DOI: https://doi.org/10.53350/pjmhs22162759

ORIGINAL ARTICLE

Vitamin D significance in Combating; Progression and Austerity of COVID-19

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ABSTRACT

Humankind on our planet is under high pressure at present, facing an alarming pandemic in the form of coronavirus infection 2019 (Covid-19), which is known to be stimulated by severe acute respiratory syndrome coronavirus 2 (SARS‑CoV‑2). Covid-19 can lead to acute respiratory distress syndrome (ARDS). Due to the minimal treatments or research, it is essential to consider therapeutic strategies with immunomodulatory effects. According to past studies, supplementing with vitamin D has been shown to minimize or even prohibit respiratory infections in some situations, according to some studies. Recent research has also demonstrated an association concerning vitamin D imbalance and adverse COVID-19 outcomes. It is a debatable situation because vitamin D deficiency is an important health issue worldwide. There may be a benefit in supplementing the low vitamin D levels in COVID-19 infected persons to assist in preventing the disease from more complicating matters. Covid-19 may benefit from vitamin D's immunomodulatory properties, and a comprehensive examination of the effects of vitamin D on Covid-19 is outlined in this brief review.

Keywords: Covid-19, Acute respiratory disease syndrome (ARDS), Vitamin D, Cardiovascular disorder (CVD), Dipeptidyl peptidase-4 receptors (DPP-4/CD26)

INTRODUCTION

The Covid-19 pandemic has now firmly established itself as the root cause of a worldwide crisis in public health. The preventive factors for this infection are hardly documented. Preventive health interventions are also urgently required in order to reduce the possibility of viral infections, persistence, and severity. Caused by SARS-CoV-2, the Covid-19 pandemic is a worldwide health risk and spreading rapidly with unpredictable effects worldwide. Antiviral properties of vitamin D have recently been documented, which can directly inhibit viral replication and have anti-inflammatory and immunomodulatory efficacy[1]. SARS-CoV-2 tends to be a recognized pathogenic sequence of acute respiratory disease syndrome (ARDS) progression in some patients, after infection with the immune evasion process accompanied by hyper reactions and cytokine storm[2–4]. During winter, particularly at the north latitude, respiratory tract infections are more prevalent than in summer[5]. COVID-19 pandemic has transmitted promptly during winter months and turns out to be a worldwide pandemic [6,7]. Vitamin D deficiency, which frequently occurs during this time, is widespread in the winter season and in residents of northern countries[8]. This leads to the cross-examination of whether an insufficient amount of vitamin D impacts the development and seriousness of COVID-19.

Vitamin D is considered influential in sustaining bone integrity and calcium-phosphorus metabolism. However, several other functions, such as immune response control for viral and autoimmune diseases, have been recently speculated[9,10]. Vitamin D contains a wide variety of immunomodulatory, anti-inflammatory, antioxidant, and antifibrotic functions, including fat-soluble secosteroids. The two most prevalent forms of vitamin D in humans are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Vitamin D_3 has been transformed into calcifediol (25-hydroxycholecalciferol), and D_2 subtype into 25-hydroxyergocalciferol. These two vitamins' critical vitamin D metabolites, 25-hydroxyvitamin D or 25(OH)D, can be evaluated using a serum to identify a person's vitamin D level[11]. The active ingredient in vitamin D produced by the 1α hydroxylase enzyme in the kidney is called calcitriol (1,25-(OH)2D)[12,13]. Calcitriol enters the bloodstream as a hormone that plays a significant role in calcium and phosphate balance and facilitates safe bone reconfiguration. In addition to calcitriol, neuromuscular functions have a significant role in cell proliferation and immune responses, especially anti-inflammatory activity. It prevents inflammatory cytokine production (e.g., IL-1α, IL-1β, tumor necrosis factor-α), and its absence is related to the excessive expression of Th1 cytokines[14]. Lack of vitamin D is calculated based on plasma level transport in the state of vitamin D, 25(OH)D. Vitamin D deficiency is widely distributed globally and appears primarily in north and south countries[15]. Vitamin D deficit is frequent in Europe during the cold season, particularly in senior people and immigrants. The approximate mortality rate of 12 countries in Europe with COVID-19 reveals a substantial inversion in the presumed plasma concentration of 25(OH)D (P=4046)[16].

