IJBPAS, June, 2020, 9(6): 1376-1384

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

VITAMIN D SUPPLEMENTATION AS A SUPPORTIVE THERAPY FOR COVID-19: A REVIEW ARTICLE

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Received 10th May 2020; Revised 15th May 2020; Accepted 26th May 2020; Available online 1st June 2020

https://doi.org/10.31032/IJBPAS/2020/9.6.5094

ABSTRACT

Coronavirus is caused by severe acute respiratory syndrome; coronavirus 2 has caused a widespread pandemic which is hard to treat as the layers of the virus cause it difficult for the medicines to show effect rapidly. This virus spreads through direct contact with the infected person or coughing, sneezing of the infected person and it causes suppression of immunity that allows the virus to grow rapidly. Several immune modulators can be used out of which one is the vitamin D that is involved in several processes in the body mainly providing the innate and acquired immunity through the activation of B-cells and T-cells. Several studies have shown that vitamin D can be beneficial for patients of COVID-19. One such was a meta-analysis study that reviewed that group administered with vitamin D had less incidence of respiratory diseases compared to those on placebo. Other studies have reviewed that administration of vitamin D during winters can help avoid respiratory conditions. Some adverse effects include hypercalcemia and renal stones at doses administered at single high doses. It shows effect better when administered in daily or weekly doses rather than a single high dose.Overall vitamin D can be used both in the treatment and prevention of COVID-19.

Keywords:COVID-19, SARS-CoV-2, vitamin D, pandemic, immunity, respiratory distress syndrome

INTRODUCTION

The world is suffering from its third global pandemic that has lead to destruction all over the world with a mortality rate of 3.4 –4.9%. Coronavirus disease (Covid-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) is causing a

serious illness that is dangerous and has caused many deaths. Most of the infected individuals have mild to moderate respiratory illness that starts with a sore throat, coughing, and gradually causes pulmonary fibrosis that affects the breathing of the person. According to preclinical research the coronavirus enters the cell via the Angiotensin Converting Enzyme 2 (ACE 2) by downregulating the enzyme by its replication and affecting the regulation of rennin angiotensin system (RAS) causing the release of various cytokines that leads to respiratory distress **[1]**. Also there is rapid and thick production of mucus in the patients affected with COVID-19. All the parameters are in a way affected bythe loss of the immunity to fight against the infection. Vitamin D is a secosteroid hormone that is a fat-soluble vitamin produced by the skin during exposure to UV-B rays **[1]** and regulates the calcium-phosphate hemostasis and cell proliferation. The inactive form of vitamin D is activated mainly by the liver and other organs involved are the lungs, kidney, brain, and immune cells. The active vitamin D produced by the brain and immune cells provides immune system actions and lung calciferol is involved in acting against lung infections. Mainly the vitamin D is involved in enhancing the innate immunity **[2]**. The deficiency of vitamin D has been reported to cause increased autoimmunity and increased chances of infection **[3]**.

COVID-19 (Coronavirus disease 2019) and its pathology

Coronavirus disease is a respiratory infection caused by severe acute respiratory syndromecoronavirus 2 (SARS-CoV-2). They are a family of enveloped virus that consists of single-stranded RNA. It is approximately 125 nm in diameter and is the largest of all the RNA viruses. It consists of four proteins that are important for its structure: spike (S), membrane (M), envelope (E), nucleocapsid (N), and hemagglutinEsterase Protein.

The N forms a complex with RNA and helps to form viral assembly, and the S,E,M proteins create the viral envelope and S is responsible for the virus entry into the human cell and it then uses various human enzymes like the ACE-2 and transmembrane protease serine 2 (TMPRSS2) for it entry and development. This virus is mainly transmitted via the inhalation of the aerosol droplets from the coughing, sneezing, or talking of the symptomatic people or through direct hand-to-face contacts making it a highly contagious disease. The first case was seen in Wuhan, China in November 2019 with later in December caused outbreak

leading to pandemic affecting 3,206,333 people worldwide till now and is increasing each day. The incubation period may range from 2-14 days and can be symptomatic or asymptomatic. But generally, the symptoms may include dry cough, moderate fever, runny nose, fatigue, nasal congestion, sore throat, and rare symptoms including diarrhea, vomiting, muscle and joint pain, headache, and development of productive cough. It mainly corresponds to the symptoms of pneumonia. In severe cases the patients can develop dyspnea, high fever, chest pain, hemoptysis, respiratory crackles, and progressive respiratory failure. The recovery time may vary from 2-6 weeks. The complications that can increase the risk for COVID-19 include immunosuppression, age above 65 years, pregnancy, and various chronic diseases like DM, CAD, hypertension, and cerebrovascular diseases **[4, 5]**.

