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Research Paper

Role of Vitamin D in Prevention of Covid 19

Mohammed Salih C.P[1*], Sumitha S.K[2], Sambath Kumar .R[3]
[1]*Student, Department of Pharmacy Practice, J.K.K Nattraja College of Pharmacy, Kumarapalayam-638183,*
[2]*Lecturer, Department of Pharmacy Practice, J.K.K Nattraja College of Pharmacy, Kumarapalayam-638183,*
[3]*Professor and Head, Department of Pharmaceutics, J.K.K Nattraja College of Pharmacy, Kumarapalayam-*
**Correspondence To: Mohammed Salih C.P*

ABSTRACT
The outbreak of COVID-19 has created a global public health crisis. WHO declared SARS-CoV-2 a global pandemic. Little is known about the protective factors of this infection. Therefore, preventive health measures that can reduce the risk of infection, progression and severity are desperately needed. This become one of the most important epidemiological events within the last 100 years, causing devastating consequences for the public health systems and the socio economical tissue around the world. Infection with SARS-CoV-2 can lead to a mild or highly acute respiratory syndrome fuelled by altered secretion of inflammatory cytokines (cytokine storm) that can be fatal within children, elderly populations, patients with chronic pulmonary or hypertension diseases, and people living in cities with poor air quality. Evidence recommends that vitamin D might be an important supportive agent for the immune system, mainly in cytokine response regulation against COVID-19. Vitamin D supplementation could be especially important for older people as they are at high risk of poor outcome from COVID-19 and of vitamin D deficiency. Thus this review discussed the possible roles of vitamin D in reducing the risk of COVID-19 and other acute respiratory tract infections and severity.

KEYWORDS: *vitamin D, Covid 19*
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I. INTRODUCTION

The novel coronavirus (nCoV) 2019, also called SARSCoV-2 (severe acute respiratory syndrome), was so named by the World Health Organization (WHO) because the first case of this unusual coronavirus was reported on December 31, 2019 from China. The word "novel" was used because it was not like the earlier coronaviruses, viz., severe acute respiratory syndrome or SARS-CoV (2002) and Middle East respiratory syndrome or MERS (2012). In fact, it belongs to the family of Betacorona RNA (positive sense) viruses, of which there are seven, and four of these viruses cause symptoms and signs, similar to those of a common cold. This unprecedented (in scale, scope) coronavirus disease 2019 (COVID-19) pandemic has taken the world by storm. Cases and case fatality rates are mounting and in this panic-stricken environment, where there are no specific antinovel corona viral drugs or vaccines, doctors are experimenting with drugs that have not been specifically approved for this virus.[1]

In this regard, one of the hottest topics these days is the role of Vitamin D in prevention or treatment of COVID-19. Several functions such as modulating adaptive immune system and cell-mediated immunity, as well as increase of antioxidative-related genes expression have been proven for Vitamin D as an adjuvant in the prevention and treatment of acute respiratory infections.[2] Interest in a potential role for vitamin D in the prevention or treatment of acute respiratory infections dates back to the 1930s, when cod liver oil was investigated as a means to reduce industrial absenteeism due to the common cold.[3] Vitamin D is not only a micronutrient or vitamin, but also a hormone that has vitamin D receptors on cells all over the body. Considering the differences in the severity and fatality of COVID19 in the globe, it is important to understand the reasons behind it. Improvement of immunity through better nutrition might be a considerable factor. The nutrient such as vitamin D shows significant roles in immune function. However, little is known about the role of vitamin D in preventing COVID-19 infection and fatality.[4] Several studies demonstrated the role of vitamin D in reducing the risk of acute viral respiratory tract infections and pneumonia. These include direct inhibition with viral replication or with anti-inflammatory shown as safe and effective against acute respiratory tract infections.[5] This review focus on possible preventing role of vitamin D in covid 19.