The question emerges whether a deficiency in vitamin D influences COVID-19 or not. A study of COVID-19 outbreak incidence revealed that geographical position (30 to 50° N+), average temperature between 5 to 11°C, and little moisture are interlinked. Latitude dependence is apparent in mortality rates of COVID-19 (Cases/Million Population). Mortality decreases significantly below latitude 35[17]. Considering disparities in COVID-19 seriousness and deaths globally, its motives are essential to consider. Enhancing immunity via better nutrition might be a significant factor. Natural foods containing vitamin D are a fundamental cause for enhanced immunity functions. However, the performance of Vitamin D in infection control and fatality by COVID-19 is seldom known. The connection between vitamin D status with COVID-19 and fatalities per million people in European communities were analyzed with the information collected from the COVID-19 pandemic

information center. The possible involvement of vitamin D was also discussed in this mini-review during severe airborne infections. Several discussions on the accessible investigations somehow verified the significance of vitamin D in COVID-19 seriousness and deaths. The function, intensity, and fatality of vitamin D in COVID-19 infected individuals were investigated using Web of Science, PubMed, Scopus, Google Scholar, Cochrane Central Register of Controlled Trials, and medRXiv, among other sources.

2 Vitamin D necessity and influences

2.1 Vitamin D possible effects: Vitamin D is a steroid hormone released uncontrolled with ultraviolet exposure on the skin, extracellular food source, or nutritional supplement. Inadequacy of vitamin D is an issue for public health that impacts more than one billion people worldwide[18]. Several investigations have shown a potential link with lower vitamin D and numerous diseases over the past decade, including severe infections[19]. Inadequate vitamin D influences the operation of the immune system as vitamin D is an immunomodulating effect[20]. The growing immune response from antiviral peptide release [21], strengthens protection against the mucosal defense. Low serum vitamin D concentrations in clinical trials were linked to acute respiratory tract infections, particularly infectious influenza[22]. Figure 1 illustrates risk factors for vitamin D insufficiency. Vitamin D has recently addressed the skeletal and additional skeletal impacts[23]. Vitamin D has an impact on gene expression, both genomically and non-genomically. Non-genomic consequences include the triggering in the associated areas of Vitamin D responsive genes of several signal molecules associated with Vitamin D response element (VRE)[24]. The significance of mucous membranes as a barrier in the respiratory system is crucial for vitamins A and D[25].

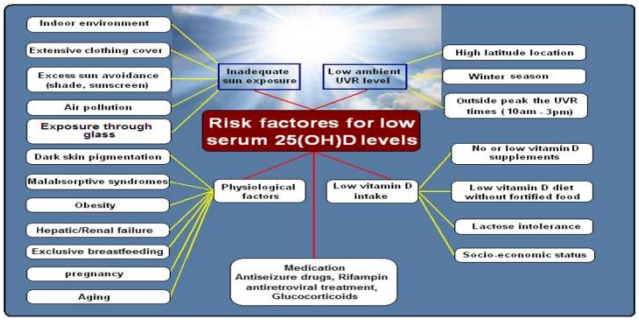

Figure 1: discusses the probability of vitamin D deficiency and the risk factors. Reprints with permission [26]

