

Preventive and Therapeutic Role Played by Vitamin D in Individuals with Covid-19

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ABSTRACT

The coronavirus pandemic has created public health crises around the globe and the research for possible preventive and protective factors is still underway in many countries. Elderly patients, and those patients with comorbidities like hypertension and diabetes mellitus, are at higher risk of developing pneumonia which can further lead to complications like pulmonary fibrosis and ARDS (Acute Respiratory Distress Syndrome). At times, even children are not spared by Covid 19 and they acquire a less extreme manifestation of the disease. This review article talks about the preventive role of Vitamin D in individuals that are prone to develop Corona Viral Disease.

Vitamin D is an essential micronutrient, which is provided by sources such as sunlight and other sources such as cod liver oil, yolk from cooked eggs and liver of beef. Hypovitaminosis D has been shown to be a causative factor of Corona viral disease, thus implicating Vitamin D as a promising medium for fighting the Corona Virus. Vitamin D supplementation for risk groups (those with hypovitaminosis D), is recommended to maintain an optimal level of serum vitamin D for Corona viral disease prevention and treatment. This vitamin also has a direct antiviral effect on viruses with envelopes, and the novel corona virus is an enveloped virus. Vitamin D is a vitamin which also has a role in modulating the immune responses and signaling pathways that has a role in the pathogenesis of Corona viral disease. Thus, in this article, we review the preventive and therapeutic part played by Vitamin D in the disease caused by the novel coronavirus.

Key words: Covid-19, Vitamin-D, Prevention

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INTRODUCTION

The Coronavirus pandemic has caused a global medical crisis, even in the most developed countries, and this has led to a frantic search for therapeutic agents which could be useful in the treatment of Corona Viral Disease. Several vaccines such as Covaxin and covishield have been created to prevent the development of Corona Viral Disease. Newer antiviral drugs such as Remdesivir have been given a green signal to be used in the treatment of Covid 19. Corticosteroids and immunoregulatory agents such as hydroxychloroquine have also been used by some, as a therapeutic agent in covid 19 [1].

Apart from the rise in research for potential therapeutic agents, local governments have taken frantic steps such as lockdown of entire nations, and quarantine and isolation of patients infected with the Virus. Development of new vaccine and drugs, have taken a long time to be available commercially due to human testing and clinical trials and at the same time, already available pharmaceutical agents have been tested for their action against the novel

coronavirus [2]. One such already available agent is Vitamin D. Studies have observed that Vitamin D supplementation in Corona Viral Disease could be a therapeutic as well as a preventive agent. There are ongoing trials and studies to find out the possible part played by Vitamin D in Corona Viral Disease [3].

For humans, the principal source of vitamin D is sunlight, and there occurs two steps of hydroxylation, the first one in the liver and the final one in the kidneys, and this leads to development of the active form of the vitamin, Calcitriol [4]. Vitamin D, which is a fat-soluble vitamin has been seen as a marker for healthy bones, and is also required for the health of many other organs and tissues. Low Vitamin D levels predisposes to diseases affecting the heart, Type 2 DM, metabolic syndrome and cancer as well. Low levels of this Vitamin, has been implicated in increased mortality due to ARDS. Vitamin D's protective role in respiratory infections has been implicated due to stimulation of innate immunity and the increased production of IL-37, cathelicidins and defensins. Not only does it increase innate immunity, but it also reduces the severity of cytokine storm and decreases the production of inflammation causing cytokines like Interferon gamma and Tumour Necrosis Factor Alpha [5-7].

It has been seen that cells of the reticuloendothelial system, which are antigen presenting cells, synthesize the 1,25-dihydroxyvitamin D, which is the active form of the Vitamin from the precursor form, 25-hydroxyvitamin D (25-OHD) . This property of reticuloendothelial cells, which was earlier considered to be a pathological response to diseases such as Sarcoidosis, Tuberculosis and other granulomatous diseases, but now it has been proven that this property is needed for the normal development of the reticuloendothelial cells [8].

