Review Article

International Journal of Research in Pharmaceutical Sciences

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

Role of Vitamin D in Boosting Immunity against COVID- 19

Roselin C[1], Parameshwari S[*2]

[1]Department of Nutrition and Dietetics, Bishop Heber College, Trichy-17, Tamil Nadu, India
[2]Department of Nutrition and Dietetics, Periyar University, Salem-11, Tamil Nadu, India

Article History:

Received on: 20 Jun 2020
Revised on: 18 Jul 2020
Accepted on: 22 Jul 2020

Keywords:

Covid-19, infections, micronutrients, vitamin D, cholecalciferol, calcitriol

Abstract

The world is now in the state of contingency and is facing one common enemy, COVID 19. Front developed countries to the developing and under developed countries, all are fighting against this common enemy which is a virus that is 0.125 microns (1 25 nm) with the size ranging from 0.06 to 0.14 microns. The world is now looking for a vaccine to prevent the infection, while the need of the hour is to boost the immunity of individuals against the disease through readily available nutrients. With the increase in incidence of the COVID-19 pandemic, scientists to common public have started to ponder the ways out of it, while boosting the immunity has become the only resolve as no vaccine has been invented until date. It is obvious that there is a correlation between nutrition and immune system; it is a common understanding that people who are well-nourished have a better immunity compared to poorly nourished people with a weak immunity. It is to be noted that people suffering from chronic diseases and elderly will have a weak immunity and are more prone to any disease let alone COVID-19. Though general immunity can be boosted through vitamin C, zinc and other micronutrients, vitamin D is required to boost overall immunity and also strengthen lungs. This review aims at laying emphasis on the need of vitamin D in strengthening immunity against the deadly common enemy COVlD- 19.

[*]Corresponding Author

Name: Parameshwari S
Phone: 9965954456
Email: sparameshwari2009@gmail.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11iSPL1.2803

Production and Hosted by

IJRPS | www.ijrps.com

INTRODUCTION

The immunity is the capacity of an organism to resist against an infection caused by a pathological microorganism or toxin, by the action of relevant antibodies or WBCs that are sensitized. Biologically speaking, immunity is nothing but the balanced state of a multi cellular organism having sufficient defense against infection, disease or any other invasions biologically, with adequate tolerance of the organisms in avoiding allergy and autoimmune disorders. Immunity has become a common man's term on the advent of the recent scenario of COVlD-19.

According to WHO, corona virus is the causative organism of the Novel Corona virus disease (COVlD-19). Generally speaking, once a person is infected with virus, there is no treatment for the infection as such, but only the symptoms are treated; but body's defense mechanism fights against the virus and 'kills' it and also through the formation of antibodies by adaptive immunity, the virus is recognized immediately once it enters the system for a second time and relapse of the infection is prevented. With regards to COVlD- 19, its easy spread from person-to-person is the reason for it becoming a Pandemic' from an 'epidemic. It can spread mainly through

close contact between persons and also persons who are asymptomatic can also act as a carrier of the disease. Severe infection can lead to the exacerbated inflammation of the lung tissue leading to necrosis and hyperplasia of the affected tissue causing severe pneumonia which has proven to be fatal and this is the main reason for death of patients infected with corona virus world over. Moreover, in patients over 60 years and with co-morbidities such as diabetes, blood pressure and Cardio Vascular Diseases, there seems to be disturbances in the normal plasma levels of lymphocytes, CRP, thrombocytes and LDH and also the more vulnerable is the older adults with a higher risk of death. As there is a lack of specific treatment for this infection, it is now felt that the disease can only be controlled through the strengthening of the immune system of the people globally until a vaccine is invented. Studies show that vitamin D which is a vitamin that is soluble in fat and is important for healthy bones, plays a major role in immune strengthening and can be protective against lung infections. This review tries to throw light on the protective function of vitamin D in improving the immunity of the system and the role of vitamin D supplementation in boosting the immunity of individuals affected with COVlD- 19.