2.2 Vitamin D and immunity: The importance of vitamin D in maintaining a healthy immune system cannot be overstated[27]. Vitamin D impairs the significant immune system cells, including neutrophils, B and T lymphocyte cells, macrophages, and dendritic cells that explicit VDRs Vitamin D interferences. Cathelicidin, a peptide generated by vitamin D-mediated activation, exhibits antimicrobial activity toward bacteria and fungi[28]. In comparison, vitamin D reduces pro-inflammatory cytokines development and improves anti-inflammatory cell proliferation[29]. The successful metabolite vitamin D in dendritic and macrophages cells from receptor 25(OH)D helps activate the VDR and induces the activities of different inherent and receptive proteins of the immune system. (pattern recognition receptors, cytokines, Treg cells, defensins, etc.)[30]. Vitamin D acts against the adaptive (inhibiting) and endogenous (promoting) immune systems; this corresponds to anti-inflammatory reactions and regulates immune function[31]. Activated vitamin D 1, $25(OH)_2D_3$ metabolite can be produced in T and B lymphocytes, which prevents the growth and the stimulation of T cells[32]. Vitamin D can thus inhibit T-cell inflammation and activate Treg cells by intensifying IL-10 production in DC cells[33].

2.3 Vitamin D immune modulation pathway for viral infections: Immune cells are known to be an expression in Vitamin D receptor (VDR), and different immune cells can transform Vit D (25OHD) 25 hydroxy into active 1,25-$(OH)_2$ D. This requires local monitoring at inflammatory sites of 1,25-$(OH)_2$ D[34]. 1,25-$(OH)^2$ D linkage with VDR translocation complex in the cell nucleus, thus altering expression for hundreds of genes, cytokine formation[35]. The complex also contributes to antimicrobial peptides such as cathelicidin and defensins. Figure 2 describes the immunomodulatory effects and the production of antimicrobial proteins. A recent study observed the insufficiency in rotavirus reproduction by Vitamin D treatment at 5000 IU/kg in vitro and in vivo. Vitamin D limits the induction of cytokine storm[36]. The body's immune response contains anti-inflammatory cytokines and pro-inflammatory in COVID-19 victims[37]. Cytokines, including tumor necrosis factor-α (TNF-α) and interferon-γ of T helper cell types 1 (Th1), may decline development. Often, macrophages decrease the secretion of cytokines that promote inflammation and the application of Vitamin D to improve anti-inflammatory cytokines. Virulence-inducing molecular pathways that CoV is used to bind dipeptidyl peptidase-4 receptors (DPP-4/CD26). The S1 domain of glycoprotein SARS-COV-2 spike has been found to interact with human DPP-4 / CD26. In this sense, the satisfaction of Vitamin D insufficiency has accompanied that the manifestation of DPP4/CD26 in vivo receptors has decreased considerably, and Vitamin D is a potent autophagic modulator[29,38,39].

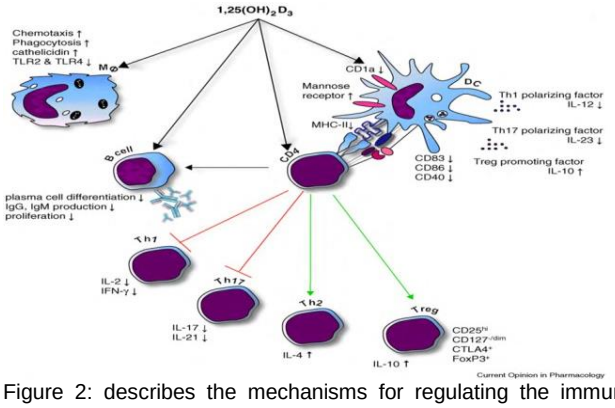

Figure 2: describes the mechanisms for regulating the immune system of $1,25(OH)_2D_3$. Cathelicidin, an antibacterial protein produced by macrophages, is stimulated by 1,25(OH)2D3 in the innate immune system. This increases macrophage chemotactic and phagocytotic responses. Reprints with permission [31]

2.4 Role of Vitamin D insufficiency in COVID-19 and dose recommendations: Two major physiological factors cause inadequate vitamin D levels: little UVB radiations in northern territories, especially during the cold season and in the presence of a high complexion, as well as decreased skin vitamin synthesis as a consequence of aging[40]. Moreover, inadequate health, low amounts of fish, and fortified food are the main reasons for old age malnutrition and hunger. Over the years, women with low or no sunshine (entire-body coverage), no interaction outside the globe, and population with a dark complexion, particularly in Europe and the United States of America, form the principal class of risk, aside from female pregnant and babies under the age of five.