Vitamin d and its role to decrease viral infection

Vitamin D is a steroid hormone, produced endogenously with the effect of ultraviolet radiation on the skin or available from exogenous food sources or dietary supplements. Vitamin D insufficiency is a public health problem affecting over a billion people across all life stages worldwide.[6] Vitamin D insufficiency affects the immune functions as vitamin D exerts an immunomodulation role increasing innate immunity by secretion of antiviral peptides, which improves mucosal defences.[7] It seems that SARS-CoV-2 primarily uses the immune evasion process during infection, which is followed by hyper reaction and cytokine storm in some patients, as a known pathogenic process of acute respiratory disease syndrome (ARDS) development. SARS-CoV-2 uses angiotensin converting enzyme 2 as the host receptor to enter into alveolar and intestinal epithelial cells. Subsequent dysregulation of the renin–angiotensin system may lead to excess cytokine production resulting in prospective fatal ARDS. Considering the differences in the severity and fatality of COVID19 in the globe, it is important to understand the reasons behind it. Improvement of immunity through better nutrition might be a considerable factor. [8]

Vitamin D is usually known for its role in the maintenance of bone health and calcium–phosphorus metabolism, yet many other roles of this hormone have been recently discovered, such as modulation of the immune response in both infectious and autoimmune diseases. Vitamin D follows different mechanisms in reducing the risk of viral infection and mortality. [9] To reduce the risk of common cold, vitamin D uses three pathways: physical barrier, cellular natural immunity, and adaptive immunity. These comprise maintaining of cell junctions, and gap junctions, increasing cellular immunity by decreasing the cytokine storm with influence on interferon and tumor necrosis factor and regulating adaptive immunity through inhibiting T helper cell type 1 responses and stimulating of T cells induction.[10] Vitamin D supplementation was also found to enhance CD4+ T cell count in HIV infection. The other potential role of vitamin D is reduction of inflammatory induced following SARS-CoV-2 infection. In fact, vitamin D affects the renin–angiotensin system pathway and promotes the expression of angiotensin-converting enzyme 2 (ACE2), which down regulates by SARS-CoV-2. [11]

Most people depend on sunlight exposure to produce the required amount of vitamin D. Differences in sunlight-dependent production of vitamin D is greatly influenced by season, latitude, time of day, skin pigmentation, sunscreen use, and age, with the elderly generating 25% of the vitamin D produced by younger ones in the same amount of time. As very few nutrients naturally contain vitamin D, dietary intake of vitamin D is generally insufficient. Thus, fortification of food and/or oral supplementation is often necessary. In adults, vitamin D supplementation is recommended for all ages (600 UI/day from 19 to 70 years of age; 800 UI/day >70 years of age; up to 1500/2000 UI/day to maintain a blood level of vitamin D above 30 ng/mL), with a higher dosage required for pregnant or lactating women and subjects at risk of osteoporosis. [12] In the paediatric population, vitamin D supplementation (400 UI/day from birth to 12 months of age and 600 UI/day beyond 12 months of age) is usually recommended for the prevention of rickets and osteomalacia.

The ultraviolet B radiation is absorbed by 7-dehydrocholesterol in the skin, leading to its conversion to pre vitamin D3, which is rapidly transformed into vitamin D3 (cholecalciferol). The molecule then undergoes further processing in the liver [25-hydroxy cholecalciferol or calcifediol] by cytochrome CYP2R1 and in the kidney (1,25-dihydroxy cholecalciferol or calcitriol) by cytochrome CYP27B1, before reaching its cellular targets. Here, the activated vitamin D binds to the nuclear vitamin D receptor (VDR) and forms an heterodimeric complex with the retinoic acid X receptor that recognizes specific DNA sequences, known as vitamin D responsive elements (VDRE), resulting in the expression of the vitamin D responsive genes via a variety of transcriptional factors. [13]

Although vitamin D is usually acknowledged for the maintenance of bone health and calcium–phosphorus metabolism, many other roles of this hormone have been recently discovered, such as stimulation of insulin production, effects on myocardial contractility, prevention of inflammatory bowel disease (IBD), and promotion of thyroid-stimulating hormone (TSH) secretion.[14]