Renin Angiotensin system (RAS) plays an important role in blood pressure regulation. When flow of blood to the kidneys decreases, the juxtaglomerular cells of kidney secretes Renin, which aids in the conversion of plasma angiotensinogen to Angiotensin 1, and then the conversion of Angiotensin II by Angiotensin Converting Enzyme (ACE) (Ren *et al.*, 2019). Angiotensin-II increases water and sodium re-absorption in the kidney leading to vasoconstriction. Studies show that vitamin D plays a main role in the regulation of Renin Angiotensin System (RAS) (Nehme *et al.*, 2019). A number of studies have documented the inverse relationship of serum 25(OH) D levels and blood pressure. (Forman *et al.*, 2010) did an investigation in a cross-section of the population and came to a conclusion on the correlation between 25(OH) D and RAS in 184 subjects who have normal blood pressure. Results revealed that in comparison with vitamin D insufficient individuals, Angiotensin-II levels were high in Vitamin D insufficient individuals had an increased plasma Renin activity. Additionally, in the kidney, on infusion of Angiotensin-II, the RAS assessed through renal plasma flow was found to be increased in patients deficient in vitamin D, in comparison to the ones who had sufficient plasma vitamin D. These results suggest that the decrease in plasma 25(OH) D levels can be correlated to be increased RAS.

Relationship between COVID-19, vitamin D and lung fibrosis

Though, the term corona virus is new to us, they have been recognized by virologists for over 50 years. Corona viruses were first identified by a group of virologists, who relayed their findings in 1968 to the journal Nature, which published a brief annotation. According to the journal Nature reported in 1968, "these viruses belong to a previously unrecognized group which [the virologists] suggest should be called the corona viruses, to recall the characteristic appearance by which these viruses are identified in the electron microscope." Though the word "corona" has a number of meanings the virologists June Almeida and David Tyrell chose the name "corona virus" as they found that the fringe or outer projection of the virus were comparable to that of solar corona or the "halo" seen around the sun at the time of eclipse.

This is a single-stranded RNA virus, about 120 nm in diameter. They can easily mutate and combine and so they are found to be increasingly diverse in nature. About 40 varieties of corona virus have been identified and their main target of infection is humans, non-human mammals and birds which are zoonotic in nature and are found to reside in bats and wild birds and are passed on to other animals and ultimately human beings. Though the origin of virus that has caused COVID-19 is not very clear, it is supposed to have originated from bats, to pangolins and snakes and from them to humans, might have been via the contamination of meat from wild animals that were sold in the meat market of Wuhan at China, where it was first identified.

Through the droplets caused through coughing or sneezing, the virus is transmitted from air and people nearby can inhale it through nose or by touching the surface of droplets and touching their mouth, nose or eyes. These particles travel quickly through the nasal passages and mucous membranes and attach itself to the receptor membrane.

The spike glycoproteins, otherwise called peplomer, which give the corona-like appearance to the virus, are responsible for the virus entering host cells. There are 2 subunits in the spike i.e. S1 which binds to the receptor on the surface of the host cell and S2 which fuses with the cell membrane. For both SARS-CoV-1 and SARS CoV-2 the cell membrane receptor is an Angiotensin Converting Enzyme (ACE-2) which is different from the enzyme that is inhibited by conventional ACE-1 inhibitors. On the surface of the cell membrane, the S1 subunit of the spike binds with ACE-2 enzyme. As a result, a host Trans membrane serine protease, TMPRSS2 activates the spike cleaves ACE-2. These TMPRSS2 acts of S2 sub-