Vitamin D is a public health concern relevant to all age groups[41]. In winter, at latitudes, insignificant radiations hit the ground surface. During winter, this enhances the chance of Vitamin D depletion. Epidemiological literature indicates that the influenza outbreak is the most widespread in the world in the first month of winter, while Vitamin D concentrations are the lowest. Adequate Vitamin D amounts were demonstrated to protect against influenza and RSV infections. Serum Vitamin D concentrations of 25-hydroxy appear to decline as they mature. It is significant as case-fatality rates (CFRs) increase at an age when COVID-19 is involved[42]. Researchers have carried out a randomized controlled trial (RCT) meta examination of Vitamin D in order to prevent respiratory tract infection (RTI). They have shown that Vitamin D prophylactic management decreases the chance of developing RTI. The mortality connection within COVID-19 per million population and regions in terms of geographical position was emphasized by Rhodes et al. [17]. Countries below the latitude of 35° North have reported low mortality levels. The insufficiency of sunshine can explain this in winter for those who live in countries over 35° north and suffer from Vitamin D deficiency. Also, in Italy, Spain, and France, the age-dependent case fatality rate (CFR) of COVID-19 was higher as compared to other countries; a severe Vitamin D deficiency has been recorded (mean 25 OHD concentration < 0.25 ng/L). The loss of memory B cells and inconsistent immunological feedback caused by overstimulating the flexible immune system in elderly persons leads to cytokine storm, as shown in COVID-19 sufferers[43].

Owing to a lower affinity for vitamin D binding protein, $25(OH)D_3$ has a half-life of 15 days, while $25(OH)D_2$ has a half-life of 13 to 15 days[44]. Consequently, prolonged indoor time spans, e.g., in nursing institutions or extended periods in quarantine, raise the possibility of vitamin D insufficiency. In terms of the COVID-19 Vitamin D supplement, there is currently no scientific data to suggest an optimum dosage. According to the Institute of Medicine, Vitamin D's recommended daily consumption is 600 international units (IU) for youngsters and 800 IU for adults over 70[45]. However, this suggestion was made in connection with skeleton fitness. According to examinational studies, strengths of at least 40-50 ng/mL are needed [46]. Additional research showed, 38 ng/mL dose was sufficient to minimize the chance of pneumonia accumulated in the population. A dosage of 2000-5000 IU/day of Vitamin D_3 should be used to attain the above concentration level. Increases in 25 OHD doses from 20 ± 6-39 ± 9 ng/mL for 4000 IU per day and 19 ± 4-67 ± 3 ng/mL for 10,000 IU per day for eight weeks of implementation of Vitamin D were recorded in previous research findings[47]. , there have been no reported side effects with taking regular amounts of less than 10,000 IU/day of vitamin D. However, based on all-cause casualties and consequences of chronic diseases, the UL value was set to 4000 IU/day[45]. Therefore, keeping the regular Vitamin D dose below 4,000 IU/day could boost immunity in the battle against COVID-19 infection.

2.5 Significance of vitamin D in connection to COVID-19: Older adults and comorbidities are concerned with the reduced availability of vitamin D. A decrease of vitamin D synthesis in the skin becomes evident after 60 years, further enhancing the aging process[48]. The skin's vitamin D source, 7-dehydrocholesterol, drops by around 50 percent from 20 to 80 years. Furthermore, the rise of cholecalciferol in serum after UVB exposure to the body complexion indicates more than 4-fold variation in adults ages 60–80 years. The controls (20–30 years) are comparable, which describes a large number of older people with low vitamin D status[49]. However, the virulence processes of COVID-19 should be thoroughly understood; several cellular pathways have been established in a strongly linked COVID-MERS virus, namely Papain-like Protease (PLpro)-intermediated xerox, binding dipeptidyl peptidase-4 receptor (DPP-4/CD26)[50]. The spike glycoprotein domain S1 of COVID-19 was reported to bind with human DPP-4/CD26, indicating that virulence may be an important factor in the infectious disease caused by COVID-19. Vitamin D deficiency causes a significant reduction in control of the DPP-4/CD26 receptor in vivo[39]. It is evident that vitamin D management can minimize a few unhealthy downstream immunological consequences of Covid-19 infection to retrieve weaker clinical results, for example, Interferon-gamma reaction interruption, interleukin 6 accumulation[51], and, Negative prognostic predictor in individuals having critically ill pneumonia, particularly those affected with Covid-19[52]. Figure 3 shows MERS-CoV pathogenesis in animals and humans: molecular mechanisms.

