



## VITAMIN D, ITS STATUS AND IMPACT ON IMMUNITY AND ITS ROLE IN COVID-19 AND RELATED VIRAL PANDEMICS – “A CRITICAL ANALYSIS”

<b>Dr Naresh Rathod</b>	Resident, Department of Pharmacology, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka India.
<b>Dr Jyothi DB</b>	Tutor/Senior Resident, Department of Pharmacology, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka India.
<b>Dr Fouzia M*</b>	Resident, Department of Pharmacology, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka India.*Corresponding Author
<b>Dr Aashish Singh Rajput</b>	Resident, Department of Pharmacology, MGIMS, Sevagram, Maharashtra, India
<b>Dr K Lakshminarayana</b>	Prof & HOD, Department of Pharmacology, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka India.

**ABSTRACT** The globe is under the grip of Covid-19, which is a dreadful pandemic caused by a novel virus belonging to family of coronaviruses. This is supposed to begin as a cross species transmission from bats to humans, originating from the city of Wuhan, in the Hubei province of the country of china in the late 2019. This pandemic has caused a widespread impact on human lives and the economy, the mortality rates are increasing steadily. Impaired or weakened immune responses have shown to cause increased susceptibility and subsequent mortality in the viral pandemics of the past. In the pretext of non-availability of vaccines and other drugs to treat these conditions, Social distancing and related Non-Pharmaceutical Intervention strategies go a long way in limiting the spread. Keeping the immunity intact and strong, helps in reducing the chances of succumbing to such pandemics. Vitamin D, a versatile fat soluble vitamin is known to have immune-enhancing properties and it helps to reduce the incidence of respiratory infections through varied mechanism, which includes protection via strengthening the three immune barriers viz: strengthening physical barriers via occludins, gap junctions and E-cadherins, strengthening the cellular and adaptive immunity responses. Induction of cathelicidins and defensins by Vitamin D is known to lower viral replication rates and reducing concentrations of pro-inflammatory cytokines and increase anti-inflammatory cytokines that may prevent the development of ARDS and subsequent mortality. Vitamin D is also known to have preventive effect in the development of cytokine release syndrome. A recent study by Alipio M and colleagues on Covid-19 infected individuals, gives an indication that higher levels of Vitamin D [25(OH)D] will possibly have less severe symptoms and vice-versa. More clinical trials with stringent protocols studying the effects of Vitamin D in Covid-19 patients needs to be carried out on large scale. In the absence of clinical studies at large, maintaining adequate Vitamin D levels among general public under lockdown, patients of Covid-19 and healthcare professionals may lessen the effects of the virus, by its immune boosting and viral disintegrating properties viz a viz, may lessen the severity of the symptoms caused by Covid-19 virus and could help us to save more lives.

**KEYWORDS :** Covid-19; Viral pandemic; Vitamin D; Synthesis; Immunity; Lockdown and Vitamin D; Immune response.

### INTRODUCTION

The mankind across the globe is presently experiencing a major pandemic of coronavirus infection. A virus that is supposed to have begun as an epidemic in the city of Wuhan in the Hubei province of the country of china in the late 2019, which was originally called as the 2019- nCoV, to be later renamed by the World Health Organisation (WHO) on February 11, 2020 as COVID-19, Which essentially means Corona Virus Disease of 2019.<sup>1</sup>

The world has witnessed several epidemics and pandemics in the past. The corona virus epidemic of 2003 named as the Severe Acute Respiratory Syndrome (SARS-CoV) that started in china, similarly the Middle East respiratory syndrome (MERS-CoV) that started in the Middle East in 2012 were generally caused by cross transmission from animal to humans, wherein the mortality rates were reported to be >10% for SARS and >35% for MERS.<sup>2,3,4</sup>

The direct cause of death in the sufferers of these viral infections were studied to be due to lower respiratory infection leading to severe atypical pneumonia. In people who developed influenza, pneumonia was implicated as a cause of death, although the mortality rates were tabulated to be lesser around 1%–3% H5N1 influenza a pandemic of 1918–1919 that happened in the United States.<sup>5</sup>

In the past four types of Corona Virus infections are also implicated in the seasonal respiratory tract infections (RTIs) which includes human CoV 229E (HCoV-229E), human CoV OC43 (HCoV-OC43), human CoV NL63 (HCoV-NL63) and human CoV HKU1. Surveillance reports conducted during these outbreaks between 2014–2015, three strains of these viruses were detected among childrens that crossed borders from China to Hongkong from months or January to February,

whereas human CoV NL63 (HCoV-NL63) was detected only in summer and fall. In the present context, the Covid-19 (Novel corona virus) is presumed to have emerged in the later months of 2019 around the winter of December, but the exact dates of origin and its outbreak is a matter of controversial discussion till date.