Relevance of vitamin D in Covid 19

It is important to fully elucidate the virulence mechanisms of COVID-19, several cellular mechanisms including Papain-like protease (PLpro)-mediated replication, dipeptidyl peptidase-4 receptor (DPP-4/CD26) binding, disruption of M-protein mediated type-1 IFN induction and MDA5 and RIG-I host-recognition evasion have been recognized in the closely-related COVID-MERS virus. Of the above processal, human DPP-4/CD26 has been exhibited to connect with the S1 domain of the COVID-19 spike glycoprotein, suggesting that it could also be a salient virulence factor in Covid-19 infection. [15] The expression of the DPP-4/CD26 receptor is reduced significantly in vivo upon the correctness of vitamin D insufficiency. There is also an indication that maintaining of vitamin D may reduce some of the unfavourable downstream immunological sequel thought to extract poorer clinical outcome in Covid-19 infection, such as interleukin 6 elevation, delayed interferon-gamma response, and, a negative prognostic marker in subjects with acutely-ill pneumonia, including those having Covid-19. [16]

It is also known that vitamin D enhances the expression of two antimicrobial peptides called cathelicidin and β-defensin, and that play a key role in innate immunity. These peptides are involved in direct microbicidal effects and have also shown pleiotropic efects in inducing immune modulatory responses to pathogen stimuli. [17] Vitamin D also promotes self-tolerance by shifting the cytokine patterns from a Th-1 to a Th-2 environment. This results in a reduction in Th1- and Th17-stimulating cytokines with depletion of Th-17 cells (which are known to be linked to tissue damage and inflammation) and up regulation of regulatory type-2 (T reg) cells. It has also been demonstrated that vitamin D is capable of inducing autophagy and apoptosis in infected cells, throughout several mechanisms. [18] Finally, 25-hydroxyvitamin D and 1,25(OH)2D also modulate T-cell immunity, reducing pro-inflammatory type 1 cytokines (such as, IL-8, IFN-γ, IL-12, IL-6, TNF-α, and IL-17) and increasing anti-inflammatory type 2 cytokines (such as, IL-4, IL-5, and IL-10). It has also been demonstrated that high levels of vitamin D seem to reduce aromatase activity (which is in turn increased by high levels of pro-inflammatory cytokines levels), thus containing the effects related to increased peripheral estrogen metabolism, such as B cell over activity. [19] Vitamin D supplementation has been shown to have protective effects against respiratory tract infections; therefore, people who are at higher risk of vitamin D deficiency during this global pandemic should consider taking vitamin D supplements to maintain the circulating 25(OH)D in the optimal levels (75–125 nmol/L).[20] Also COVID-19 is caused, beside the virus virulence by the release of pro-inflammatory cytokines. Vitamin D has been found to modulate macrophages' response, preventing them from releasing too many inflammatory cytokines and chemokine. Recent studies found significant crude relationships between vitamin D levels and the number COVID-19 cases and especially the mortality caused by this infection. The most vulnerable group of population for COVID-19, the aging population, is also the one that has the most deficit Vitamin D levels. [21]

Risk factors for severe courses of COVID-19

Older age and co-morbidities are linked to an insufficient vitamin D supply. Over 60 years of age, a reduction in the synthesis of vitamin D in the skin becomes apparent, which further increases getting older. [22] The precursor of vitamin D, 7-dehydrocholesterol in the skin declines about 50% from age 20 to 80, and the elevation of cholecalciferol levels in serum following UVB radiation of the skin shows more than a 4-fold difference in individuals aged 62–80 yrs. compared with controls (20–30 yrs). This explains the high number of older individuals with an inadequate vitamin D status. Co-morbidities and old age show a relationship with Renin Angiotensin-Aldosteron-System (RAAS), vitamin D status and COVID-19 infection. RAS plays an important role in maintaining vascular resistance and extracellular fluid homoeostasis. [23] Infection with SARS-CoV-2 causes the virus spike protein to come into contact with ACE2 on the cell surface and thus to be transported into the cell. This endocytosis causes upregulation of a metallopeptidase (ADAM17), which releases ACE2 from the membrane, resulting in a loss of the counter regulatory activity to RAS. As a result, pro inflammatory cytokines are released extensively into the circulation. This leads to a series of vascular changes, especially in the case of pre-existing lesions, which can promote further progression of cardiovascular pathologies. [24]