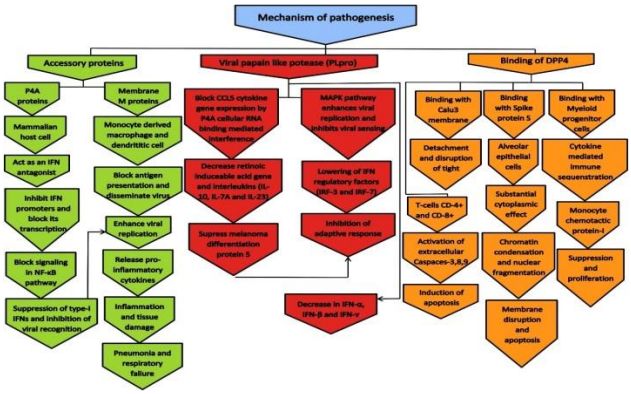

Figure 3: shows MERS-CoV pathogenesis in animals and humans: molecular mechanisms. Pathogenesis is primarily mediated by DPP4, the papian-like protease PLpro, and associated proteins such as p4a and membrane M protein. Reprints with permission [50,53]

In the present COVID-19 pandemic, we cannot disregard new findings that vitamin D intakes combat against acute respiratory infections (ARI) [32]. A meta-analysis of 25 RCTs featuring approximately 11,000 clinical practices for individual patients was conducted, and the results are now accessible. Those who received regular (e.g., daily) vitamin D dosages had an advantage over bolus doses. Both innate and acquired immunity have been certainly benefited from vitamin D[54], which may help it combat acute respiratory infections. COVID-19 is an ARI induced by SARS-CoV-2; On the basis of the existing data, vitamin D supplementation does not appear to be a viable way of protecting against COVID-19. However, vitamin D insufficiency is a readily controllable indicator of the probability for ARI and should be actively addressed using inexpensive, safe, and widely available vitamin D supplements. This strategy would be easily justified if COVID-19 infections were minimized [55].

Radujkovic et al. looked into vitamin D insufficiency and COVID-19 patient outcomes to determine any relationships between vitamin D levels and the severity of symptoms and survival. Their data show an association between vitamin D and COVID-19 survival/mortal, emphasizing the necessity for Vitamin D supplements outcome measures in people with SARS-CoV-2 infections [56]. Nurshad Ali analyzed the role of vitamin D in the prevention, progression, and severity of COVID-19 infection and discovered a negative correlation (p=0.033) between average vitamin D levels and COVID-19 infections per million people in Europe. Consequently, the data correlating vitamin D levels and COVID-19 severity and fatality is unclear. RCTs and prospective investigations are necessary to explore this hypothesis[57].

2.6 Vitamin D, hypertension, and COVID-19 severity: The intake of vitamin D decreases hypertension in infected persons with normal blood pressure. To reduce blood pressure in patients with hyperparathyroidism, plasma renin release in the bloodstream and blood angiotensin II levels are essential [58]. Low vitamin D will increase renin-angiotensin-system (RAS) operation and higher blood pressure afterward. In hypertensive and normotensive individuals, It was discovered that the blood pressure and the active metabolite concentration 1,25(OH)2D3 had an anti-parallel relationship[59]. The Mendelian randomization method was used in 35 experiments (146,581 participants) with 4 individual Nucleotide Polymorphism (SNPs); Vitamin D insufficiency is associated with an increased risk of hypertension in patients with elevated 25(OH)D levels of inherited factors. Following past research findings, the percentage of patients with hypertension COVID-19 was 20 to 30%, and the proportion of diabetes was 15 to 22%. The most significant corresponding morbidity in patients suffering from extreme course disorder was accompanied by diabetes (16.2%)[60].

