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Review Article

Role of Vitamin D in Recovery from Covid 19 infection

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ABSTRACT

Initially, COVID- 19 occurs in 2019 in the city of Wuhan China and began to spread. The common indications of COVID-19 are dyspnea, sore throat, cough, and fatigue. Many drugs have been used to decrease the overwhelming results such as Ivermectin, Colchicine, Metformin, and Fluvoxamine are the most affected anti-parasite. Anti-parasitic drugs also contain some side effects. Numerous dietary factors have been used but deficiency of vitamin D has been allied with an intensification in ICU treatment of patients infected with COVID-19. The central role of vitamin D in the human body is to sustain immunomodulatory, and calcium homeostasis and have anti-inflammatory, anti-fibrotic properties. Past studies show that vitamin D has a role in the reduction of respiratory diseases in adults and children. The common sources of vitamin D are meat, fish, milk products, eggs, mushrooms, sunlight, etc. Corona-viruses are enveloped by membranes, contain positive Single-Stranded RNA (+ssRNA), or can cause infection in equally animals and humans. S protein in the COVID- 19 binds to the ACE 2 receptor, leading to the virus's entry into the body. A host with a sufficient level of vitamin D has been allied with amplified excretion of anti-microbial peptides or depressing the menace of *hypercytokinemia*, also tangled in the stimulation of macrophages i.e., defensive cells or protected response of Th2 cells. Various studies have determined that there is no protagonist of vitamin D in managing of hazards of COVID-19. Thus, this review aims to clarify the immune-modulatory effects of vitamin D in the control of COVID-19.

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Introduction

Calciferol (vitamin D) is a fat-soluble vitamin (Chang 2019). The main source of vitamin D is sunlight and could be obtained from supplements or diet in a minor amount (Fraser 2021). Although vitamin D plays a role in bone or calcium stability, it is recognized that it has anti-inflammatory, immunomodulatory, and anti-fibrotic properties and also participates in the regulation of differentiation, and cell multiplication. It is also involved in the treatment of chronic liver disease(Kitson et al. 2012). Vitamin D has a vigorous role against upper respiratory infections. Estimating vitamin D level in laboratory studies seems related to immune function and the protagonist in critical respiratory tract infections (RTIs)(Shoemaker et al. 2022). More than one billion population has been affected by vitamin D Shortage or becomes a worldwide health issue(Pérez-Castrillón et al. 2021). Vitamin D deficiency may also affect the respiratory system which causes the intensification of the menace of COVID-19 infection(Ali 2020). Past studies of 1918 manifest that vitamin D has no role in decreasing pneumonia but now interventional studies showed that respiratory tract diseases reduce in children or adults by vitamin D supplementation(Xu et al. 2020). A novel coronavirus infection has been spread in a large area in Wuhan, China from the mid since December 2019(She et al. 2020). According to WHO global situation of confirmed cases is 760 million and the death rate is 6 million. In Europe 274 million, in America 190 million and in Africa 9 million. In Pakistan from 3 January 2020 to 16 march 2023, 1 million confirmed cases or 30 thousand deaths were reported (WHO). The common indications of COVID-19 are sore throat, cough, fever, fatigue, or difficulty breathing. Approximately, all patients experience mild or moderate symptoms while 5-10% of patients experience life-threatening symptoms during infection (Gavriatopoulou et al. 2021) or cytokine storm (Felsenstein et al. 2020). In demand to decrease the overwhelming effect of COVID- 19 many drugs have been used without knowing its effect or used in clinical trials. There was limited data on pharmacogenomics for these drugs (Takahashi et al. 2020). Ivermectin, Colchicine, Metformin, and Fluvoxamine proved to be effective drugs against coronavirus. Some medications such as ritonavir/lopinavir, azithromycin, and hydroxychloroquine/chloroquine are not in use now for the therapeutics of COVID-19 because, after many studies with massive populations, these drugs were not giving favorable outcomes(García-Lledó et al. 2021). Several antiparasitic drugs also contain some side effects. Such as treated with hydroxychloroquine/chloroquine along with azithromycin caused extended QT interval in comparison to no conduct or defined knowledge about ritonavir /lopinavir exposed that it doesn't intensify long QT syndrome(Diaz-Arocutipa et al. 2021). Nutrition is one of the main factors for the immune system's normal functioning, which is important for human health(Albers et al. 2005). Numerous dietary strategies have been used to diminish the toxicity levels of COVID-19(Dhawan et al. 2022). Zinc, vitamin C, E, D, and omega-3 fatty acids are identified to have a valuable role in the reduction of COVID-19 infection(Shakoor et al. 2021). In case of contact with the virus during an epidemic, the appropriate consumption of vitamins D, C, and zinc supplements results in a decrease in infection (Souza et al. 2020). But this review engrossed the role of vitamin D in preventing or reducing infection. To treat or avoid COVID-19 infection vitamin D treatment has been recognized as a possible strategy. Its role also has been identified in reducing other viral infections, particularly in those with vitamin D shortage(Meltzer et al. 2020). Conflicting to all these studies there is no straight connotation of vitamin D with COVID-19 but this review aims to intricate the immunomodulatory properties of vitamin D in the managing of SARS-CoV-2 consequences.