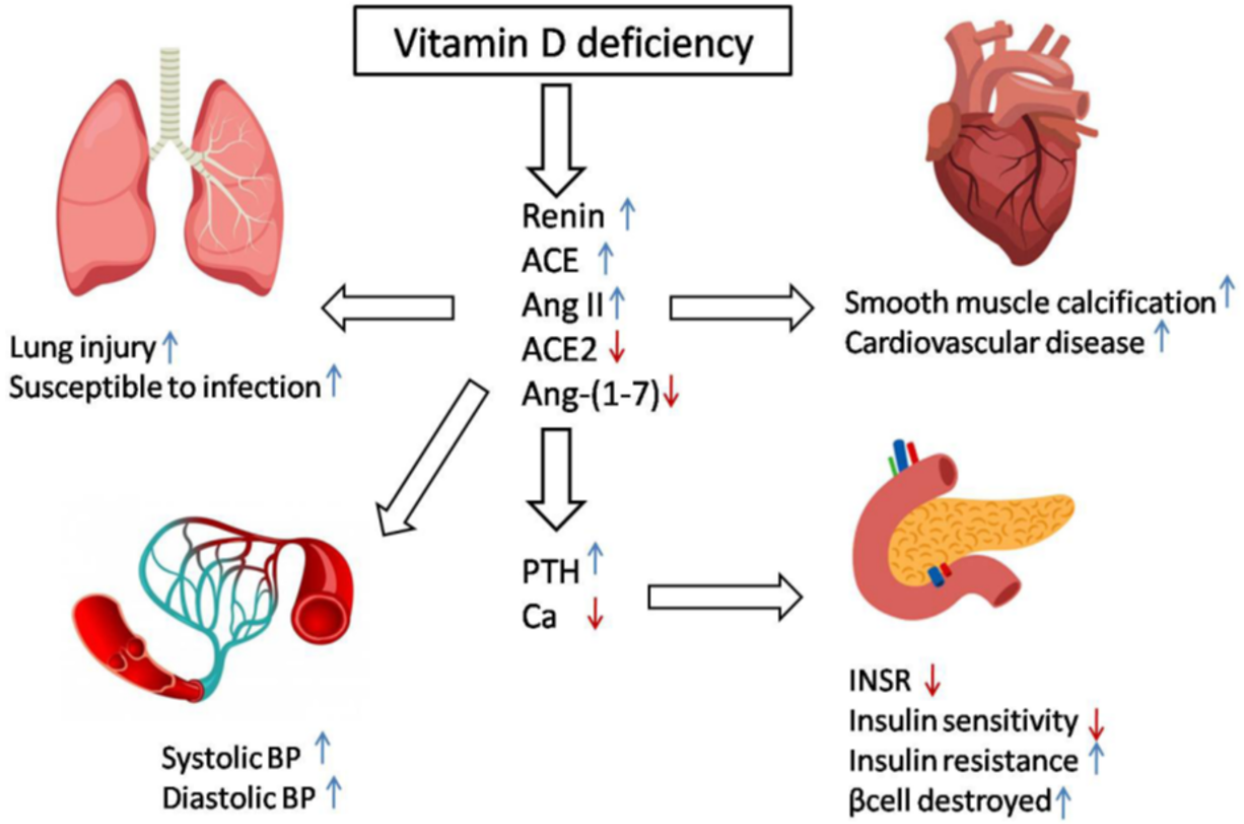

Figure 1: Deficiency of Vitamin D and its related consequences on COVID-19 infection

unit, helping the virus to fuse to the cell membrane, allowing the virus to enter the cell membrane. The virus is then release from the capsular endosome that surrounds the virus through acidification or by the action of intracellular cysteine protease and cathepsin (Aronson, 2020).

As the virus starts multiplying, they burst and infect the cells that are nearby leading to symptoms such as sore throat and dry cough. Then the virus reaches the bronchial tubules and then the lungs where the alveoli which supply oxygen to the blood and affected.

In infected patients the levels of Angiotensin II was increased and the viral load and lung damage were directly proportional (Liu *et al.*, 2020). Close correlation has been shown between COVID-19 and RAS. Organism combines to ACE 2 receptors and invades the lung epithelial cell and initiates infection. Simultaneously, an anti-inflammatory, antioxidant, anti-fibrotic and anti-hyperplasia effect is caused by ACE2 leading to degeneration of Angiotensin II (Ang II) at lung level by ACE2/Ang1-7/ Mas receptor signaling pathway, the counter-regulatory RAS axis with actions opposite to classical RAS axis (ACE/AngII/AT1 receptor pathway). Over-accumulation of toxins are prevented due to the high degradation of Angiotensin-II, which aggravate ARDS caused due to COVID-19 virus. Thus, in causing infection there is an antagonistic double action of ACE2. Moreover, the expression of ACE2 is lower in males than in females and also lower in older adults than in young people, which could be contributing to the susceptibility of elderly males to death by COVID-19 infection. Moreover, there is a worse prognosis of this group of patients, in addition to old age, they have co-morbidities such as cardiovascular diseases, diabetes, hypertension, and obesity, all of them with stimulated RAS. (Vaduganathan *et al.*, 2020).