Objective

To investigate the possible curative and preventive part played by Vitamin D in individuals suffering from Corona Viral Disease.

MATERIALS AND METHODS

There was an observational study where the laboratory, clinical and demographic data of forty-two patients suffering from an acute form of respiratory failure who were treated in Respiratory Intensive Care Unit (RICU) of the Polyclinic of Bari from March eleven to April thirty, 2020 was seen.

81 % of the individuals were seen to be suffering from hypovitaminosis D. On the basis of Vitamin D levels, the individuals were further grouped into four subgroups including no hypovitaminosis D, an insufficiency of vitamin D, moderate hypovitaminosis D, and severe hypovitaminosis D. There were no differences in the clinical and demographic background of the patients. It was seen that individuals having a grave form of hypovitaminosis D had a mortality risk of 50 % and individuals with no hypovitaminosis D had a risk of 5 % [6].

There was another study conducted in the MLB Medical college, which was a continuous prospective observational study for six weeks. Participants were Corona viral patients between the ages of 30 and 60 years. There were two groups included in the study which were asymptomatic Covid 19 patient, which was designated as Group A and severely affected patients requiring Intensive Care Unit admission, designated as Group B. Serum concentration of Vitamin D and other markers such as Interleukin 6, Tumour Necrosis Factor Alpha and serum ferritin were calculated. There were 154 patients in total out of which 91 individuals were grouped as group A and 64 individuals were grouped as group B. The mean level of vitamin D (in ng/mL) was 27.9 ± 6.2 in Group A and 14.40 ± 6.20 in Group B. The prevalence of vitamin D deficiency was 33% and 97% respectively in Group A and Group B. Thus, vitamin D deficiency was highly prevalent in Group B. Out of the 154 patients, 90 patients were found to be hypovitaminosis D. Inflammatory markers were found to be increased in patients with a decreased levels of the vitamin. The death rate was also found to be higher in patients suffering from a deficiency of Vitamin D [7].

DISCUSSION

Corona virus: Pathogenicity

Corona Virus has affected a large population of the world since its origin in China, in December 2019. It has been theorized that Corona Virus has taken its origin from bats. The proteins of the corona virus, which have been shown to play a part in the disease caused by corona virus include trimeric protein, envelop protein, membrane protein, nucleocapsid protein, and haemagglutinin esterase protein. The envelope of the virus is present underneath the surface protein, which consists of a lipid bilayer. This lipid bilayer breaks when exposed to soap and water, hence suspected contacts are told to wash hands for at least 20 seconds [9].

Corona virus has one of the hugest genome amongst Human RNA viruses, which ranges from twenty seven to thirty two kilobyte. The most important mechanism for entry of virus to host cells is receptor mediated endocytosis, and the novel corona virus uses ACE2, which is seen in the genitourinary system, Blood Vessels, the cardiovascular system, and in the respiratory system. The spike protein, that causes the viral appearance in the patient's cells, has a N and C terminal apart from its subunits S1 and S2, and either of these binds to host cell receptors and helps the virus to enter into host cells [10].

The transmission of Corona Virus is through respiratory droplets, with an incubation period of 5-6 days before the appearance of the clinical features. Once the virus has appeared in the host cells, the virus is recognized by receptors which recognize patterns such as Toll like receptor 7 and Toll like receptor 8. There is manufacture of transcription factors for interferon regulatory factor and nuclear factor-kappa B which results in the formation of Type 1 and Type 3 Antiviral interferons and a variety of cytokines [11]. There is excessive production of inflammation causing cytokines such as Tumour necrosis factor, Interleukin 6 and Interleukin 1 resulting in increase in vascular permeability, multiorgan failure and eventually death. This has been acknowledged as a cytokine storm that occurs in the Corona Viral Disease [12].

