

Educational Forum

Vitamin D micronutrient and COVID-19: the missing link

Sanjukta Mishra^{1*}, Amaresh Mishra², Swarnalata Das³

¹Department of Biochemistry, ²Department of Surgery, ³Department of Padiatrics, Kalinga Institute of Medical Science, KIIT University, Bhubaneswar, Odisha, India

Received: 24 January 2021

Revised: 05 February 2021

Accepted: 06 February 2021

*Correspondence:

Dr. Sanjukta Mishra,

E-mail: drmsanjukta@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

The current onset and expeditious increase of COVID-19, caused by severe acute respiratory distress syndrome coronavirus (SARS-CoV-2), has established a global health predicament. Declared as pandemic and public health emergency by the World Health Organization (WHO), it follows an extremely heterogeneous course from mild flu like symptoms to severe acute respiratory distress syndrome. This outbreak intimidates the public with human to human escalation, which is the primary concern worldwide with a still unforeseeable result. With limited data on plausible therapy and vaccination, it is significant to unravel the virulence mechanism of SARS-CoV-2 to delineate chemoprevention that might curb the fatal outcome. It may be acknowledged here that the primary stage of disease prevention depends on the protective immune response to eliminate the virus. This postulation kindles interest in the intervention of vitamin D micronutrient, which might unfold the feasibility of slowing disease advancement and decreasing the risk of mortality. Taking into account, the wide spectrum of beneficial effects ascribed to vitamin D like antiviral, immunomodulatory, anti-inflammatory, and antioxidant action, it can be administered to affect immune cell proliferation and angiotensin-converting enzyme (ACE) 2 expression, which is the basis of pathogenesis of transmission of SARS-CoV-2. Recently, several observational clinical and epidemiological studies underline the hypothesis regarding mean vitamin D level and COVID-19 mortality. More so some retrospective analysis reported the correlation between vitamin D level and disease severity. Nevertheless, potential clinical researches and randomised control trials are recommended in COVID-19 patients with different levels of disease extremity to appraise the useful outcomes.

Keywords: COVID-19, Immunomodulatory, Transmission, Mortality

INTRODUCTION

Emergence of novel coronavirus (2019-nCoV) pandemic is a major global health threat with an unpredictable consequence.¹ The virus was assumed to be zoonotic origin and was transmitted to humans through unidentified intermediary animals in Wuhan, Hubei province, China in December 2019.² This is the third coronavirus in the past two decades including Severe respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 and Middle East respiratory coronavirus (MERS-CoV) in 2012. This novel coronavirus was named as SARS-CoV-2 by the International Committee on taxonomy of virus (ICTV),

due to its high homology to SARS-CoV and due to its ability to use the same human angiotensin converting enzyme-2 (ACE2 receptor), which is highly expressed in the apical side of lungs epithelial cells in the alveolar space, contributing to human to human transmission by infected droplets within the incubation period.^{3,4} Corona virus disease 2019 (COVID-19) has been categorized as a global health crisis. As of 1st week September 2020, around 27 million cases have been reported worldwide and more than 9 lakh succumbed to the illness (3.26% estimated mortality rate).⁵ Based on reports, India has become the second worst coronavirus hit country with a total number of cases reaching 42 lakh with highest daily

surge of cases in world. Major causes of death comprise of severe pneumonia, acute kidney failure, and acute heart failure.⁶ Epidemiological studies have acknowledged several risk factors such as old age (more than 65 years), immunocompromised state, and pre-existing medical comorbidities like diabetes, hypertension, and kidney disease.⁷ The novel coronavirus (2019-nCoV), an enveloped, positive, single-stranded RNA virus, is confirmed to be a member of beta coronavirus with spike glycoprotein on the envelope.⁸ Spike glycoprotein on the outer surface of the virus, with S1 and S2 subunits, takes the accountability of attachment and invasion into the host cell, which is the major mechanism of transmission.⁹ Data so far available explain and support dysregulation of host immune response in patients with COVID-19 that might induce a cytokine storm, and generate a series of immune response to damage the corresponding organs leading to severity and increased mortality.¹⁰ CoV-19 infection provokes acute inflammation which is mediated by proinflammatory cytokines including interleukin (IL) (IL-1, IL-6, IL-8), tumor necrosis factor (TNF- α) which are identified to accomplish the pathogenesis and exacerbate the clinical picture of the disease.¹¹ Release of IL-1 by immune cells, fibroblasts and endothelial cells in response to pathogenic virus may provoke acute and chronic obstructive respiratory disease leading to pulmonary fibrosis. In view of unprecedented health, socio-economic crisis, and dearth of therapeutic strategies, the greatest challenge to build resilience is to reduce virus transmission and also to reduce the risk of mortality. Preventive health measures that can turn down the likelihood of infection and progression is highly desired. Potential immunomodulation may be helpful for viral clearance at early stage of disease transmission, which ameliorates disease severity and influences disease outcome.