The molecular response behind the regulation of intrarenal RAS induced through vitamin D is not clearly understood. Studies reveal that cyclic AMP response element-binding protein (CREB) is formed and 1,25 (OH)2D3 blocks the related partner complex. Transcriptional regulatory complex is also involved in the down regulation of intrarenal RAS, which is made up of nuclear receptor co repressor 1 (NCOR1), CREB1, and the vitamin D receptor that binds to cyclic AMP response element-like domain in the renin enhancer. Thus the RAS activity could be suppressed by vitamin D through the inhibition of renin and ACE/AngII/AT1R cascade 8 (Kuba *et al.*,

2005).

Vitamin D has been found to have a diverse immunomodulatory effect in reducing viral infections. These include epithelial cell junction integrity strengthening, directing the immune cells to the infection site and reducing cytokine storm caused due to innate and adaptive immune system. The viral entry of SARS-CoV-2 into human cells through ACE 2 which is a membrane exopeptidase converts Angiotensin I to nonapeptide Angiotensin. RAS is negative regulated through ACE2 by the conversion of Ang II to ANg-(1-7) and is expressed in the epithelial pathway of human airway. The RAS includes ACE and ACE 2 complex is a network and plays a major role in number of biological mechanisms. RAS activation can take place in lung fibrosis in conditions of chronic vitamin D deficiency and also 1,25(OH)2D3 might induce the expression of renin, ACE, Ang II and AT1R which could cause acute lung injury as 1,25(OH)2D3 is required for the expression of the above said elements (Li, 2003).

Studies have shown that RAS plays a significant role in various pulmonary pathologies including regulation of inflammation, proliferation and fibrosis of lung tissues including COVID-19 infections, asthma, COPD, pulmonary arterial hypertension, acute lung injury and so on. In vitro studies have shown that metabolites of vitamin D enhance immunity against a number of respiratory pathogenic organisms. Many clinical trials have also shown a intense correlation between vitamin D deficiency and are more prone to development of respiratory infections. Other clinical trials also show that vitamin D supplementation mitigates the rate of moderate and severe worsening of COPD in patients with lower vitamin D levels (lower than 25 nmol/L) but does not affect patients' with higher concentrations (Grant *et al.*, 2020).

Figure 1 gives the overall adverse effects of vitamin D deficiency.

DISCUSSION

It is observed in this review that the vulnerability to Respiratory Tract infections, with special reference to COVID-19 is reduced through the following mechanisms

1. By maintaining tight junctions and preventing the infiltration through the cells responsible for immunity in lungs and other tissues involved in respiration.
2. Destroy some viruses by stimulating antiviral techniques.
3. Reducing the pro-inflammatory cytokine synthesis by modulating immunity and the avoidance of pneumonia development (Grant *et al.*, 2020).
4. Regulating the RAS system through the balancing of ACE and ACE 2, thus maintaining pulmonary arterial blood pressure and preventing emphysema and cystic fibrosis.

Recommendations

Supplementing vitamin D can be effective in preventing and treating pulmonary infection in COVID-19 as vitamin D modulates the signalling pathways elating to anti-inflammatory, immunomodulatory, antioxidant, anti-fibrotic and anti-apoptotic effects focusing at the lung level. As this is a natural compound, it is safe to use. Vitamin D can aid to strengthen the immunity and prepare the body in overcoming severe pathological consequences of the infection and also reduce the high mortality rate in case of infection.

The risk of acute respiratory infections due to virus can be decreased by supplementing 38 ng/mL was reported in a study. Also according to certain authors the infections process can be mitigated by maintaining the range of vitamin D between 40-60 ng/mL. More recently Dr. Alipio provided sufficient information to physicians and policymakers on the importance of vitamin D supplementation in improving the patients' clinical course who are infected with COVID-19 on the basis of improved probability in having mild result when there is an increase in the serum vitamin D level while decrease in vitamin D level which is associated with worse clinical evolution. Grant and Colleagues and Rhodes et al endorsed the same recommendation and suggested that supplementing vitamin D can mitigate COVID-19 infection risk (Grant *et al.*, 2020), at least for those in the northern hemisphere who are at higher risk of severe illness and death (Rhodes *et al.*, 2020). The same is recommended by the United Kingdom Association of Dieticians and editorials in international scientific rigors.