These findings of Covid 19 bear close similarity to the Severe Acute Respiratory Syndrome which occurred due to SARS Corona Virus, a closely related coronavirus, which has also been linked to cytokine storm and dysregulated immune response [13].

Most cases of corona viral disease occurs in between the age of 30 and 79 years of age, and is highly associated with comorbidities, such as DM, raised blood pressure and diseases affecting the immune system. The most familiar clinical features of Covid 19 include a high temperature, a cough without any sputum, tiredness and dyspnoea. Other symptoms seen include a productive cough, myalgia, anosmia, anorexia, nausea, vomiting, dizziness, sore throat, and diarrhoea [14].

Treatment option for corona virus

For the treatment, of corona viral disease, various strategies and numerous drugs have been tried. Protease inhibitors, like darunavir and atazanavir used for the treatment of HIV AIDS have been tried to decrease the multiplication of the novel corona virus. The combination of Lopinavir and Ritonavir has been used in early stages of the disease and in patients treated at home. Remdesivir, a nucleotide analogue, which was earlier used in the care of Ebola Virus has been implicated in the cure of moderate to grave novel coronaviral disease. Immunomodulatory agents such as Tocilizumab, Anakinra, Baricitinib, Corticosteroids and hydroxychloroquine have also been tried. Therapeutic antibodies used from recovered patients have also been tried as a method of treatment [15].

Vitamin D and corona virus

One of the methods used to decrease the incidence and also treat the individuals with corona viral disease is the use of Vitamins, especially Vitamin D as the corona viral disease has been commonly seen in patients suffering from hypovitaminosis D. This vitamin is a steroidal vitamin with a wide role in immune responses such as immunomodulatory, antioxidant, antifibrotic and anti-inflammatory actions. Inflammation causing cytokines like Interleukin 1, Tumour Necrosis Factor, and Interleukin 6 were overexpressed in those individuals who are suffering from a deficiency of vitamin D and their expression was low in patients having a sufficient amount of this vitamin [16].

Vitamin D plays a part in many processes of the normal body physiology including osseous tissue metabolism and also extra osseous metabolism, and the function of the heart. Hypovitaminosis D is related to disordered regulation of the immune system and an increase in the graveness of infectious diseases, especially in the respiratory system. The biologically active form of Vitamin D, 1, 25-Dihydroxy Vitamin D, regulates both adaptive and innate immune responses, and hence, Vitamin D maybe considered for fighting viral infections [17].

The main source of this vitamin for humans is UV light and this has led to the association of environmental factors with the development of Corona Viral Disease. There is a resemblance in the climate and latitude among the regions that have a high incidence of Corona viral disease. Higher incidence of hypovitaminosis D and insufficiency of vitamin D was observed in regions with a higher latitude [16].

The studies for a relationship between the circulating levels of the vitamin and incidence and severity of Corona viral disease are currently limited in number though most of the studies show a higher incidence of Corona viral disease in patients having hypovitaminosis D. There are a huge number of studies that show a link between airway diseases and hypovitaminosis D. The factors limiting the use of Vitamin D in Covid 19 include the fact that the patient might already be in a hyperinflammatory

state at the time of presentation in the hospital, and it might be hard to show the use of Vitamin D above dexamethasone, which has proven anti-inflammatory effects. But still, in patients who have mild to asymptomatic Corona Viral Disease, the use of Vitamin D as a preventive medicine may be justified. There are trials which suggest that at a dose between four hundred IU and thousand IU to individuals with hypovitaminosis D, the use of this Vitamin might be useful [18].

Actions of Vitamin D

Vitamin D does its action by binding to a receptor called VDR, which is present in the nucleus of cells. It then forms a dimer with a molecule similar to the retinoid X receptor, forming VDR-RXR dimers, which then attaches to Vitamin D response elements on the promoter region of target genes. Vitamin D response elements, then promotes the transcription of antimicrobial peptides such as human cathelicidin and human beta-defensin 2. These anti-microbial peptides are synthesized endogenously and offer a first line defence against microbial pathogenic agents. These VDR-RXR dimers also replaces nuclear factors of activated T lymphocytes, which results in the suppression of cytokine related genes in humans [17].

