

Vitamin-D Supplementation in COVID-19: Existing Evidence and Gap in Literature

Muhammad Abbas Abid, Hafsa Majid and Aysha Habib Khan

Department of Pathology and Laboratory Medicine, The Aga Khan University, Karachi, Pakistan

ABSTRACT

Review of literature on effectiveness of vitamin D in COVID-19 infection demonstrated a positive effect in COVID-19 patients. However, the studies are limited either due to small sample size or are conducted in a select subset of patients. Gaps on proof-of-concept or a cause-effect relationship related to the use of vitamin D in COVID-19 infection still exist. COVID-19 related benefits of vitamin D have not been validated and are still hypothetical. Administration of high amounts of vitamin D, without clinical indication, could result in toxicity and harmful consequences. Large, multi-centre, placebo-controlled clinical trials in patients with varying severity of COVID-19 infection are needed to establish the role of vitamin D supplementation as an inexpensive therapeutic tool to fight the ongoing pandemic. Administration of vitamin D in already sufficient population should be held until concrete evidence is being established.

Key Words: COVID-19, Vitamin D, Knowledge gap, Literature review, Clinical trials, Update.

How to cite this article: Abid MA, Majid H, Khan AH. Vitamin-D Supplementation in COVID-19: Existing Evidence and Gap in Literature. *J Coll Physicians Surg Pak* 2021; **31(JCPSPCR)**:CR152-CR154.

INTRODUCTION

The severity and mortality of coronavirus disease 2019 (COVID-19) has shown wide variations globally, with countries located more northerly in the northern hemisphere reported to have higher mortality. An estimated increase of 4.4% in mortality for every 1-degree latitude north of 28 degrees north has been reported. One possible explanation proposed for this geographic disparity is the impact of vitamin D on the immune system.¹

Studies from other regions of the world have also demonstrated positive correlation between vitamin D deficiency and COVID-19 severity. A study from Iran reported higher mortality in patients with lower 25-(OH)D levels.² Similar results were reported from other South Asian countries including India.³ Similarly, a study from Africa shows that lower vitamin D levels were significantly associated with higher blood levels of inflammatory markers, higher CT chest severity score, and longer disease duration.⁴

Certain vitamin D receptor (VDR) gene alleles are associated with increased susceptibility to respiratory infections due to their role in the immune system.

The active vitamin D metabolite, calcitriol, has been shown to suppress the inflammatory cytokines of macrophages along with respiratory epithelial cells to various pathogens and respiratory viruses.⁵ A preclinical study on mouse models showed that vitamin D (calcitriol) supplementation improved outcomes of H5N1 driven lipopolysaccharide (LPS) induced lung injury and acute respiratory distress syndrome (ARDS).⁵ So, the proposed effects of vitamin D include activation of VDR signalling pathway to generate beneficial effects in ARDS by reducing the cytokine/chemokine storm, renin-angiotensin system (RAS), modulating neutrophil activity, and by preserving the integrity of the pulmonary epithelial barrier, stimulating epithelial repair and reducing coagulability.⁶ A computational model using combined molecular docking, molecular dynamics simulations and binding free energy studies to explore the possible role of vitamin D3 in inhibiting the SARS-CoV-2 receptor binding domain (RBD) from binding to angiotensin-converting enzyme 2 (ACE2), showed that vitamin D3 and its derivatives can be promising adjuvant therapy for COVID-19.⁷

Hence, there is evidence showing vitamin D deficiency as an independent risk factor for COVID-19. But these findings cannot be expanded to include the hypothesis that vitamin D could serve as a possible treatment for COVID-19. Huge knowledge gaps exist in both literature and understanding about the effects of vitamin D status before contracting the infection or treatment with vitamin D to reduce morbidity and mortality.

The possibility that vitamin D could impact the natural course of COVID-19 at multiple steps, led to an increasing interest in understanding the effects of vitamin D in different complications of COVID-19.

*Correspondence to: Dr. Aysha Habib Khan, Department of Pathology and Laboratory Medicine, The Aga Khan University, Stadium Road, Karachi, Pakistan
E-mail: aysha.habib@aku.edu*

Received: June 24, 2021; Revised: August 25, 2021;

Accepted: August 27, 2021

DOI: <https://doi.org/10.29271/jcpsp.2021.JCPSPCR.CR152>

Table I: Details of the Vitamin-D trials in COVID-19 patients.