2.7 Vitamin D correlation with cardiovascular diseases: Vitamin D is a multifunctional protective divisor for Endothelial, Artery, and Cardiac muscle cells in the cardiovascular system. An inverse correlation in 25(OH)D vitamin D plasma status (under 60 nmol/L) and cardiovascular outcomes were observed in a meta-analysis of 65,994 individuals. The Framingham and NHANES data supported these results. In terms of vitamin D supplementation's beneficial consequences on respiratory disorders, a cardiovascular disease's positive effects were documented only if vitamin D deficiency occurred before supplementation[61,62–67]. A substantial rise in renin and angiotensin II of the plasmas was found in a large randomized clinical trial in patients (n=3296) with lower 25(OH)D and 1,25(OH)D_2 amounts without mingling aldosterone amounts[68]. Vitamin D status is a self-governing fear component for CVD fatality in plasma. Vitamin D deficiency was found in 92 % of 1,801 infected people with metabolic syndrome (22.2% were seriously adequacy (25(OH)D < 25 nmol). Those with the highest levels of 25(OH)D (>75 nmol/L) had a 69 percent reduction in CVD fatality and a 75 percent reduction in overall mortality. CVD is known to be a self-governing risk component of severe consequences in COVID-19 infected persons. The percentage of survivors with CVD was 10.8 percent, while fatalities were 20 percent. One of the leading infection causes is impaired coagulation, endothelial dysfunction, and pro-inflammatory stimuli[62,69,70].

2.8 Vitamin D and viral infection reduction pathways: ARDS was the leading cause of mortality in COVID-19 patients. It was revealed that individuals with low to extremely low 25(OH) D blood levels (27.6 to 13.7 nmol/L) had severe vitamin D insufficiency [71]. Latest studies have shown various ways of reducing the possibility of microbial infection by vitamin D. To minimize the likelihood of viral infections and death; vitamin D uses multiple pathways. Vitamin D protects against the common cold in three ways: the physical barrier, the average cell immunity, and the adaptive immune response[72]. The most recent research also showed that vitamin D may effectively reduce the COVID-19 pandemic and extend human life expectancy. These involve preserving the cell linkage and space linkage, emerging cell immunity by lowering the cytokine tempest with interferon α factor and tumor necrosis factor α, and controlling flexible immunity by blocking T type 1 support cell reactions and inducing T-cell inauguration. The addition of vitamin D has also been observed in HIV infection to increase CD4+T cell count [73]. Statistics have shown in the table1 demonstrate correlations and effects of vitamin D on viral infections within confined environments.

The SARS-CoV-2 severe pandemic is notable for the emergence of lymphopenia. Vitamin D has been found to have therapeutic effects on experimental interstitial pneumonitis in mice and human cell lines [74]. Vitamin D has been shown in many in vitro experiments to be important in local 'respiratory homeostasis' by boosting antimicrobial peptide showcasing or immediately interacting with respiratory virus reproduction[51]. Vitamin D insufficiency may be correlated with ARDS and heart failure[73], the symptoms of chronically ill subjects of COVID-19. Consequently, the Renin-Angiotensin System (RAS) facilitates the deficit of vitamin D. This might lead to CVD and decreased lung function. A significant proportion of severe disease cases in COVID-19 are patients with these comorbidities[75]. Several investigations have shown vitamin D's immunomodulatory properties as well as its essential role in immunological homeostasis. Adequately planned, randomized restrained trials must explain the possible features of vitamin D in defending immune

feedback to breathing microbial and avoiding different forms of acute respiratory system infections.