Pandemics has an enormous impact on human lives and the economy at large, while the disaster mitigation strategies like Non Pharmaceutical Interventions which includes Social Distancing, Hand Hygiene, Cough and Sneezing protection, Quarantine and isolation are at place and functioning, we have to look into ways and solutions that can help us fight against this viral pandemic at large and at a comparatively low cost.

Vitamin D is one such vitamin that has demonstrated enormous antiviral properties in the past, this vitamin is largely studied in different Randomised Controlled Trials to have demonstrated significant antiviral and antimicrobial activity and has also immune boosting properties, that would enable one to fight against bacteria and viruses causing Lower Respiratory Infections and its associated complications like pneumonia.<sup>7,8,9,10,38</sup>

### VITAMIN D SYNTHESIS

Vitamin D is an important fat soluble vitamin required to carry out various bodily functions and to maintain calcium homeostasis. The principal provitamin found in animal tissue is 7-dehydrocholesterol which is synthesized in the epidermal layer of the skin. Exposure of skin to direct sunlight containing UV-B within wavelengths 290-315 nm, results in the conversion of 7-dehydrocholesterol to pre-cholecalciferol (pre vitamin D<sub>3</sub>) which undergoes spontaneous isomerisation to cholecalciferol (vitamin D<sub>3</sub>). Cholecalciferol

undergoes double hydroxylation, first in the endoplasmic reticulum of liver hepatocytes to form calcifediol (25-hydroxycholecalciferol) followed by second hydroxylation in the kidneys to form Calcitriol (1-25-dihydroxycholecalciferol). Calcitriol is the active form of circulating Vitamin D in human body.<sup>11</sup>

### VITAMIN D DEFICIENCY GLOBAL AND INDIAN SCENARIO

Vitamin D deficiency is now recognised as a global pandemic. About 1 billion people worldwide have vitamin D deficiency. The major cause is attributed to the lack of appreciation that sun exposure in moderation is the major source of Vitamin D for most human beings. Increased indoor lifestyles also prevents adequate exposure to sunlight, increased pollution that cuts of UV-B penetration into the atmosphere, low dietary intake of foods rich in calcium and Vitamin D, Phytates and Phosphates present in fibre rich diet, Pigmented skins, application of sunscreen lotions, unspaced and unplanned pregnancies can all lead to Vitamin D deficiency in children, adults, elderly, pregnant and lactating mothers.<sup>12</sup> The prevalence of patients with vitamin D deficiency is highest in the elderly, the obese patients, nursing home residents, and hospitalized patients. Prevalence of vitamin D deficiency was 35% higher in obese subjects irrespective of latitude and age.<sup>14</sup>

In India, Vitamin D deficiency is widespread. However, the clinically diagnosed cases represent only the tip of the iceberg. The prevalence of Vitamin D deficiency is estimated to range from 40% to 99% according to the study conducted by P Arpana et al. As per the report of International Osteoporosis Foundation, in North India, 96% of neonates, 91% of healthy school girls, 78% of healthy hospital staff, and 84% of pregnant women were found to have hypovitaminosis D.<sup>13</sup>

### COVID-19, LOCKDOWN AND IMPACT ON VITAMIN D STATUS

Globally and in most of the countries which are presumed to receive abundant sunlight which is the key driving factor for synthesis of Vitamin D, the deficiency profile is paradoxically profound and the most vulnerable groups includes the healthcare professionals (doctors, nurses and allied), hospitalised patients, obese, elderly, neonates and pregnant women. In the context of Covid-19, a global pandemic, with route of transmission so challenging like aerosols and fomites, Non Pharmaceutical Interventions like social distancing and lockdown are implemented at a large scale, this further cuts down exposure to sunlight from previous levels increasing the dearth of deficiency. This may further aggravate the fragility of the immune mechanisms and body defences in Vitamin D deficient states.