Description of COVID-19

SARS nCoV is a newly arising virus that has caused an epidemic (Pinzon et al. 2020). The pneumonia of unidentified basis was expressed by the end of December 2019 which was related to the wet market of Wuhan, China. COVID-19 is a disease or SARS-CoV-2 that was named by the world health organization WHO for this newly arose novel coronavirus(Roshan et al. 2020).COVID-19 affects vertebrates and humans causing hepatic, neurologic, enteric, or respiratory diseases. Human epidemics have been caused by both SARS-CoV in 2003 and MERS-CoV in 2012. Many imperative similarities or differences have been shown in comparison with the recent virus. Equally, Middle East respiratory syndrome coronavirus (MERS-CoV) and acute respiratory syndrome coronavirus (SARS-CoV) have much high death rates that were 40% and 10%, respectively. SARS CoV 2 is spread from one to another or 79% of its genome is shared with Sars CoV (Jiang et al. 2020).

The global spread of coronavirus leads to the accomplishment of precautions such as social distancing, quarantine, isolation, lockdown, and restriction on traveling to diminish the blowout of COVID-19(Raina et al. 2021). The major risk factor of COVID-19 is age. But it is less common in people under 14 years of age(Rashedi et al. 2020). COVID-19 has a great effect on patients with co-morbid conditions such as hypertension, cardiac, obesity, diabetes, cancer, HIV, and AIDS. The most common symptom of a patient infected with COVID-19 is the damage of the alveolar membrane as common in Middle East Respiratory Syndrome Coronavirus or severe acute respiratory syndrome. Respiratory distress syndrome pulmonary hyperplasia is common. The occurrence of platelet fibrin thrombin in small arterioles is the cause of hypoxia which is one of the targets for therapy(Carsana et al. 2020).

S_1 subunit of spike protein in the COVID-19 bind to the ACE 2 (Angiotensin-converting enzyme 2) receptor. (TMPRSS2) Transmembrane protease serine 2 protease smites the S protein or triggers the S2 domain which causes the entry of a virus characterized by the fusion of plasma or viral membranes. The uncoating of the virus releases +ssRNA. Polypeptides pp1a or pp1b are translated from open reading frames 1a or 1b, viral RNA utilizes host ribosomal machinery. These proteins are split post-translationally and changed via PLpro or 3CLpro proteases into sixteen non-structural proteins (NSPs)

that produces the protein of transcription complex or replication which leads to viral RNA replication or the new viral genome or proteins get assembled in the Golgi apparatus or rough endoplasmic reticulum. The release of new viruses occurs by the vesicles (He et al. 2020; Kumar et al. 2022)

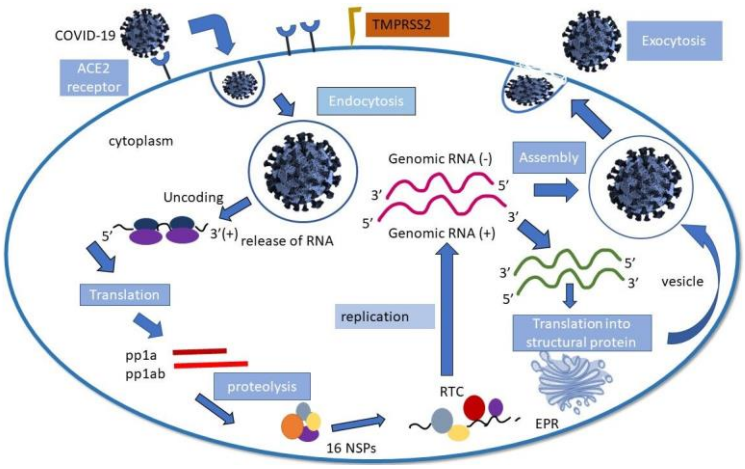

Fig. 1: Lifecycle of COVID-19: S_1 protein in the COVID-19 binds to the ACE2 receptor which leads to the viral entry characterized by membrane fusion. The uncoating of virus release + ssRNA which leads to further processes such as transcription or translation and synthesis of proteins. The viral proteins are gathered in Golgi apparatus or rough endoplasmic reticulum. The release of new viruses occurs.