Vitamin D and its process to provide immunity

Vitamin D is a fat-soluble vitamin obtained mainly by the sunlight UVB exposure and other dietary sources including fatty fish like tuna, mackerel and salmon, beef liver, dairy products, egg yolk, orange juice, and soya milk. Both exogenous and endogenous vitamin D are inactive and require two-step hydroxylation conversion to 25-hydroxylation and 1-alpha hydroxylation to be inactive form. Generally hydroxylation is carried out by the Cytochrome P450 enzyme **[2]**.

Vitamin D was accidentally looked into in the people who had pneumonia, so there was an observation that people who had less vitamin D or hypovitaminosis D were more prone to develop pneumonia. According to the study SARS-CoV2 is an enveloped virus and these enveloped viruses can be affected by the proteins that Vitamin D activates.

In our body innate immunity is activated when any pathogen binds with a macrophage receptor (PAMP & TLRs) when this receptor is activated, the pathogen becomes internalized but at the same time Vitamin D receptor is activated inside the macrophages, Now the inactive form of vitamin D (25 Hydroxylated vitamin D3) is picked up by the macrophages and converted to the active form that is 1, 25Dihydroxy Vitamin D3. The immune cells (T cell, B cell, Macrophages, and Dendritic cells) have their enzymes to convert Vitamin D into an active form. When vitamin D is activated in Immune cells it helps to produce proteins called Beta defensins, Cathelicidin, and Nuclear Factor Kappa B (NFK-B).

SARS- CoV 2 is an enveloped virus so these proteins specifically Beta defensins when they are released they can enter the cell membrane (Generally viruses are naked but this SARS-CoV 2 have membrane), and create holes in that membrane and then go in the cell, in this process the hole they create causes the membrane to become disrupted and the material from inside can be leaked out. Secondly when the membrane is damaged the virus can die. But for the production of Beta defensinsneeds NFK-B and for that Vitamin D is needed.

Now another Protein called Cathelicidin does chemotaxis (attracts immune system cells to the area of infection) and this leads to an increase in the immune response. It also activates macrophages activity for phagocytosis (macrophages eating up the pathogens and killing them). Cathelicidin leads to increase vascular permeability (more amounts of blood moving and coming into the area of infection) to help combat and provide nutrition and oxygen and take waste products away. It also proliferatesTcells and Bcells **[2, 3, 6]**.