Author	Country	Date published	Study design	Population type	Sample size	Treatment group size	Treatment given	Dose of vitamin D	Results	Limitations
Annweiler <i>et al.</i>	France	October, 2020	Quasi experimental	Geriatric	66	57	Bolus vitamin D3	80,000 IU every 2-3 months	Less severe COVID-19 and ↑ survival rate	Small sample size Only nursing home residents Less robust than RCT Not placebo-controlled Not randomized
Annweiler <i>et al.</i>	France	November, 2020	Quasi experimental	Geriatric	77	45	Bolus vitamin D3	50,000 IU every month or 80,000, 100,000 IU every 2-3 months	Less severe COVID-19 and ↑ survival rate	Small sample size Only hospitalized frail elderly patients Less robust than RCT Not placebo-controlled
Castillo <i>et al.</i>	Spain	October, 2020	Pilot randomized clinical trial	All ages	76	50	Oral Calcifediol	0.532mg at admission, followed by 0.266 weekly	↓ ICU treatment need	Small sample size Not double blind Not placebo-controlled
Tan <i>et al.</i>	Singapore	September, 2020	Cohort observational	≥50 years	43	17	Oral vitamin D, magnesium, vitamin b12	1000 IU daily	↓ Clinical deterioration	Small sample size Retrospective cohort design Not randomized
Rastogi <i>et al.</i>	India	November, 2020	RCT	36-51	40	16	Oral Cholecalciferol	60,000 IU daily for 7 days	Quicker seronegativity. Significant ↓ fibrinogen	Small sample size. Short duration. Mildly symptomatic or asymptomatic population.

RCT = Randomised controlled trial; 25 (OH) D = 25-hydroxyvitamin D (Pubmed: March 11, 2021).

The National Institute of Health (NIH) clinical trials database (www.clinicaltrials.gov) has 39 registered clinical trials (as on December 1st, 2020) of vitamin D in COVID-19 patients. Only three of these trials have been completed. A search of PubMed (March 11, 2021) with search terms “COVID-19, vitamin D” and “COVID-19, 25 (OH)D” produced 482 and 4 results, respectively. Only five studies reported the results of intervention with vitamin D in COVID-19 patients.

One quasi-experimental study with 66 subjects from a French nursing home reported decreased severity of COVID-19 and higher survival rates in patients receiving vitamin D supplementation prior to or during the COVID-19 infection.⁸ The same group presented similar results in another quasi-experimental study with vitamin D supplementation in 77 patients of COVID-19 in a geriatric unit.⁹ A randomised pilot study consisting of 76 subjects showed that administration of bolus vitamin D3 significantly reduced admissions to the intensive care unit (ICU) among hospitalised COVID-19 patients.⁶ Another study on cohort of 43 patients, 17 of whom received a combination of vitamin D, magnesium, and vitamin B12 and demonstrated a significant reduction in clinical deterioration and the need for supplemental oxygen and ICU admission.¹⁰ Rastogi *et al.* performed a short-term, high-dose vitamin D, randomised, placebo-controlled trial. They reported significantly quicker COVID-19 seronegative results in the intervention arm with significant reduction in fibrinogen levels.¹¹ Although all five studies demonstrate a positive effect of vitamin D in COVID-19 patients, these studies are limited either due to small sample size or were conducted in a select subset of patients.

The characteristics of these studies are outlined in Table I. Other studies, suggesting a positive correlation in vitamin D deficiency and mortality and severity of COVID-19, are retrospective and exhibit inherent biases.

A recent study from Spain, the Barna-COVIDIOL study, was published as a preprint with The Lancet Infectious Diseases, on January 22 2021. The study reported that 36 of 551 (6.5%) patients treated with calcifediol at admission died, compared with 57 of 379 (15%) controls who did not receive calcifediol ($p = .001$). Similarly, of the calcifediol-treated patients, 30 (5.4%) required admission to ICU, compared with 80 of 379 controls (21.1%; $p < .0001$). However, the study met with a raft of criticism due to a lack of detail regarding methodology, specifically the randomization process, and was eventually removed from Lancet server. [HYPERLINK \l "12](#) This preprint was a first, large-scale, randomized controlled trial, reporting the impact of vitamin D in COVID-19 patients and reported that vitamin D (calcifediol, [25(OH)D3]) administration in patients hospitalized with COVID-19 reduced mortality significantly.

Gaps in knowledge exist regarding the association that vitamin D administration will result in improvement of COVID-19 patients; and the notion that vitamin D could be used for the treatment of COVID-19 patients is still a hypothesis. No study, to date, has established proof-of-concept or demonstrated a cause-effect relationship including reports from Pakistan. Furthermore, vitamin D is not a harmless drug. Administration of high amounts of vitamin D without clinical correlation could result in toxicity and harmful consequences. Care in vitamin D replacement is warranted to

avoid abnormalities in the calcium-vitamin D-parathyroid hormone (PTH) axis. Food sources and lifestyle factors should be encouraged. This will aid in improving the immune system, while also providing long-term health benefits till the time evidence is established regarding the role of vitamin D in the management of COVID-19.