Vitamin D and its physiology and its Metabolism

Although the role of vitamin D is significant for bone homeostasis and also necessary for many body functions such as immune deficiency and immunomodulation concerning the innate or adaptive immunity (Aranow 2011). Vitamin D is a corticosteroid hormone also helpful in the anticipation of numerous ailments like diabetes, cancer, hypertension, obesity, hypertension, or autoimmune diseases (Mu et al. 2021). Vitamin D is a micronutrient and very few foods contain little amount of vitamin D (Fraser 2021). Vitamin D is a pioneer of steroid hormone that synthesis the biologically active compound calcitriol after undergoing two metabolism steps in the kidney and liver to undergo potent physiological processes (Jeon et al. 2018).

Here are three core phases of vitamin D metabolism that are accomplished by cytochrome p450 that are 25-hydroxylation, 1a-hydroxylation, and 24-hydroxylation. These enzymes are found in also mitochondria (e.g., CYP27A1, CYP27B1, and CYP24A1), and endoplasmic reticulum (e.g., CYP2R1) (Bikle 2014). The epidermis (skin) absorbs UVB radiations of range (290-315nm)(NIH) from the sun and pre-vitamin D_3 is transformed from 7-dehydrocholesterol (7-DHC) which is instantly changed into vitamin D3 or transferred to the liver through circulation. Nutritive vitamins D3 or D_2 are transferred to liver from the intestine by chylomicrons. In the liver vitamin D is hydroxylated to 25-hydroxyvitamin D (25(OH)D), this conversion is accomplished by (CYP2R1) cytochrome p450 enzyme. When 25-hydroxyvitamin D is released in the circulation transferred towards the kidney or other tissues by binding to vitamin D binding protein. 1a-hydroxylation (CYP27B1) of 25-hydroxyvitamin D consequences in the creation of the active $1,25(OH)_2D$ calcitriol in the kidney proximal tubules. The expression of the 24-hydroxylase enzyme encoded by gene CYP24A1 persuade by $1,25(OH)_2D$, which catalyzes the conversion of $1,25(OH)_2D$, 25(OH)D to inactive 24-hydroxylated products, $1,24,25(OH)_3D$ + $24,25(OH)_2D$ subsequently (McCartney et al. 2021; Garbossa et al. 2017; Chun et al. 2019; Sosa-Diaz et al. 2022).

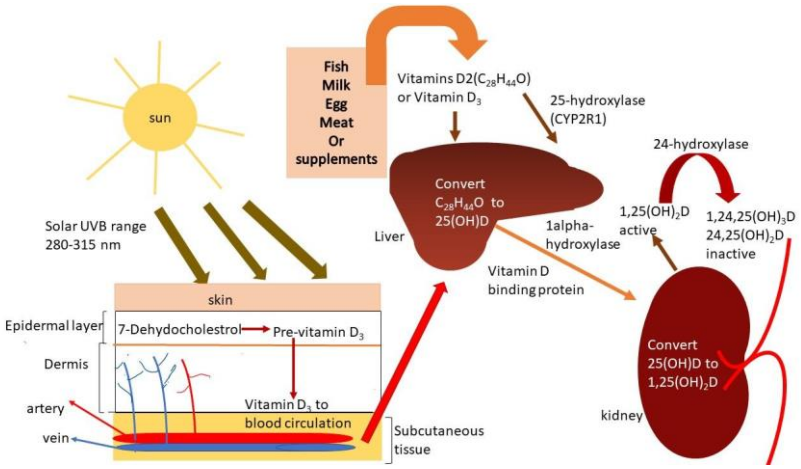

Fig. 2: Metabolism of vitamin D in the liver or kidney:7-dehydrocholestrol converted to pre-vitamin D_3 by absorbing UVB rays (280-315nm) which through blood circulation transfer to liver. In the liver vitamin D hydroxylated to 1,25(OH)D by CYP2R1. 25(OH)D is transferred towards kidney or other tissues by binding to vitamin D binding protein.1a-hydroxylation (CYP27B1) of 25(OH)D results in active $1,25(OH)_2D$ vitamin calcitriol in the kidney.24-hydroxylase enzyme catalyze the conversion of $1,25(OH)_2D_3$,25(OH)D to inactive 24-hydroxylated products $1,24,25(OH)_3D$+$24,25(OH)_2D$ consequently.