### VITAMIN D AND IMMUNITY

Calcitriol, the active form of Vitamin D after synthesis, enters the blood and reaches its target cell and thereby entering the nuclear VDR (Vitamin D Receptor) and exerting its action. Several review literatures in the past have demonstrated the mechanism of by which Vitamin D reduces the risk of microbial infections more specifically the viral infections and associated mortalities.<sup>14-22</sup>

In a recent study conducted by Rondanelli M et al, to explain the three main immune interactive clusters in the causation of common cold and respiratory tract infections, the role of Vitamin D in reducing the risk of common cold and related infections was grouped into three probable categories: The physical barrier, Cellular natural immunity and the Adaptive immunity.<sup>21</sup>

### VITAMIN D AND THE FIRST IMMUNITY BARRIER: "PHYSICAL BARRIER"

The foremost barrier in any immune mediated response is the physical barrier. The active hormone form of Vitamin D is important in upregulating the genes via the 1 $\alpha$  hydroxylase enzyme, which subsequently encodes the proteins that is required for the formation of tight junctions like occludins, the tight junctions helps in the sealing of the adjacent epithelial cells in a narrow band just beneath their apical surface and includes a network of claudins and other related proteins, Similarly Vitamin D helps in the approximation of gap junctions and adherens junction like E-cadherins, the adherens junction are known to provide strong mechanical attachments between adjacent cells, they hold the epithelial cells together as narrow bands and are responsible for the contact inhibition. These barrier when strong, would enhance the defences against invading microbes and viruses in particular and hence prevent easy penetration and subsequent pathogenetic effect.<sup>23</sup>

### VITAMIN D AND THE SECOND IMMUNITY BARRIER: "CELLULAR IMMUNITY"

Several studies conducted in the past, concludes that Vitamin D enhances cellular immunity by varied mechanisms like the induction of antimicrobial peptides, that includes human cathelicidin and LL-37. Cathelicidins are small, cationic, antimicrobial peptides found in humans and other species of farm animals. These proteolytically activated peptides are part of the innate immune system of many vertebrates. These peptides shows a broad spectrum antimicrobial activity against a variety of microbes, including Gram-positive and Gram-negative bacteria, enveloped and non-enveloped viruses, and fungi. Apart from exerting direct antimicrobial effects, cathelicidins can also trigger specific defence responses in the host. Their roles in various pathophysiological conditions have been studied in mice and humans.

Cathelicidins were originally found in neutrophils, but now they are known to be present in many other cells that includes epithelial cells and macrophages. Covid-19 virus is believed to interact with respiratory epithelial cells and cause its subsequent pathogenesis. The general rule of action of the Antimicrobial Peptides (AMPs) like Cathelicidins, is that, when these peptides are induced by bacteria, viruses or other substances, they cause disintegration of the cell membranes of the organisms towards which these peptides are active. Disintegration results in damaging and puncturing of the triggering organism, that may kill them or render them pathologically inactive or by neutralising their endotoxins. Cathelicidins are also known to rapidly destroy the lipoprotein membranes of the microbes that are enveloped in the phagosomes after their fusion with the lysosomes in macrophages.<sup>24,25</sup>

A clinical trial reported that supplementation with 4000 IU/d of vitamin D decreased dengue virus infection.<sup>26</sup> Additionally a review conducted by Hewison et al. showed that Vitamin D supplementation was successful in raising the serum levels of 25OHD in patients with tuberculosis and it may also play a role in promoting the innate immune responses to enhance monocyte phagocytosis and degradation of the beta amyloid. The effects of Vitamin D3 on the macrophage phagocytosis may be related to the ability of that vitamin to alter monocyte maturation. Thus it may enhance the immunoglobulin and complement-mediated phagocytosis by human monocytes through its stimulation of monocyte maturation to macrophages.<sup>27</sup> It is understood that enhancing innate immune responses through Vitamin D supplementation would help maintain self-tolerance by dampening over zealous adaptive immune responses. Similarly another study on Vitamin D supplementation in postmenopausal women, showed a significant benefit in the reduction of systolic blood pressure and improvement in lower extremity function, and also the reduction in several inflammatory and innate immunity markers.<sup>28</sup>