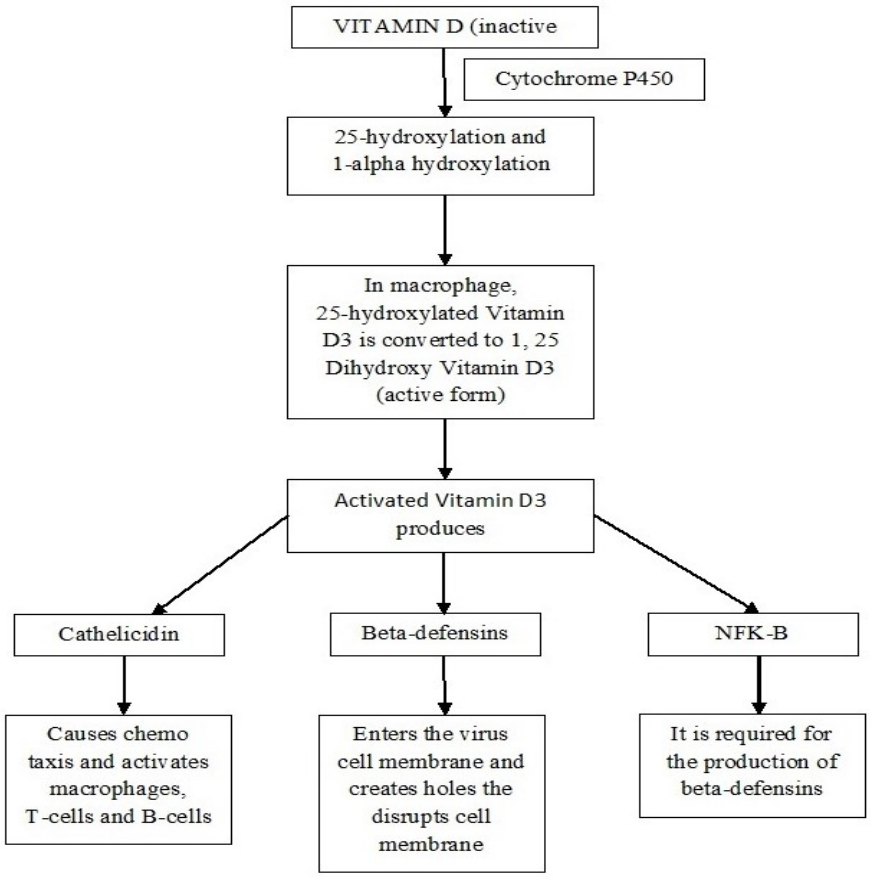

Figure 1: Innate Immunity by Vitamin D

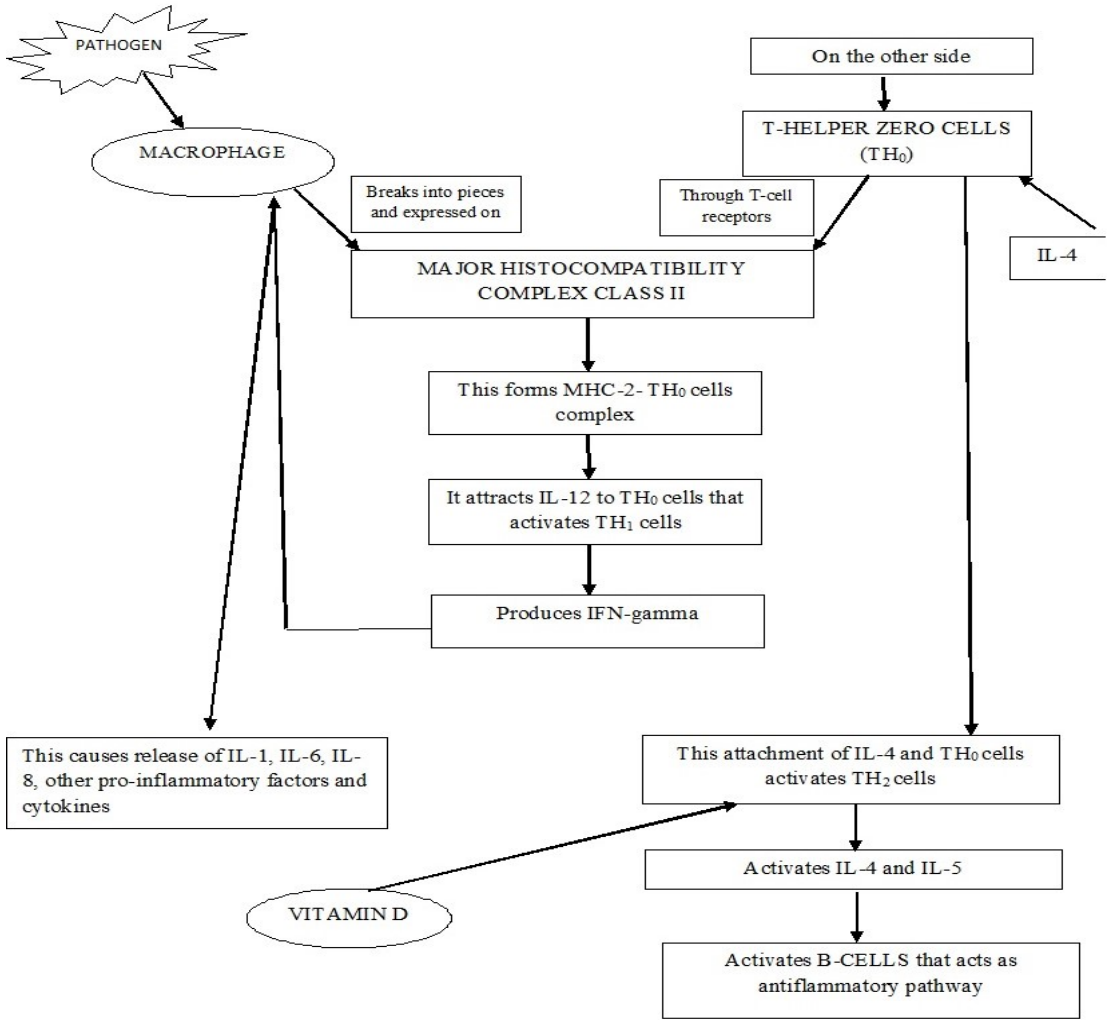

Figure 2: Acquired Immunity by Vitamin D

Secondly our immune system has an innate arm and then acquired arm. The innate arm consists of normal monocytes, macrophages, and other cells of this kind, and the acquired arm has B cells and T cells. When a pathogen enters into a macrophage, it will break it into smaller pieces and then they are expressed on MHC 2 (Major histocompatibility complex). On the other side in acquired arm we have T helper zero cells this T cell connects through the T cell receptor on MHC 2 (called as an antigen-presenting cell) and co-stimulation and exchanges of enzymes occur. Once this engagement occurs and an IL-12 attracts to T helper Zero cell it would cause TH-1 cell (T helper one cell) to become active and when this becomes active it produces IFN-Gamma that is sent back to macrophages. When macrophage becomes active with this IFN-Gamma it releases a lot of IL-1,IL-6,IL-8,

and other Pro-Inflammatory and other cytokines. Now if IL-4 attaches to T helper zero cells rather than IL-12 then it activates TH-2 cell (T helper two-cell), which in turn activates by IL-4 and IL-5 so it activates the B cell on the acquired arm. When vitamin D is present it causes the immune system to move in the TH-2 cell activation direction because it somewhat acts as Anti-inflammatory.

In the COVID-19 in serious cases when the patient is on a ventilator we give them IL-6 inhibitors and other drugs, IL-6 coming from the activation of TH-1 cell pathway and this sending IFN-Gamma to macrophage and it releases the IL-6 and other Pro-Inflammatory. The presence of vitamin D helps move towards T helper 2 cells which are more