Table 1: Findings based on considering the correlations and effects of vitamin D on enclosed viral infections. Reprints with permission (Ref. [73])

Virus	Vitamin D Effect	References
Dengue	Vitamin D mechanisms discussed	[76]
Dengue	Inverse association between 25(OH)D concentration and progression of disease state	[77]
Dengue	Vitamin D supplementation trial with 1000 and 4000 IU/d. 4000 IU/d resulted in higher resistance to DENV-2 infection. MDDCs from those supplemented with 4000 IU/d showed decreased mRNA expression of TLR3, 7, and 9; downregulation of IL-12/IL-8 production; and increased IL-10 secretion in response to DENV-2 infection	[78]
Hepatitis C	1,25-hydroxyvitamin-D3-24-hydroxylase, encoded by CYP24A1 gene, is a key enzyme that neutralizes 1,25(OH)2D. This study found that alleles of CYP24A1 had different effects on the risk of chronic hepatitis C infection.	[79]
CHB	25(OH)D concentrations were lower in CHB patients than that of healthy controls and inversely correlated with HBV viral loads	[80]
KSHV	Found that cathelicidin significantly reduced KSVH by disrupting the viral envelope.	[81]
HIV-1	Review of 29 clinical studies of vitamin D supplementation showed there was a decrease in inflammation. In 3 of 7 studies, CD4+ T cell count increased, but the effect on viral load was inconclusive since most patients were on cART.	[82]
H9N2 influenza	In a lung epithelial cell study, calcitriol treatment before and post-infection with H9N2 influenza significantly decreased expression of the influenza M gene, IL-6, and IFN-β in A549 cells but did not affect virus replication.	[83]
RSV	Demonstrated that the human cathelicidin LL-37 has effective antiviral activity against RSV in vitro and prevented virus-induced cell death in epithelial cultures,	[84]
RSV	Performed a laboratory study that identified the mechanism by which vitamin D reduced the risk of RSV.	[36]
RSV	Found that the T-allele of the vitamin D receptor has a lower prevalence in African populations and runs parallel to the lower incidence of RSV-associated severe ALRI in African children, 1 year.	[85]
Rotaviral diarrhea	Found serum 25(OH)D <20 ng/mL associated with an odds ratio of 6.3 (95% CI, 3.6 to 10.9) for rotaviral diarrhea	[86]

2.9 Positive effects of vitamin D enrichment: COVID-19 has been declared a worldwide pandemic by the World Health Organization. However, information on the possible defense mechanisms of this infectious disease is minimal. There is no evidence that vitamin D supplementation prevents COVID-19 from becoming severe and fatal. Several randomized studies have been conducted to evaluate the effectiveness of vitamin D in the medication of COVID-19 infection and severity, but the findings have yet to be released. Small cohort research has been identified above to show protective benefits from the clinical decay of COVID-19 from mingled vitamin D, Mg, and vitamin B_{12}. In a prior meta-analysis, vitamin D supplementation was proven to be beneficial and dependable in preventing acute respiratory tract infectious diseases[32].

Additionally, people with severe vitamin D insufficiency reaped the most advantages from supplementation. The preventive impact of vitamin D was similarly substantial in participants with a serum 25 (OH)D of less than 25 nmol/l, compared to serum 25(OH)D of more than 25 nmol/L[32]. A subgroup evaluation in the same article revealed that regular or weekly vitamin D consumption (exclusive of any added bolus) provided supportive benefits against ART infection, particularly in patients with vitamin D insufficiency. Antioxidant gene expression (subunit glutathione reductase modifier) is improved by vitamin D treatment as well [87]. Increased glutathione production reduces vitamin C consumption, perhaps resulting in antimicrobial action, and is recommended as a way to prevent and treat COVID-19 infection. Limited evidence has been gathered That the 20–50 µg/day vitamin D supplement has some harmful health effects. Adults are in reality safe to supplement vitamin D in doses up to 100 µg/day, and now several specialist groups are considering intake in older adults, though at levels smaller than this. One research found that the consumption of vitamin D supplements over 6 weeks of 100-250 µg/day raises the serum strength of 25(OH)D from 2-3 times exclusive of any adverse medical consequences, respectively[88].

