Vitamin D and COVID-19: Insight on Mechanism and Implementation in Equatorial Countries

Indah Bachti Setyarini, Nurul Ratna, Ninik Mudjihartini

Department of Nutrition, Faculty of Medicine Universitas Indonesia-Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia
Department of Biochemistry, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

Introduction

Since March 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic and since then it has infected more than 58 million people worldwide, attributing to at least 1.3 million deaths.[1] The degree of disease manifestation ranges in severity from asymptomatic to multi-organ failure. According to Benskin et al approximately 89% of COVID-19 patients are in a state of vitamin D insufficiency or deficiency.[2] This observation sparks the notion to the potential benefit of vitamin D supplementation in improving the patient's outcome, and even prevent the infection before it happened.

This moment, the treatment for COVID-19 still focuses on symptomatic relief.[3,4] Current existing guidelines classified therapy intervention depending on the degree of severity.[3,4]

Malnutrition, which are induced by prolonged inflammation, malabsorption, and low appetite, influences COVID-19 prognosis. Dysregulation to the immune system was shown to be more noticeable in malnourished patients. Hence, a balanced diet – containing macro and micronutrients, vitamins, antioxidants, and minerals – is one of the main principles of therapy. Some studies highlighted that an insufficiency of vitamin D significantly correlates with the degree of severity in COVID-19 patients.[5,6] In addition, a retrospective study in Israel also underlines the importance of adequate vitamin D supplementation in accordance to the severity of COVID-19 infections.[7]

Thus, this article aims to elaborate on the mechanisms by which vitamin D may affect COVID-19 patients, whilst exploring the potential benefit of being near the equator towards vitamin D concentration.

Vitamin D Biosynthesis

Vitamin D synthesis are primarily aided by ultraviolet-B (UVB) radiation and, to a lesser extent, obtainable from dietary sources.[8] Factors attributing to the synthesis of vitamin D include age, liver and kidney disease, and UVB radiation quality. Skin pigmentation, clothing and, sunscreen lotion disallow maximum UVB penetration, hence decreasing the synthesis of precalciferol. In addition, the custom of sun-seeking behavior may greatly influence vitamin D synthesis.[9]

Korespondensi: **Ninik Mudjihartini**
E-mail: *ninikbiokim@gmail.com*

Vitamin D Measurement

The state of vitamin D adequacy is divided into 3 categories; normal, insufficient, and deficient. Insufficiency and deficiency are defined with measures of serum 25(OH)D of < 50nmol/L and <30nmol/L respectively.[10] Current supplementation guideline recommends 400-800 IU/day with an upper tolerated dose of 4,000 IU/day.[11,12] To ensure prime treatment or even prevent COVID-19, several studies recommend maintaining 40-60nmol/L of vitamin D which can be achieved by giving dose of 1,000 IU/day.[13,14] For individuals deficient of vitamin D, up to 4,000 IU/day can be prescribed followed by 25(OH)D measurements following 1.5 months of intervention.[14]

Role of vitamin D as an immunomodulator

The immunomodulatory roles of vitamin D are mainly mediated by binding of Vitamin D Receptor (VDR) and Retinoid X Receptor (RXR) heterodimer at the promoter region of Vitamin D Receptor Element (VDRE).[8]

Its' immunomodulatory role encompass both innate and adaptive immune response. In the innate immune system, it downregulates the gene responsible for monocyte proliferation, it also diverts monocyte differentiation into macrophages. Enhancing phagocytosis and antimicrobial peptides production. Also, binding of calcitriol with VDR in Antigen Presenting Cell (APC) keeps them in an immature state, hence the low expression of Major Histocompatibility Complex (MHC) class-II.[15]

Consequently, minimal antigen presentation activity diminishes adaptive immune response. Upon stimulation by the innate immune system, naïve T-helper (Th) cell differentiates into Th0. Vitamin D promotes the formation of anti-inflammatory T cells; Th2 and regulatory T-cell (Treg). An increase in Th2 activity is linked to the production of anti-inflammatory mediators IL-4, 5 and, 10, while Treg can prevent exaggerated immune response.[15]