This hypothesis brings about the concept of vitamin D, the sunshine vitamin, produced endogenously with the effect of UV rays on the skin or supplied through an exogenous dietary source. It is well known for its role in maintenance of mineral and skeletal homeostasis. High prevalence of vitamin D deficiency (VDD) is a worldwide plight with more than a billion cases, which can mainly attributed to lifestyle and environment factors like low latitude areas, air pollution, as well as cultural factors that lead to skin being covered.¹² The field of vitamin D research has grown exponentially in recent years with a much improved understanding of its biological importance. Vitamin D might be considered as an independent risk factor for total mortality in the general population, as several research works substantiate the likely contribution of vitamin D against chronic diseases like type 2 diabetes mellitus, cancer, cardiovascular disease, depression, auto-immune diseases, systemic infection and many more.^{13,14} Accumulating evidence suggests that vitamin D has antiviral, immunomodulatory, and anti-inflammatory and antioxidant actions.^{15,16} Current literature and circumstantial evidence emphasize the outcome of COVID-19 and vitamin D status.¹⁷ Association between vitamin D and respiratory health has already been

hypothesized. So it may be contemplated that vitamin D may play a protective role for COVID-19 by affecting immune cell proliferation and ACE2 expression, which is the basis of pathogenesis of transmission of SARS-CoV-2. In the present scenario, saving lives and slowing down the worldwide pandemic is given the utmost importance for the public as well as health care professionals. In view that, a comprehensive, relevant literature review was performed using a digital database about the association of vitamin D and disease progression, severity, and mortality in COVID-19. This brief report aims to provide an accurate, evidence based view on association of vitamin D and COVID-19 severity, which may help to establish the validation of vitamin D therapy in improving disease status and outcome. However, further randomised clinical controlled trials are needed to reconfirm its role as adjuvant therapy in COVID-19.

VITAMIN D MICRONUTRIENT AND THE IMMUNE SYSTEM

Endogenous skin synthesis of vitamin D contributes up to 80% in healthy individuals till the age of 65 years. Extrarenal production of vitamin D occurs in bone, lungs, colon, immune cells, especially activated macrophages. Vitamin D status is observed to be poor in elderly and institutionalized persons. Research during the past two decades has established the diverse biological functions of vitamin D.¹⁴ General mechanism by which vitamin D reduces the risk of microbial infection include physical barrier, natural immunity, and adaptive immunity.¹⁶ According to recent advances, therapeutic use of vitamin D to enhance immune status is a stirring possibility. Immunoregulatory function exerted by micronutrient vitamin D is mediated through promotion of innate immunity. This happens through the induction of 1,25-dihydroxy vitamin D₃ (1,25-DHD), which plays a pivotal role in monocyte/macrophage response to infection. Mitochondrial enzyme 1- α hydroxylase (CYP27B1), essential for active metabolite 1,25-dihydroxy vitamin D₃ (1,25-DHD), can be induced by immune activation of macrophages and cytokines present in the respiratory tract. Genomic action of 1,25-DHD is modulated through vitamin D receptor (VDR), a transcription factor belonging to the steroid receptor family. VDR is expressed widely in non-skeletal tissues like respiratory epithelial cells and immune cells like T cell, B cell, dendritic cell, and macrophages, which explains its immunomodulatory action.¹⁸ Vitamin D-cathelicidin pathway is evolved as an important immune response mechanism for protection against a spectrum of microbes, including gram-positive and gram-negative bacteria, enveloped and nonenveloped viruses, and fungi.¹⁹ Cathelicidin (LL-37), an antimicrobial protein-18, is synthesized and secreted in a significant amount by tissues exposed to microbes. These host-derived peptides kill the invading pathogens by perturbing their cell membranes and can neutralize the biological activities of endotoxins.²⁰ Moreover, this can act as a signalling molecule to induce expression of several cytokines and chemokines, thus provides another