### VITAMIN D AND THE THIRD IMMUNITY BARRIER: "ADAPTIVE IMMUNITY"

Recent epidemiological studies, suggest that Active form of Vitamin D supplementation serves as an independent protective factor that influences the occurrence of T-1 mediated autoimmunity.<sup>29</sup> The effect of Vitamin D supplementation on the immune system includes, decreasing of T1/T17, CD4+ T cells and cytokines, increasing of the regulatory T cells, down regulation of the Ig G Production which is T cell driven and the inhibition of the dendritic cell differentiation.<sup>30</sup> The adaptive immune effects of Vitamin D is multifaceted and is just not related to only effector T cells but also has its action of suppressor or regulatory T cells (Treg), which are a group of CD4+ T cells that are known for inhibiting the proliferation of other T cells. Regulatory T cells are studied widely for their beneficial effects in autoimmune disease and graft vs host rejection reactions.<sup>31</sup>

In a study conducted on reproductive age group females, it was seen that, Vitamin D deficiency or insufficiency has immunological implications in the patients who had recurrent miscarriages, in these females the percentage of B cells, TNF- $\alpha$  producing Th cells and Natural killer cell mediated cytotoxicity were significantly reduced under 0.5 $\mu$ g/day of Vitamin D [1,25 (OH)<sub>2</sub>D] supplementation for 2 months. Subsequent treatment with 4000 IU of Vitamin D3 significantly reduced the CD4+ T cell activation when compared to low dose Vitamin D3, this very important observation provides a human evidence that Vitamin D can influence the cell-mediated immunity on a multipronged dimensions.<sup>32,33</sup> Vitamin D is also

known to reduce the cytokine storm induced by the innate immune system, it helps to reduce the production of pro-inflammatory Th1 cytokines, such as tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) and interferon  $\gamma$  (IF $\gamma$ ) that increases the expression of anti-inflammatory cytokines by macrophages.

### COVID-19, IMMUNE RESPONSE AND VITAMIN D

The immune responses induced by the Covid-19 virus are two phased, the incubation phase, which is generally a non-serious phase. The development of an endogenous protective immune response requires the host to be in a good general health with adequate immunity and an appropriate genetic background that elicits specific antiviral immunity. Vitamin D plays an important role in boosting the overall immunity of the patient as evidenced by previous studies.<sup>27-33</sup>

Covid 19 is presumed to effect the organs and tissues that have high ACE2 expression, such as intestines, kidneys and lungs, It is known to cause massive destruction of these tissues. These damaged cells induce innate inflammation in the lungs that is mediated largely by the pro-inflammatory macrophages and granulocytes, Lung inflammation is the main cause of life threatening respiratory disorders that leads to the severe stage. Hence good general immunity may be beneficial to prevent the advancement of the patients to severe stages but once they progress to severity it may be of no help. The role of Vitamin D with innate immunity boosting activity has some consideration here.<sup>29,35</sup>

The cytokine release syndrome (CRS) seems to affect patients with severe conditions and lymphocytopenia is commonly seen. Hence the CRS has to be mediated via the leucocytes other than T cells. In such conditions blocking, IL-1, IL-6 and TNF may prove beneficial. Vitamin D from the previous studies has been known to enhance cellular immunity, in part by reducing the cytokine storm induced by the innate immune system. The innate immune system generates both pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections.<sup>36</sup> Vitamin D can reduce the production of pro-inflammatory Th1 cytokines, such as tumour necrosis factor  $\alpha$  and interferon  $\gamma$  <sup>37</sup>. Administering vitamin D reduces the expression of pro-inflammatory cytokines and increases the expression of anti-inflammatory cytokines by macrophages.

