory infection including Covid-19 and recommend that all older adults, hospital inpatients,

nursing home residents and other vulnerable groups (e.g. those with diabetes mellitus or compromised immune function, those with darker skin, vegetarians and vegans, those who are overweight or obese, smokers and healthcare workers) be urgently supplemented with 20-50µg/d of vitamin D to enhance their resistance to Covid-19, and that this advice be quickly extended to the general adult population [19]. David O Meltzer had conducted a single-center, retrospective cohort study found that deficient vitamin D status was associated with increased COVID-19 risk, and also that suggests that randomized trials may be needed to determine whether vitamin D affects COVID-19 risk [20].David A Jolliffe et al,had conducted a systematic review and meta-analysis of data from randomised controlled trials (RCTs) of vitamin D for acute respiratory tract infection prevention using a random effects model. Vitamin D supplementation was safe and reduced risk of acute respiratory tract infection, despite evidence of significant heterogeneity across trials. Protection was associated with administration of daily doses of 400-1000 IU vitamin D for up to 12 months. The relevance of these findings to COVID-19 is not known and requires investigation [21]. K Shah had conducted meta-analysis to understand the effect of oral supplementation of vitamin D on intensive care unit (ICU) requirement and mortality in hospitalized COVID-19 patients. The findings indicate that potential role of vitamin D in improving COVID-19 severity in hospitalized patients, more robust data from randomized controlled trials are needed to substantiate its effects on mortality [22].

V. CONCLUSION

The meta-analysis study concluded that vitamin D supplementation is needed for the treatment of COVID-19 patients to decrease the mortality and morbidity. Vitamin D is not expensive, less side effects and safest therapeutic intervention for better outcome of COVID 19 treatment. However more clinical trial or randomized control trail with large sample isrequired tocalculate the exact dosage according to the age, comorbid conditions and severity of COVID 19 infection.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

[1]. Raoult D, Zumla A, Locatelli F, et al. Coronavirus infections: epidemiological, clinical and immunological features and hypotheses. Cell Stress, 2020;4(4):66-75.
[2]. Aranow C. Vitamin D and the immune system. Journal of Investigative Medicine, 2011;59(6):881-886.
[3]. https://www.news-medical.net/health/Vitamin-D-and-COVID-19.aspx
[4]. Arnljots R, Snaebjo¨rnssonArnljots E, Thorn J, et al. Bacteriuria and vitamin D deficiency: a cross sectional study of 385 nursing home residents. BMC Geriatrics, 2019;19(1):381.
[5]. Rie B. Jäpelt, JetteJakobsen. Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. Frontiers in Plant Sceinces, 2013; 4: 136.
[6]. Mansur JL, Tajer C, Mariani J, et al. Vitamin D high doses supplementation could represent a promising alternative to prevent or treat COVID-19 infection. Clínica e Investigación en Arteriosclerosis,2020;32(6):267-277.
[7]. D. De Smet, K. De Smet, P. Herroelen, S. Gryspeerdt, G.A. Martens. Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. medRxiv preprint Server for Health Sciences, 2020. doi: https://doi.org/10.1101/2020.05.01.20079376
[8]. RoyaGhasemian, Amir Shamshirian et al. The Role of Vitamin D in The Age of COVID-19: A Systematic Review and Meta-Analysis Along with an Ecological Approach. medRxiv preprint Server for Health Sciences, 2020. doi: https://doi.org/10.1101/2020.06.05.20123554
[9]. Anshul Jain, RachnaChaurasia, Narendra Singh Sengar, Mayank Singh, Sachin Mahor,5 SumitNarain. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Scientific Reports, 2020; 10: 20191.
[10]. Nurshad Ali. Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of infection and public health. 2020 Oct; 13(10): 1373–1380.

[11]. VadirBaktash, Tom Hosack, Nishil Patel, et al. Vitamin D status and outcomes for hospitalised older patients with COVID-19. Postgraduate Medical Journal, 2020-138712.

[12]. William B Grant, Henry Lahore, Sharon L McDonnell, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients2020 Apr 2;12(4):988.

[13]. PetreCristianIlie, SiminaStefanescu, Lee Smith. The role of Vitamin D in the prevention of Coronavirus Disease 2019 infection and mortality. Research Square, DOI:10.21203/rs.3.rs-21211/v1

[14]. F. M. Panfili, M. Roversi, P. D'Argenio, P. Rossi, M. Cappa, D. Fintini. Possible role of vitamin D in Covid-19 infection in pediatric population. Journal of endocrinological investigation. 2020 Jun 15 : 1–9

[15]. Marcos Pereira, AlialdoDantasDamascena, LayllaMirellaGalvãoAzevedo, et al. Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Critical reviews in food science and nutrition, 2020 Nov 4;1-9. doi: 10.1080/10408398.2020.1841090.

[16]. RuhulMunshi, Mohammad H Hussein, Eman A Toraih , Rami M Elshazli, et al. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. Journal of medical virology, 2021 Feb;93(2):733-740.

[17]. PetreCristianIlie, SiminaStefanescu, Lee Smith.The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging clinical and experimental research.. 2020 May 6 : 1–4.

[18]. Frank H. Lau, RinkuMajumder, RadbehTorabi, FouadSaeg, Ryan Hoffman, Jeffrey D. Cirillo, Patrick Greiffenstein. Vitamin D insufficiency is prevalent in severe COVID-19. medRxiv preprint Server for Health Sciences, 2020. doi: https://doi.org/10.1101/2020.04.24.20075838.

[19]. D M McCartney, D G Byrne. Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Irish medical journal, 2020 Apr 3;113(4):58.

[20]. David O Meltzer, Thomas J Best, Hui Zhang, Tamara Vokes, VineetArora, Julian Solway. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. JAMA Netw Open, 2020 Sep 1;3(9):e2019722.

[21]. David A Jolliffe, Carlos A Camargo Jr, John D Sluyter, et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials. medRxiv, 2020 Nov 25;2020.07.14.20152728.

[22]. K Shah, D Saxena, D Mavalankar. Vitamin D supplementation, COVID-19 and disease severity: a meta-analysis. An International Journal of Medicine, 2021; 114(3):175–181