This also calls for large, multi-centre, placebo-controlled clinical trials that study COVID-19 patients with different severity of the disease. Randomised clinical trial documentation of vitamin D supplementation being associated with a positive outcome in COVID-19 patients would provide an inexpensive and accessible addition to current treatment protocols that is easy to disseminate to a larger population considerably rapidly as compared to other more complex interventions. Furthermore, the possible improvement of COVID-19 patients is just one aspect served by vitamin D. Its overall benefit on individuals' and the community's general well being is substantial.

As the COVID-19 related benefits of vitamin D have not been validated yet, so its supplementation to replace preexisting deficiency should be the cornerstone in patients suffering from COVID-19. Administration of vitamin D in already sufficient population should be held until concrete evidence has been established. Prospective, community-based studies are needed urgently to establish the efficacy of vitamin D supplementation as an inexpensive therapeutic tool to fight the ongoing pandemic.

ETHICAL APPROVAL:

Not applicable.

PATIENTS CONSENT:

Not applicable

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

MAA: Literature search, and write-up.

HM: Literature search, and review.

AHK: Idea, literature search, review and critical input.

REFERENCES

- Rhodes JM, Subramanian S, Laird E, Griffin G, Kenny RA. Perspective: Vitamin D deficiency and COVID-19 severity-plausibly linked by latitude, ethnicity, impacts on cytokines, ACE2 and thrombosis. *J Intern Med* 2021; **289**(1):97-115. doi: 10.1111/joim.13149.
- Shakeri H, Azimian A, Ghasemzadeh-Moghaddam H, Safdari M, Haresabadi M, Daneshmand. Evaluation of the relationship between serum levels of zinc, vitamin B12, vitamin D, and clinical outcomes in patients with COVID-19. *J Med Virol* 2021. doi: 10.1002/jmv.27277.
- Nimavat N, Singh S, Singh P, Singh SK, Sinha N. Vitamin D deficiency and COVID-19: A case-control study at a tertiary care hospital in India. *Ann Med Surg* 2021; **68**:102661. doi: 10.1016/j.amsu.2021.102661.
- Teama M, Abdelhakam DA, Elmohamadi MA, Badr FM. Vitamin D deficiency as a predictor of severity in patients with COVID-19 infection. *Sci Prog* 2021; **104**(3): 368504211036854. doi: 10.1177/00368504211036854.
- Huang F, Zhang C, Liu Q, Zhao Y, Zhang YT, Qin Y, et al. Identification of amiripityline HCl, flavin adenine dinucleotide, azacitidine and calcitriol as repurposing drugs for influenza A H5N1 virus-induced lung injury. *PLoS Pathog* 2020; **16**(3):e1008341. doi: 10.1371/journal.ppat.1008341.
- Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda F. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomised clinical study." *J Steroid Biochem Mol Biol* 2020; **203**:105751. doi: 10.1016/j.jsbmb.2020.105751.
- Song Y, Qayyum S, Greer RA, Slominski RM, Raman C, Slominski AT, et al. Vitamin D3 and its hydroxyderivatives as promising drugs against COVID-19: A computational study. *J Biomol Struct Dyn* 2021; 1-17. doi: 10.1080/07391102.2021.1964601.
- Annweiler C, Hanotte B, Grandin de l'Eprevier C, Sabatier JM, Lafaie L, Célarier T. Vitamin D and survival in COVID-19 patients: A quasi-experimental study. *J Steroid Biochem Mol Biol* 2020; **204**:105771. doi: 10.1016/j.jsbmb.2020.105771.
- Annweiler G, Corvaisier M, Gautier J, Dubée V, Legrand E, Sacco G, et al. Vitamin D supplementation associated to better survival in hospitalised frail elderly COVID-19 patients: The Geria-COVID quasi-experimental study. *Nutrients* 2020; **12**(11):3377. doi: 10.3390/nu12113377.
- Tan CW, Ho LP, Kalimuddin S, Pei Zhi Chong B, Ean The Y, Yee Thien S, et al. Cohort study to evaluate the effect of vitamin D, magnesium, and vitamin B(12) in combination on progression to severe outcomes in older patients with coronavirus (COVID-19). *Nutrition* 2020; **79**(80):111017. doi: 10.1016/j.nut.2020.111017.
- Rastogi A, Bhansali A, Khare N, Suri V, Yaddanapudi N, Sachdeva N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: S randomised, placebo-controlled, study (SHADE study). *Postgrad Med J* 2020; postgradmedj-2020-139065. doi: 10.1136/postgradmedj-2020-139065.
- Nogues X, Ovejero D, Pineda-Moncusí M, Bouillon R, Arenas D, Pascual J, et al. Calcifediol treatment and COVID-19-related outcomes. *J Clin Endocrinol Metab* 2021; dgab405. doi: 10.1210/clinem/dgab405.

•••••