Other immunomodulatory effects of vitamin D are associated with junctional complexes, Natural-Killer (NK) cell activity, and Renin-Angiotensin System (RAS), in which the latter helps diminish the bradykinin effect.[16]

Correlation of Vitamin D Levels with SARS-CoV-2

Several studies have investigated the relationship between mortality of COVID-19 and level of vitamin D. Laird et al found a significant correlation between low serum 25(OH)D concentration and COVID-19 mortality rate.[5] Similar finding was observed in a European study where in addition to mortality rate, vitamin D concentration is also inversely proportional to COVID-19 incidence rate.[17] Another study focusing on the effect of vitamin D with upper respiratory tract infection revealed a significantly lower incidence rate from 42.2% to 40.3%.[17] Vitamin D has the capability to enhance body immunity, induce anti-inflammatory effect, while also preventing cytokine storm occurrence.

Aside from cytokine storm, bradykinin storm has also been pointed out as one of the mortality predictors of COVID-19 patients. SARS-CoV-2 reduce ACE RNA expression by 10 folds in conjunction with upregulation of ACE2 by 199 folds.[16] Elevated ACE2 impairs the inactivation of bradykinin as well as enhances neutrophil activation. As a result, bradykinin storm is exacerbated through ang 1-9 production followed by sensitization of BKRB2. Binding of bradykinin with drs-Arg9BK (DABK) enhances vascular permeability and induces angioedema, causing Acute Respiratory Distress Syndrome (ARDS).[18]

On the other hand, SARS-CoV-2 was shown to also counteract the protective effects induced by vitamin D. Garvin et al found a 2-fold down-regulation of VDR in COVID-19 patients, as well as upregulation of vitamin D catabolic enzymes such as CYP24A1 and CYP3A4 by 465 and 208 folds respectively. Moreover, SARS-CoV-2 was shown to reduce ACE, which is responsible for degrading excessive circulating bradykinin, by 8-folds.[16]

Impact of Vitamin D and COVID-19 in Equatorial Countries

Daily vitamin D requirements can be fully synthesized under 15-30 minutes of sunlight exposure for 3x/week. The ultraviolet index (UVI) in equatorial countries varies during the day reaching up to 13 in an equatorial country such as Indonesia. Frequent exposure to sunlight at high UVI has been associated with skin cancer and eye disorders, thus outdoor activities are suggested only when UVI is below 5.[19]

Studies have pointed out associations between vitamin D level with latitude and seasonal changes. A study investigating the effect of latitude towards COVID-19 mortality is believed to be an effect of UV radiation, where individuals living in the area of <35

degree latitude from the equator is capable of synthesizing sufficient vitamin D all year round.[9] Furthermore, a significant 4.4% increasing trend of COVID-19 mortality was observed for every 1 degree difference in latitude above 28 degree north.[13] From the perspective of the changing seasons, a Canadian study found an approximate 17% increase in adults who were lacking vitamin D during the summer compared to the winter season.[20] Nevertheless, as previously mentioned, the sufficiency of vitamin D is greatly affected by several different factors other than sunlight exposure as is shown by Laird et al. Countries closer to the equator such as Spain and Italy had higher rates of vitamin D deficiency compared to Norway, Finland, and Sweden which are located in the northern latitude.[5] This may be explained by sunlight-avoidance habit employed by many living in the equatorial countries, as well as frequent use of sunscreen lotion and darker skin pigmentation.

Conclusion

Vitamin D has been shown to have an important role in improving the survival of COVID-19 patients. Recognition of the different factors influencing the concentration of vitamin D is vital as latitude being near the equatorial countries does not guarantee the adequacy of vitamin D. Moreover, long-term studies on the impact of vitamin D supplementation in COVID-19 patients are essential to weight its risk and benefit. As knowledge upon COVID-19 is still continuously evolving, exploring other potential therapies and supplementations is essential to deduce the best course of treatment for COVID-19. Additionally, understanding the changes triggered by SARS-CoV-2 infection against vitamin D metabolism may help to evaluate the need to adjust the vitamin D requirement for COVID-19 patients in order to maximize its benefit.