Anti-inflammatory. The patient who is becoming seriously ill they have cytokines storm going and they have severe activation of their inflammatory response this causes RDS then the septic shock that leads to death so when vitamin D is present it regulates the inflammatory system downwards and it also helps the epithelial cells to make their membrane more stable and make them less permeable to water and other substances making it difficult for the pathogen to enter the cell **[2, 3]**.

DISCUSSION

Vitamin D is a fat-soluble vitamin that functions mainly in calcium metabolism and immune function modulation. It is mainly obtained from sunlight and plays a major role in regulating immunity in the body. Vitamin D is important in the body as it stimulates the immunity to fight against viral and bacterial infections. Also, it is essential for the regeneration of epithelial cells and also reduces the scope of the acquired immune response as in people who have acute respiratory distress syndrome, it occurs as the virus or bacteria enters the body and ittargets the body's immunological response that causes increased production of inflammatory fluid that collects in the alveoli and space between the capillaries and alveoli that causes a decrease in exchange of gases inside the lungs. Vitamin D disproportionate the acquired immunological response and also the lymphocytes that are involved in providing immune response have vitamin D receptors **[7]**. So, according to the biology of the SARS-CoV 2 it affects the lungs causing the main symptom as pneumonia as the immune cells fail to give the response as the virus also affects the immune system. Therefore, vitamin D supplements can be used for increasing immunity in patients. Sunlight being the main source of this