Studies have proven the association of Respiratory tract infections causes by viruses, in individuals with hypovitaminosis D. A vitamin D agonist, calcitriol showed protective responses in patients with injury to the lung, by regulating members of the Renin-Angiotensin System, especially the ACE-2, present inside the lungs, which has been proven to have a role in Corona Viral Disease. Not only does Vitamin D modulate the ACE2 enzyme, but it also increases the production of surfactant in the alveolar cells (type 2) and these alveolar cells are the primary target of corona virus, which exerts its action by decreasing surfactant production and increasing surface tension [16].

One of the main virulence mechanisms employed by the novel corona virus in its pathogenicity is binding to dipeptidyl peptidase 4 (DPP-4/CD 26) receptor. This receptor interacts with the S1 domain of corona virus spike glycoprotein. This occurs more in vitamin D deficient individuals and fulfilment of the deficiency of Vitamin D has been shown to significantly decrease the expression of this receptor in vivo [19].

Not only does hypovitaminosis D increase the risk of Corona Viral Infections, but it also increases the seriousness of infections caused by it. The patients with Vitamin D deficiency suffered from bilateral lung infections, ARDS, and multi organ failures. They were shown to be suffering from an abnormal immune and inflammatory response including both B and T cells [20].

Vitamin D, Covid 19 and other comorbidities

Another factor that supports the association of Vitamin D deficiency and coronal viral disease, is that hypovitaminosis D is commonly seen in the older population. After 60 years of age, there is an apparent

reduction in the production of Vitamin D in the skin. Thus, the presence of comorbidities and old age, suggests a relationship between Vitamin D status, the Renin-Angiotensin-Aldosterone system and Covid 19 infection. There are also studies that have shown the increased Plasma Renin activity, higher angiotensin 2 activity, and higher Renin-Angiotensin-Aldosterone activity occur as a consequence of hypovitaminosis D. This is consistent with the fact that when vitamin D is given to individuals with essential hypertension, it decreases the blood pressure. Similarly, there is also a positive correlation between other comorbidities like DM type 2 and obesity, and Vitamin D deficiency [21].

Vitamin D and its preventive and therapeutic role in Covid 19

Vitamin D acts as by generally blocking the viral replication by nonspecific responses. This way Vitamin D plays a part in the prophylaxis of Covid 19. Once the infection has been acquired, vitamin D could play a part by interacting with cellular as well as viral factors. Vitamin D impacts both adaptive and innate immune responses, and thus vitamin D plays a role in improving immune responses in the fight against the virus. Uncontrolled immune response plays a major role in the corona viral disease thus leading to cytokine storm, and this could be stopped by the use of vitamin D [3].

CONCLUSION

Coronavirus has caused global medical crises, and scientists from all countries around the world have been trying to find out possible therapies for the viral disease. Not only has it led to a medical crises, it has also led to a widespread lockdown of essential commodities, schools and offices all around the world. Scientists have found various therapies for the viral disease which include antiviral drugs like darunavir, drugs used against ebola virus like Remdesivir, and immunomodulatory drugs like corticosteroids and hydroxychloroquine. One such agent that has come of use in the ongoing global pandemic is vitamin D. Vitamin D has been widely reported to have immunomodulatory properties that decrease the severity of cytokine storm that occurs in Coronaviral disease. Not only that, but vitamin D levels have an inverse correlation with the severity of the disease with those having low vitamin D levels suffering from severe disease and its complications like Bilateral lung infections and Acute respiratory distress syndrome. Thus, it has emerged that the use of Vitamin D could be of help in the prevention and treatment of Covid 19.

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