Sources of Vitamin D

About 95% of vitamin D is gained from sunlight whereas, the rest of the requirement is fulfilled through diet (Quah et al. 2018).The most suitable way to improve the dietary intake of vitamin D is by increasing breakfast or cereal consumption. The strategy to help an individual to meet the recommended dietary allowance (RDA) is to increase milk consumption (Hill et al. 2012). Vitamin D is particularly occur in oily fish (Darling et al. 2017), eggs, some plants, mushrooms, fatty fish, dairy products, liver (Lundqvist et al. 2016). Milk is the major source of vitamin D (Yogal et al. 2022). Other nutritional sources are dairy products especially yogurt, orange juice, margarine, plant-based beverages, beef liver, dark chocolate (Benedik 2021; Buttriss et al. 2020).

Infectious or autoimmune diseases caused by deficiency of vitamin D

Although TB shows a link with the low concentration of 25(OH)D. But studies show that deficiency of vitamin D also links to lower and upper respiratory tract infections such as bronchiolitis, and influenza, pharyngotonsillitis, pneumonia, otitis media, rhinosinusitis. These are lower tract infections owing to a deficiency of vitamin D (Zisi et al. 2019). The susceptibility to autoimmune diseases has been related to deficient serum level of 25(OH)D. The autoimmune diseases are rheumatoid arthritis (RA), multiple sclerosis (MS)systemic lupus erythematosus (SLE) (Dupuis et al. 2021).

Role of Vitamin D in Immunity

The central role of vitamin D is immunity in addition to maintaining bone homeostasis. Vitamin D is expressed on immune cells that are B or T cell/s or antigen-presenting cell/s as they are intricated in the synthesis of vitamin D metabolite. Autoimmunity or risk of infections increases due to a deficiency of vitamin D as Vitamin D is concerned in the activation of innate or adaptive immunity (Aranow 2011).

Although studies clearly illustrate the role of vitamin D in COVID-19 infection is inadequate but its protagonist in innate or adaptive immunity undeniably demonstrate that it could be. The first line of defense is innate immune system or its activation depend on manifestation of PRR (pattern-recognition receptor) such as TLRs (Toll-like receptors) to identify microbes. Defense by AMPs (anti-microbial peptides) such as cathelicidin or β-defensive 4 is persuade by 1,25-dihydroxyvitamin D (exhibit 1a-hydroxylase enzyme in alveolar macrophages or respiratory epithelium or generate both $1,25(OH)_2D$ or VDR which persuade the innate immunity) leading to viral demolition or clearance/removal by many mechanisms, recruiting macrophages, dendritic cell/s, neutrophils, or influence the adaptive immune response. Even though, innate immunity is not persistent or cytokine storm take place. 1,25-Dihydroxyvitamin D diminish the chronic/continual innate immunity response through many mechanisms such as suppressing adjustment of TLRs and prohibit IFNγ and NFκB/TNF signaling pathways. Adaptive immunity takes time but once develop provide more precise response, against pathogen. In spite of that, response can be destructive if not controlled. Adaptive immunity is regulated by active metabolite of vitamin D i.e.$1,25(OH)_2D$ by restricting the dendritic cell maturation, restraining their potential to show antigens to T cell/s (T cell proliferation) (Bikle 2022; Duntas et al. 2022).

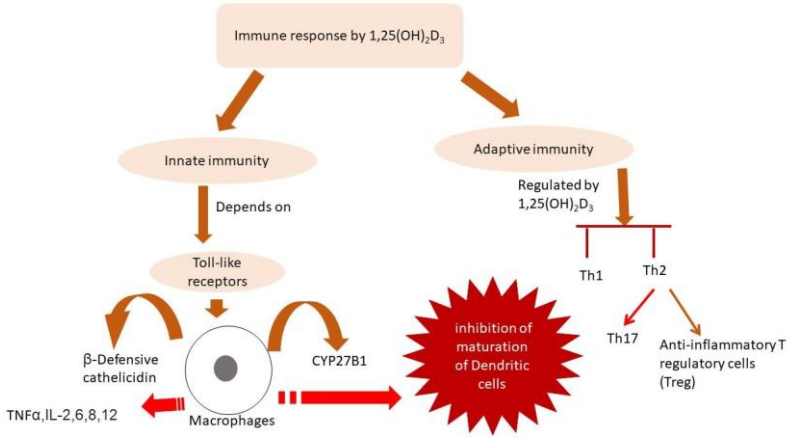

Fig. 3: Role of vitamin D in immunity; Innate immunity is the first line of defense its activation depends on PRR like TLRs to detect pathogen. 1,25-dihydroxyvitamin D influence the defense by AMPs like β-defensive or cathelicidine, leading to viral demolition or removal by many mechanisms.1,25(OH)2D (active) regulate the adaptive immunity by restricting dendritic cell maturation, limiting T cell proliferation. Red arrows show inhibition or brown arrows shows positive influence.