It's worth mentioning that serum 25(OH)D levels should be elevated to the optimal range of 75-125 nmol/L. After one month, To maintain 25(OH)D circulation values, the intake should be reduced to 100 g/day [89]. However, prospective clinical trials may make it worth assessing, for example, once a week, the strength of multiple vitamin D dosing plans for acute respiratory tract contamination, which may be easier to carry out. Due to demographic and biological distinctions, e.g., race, age, exposure length, seasonal fluctuations, body mass index, consumption of some drugs, base vitamin D level, physiology, and form of vitamin D supplement[90], the serum reaction to the prescribed doses are varied mainly between individuals. In addition, the population variability and the dosage of vitamin D must be addressed during the assessment of the vitamin D preventive function of the COVID-19. In randomized controlled experiments, the attention should be on the sample's design focused solely on serum accumulation levels of 25(OH)D and not on the dosage administered[91]. A new study has recommended supplementing vitamin D with magnesium to control phosphate and calcium homeostasis. Magnesium supplementation appears to be required for the enzymes engaged in vitamin D metabolism, which is a significant factor in enzymatic responses, particularly in the kidney and liver[92].

Limitations: A significant drawback in all research concerned with insufficiency of vitamin D and disease, few reports are available to indicate a fundamental linkage. Several experiments suggest that vitamin D status interactions and evidence on the effect of COVID-19 are incomplete. Moreover, along with vitamin A, the impact of vitamin D on immunological gene expression should be considered appropriately. It has not been investigated in connection to vitamin A insufficiency in COVID-19. In contrast, vitamin A insufficiency and combination deficits are not only common in low-income nations that lack vitamin D or other minerals.

CONCLUSIONS AND RECOMMENDATIONS

In arbitrary trials and meta-analytical examinations, vitamin D intake was observed to protect against respiratory infections. Thus, the population at higher risk of having insufficiency should begin to take vitamin D supplements to ensure optimal amounts of circulating 25(OH)D (75-125 nmol/L). According to a number of independent studies, a link has been originated within vitamin D and COVID-19; however, some results have not demonstrated an association owing to changing confounding factors. There is limited data linking vitamin D to COVID-19 prevalence and death. Consequently, RCTs and extensive cohort studies are needed to confirm this theory.

Vitamin D deficiency has been connected to various non-communicable diseases (high blood pressure, diabetes, CVD, and metabolic disorders). These comorbidities, when combined with corresponding vitamin

D insufficiency, exacerbate COVID-19. Vitamin D strength should consequently be given equal importance in the pathogenesis and progression of Covid-19. Due to limited sun exposure, natural skin vitamin D synthesis is significantly inhibited by the measures employed to control the pandemic (lockdown), raising the risk of vitamin D insufficiency. Appropriate nutritional treatment, mild supplements, or food compliance may help to reduce this shortcoming. The vitamin D status should be checked as soon as possible and changed in the case of hospitalization. Meanwhile, in COVID-19 illness, several studies have started investigating the effects of vitamin D intake at varying dose levels (up to 200 000 IU). The goal is to understand whether supplementing with vitamin D at different doses alters the disease's progression or immunological response.

In summary, studies have shown that vitamin D increases immunity, both in those born with it and those who acquire it over time, perhaps assisting in the fight against acute respiratory infections. SARS-CoV-2 is the source of ARI COVID-19, although evidence for vitamin D supplementation against COVID-19 disease is equivocal. However, vitamin D insufficiency is a readily controllable probability factor for ARI and should be aggressively treated using affordable, safe, and readily accessible supplements. Several new investigations also reinforced the possible performance of vitamin D in minimizing the COVID-19 pandemic and life expectancy. This strategy would be easily justified if COVID-19 infections were minimized

Acknowledgment: Dr. Umair Yaqub Qazi extends his appreciation to the Deanship of Scientific Research, University of Hafr Al Batin, for funding this work through the research group project number S-1443-0053.

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