CONCLUSIONS

Lack of treatment for COVID-19 ultimately has left us with no choice but to follow preventive and prophylactic measures in fighting the pandemic. One such immune booster is vitamin D which seems to be having an advantage over other immune modulators. There are proven studies to show that vitamin can fight against acute respiratory infections and is also safe to use. Moreover, there is enough evi-

dence to show the correlation between plasma vitamin D levels and various other non-communicable diseases which are aggravated by COVID-19 such as diabetes, CVD, hypertension and other metabolic syndromes. Also there is ample proof that the risk of COVID-19 infection is increased by all the above mentioned co-morbidities and so maintaining sufficient vitamin D plasma level becomes inevitable. There are also chances of warding off the infection without mortality if the plasma vitamin D level is maintained. In order to improve the vitamin D plasma level, apart from taking supplementation, people should be encouraged in getting natural vitamin D (vitamin D synthesized by exposure to sunlight), as people are confined to their homes due to the stay-in-shelter lockdown due to this pandemic. Thus, proper diet advice, intake of vitamin D fortified foods and exposure to sunlight can help in preventing vitamin D deficiency and help in overcoming this pandemic.

ACKNOWLEDGEMENT

We prepared this article with the help of many journals and websites. We pay our sincere gratitude to all authors and experts for their efforts and contributions.

Funding support

No funding support required for this article.

Conflict of Interest

The authors declare that they have no conflict of interest.

REFERENCES

Aronson, J. K. 2020. Corona viruses - a general introduction Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, University of Oxford.

Forman, J. P., Williams, J. S., Fisher, N. D. 2010. Plasma 25-Hydroxyvitamin D and Regulation of the Renin-Angiotensin System in Humans. *Hypertension*, 55(5):1283–1288.

Grant, W. B., Lahore, H., McDonnell, S. L., Baggerly, C. A., French, C. B., Aliano, J. L., Bhattoa, H. P. 2020. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*, 12(4):988–988.

Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, G. F. B., Huan, P. Y., Yang, Y., Zhang, W., Deng, L., Bao, B., Zhang, G., Liu, Z., Wang, M., Chappell, Y., Liu, D., Zheng, A., Leibbrandt, T., Wada, A. S., Slutsky, D., Liu, C., Qin, C., Jiang, J. M. 2005. A crucial role of Angiotensin converting enzyme 2 (ACE2) in SARS Corona virus-induced lung injury. *Nat. Med*, pages 875–879.

Li, Y. C. 2003. Vitamin D regulation of the renin-angiotensin system. *Journal of cellular biochemistry*, 88(2):327–358.

Liu, Y. Y. Y., Zhang, C., Huang, W. F. F., Yuan, J., Wang, Z., Li, J., Li, J., Feng, C., Zhang, Z., Wang, L., Peng, L., Chen, L., Qin, Y., Zhao, D., Tan, S., Yin, L., Xu, J., Zhou, C., Jiang, C., Liu, L. 2020. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury Sci. *China Life Sci*, 63:364–374.

Nehme, A., Zouein, F. A., Zayeri, Z. D., Zibara, K. 2019. An Update on the Tissue Renin Angiotensin Systemand Its Role in Physiology and Pathology. *Journal of Cardiovascular Development and Disease*, 6(2):14–14.

Ren, L., Lu, X., Danser, A. H. J. 2019. Revisiting the Brain Renin-Angiotensin System—Focus on Novel Therapies. *Current Hypertension Reports*, 21(4):28–28.

Rhodes, J. M., Subramanian, S., Laird, E., Kenny, R. A. 2020. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. *Alimentary Pharmacology & Therapeutics*, 51(12):1434–1437.

Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J. J., Pfeffer, M. A., Solomon, S. D. 2020. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19. *New England Journal of Medicine*, 382(17):1653–1659.