Vitamin D supplementation and deficiencies

Fewer than 20ng/ml of 25-hydroxy cholecalciferol or lower than 18ng/mL of 1,25-dihydroxycholecalciferol before COVID -19 testing marked as vitamin D shortage(Meltzer et al. 2020). The supplementation of vitamin D is useful to lessen Acute respiratory infection or is safe to consume compared with a placebo. For protection, the administration of a daily dose was 400–1000 IU for ages 1·00–15·99 years up to 12 months (Jolliffe et al. 2021). People with a low level of 20ng/mL or 50nmol/L of serum 25(OH)D were 2.42 times more susceptible to COVID- 19 or deficient level of vitamin D does not affect COVID-19 death. The supplementation of vitamin D can prevent COVID-19, otherwise, deficiency can increase the chance of COVID-19 (Kaya et al. 2021). The requirement of vitamin D depends on your age from birth to till 12 years is 400 IU, 14 to 70 years is 600 IU for older than 71 years is 800IU pregnant breastfeeding women is 600IU (NIH).

How Vitamin D can relate to acute respiratory syndrome and COVID-19

Lockdown has affected the lifestyle of people bi-directionally. These changes are both positive and negative. Quarantine has affected adults that are above 40 years of age those existing in a region with high GDP, living with children, not taking home meals, are unemployed. As the coronavirus is still spreading globally so it's necessary to spread the message to be active or to adopt healthy habits to prevent chronic infection (Górnicka et al. 2020).

According to the study vitamin D shows a sturdy - association with COVID- 19 infection or death rate. The study shows that mortality or infection rate is higher in the adult group because they are deprived of vitamin D. so, vitamin D is essential for reducing infection (Ilie et al. 2020). The recommended way of taking 10,000 IU/d for limited weeks and 5000IU/d especially for those in danger of flu or COVID-19. The target is to increase the concentration of vitamin D (100-150nmol/L) to 40 -60ng/mL (Grant et al. 2020). The ICU COVID- 19 infected patients show thrombophilia or homeostatic disorder up to 43%. Where laboratory testing in COVID-19-associated coagulopathy (CAC) shows an increment of fibrinogen, the irregularities in the coagulation test show a low number of platelets (Pluta et al. 2021). Multiorgan failure or organ hyper fusion is caused by the initiation of the clotting process during the immune response to COVID-19. So, that vitamin D has a significant role in homeostatic disorders. The anticoagulant result in a decrease in tissue thromboplastin (blood coagulation factor III) or an increase in thrombomodulin and glutathione (Tomaszewska et al. 2022). According to the study of 77 patients of mean age (80 or 85) are divided into 3 groups. Group 1 has taken supplementation in the previous year. Group 2 is supplemented later by the analysis of COVID- 19. Group 3 was non-supplemented. After monitoring for about 14 days, patients with regular supplementation have to cope with the severity of the infection. All patients are treated in the same way combination of azithromycin (500 mg for 5 days orally) hydroxychloroquine (400 mg on the first day every 12h, or for 5 days following 200 mg every 12 h). In the calcifediol treatment group patients are orally administrated on days 3 and 7 with calcifediol (0.266 mg) or weekly till they are discharged from the hospital (Annweiler et al. 2020). The study shows that 25-hydroxyvitamin D or calcifediol, the endocrine system's main metabolite compacts the requirement of ICU treatment for COVID-19 patients. Calcifediol seems to be effective in plummeting the menace severity of infection (Castillo et al. 2020). Acute respiratory syndrome is an acute, inflammatory, life-threatening condition of ill patients that is characterized by poor oxygenation. On the microscopic level, it shows damage to the alveoli (Diamond et al. 2021).

Conclusion

Vitamin D is intricate in sustaining body functions as well as vitamin D has an immune-improving effect in other respiratory tract infections, we can consider that it will have an immune-enhancing effect for Coronavirus as well. The shortage of vitamin D has a strong link with severe respiratory tract infections including COVID-19 as well. The proper dosage of vitamin D can aid in managing the harmful consequences of COVID-19 and reduce mortality or ICU treatment. The recommended method of taking vitamin D is 10,000 IU/d or 50,000 IU/d for those at risk of COVID-19 infection target is to increase the concentration to 40-60ng/mL or must be taken during treatment of COVID-19 infection. But numerous cohort studies are necessary to find the direct role of vitamin D in COVID-19.

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