vitamin can be obtained by sitting in sunlight early morning. Taking an example of tuberculosis, in the early days patients of TB were advised to go and live at higher altitudes where ample sunlight is present so that they can get enough sunlight that can help activate vitamin D and help in TB infection **[7]**. But considering the respiratory tract infection they occur more during the winter seasons when the intensity of sunlight is less. According to a study published in BMJ in 2017, most of the respiratory tract infections commonly being common cold and others like bronchitis, pneumonia,etc has more evidence to occur during winter and occurs more in individuals having low vitamin D levels. But the study reviewed that administering Vitamin D supplements can cut the proportions for people getting such infections by 12% but the exact effect of vitamin D supplements is not proved to show effect in all the patients **[6]**. Another systemic review and meta-analysis that studied individual patient data included 10,933 patients that were divided into two groups in which one group was administered vitamin D3 and the other group was given a placebo. Both the groups received the treatment in the same way and the results showed that the 1st group that was administered vitamin D3 did not have respiratory tract infection and if also if occurred were less severe with an adjusted odds ratio (AOR) of 12% and P-value 0.05. The benefits were greater in those receiving daily or weekly doses of vitamin D without additional doses with AOR for not getting respiratory tract infection of 19% whereas in cases that included large bolus doses being administered did not. Also, the safety and efficacy of administering supplement were studied and it revealed that use of vitamin D supplement did not influence the risk of serious adverse events of any cause and also did not increase the risk of death but some complications that were seen in some patients was hypercalcemia (0.5%) and renal stones (0.2%) with the same percentage of occurrence in both the groups that were studied. Therefore, vitamin D supplement was considered to protect against ARTI with a dose of 1mcg (40 IU) to 25 mcg (1000 IU) **[6]**.

According to another recent study done in 2020, revealed that the infection outbreak occurred in winter when the levels 25-hydroxyvitamin D are the lowest, and the cases of mortality were more due to increased age and disease co-morbidity in which the levels of vitamin D are low. So it was recommended that vitamin D supplements should be administered with

magnesium supplements as magnesium helps to activate vitamin D and also regulates calcium and phosphate hemostasis that helps maintain bones. Also all the enzymes that metabolize vitamin D require magnesium that acts as co-factor. For this it was recommended that vitamin D should be administered by selecting the appropriate dosage after checking that baseline level of vitamin D in the patients that are suggested to have low levels like in cases of increased age, pregnancy, obesity, etc. and it was found that for about half of the population 5000 IU/day or 30,000-35,000 IU/week had raised vitamin D concentration to 40ng/ml. It was also studied that the supplementation can reduce the risk of influenza and COVID-19 incidence and the RCT in ventilated ICU patients was conducted. The main goal should be to raise 25 (OH) D concentrations above 40-60 ng/ml and a conclusion was made that people infected with COVID-19, higher vitamin D3 doses can be used as it can show effect **[8]**.

CONCLUSION

According to various clinical trials and studies it can be said that vitamin D supplementation can help in both preventions and as supportive care in the treatment of COVID-19 cases.

Vitamin D has many roles to play in the body mainly in regulating both innate and acquired immunity that can help to restrict the viral infection and has also reportedshowing effect in restricting the respiratory tract infections mainly ARTIthrough activating various receptors at different stages that are the mainstay where this COVID-19 virus affects causing the formation of rapid and thick mucus that causes the host immune system to suppress allowing the bacteria to multiply rapidly causing a worldwide pandemic.

Using vitamin D in daily or weekly doses by checking the levels of vitamin D in patients and taking into consideration the side effect of hypercalcemia and renal stones studied in few individuals at very high doses it can be used to increase the immunity in the patients especially in the areas having winters and low intensity of sunlight and hospitalized patients who cannot be advised to obtain natural vitamin D. Covid-19 being an enveloped virus cannot be easily destroyed and along with other medication, it is necessary to activate the host immune system to fight against the virus. So, vitamin D supplementation can be suggested to be used in increasing immunity in patients and also can be used as a tool for the prevention of this worldwide pandemic.

AUTHOR CONTRIBUTION: All the authors have equal contribution in literature review, drafting the manuscript and edits.

FUNDING INFORMATION: No funding was received from any agency.

CONFLICT OF INTEREST: None Declared

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