mechanism to activate the adaptive immune system. That apart, administration of vitamin D can diminish expression of pro-inflammatory cytokines (TNF- α , IFN- γ) and increase expression of anti-inflammatory cytokines by macrophages, which also justifies the role of vitamin D in recent pandemic.²¹ It is worth mentioning here that after viral infection in COVID cases, the innate immune system triggers the production of both pro-inflammatory and anti-inflammatory cytokines, which is the underlying pathogenesis of cytokine storm. Vitamin D also plays a role to modulate adaptive immunity by suppressing T helper cell type 1 (Th1), which repress inflammatory cytokines IL-2 and interferon gamma (IFN- γ). It also enhances the activity of T helper cell type 2 (Th2), thus producing cytokines that further suppress Th1 by complementing with regulatory cells.²² Moreover, the association between vitamin D and inflammation is widely accepted as it plays an important role in the modulation and production of inflammatory cytokines (IL-1 α , IL-1 β , TNF- α).²³ In addition to regulating innate and adaptive immunity, the active metabolite of vitamin D exhibits a protective role in COVID-19 by modulating ACE2 receptor that is highly expressed in type II pneumocytes.²⁴ That apart evidence supporting the association of vitamin D with several other types of infections like rotavirus, dengue virus, and other enveloped virus has been documented previously.²⁵ Reasons include direct inhibition with viral replication or with anti-inflammatory or immunomodulatory ways. This raises a question whether vitamin D deficiency is contemplated as a virulence factor in COVID infection or vitamin D supplementation is beneficial by decreasing severity and mortality. It is essential to mention here that there are some crucial determinants of COVID-19 severity and mortality, such as age, sex, ethnicity, associated comorbidities, and co-infection. This is an important notion that must not be ignored. It is worth mentioning here that vitamin D synthesis gradually decreases with increase in age. Interestingly, some pharmaceutical drugs also reduce serum 1,25DHD concentrations by activating the pregnane-X receptor.²⁶ So also COVID-19 mortality increases with age. Epidemiological data reported a high prevalence of VDD previously in regions of highly affected COVID areas.²⁷ Irrespective of this, current evidence strongly supports the association of VDD and increased risk of COVID-19.

CLINICAL TRIALS ON VITAMIN D EFFECTS

Several retrospective studies outlined the correlation between vitamin D deficiency and poorer clinical outcomes in COVID cases due to immunological consequences. Recent review by Grant et al supported the function of vitamin D in reducing the risk of COVID-19 by increasing cellular immunity, which can be explained by decreasing cytokine storm with effect on IFN- γ and TNF- α (tumor necrosis factor α).²⁵ Ilie et al observed a negative correlation between mean vitamin D level (average 56.79 nmol/l) and number of COVID cases per 1 million population in different European country (average