SARS-CoV-2 not only reduces the ACE2 expression, but also leads to further limitation of the ACE2/Ang 1–7/Mas axis via ADAM17 activation, which in turn promotes the absorption of the virus. This results in an increase in Ang II, which further upregulates ADAM 17. [25] Thus a vicious circle is established turning into a constantly self-generating and progressive process. This process may contribute not only to lung damage (Acute respiratory distress syndrome - ARDS), but also to heart injury and vessels damage, observed in COVID-19 patients. Thus, previous lesions of the cardiovascular system represent a risk factor, since coexisting pathologies can progress as a result of the virus infection. [26]

An inadequate supply of vitamin D has a variety of skeletal and non-skeletal effects. There is ample evidence that various non-communicable diseases (hypertension, diabetes, CVD, metabolic syndrome) are associated with low vitamin D plasma levels. These comorbidities, together with the often concomitant vitamin D deficiency, increase the risk of severe COVID-19 events. [27] Thus role for vitamin D in the response to COVID-19 infection could be twofold. First, vitamin D supports production of antimicrobial peptides in the respiratory epithelium, thus making infection with the virus and development of COVID-19 symptoms less likely. Second, vitamin D might help to reduce the inflammatory response to infection with SARS-CoV-2. Deregulation of this response, especially of the renin– angiotensin system, is characteristic of COVID-19 and degree of over activation is associated with poorer prognosis. Vitamin D is known to interact with a protein in this pathway—angiotensin converting enzyme 2 (ACE2)—which is also exploited by SARS-CoV-2 as an entry receptor. While SARS-CoV-2 down regulates expression of ACE2, vitamin D promotes expression of this gene. [28] Much more attention should be paid to the importance of vitamin D status for the development and course of the disease. Particularly in the methods used to control the pandemic (lockdown), the skin's natural vitamin D synthesis is reduced when people have few opportunities to be exposed to the sun. The short half-lives of the vitamin therefore make an increasing vitamin D deficiency more likely. Specific dietary advice, moderate supplementation or fortified foods can help prevent this deficiency. [29]

Although comparing global statistics of COVID-19 outcomes is difficult, it is clear that the mortality rate is higher in several countries. It seems that various factors such as age, healthcare system quality, general health status, socioeconomic status, etc. Nonetheless, one of the underestimated factors, which might be associated with COVID-19 outcome is the vitamin D status in every populations. Investigations on respiratory infections indicated that 25- hydroxyl vitamin D can effectively induce the host defense peptides against bacterial or viral agents and vitamin D insufficiency/deficiency can lead to non-communicable as well as infectious diseases. [30] The other potential role of vitamin D is reduction of inflammatory induced following SARS-CoV-2 infection. In fact, vitamin D affects the renin–angiotensin system pathway and promotes the expression of angiotensin-converting enzyme 2 (ACE2), which down regulates by SARS-CoV-2. Unfortunately, there were no clinical trials and high-quality data regarding the role of vitamin D in COVID-19. According to available data we could find that approximately more than one-third of the patients infected with SARS-CoV-2 were suffering from vitamin D deficiency and this vitamin was insufficient in about 32% of them. [31] The conditional evidence recommends that vitamin D might be an important supportive agent for the immune system, mainly in cytokine response regulation against pathogens. There is 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. Altogether, it seems that populations with lower levels of vitamin D might be in higher risk of SARS-CoV-2 infection. [32]

II. CONCLUSION

Covid-19 is a pandemic of unprecedented proportion, whose understanding and management is still under way. In the emergency setting new or available therapies to contrast the spread of COVID-19 are urgently needed. In this review, we suggest 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 paediatric population. There is significant crude relationships between vitamin D levels and the number COVID-19 cases and especially the mortality caused by this infection. The most vulnerable group of population for COVID-19, the aging population, is also the one that has the most deficit Vitamin D levels. Vitamin D has already been shown to protect against acute respiratory infections and it was shown to be safe. It should be advisable to perform dedicated studies about vitamin D levels in COVID-19 patients with different degrees of disease severity.