References

1. WHO coronavirus disease (COVID-19) dashboard [Internet]. World Health Organization. Available from: https://covid19.who.int/
2. Benskin LL. A basic review of the preliminary evidence that COVID-19 risk and severity is increased in vitamin D deficiency. Front Public Health. 2020 Sep 10;8.
3. Pedoman pencegahan dan pengendalian coronavirus disease (COVID-19) revisi ke-5 [Internet]. Kementerian Kesehatan Republik Indonesia. 2020. Available from: https://covid19.go.id/p/protokol/pedoman-pencegahan-dan-pengendalian-coronavirus-disease-covid-19-revisi-ke-5
4. Diagnosis and treatment plan of corona virus disease 2019 (tentative sixth edition). Glob Health J. 2020 Mar;4(1):1–5.
5. Laird E, Michael Rhodes J, Kenny RA. Vitamin D and Inflammation: Potential Implications for Severity of Covid-19. Ir Med J [Internet]. 2020;113(Ir Med J; Vol 113; No. 5; PB1). Available from: https://www.researchgate.net/publication/341234461_Vitamin_D_and_Inflammation_Potential_Implications_for_Severity_of_Covid-19
6. 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 Jul;32(7):1195–8.
7. Merzon E, Tworowski D, Gorohovski A, Vinker S, Golan Cohen A, Green I, et al. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: An Israeli population-based study. FEBS J. 2020 Sep;287(17):3693–702.
8. Gil Á, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and novel actions. Ann Nutr Metab. 2018;72(2):87–95.
9. Roth DE, Abrams SA, Aloia J, Bergeron G, Bourassa MW, Brown KH, et al. Global prevalence and disease burden of vitamin D deficiency: A roadmap for action in low- and middle-income countries. Ann N Y Acad Sci. 2018 Oct;1430(1):44–79.
10. Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19? Clin Med. 2020 Jul;20(4):e107–8.
11. Lanham-New SA, Webb AR, Cashman KD, Buttriss JL, Fallowfield JL, Masud T, et al. Vitamin D and SARS-CoV-2 virus/COVID-19 disease. BMJ Nutr Prev Health. 2020 Jun;3(1):106–10.
12. Bender D, Rodwell V, Botham K, Kenelly PJ WP. Harper's illustrated biochemistry. 30th ed. Chicago: McGraw Hill; 2015.
13. 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. 2020 Jul 22.
14. Bleizgys A. Vitamin D and COVID-19: It is time to act. Int J Clin Pract [Internet]. 2020 Oct 27 [cited 2020 Nov 29]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/ijcp.13748
15. Prietl B, Treiber G, Pieber T, Amrein K. Vitamin D and immune function. Nutrients. 2013 Jul 5;5(7):2502–21.
16. Garvin MR, Alvarez C, Miller JI, Prates ET, Walker AM, Amos BK, et al. A mechanistic model and therapeutic interventions for COVID-19 involving a RAS-mediated bra-

dykinin storm. eLife. 2020 Jul 7;9.
17. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;i6583.
18. Sodhi CP, Wohlford-Lenane C, Yamaguchi Y, Prindle T, Fulton WB, Wang S, et al. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg 9 bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. Am J Physiol-Lung Cell Mol Physiol. 2018 Jan 1;314(1):L17–31.
19. Judistiani RTD, Nirmala SA, Rahmawati M, Ghrahani R, Natalia YA, Sugianli AK, et al. Optimizing ultraviolet B radiation exposure to prevent vitamin D deficiency among pregnant women in the tropical zone: Report from cohort study on vitamin D status and its impact during pregnancy in Indonesia. BMC Pregnancy Childbirth. 2019 Dec;19(1).
20. CaMos Research Group, Greene-Finestone LS, Berger C, de Groh M, Hanley DA, Hidiroglou N, et al. 25-Hydroxyvitamin D in Canadian adults: Biological, environmental, and behavioral correlates. Osteoporos Int. 2011 May;22(5):1389–99.