1393.4, STDEV 1129.984, r (20) = -0.4435; p value = 0.050), and between the mean vitamin D levels and the number of deaths caused by COVID-19/1 M (average 80.42, STDEV 94.61, r (20) value = -0.4378; p value = 0.05).²⁸ An Israeli population based study with 782 COVID positive patients (10.02%) concluded a link between low level of vitamin D and increased COVID-19 susceptibility. They found that the mean plasma vitamin D level was significantly lower among those who tested positive than negative for COVID-19 (19.00 ng/ml (95% confidence interval (CI) 18.41–19.59) versus 20.55 (95% CI: 20.32–20.78)).²⁹ Univariate analysis of this study documented an association between the low 1,25 DHD and feasibility COVID-19 infection (crude odds ratio (OR) of 1.58 (95% CI: 1.24–2.01, p < 0.001)), and of hospitalization due to the SARS-CoV-2 virus (crude OR of 2.09 (95% CI: 1.01–4.30, p < 0.05)). In another retrospective data analysis, Daneshkhah et al analysed data showing association between severity in COVID-19 and C-reactive protein (CRP), a surrogate marker for cytokine storm. They also determined a possible link between high CRP and vitamin D deficiency (odds ratio 1.8 with 95% CI).³⁰ In a recently published cohort study of 489 patients by Meltzer et al, the relative risk of testing positive for covid-19 was 1.77 times greater than compared deficient vitamin D status was statistically significant.³¹ Ciu et al had shown a pronounced impact of vitamin D on the renin-angiotensin system with enhanced expression of ACE2 in an experimental animal model.³² Alipio et al conducted retrospective logistic regression study on 212 COVID-19 patients in south-Asian countries and their statistical analysis showed a decrease in 1,25-DHD level with increase in severity of the disease (31.2 ng/ml to 17.1 ng/ml, p < 0.001).³³ Out of the total participants, 80 exhibited vitamin D insufficiency (25 OHD < 21–29 ng/ml) and 77 exhibited vitamin D deficiency (25 OHD < 20 ng/ml). The odds of having mild clinical outcome increases and critical outcome decreases (OR = 0.051, p < 0.001), with increase in serum 25 OHD level. Such correlative evidence has strengthened studies on whether vitamin D supplementation can prevent or treat COVID-19. But there is conflicting report from a study of people in United Kingdom by Hastie et al who tried to explore COVID-19 likelihood in black and south Asia people. They found no evidence that would explain susceptibility to COVID infection either overall or between ethnic groups.³⁴ Observational studies in the past have also connected low vitamin D and susceptibility of acute upper respiratory tract infection. In an attempt to explore the said effect, Charan et al did a meta-analysis trial showing the effect of vitamin D supplementation in the prevention of respiratory tract infection. There was significant reduction in incidence of respiratory tract infection as compared to placebo group (odds ratio = 0.582 (0.417–0.812), p = 0.001) in random model. Similar values were noted with fixed model also (odds ratio = 0.615 (0.488–0.776), p = 0.000).³⁵ Another striking evidence is the recently performed randomised control trial including 1300 healthy children and adolescent population aged 3 to 17 years. 650 of them

were assigned to vitamin D and the rest 650 to placebo. A significant effect was noted in reducing all respiratory virus infections (HR: 0.81, 95% CI: 0.66-0.99).³⁶ A Cochrane review of randomised controlled trials including 435 children and 658 adults with mild to moderate asthma, reported that no participant in the trial suffered a fatal asthma exacerbation. Vitamin D supplementation can lessen the possibility of severe asthma exacerbations, which are commonly precipitated by viral upper respiratory tract infections.³⁷

One more happening result was noted in the double-blind randomised controlled trial including 140 patients with antibody deficiency and increased susceptibility to respiratory tract infection. They were given daily vitamin D supplementation, which could reduce infectious score compared to placebo (adjusted relative score 0.771, 95% CI 0.604–0.985, $p=0.04$).³⁸ From a mechanistic point of view, there are acceptable grounds to suggest that vitamin D supplementation modulates host response to SARS-CoV-2 both in early viremia and later stage of COVID. The data reviewed here reinforce higher vitamin D level (40–60 ng/ml) as a measure of protection. For a greater benefit and to attain the desired level, a dose of 2000–5000 IU/day can be taken to lower the risk of infection severity.²⁵ The U.S. Institute of Medicine has recommended <10,000 IU/day vitamin D supplementation without any adverse effects.³⁹

However, the value for upper limit (UL) was corrected to 4000 IU/day based on all-cause mortality and chronic disease outcomes. SOP it is recommended to take 4000IU/day to boost immunity and to fight against COVID. A recent review suggested using vitamin D loading doses of 200,000–300,000 IU in 50,000-IU capsules to reduce the risk and severity of COVID-19.⁴⁰ So based on finding in several studies discussed here, it can be concluded that vitamin D deficiency can be considered as virulence factor which may enhance the risk of COVID severity. In our view, well-powered randomised control trials of vitamin D supplementation for both prevention and treatment are now needed to validate the hypothesis.

ROLE OF OTHER MICRONUTRIENTS

Apart from vitamin D, several other micronutrients like vitamin C, vitamin A, selenium, and zinc also play a vital role in modulating the risk and clinical course of COVID-19. The immune supporting role of a mega dose of vitamin C has been well documented.⁴¹ Furthermore the role of vitamin A in cytokine expression and enhanced activity of macrophage, T cell cannot be ignored.⁴² Being an integral part of glutathione peroxidase, selenium plays an important role in viral infection as an antioxidant. So selenium supplementation along with vitamin D, A, and C helps in COVID prevention. Also, it is recommended to take magnesium (Mg) supplementation along with vitamin D as it activates vitamin D and acts as a cofactor in many enzymatic reactions. Vitamin D also affects metabolism of zinc, which decreases replication of coronaviruses.⁴³