REFERENCE

[1]. Wu D et al. The SARS-CoV-2 outbreak: What we know. Int J Infect Dis 2020; 94:44-8.
[2]. Ghasemian R 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 2020: 1-7.
[3]. Martineau AR. Vitamin D for COVID-19: a case to answer? lancet 2020: S2213-8587
[4]. Suvarna VR, Mohan V. Vitamin D and Its Role in Coronavirus Disease 2019 (COVID-19). Journal of Diabetology 2020; 11:71-80
[5]. Ali N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. J Infect Public. 2020
[6]. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocrine Metab Disord 2017; 18:153–65.
[7]. Gombart AF et al. Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3. FASEB J 2005; 19:1067–77
[8]. Jakovac H. COVID-19 and vitamin D is there a link and an opportunity for intervention? Am J Physiol Endocrinol Metab 2020; 318:E589.
[9]. Alvarez N et al. The potential protective role of vitamin D supplementation on HIV-1 infection. Front Immunol 2019; 10:2291.
[10]. Grant WB & Giovannucci E. The possible roles of solar ultraviolet-B radiation and vitamin D in reducing case-fatality rates from the 1918-1919 influenza pandemic in the United States. Dermato-endocrinology 2009; 1:215-19.
[11]. Gombart A F et al. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection 2020; 12(1):236.
[12]. F. M. Panfli et al. Possible role of vitamin D in Covid-19 infection in pediatric population. Journal of Endocrinological Investigation. 2020
[13]. Rossi P et al. 1,25-Dihydroxyvitamin D3 and phorbol esters (TPA) may induce select in vitro differentiation pathways in the HL60 promyelocytic cell line. Clin Immunol Immunopathol 1987; 44(3):308–16
[14]. Rossi P et al. 1,25-Dihydroxyvitamin D3 and phorbol esters (TPA) may induce select in vitro differentiation pathways in the HL60 promyelocytic cell line. Clin Immunol Immunopathol 1987; 44(3):308–16
[15]. Skariyachan S et al. Recent aspects on the pathogenesis mechanism, animal models and novel therapeutic interventions for Middle East respiratory syndrome coronavirus infections. Front Microbiol 2019;10
[16]. Zdrenghea MT et al. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol 2017; 27:e1909.
[17]. Lemire JM. Immunomodulatory role of 1,25-dihydroxyvitamin D3. J Cell Biochem. 1992; 49(1):26–31.
[18]. Teymoori-Rad M et al. The interplay between vitamin D and viral infections. Rev Med Virol. 2019; 29(2):e2032.
[19]. Eckard AR et al. Vitamin D supplementation decreases immune activation and exhaustion in HIV-1-infected youth. Antivir Ther 2018; 23(4):315–24.
[20]. Ilie PC et al. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clinical and Experimental Research. 2020; 32:1195–98
[21]. Zou Z et al. Angiotensin-converting enzyme 2 protects from lethal avian infuenza A H5N1 infections. Nat Commun. 2014; 5:3594.
[22]. Biesalski HK. Vitamin D deficiency and co-morbidities in COVID-19 patients – A fatal relationship?. NFS Journal 20. 2020; 10–21
[23]. R. Heaney. Barriers to optimizing vitamin D3 intake for elderly, Nutrtion 136 2006; 1123–25.

[24]. J. MacLaughlin, M.F. Holick, Aging decreases the capacity of human skin to produce vitamin D3, J. Clin. Invest 1985; 76:1536–38.
[25]. M.F. Holick, L.Y. Matsuoka, et al. Age, vitamin D, and solar ultraviolet, Lancet ii. 1989; 1104–05.
[26]. A. Zittermann et al. Effects of vitamin D supplementation on renine and aldosterone concentrations in patients with advanced heart failure: the EVITA trial, Int. J. Endocrinol. 2018; 5015417.
[27]. L.M. Resnick, et al. Calcium-regulating hormones in essential hypertension: relation to plasma renin activity and sodium metabolis, Ann. Intern. Med 1986; 105: 649–54.
[28]. J.P. Forman et al. Fisher, Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans, Hypertension 2010; 55:1283–88.
[29]. L. Lind et al. Reduction of blood pressure during long term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status. A double blind, placebo-controlled study. Am. J. Hypertens 2002; 2:20–25.
[30]. Greiller CL & Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients 2015; 7: 4240-70
[31]. Hansdottir S et al. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. Journal of immunology 1950; 181:7090-99.
[32]. Olliver M et al. Immunomodulatory effects of vitamin D on innate and adaptive immune responses to Streptococcus pneumoniae. The Journal of infectious diseases. 2013; 208: 1474-81.