Covid-19 infection and the innate immune response to tissue damage caused by the virus is supposed to cause Acute Respiratory Distress Syndrome (ARDS) in which the respiratory failure is characterised by the rapid onset of widespread inflammation in the lungs and subsequent fatality. Recent epidemiological studies, suggest that Active form of Vitamin D supplementation serves as an independent protective factor that influences the occurrence of T-1 mediated autoimmunity. And adequate levels in the infected patients may be helpful in preventing the progression of the disease to ARDS and fatality thereof.<sup>29,35</sup>

In the dawn of the possible immune enhancing effect of Vitamin D in patients with Confirmed Covid-19 infection. A retrospective analysis was undertaken by Alipio M and colleagues, using the database from three hospitals of the Southern Asian Countries, wherein they categorised 212 cases of Covid-19 cases into mild, ordinary, severe and critical and matched them to see the levels of their Vitamin D [25(OH)D] status. The cut offs were taken as Normal levels, 25(OH)D > 30ng/ml, insufficient, 21–29ng/ml and deficient as <20ng/ml. the subsequent analysis revealed that for the category of mild infections the mean levels of Vitamin D [25(OH)D] were 31.2ng/ml, ordinary, 27.4 ng/ml, severe, 21.2ng/ml and critical the lowest at 17.1ng/ml. These variations and differences in the values were found to be statistically significant and hence gives an indication that possibly the patients with higher levels of Vitamin D [25(OH)D] will have less severe symptoms and vice-versa.<sup>34</sup>

### CONCLUSION

Covid-19 is the havoc that the world is fighting today, with lots of sacrifices and lives on the line, worst hits encompass the vulnerable population with extremes of age and with weakened immunity. Healthcare professionals and other frontline warriors against Covid-19 are at maximum risk of exposure, hence every possible move that could boost up their immunity and help them to combat this dreaded virus is justified. Vitamin D is one such versatile Vitamin that has known to have multiple benefits to mankind, boosting the immune system is one such advantage. Many studies and trials in the past, when the world has faced dreaded viral pandemics, studied the advantage of

this Vitamin and its role in combating these infections via varied mechanisms. This Vitamin is known to strengthen the three most important immunological barriers that prevents any bacteria, virus or other microbes from invading our organ system and causing their dreaded effects. It strengthens the physical barriers via occludins, gap junctions and E-cadherins, it also strengthens the cellular and adaptive immunity responses, causes the induction of cathelicidins and defensins that is known to lower viral replication rates and also disintegration of bacteria and viruses (both capsulated and uncapsulated). Vitamin D also reduces the concentrations of pro-inflammatory cytokines and increase anti-inflammatory cytokines that may prevent the development of ARDS and subsequent mortality. Vitamin D is also known to have preventive effect in the development of cytokine release syndrome.

Although Vitamin D is known to enhance immunity as evidenced by large number of studies carried out in the past to gauge its role in immune responses. But in the context of Covid-19, as no concrete clinical data is available, the value of Vitamin D supplementation and its subsequent maintenance to reduce the symptom burden in those patients with Covid-19 remains largely unclear. Nevertheless based on the retrospective analysis by Alipio M and colleagues with favourable results, would seem important and valuable for the clinicians to ensure that those with Covid-19 infection should have adequate Vitamin D levels, as it may lessen the effects of the virus, by its immune boosting and viral disintegrating properties viz a viz, may lessen the severity of the symptoms caused by Covid-19 virus and could help us to save more lives.<sup>34</sup>

### ACKNOWLEDGEMENTS

We would like to thank Dr.SurendraNaik, MD (Internal Medicine), Dr.Harish H.S, Ophthalmologist Delhi and Dr.M.K.Srinivas, IRMS, Bangalore, for reviewing the article and giving opinions, comments and corrections as appropriate. We extend our thanks to Dr. B. Devanand, Director, VIMS, Ballari, Dr. D. Krishnaswamy, Principal, VIMS, Ballari, Dr. J. Mariraj, Medical Superintendent, VIMS, Ballari, Dr.Y.Vishwanath Professor, Department of Pharmacology, for constantly encouraging us to contribute back to medical fraternity and other Faculties of Department of Pharmacology, VIMS, Ballari for their encouragement, our families for their continued support and friends for their appreciation and valuable views.

### CONFLICT OF INTEREST

The authors does not declare any competing conflict of interest.

### FUNDING AND SPONSORSHIP

No funds or sponsorship was availed for carrying out this research work.

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