CONCLUSION

COVID-19 pandemic has taken a firm hold over the world. Vitamin D deficiency is a global health problem. Reviewing the direct effect of vitamin D on immune system, ACE2 expression, and antimicrobial action against viruses, and more importantly looking at dearth of management, vitamin D unfolds the possibility of improvement in clinical status and better survival of patients. Vitamin D micronutrient is a unique prohormone, which is synthesized by the skin on exposure to sunlight. So dark skinned people having low melanin and aged persons are more likely to be deficient of this vitamin. Even in a sunnier country like India, VDD prevails due to less exposure of skin to sunlight. That apart, due implementation of lockdown for weeks together, people are forced to stay indoors, which might have resulted in less vitamin D synthesis. More so lifting of lockdown during monsoon time lowers sun exposure due to cloudy sky. In the context of recent pandemic, good nutrition (both micro and macro) and regular physical activity may accredit a good impression on immunity, which combat infection. Circulating level of active vitamin D metabolite has long been identified to assist innate antiviral effector system. Ability of vitamin D to modulate cellular innate immunity is by the phagocytic activity of macrophages and natural killer cells through induction of cathelicidin, defensin, and 1,25-DHD. It has been contemplated that there is a prospective connection between mean vitamin D level and COVID-19 mortality as vitamin D modulates immune response of white blood cells (WBC) so that too many inflammatory cytokines are not released from them. It is worth mentioning here that cytokine storm is one of the complications associated with COVID-19. Observational studies in the past have also connected low vitamin D and susceptibility of acute upper respiratory tract infection. This raises questions about whether insufficient vitamin D influences the course of COVID-19. Observational studies and anticipations have to be validated by human randomised control trials to evaluate the therapeutic potency of vitamin D in preventing infection.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395(10223):470-3.
2. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol*. 2020;215:108427.
3. Harpan H, Itoh N, Yufika A, Winardi W. Coronavirus disease 2019 (COVID-19): A Literature review. *J Infect Public Health*. 2020;5(13):667-73.
4. Hoffmann M, Klein-Weber H, Schroeder S, Kruger N. SARS-CoV-2 cell entry depends on ACE2 and

- TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020.
5. Coronavirus outbreak. Available at: <http://www.wordometers.info/coronavirus/>. Accessed on: 24 August 2020.
 6. Du R, Liang L, Yang C, Wang W, Cao T, Li M, et al. Predictors of mortality for patients with COVID-19 Pneumonia caused by SARS-CoV-2: A prospective cohort study. *Eur Respir J*. 2020.
 7. Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review. *Diabet Metab Syndr*. 2020;14(5):1133-42.
 8. Lu R, Zhao X, Li J, Niu P. Genomic characterisation and epidemiology of 2019 novel coronavirus: implication for virus origin and receptor binding. *Lancet*. 2020;395(10224):565-74.
 9. Wall AC, Park YJ, Tortorici MA, Wall A. Structure, function, and antigenicity of SARS-CoV-2 glycoprotein. *Cell*. 2020;16:281-92.
 10. Qin C, Zhou L, Hu Z, Zhang S, Yang Y, Tao C, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. 2020;12:248.
 11. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regulators and Homeostatic Agent*. 2020;14:34(2).
 12. Mendes MM, Charlton K, Thakur S. Future perspectives in addressing the global health issues of vitamin D deficiency. *Nutr Soc*. 2020;79:246-51.
 13. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxy vitamin D levels, and the risk of mortality in the general population. *Arch Intern Med*. 2008;168:1629-37.
 14. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment, and prevention. *Rev Endocrine Metab Disord*. 2017;18:153-65.
 15. Coussens AK, Martineau AR, Wilkinson RJ. Anti-inflammatory and antimicrobial actions of vitamin D in combating TB/HIV. *Scientifica (Cairo)*. 2014;903680.
 16. Skrobot A, Demkow U, Wachowsks M. Immunomodulatory role of vitamin D: A review. 2018;1108:13-23.
 17. Mitchell F. Vitamin D and COVID-19: do deficient risk a poorer outcome. *The Lancet*. 2020;8(7):570.
 18. Di Rosa M, Malaguarnera M, Nicoletti F, Malaguarnera L. Vitamin D3: a helpful immunomodulator. *Immunology*. 2011;134:123-239.
 19. Gombart AF. The vitamin D- antimicrobial peptide pathway and its role in protection against infection. *Future Microbiol*. 2009;4:1151.
 20. Agier J, Efenberger M, Brzezinska-Blaszczyk E. Cathelicidin impact on inflammatory cells. *Cent Eur J Immunol*. 2015;40:225-35.
 21. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. *Nutrients*. 2020;12:236.
 22. Cantorna MT, Snyder L, Lin YD, Yang L. Vitamin D, and 1,25-(OH)₂D regulation of T cells. *Nutrients*. 2015;7:3011-21.
 23. Ebadi M, Bhanji RA, Mazurak VC, Lytvyak E, MNason A, et al. Severe vitamin D deficiency is a prognostic biomarker in autoimmune hepatitis. *Aliment Pharmacol Ther*. 2019;49:173-82.
 24. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. 2020;13(10):1373-80.
 25. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, et al. Evidence that vitamin D supplementation could reduce the risk of influenza and COVID-19 infections and death. *Nutrient*. 2020;12:988.
 26. Gröber U, Kisters K. Influence of drugs on vitamin D and calcium metabolism. *Dermatoendocrinol*. 2012;4(2):158-66.
 27. Ebadi M, Montano-Loza AJ. Perspective: Improving vitamin D status in the management of COVID-19. *Eur J Clin Nutr*. 2020;74:856-9.
 28. Ilie PC, Stefanescu S, Smith L. Role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res*. 2020;32:1195-8.
 29. Merzon E, Tworowski D, Gorohovski A, Vinker S, Cohen AG, et al. Low plasma 25(OH) vitamin D is associated with increased risk of COVID-19 infection: an Israeli population based study. 2020;287(17):3693-702.
 30. Daneshkhah A, Agrawal V, Eshein A, Subramanian H, Roy HK, Backman V. The Possible Role of Vitamin D in Suppressing Cytokine Storm and Associated Mortality in COVID-19 Patients. *MedRxiv*. 2020;4(8):20058578.
 31. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. *JAMA Netw Open*. 2020;3(9):2019722.
 32. Cui C, Xu P, Li G, Qiao Y, Han W, et al. Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: role of the renin-angiotensin system. *Redox Biol*. 2019;26:101295.
 33. Alipio M. Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19). 2020;3571484.
 34. Hastie CE, Mackay DF, Ho F, Celis-Morales CA, Katikireddi SV, et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr*. 2020;14(4):561-5.
 35. Charan J, Goyal JP, Saxena D, Yadav P. Vitamin D for prevention of respiratory tract infection: A systematic review and meta-analysis. *J Pharmacol Pharmacotherap*. 2012;3(4)300-3.

36. Loeb M, Dang AD, Thiem VD, Thanabalan V, Wang B, Nguyen NB, Tran HTM, Luong TM, Singh P, Smieja M, et al. Effect of Vitamin D supplementation to reduce respiratory infections in children and adolescents in Vietnam: A randomized controlled trial. *Influenza Other Respir. Viruses*. 2019;13:176-83.
37. Martineau AR, Cates CJ, Urashima M. Vitamin D for the management of asthma. *Cochrane Database Syst Rev*. 2016;9(9):CD011511.
38. Bergman P, Norlin AC, Hansen S. Vitamin D3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. *BMJ Open*. 2012;2(6):e001663.
39. Ross AC, Manso JE, Abrams SA. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96:5-8.
40. Wimalawansa SJ. Global epidemic of coronavirus: What can we do to minimize the risks. *Eur J Biomed Pharm Sci*. 2020;7:432-8.
41. Manning J, Mitchell B, Appadurai DA. Vitamin C promotes maturation of T-cells. *Antioxid Redox Signal*. 2013;19(17):2054-67.
42. Patel N, Penkert RR, Jones BG, Sealy RE, Surman SL, Sun Y, Tang L, et al. Baseline serum vitamin A and D levels determine the benefit of oral vitamin A & D supplements to humoral immune responses following pediatric influenza vaccination. *Viruses*. 2019;11:907.
43. Velthuis AJ, vanden Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog*. 2010;6(11):e1001176.

Cite this article as: Mishra S, Mishra A, Das S. Vitamin D micronutrient and COVID-19: the missing link. *Int J Adv Med* 2021;8:474-9.