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Review Article

Vitamin D nemesis of COVID-19

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ABSTRACT

The surge in the spread of the corona virus disease (COVID-19) pandemic alerted us to opt for the preventive medicine, as prevention is always better than cure. Apart from wearing mask, frequent hand washing and social distancing, strengthening our immune response plays a pivotal role in preventing infections. Vitamin D not only aids in calcium and phosphate homeostasis but also acts as an immunomodulator; the deficiency of which is linked with various respiratory and systemic infections. Hence we took up this review to study the effect of vitamin D in corona illness. Vitamin D exerts the expression of pro-inflammatory cytokines, hinders zinc metabolism, lowers Interleukin 6 levels and thereby inhibits cytokine storm in covid patients. Studies have proved that the covid patients have vitamin D deficiency and its supplementation improves the disease severity as well as the length of hospital stay. To conclude, Vitamin D supplementation can protect as well as halt the progression of corona virus disease. Further trials are needed to set the therapeutic levels in various stages of corona illness.

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1. Introduction

Vitamin D, a fat soluble prohormone required for calcium and phosphate metabolism plays a pivotal role in maintaining bone and muscle health.¹ It is also involved in cellular proliferation and differentiation,² regulating gene expression and signal transduction. Vitamin D, by binding with its receptor secures against endogenous and exogenous stresses and possess non calcaemic role like immunomodulation in regulating innate immunity and autoimmune response.³

The outbreak of COVID-19 has set in a global pandemic - a health crisis situation; thereby making it a mandate requisite to prevent the public from the jaws of corona virus infection and progression. The relationship between vitamin D deficiency and respiratory health was well-established.⁴ Vitamin D levels are lowered in acute or critical illness which sets in inflammatory episode. The corona virus enters the host cells through binding with angiotensin converting enzyme (ACE2) receptors in the respiratory tract.⁵ The virus can be eliminated at an earlier stage of infection by improving the host immune response. However strategies need to be developed to improve immune responses; one of them is to utilize a potential immunomodulator to improve

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individual immunity. One of the recent debates is about the use of Vitamin-D with the immunomodulator action in prevention and management of novel corona virus disease. So we aimed to study the role of vitamin D in Corona virus disease prevention and halting its progression.

Vitamin D, otherwise known as Calciferol, is a steroid hormone produced endogenously in the skin by the effect of ultra violet (UV) radiation from the sun, through exogenous food sources or supplements. The active form of the vitamin is 1, 25-dihydroxy Calciferol (Calcitriol). Vitamin D deficiency, globally affecting 1 billion people (6), is attributed to multifactorial causes like life style modification (less outdoor time), obesity, increased use of UV-B blockers and Smog blocking UV rays. The deficiency is associated with several diseases like cancer, cardiovascular disease, infectious diseases and diabetes. Vitamin D plays a role in reducing the risk of these diseases, microbial infections and its related death, by involving three mechanisms: physical barriers, cellular natural immunity, and adaptive immunity⁶ as shown in Figure 1. The deficiency of Vitamin D has a predisposing effect on systemic infections and auto-immune diseases which is attributed to the immunomodulatory role of Vitamin D.^{7,8}

The immunomodulatory process helps in local respiratory homeostasis mechanism by two ways viz. i) promoting the expression of antimicrobial peptides, ii) directly affecting replication of respiratory viruses. It plays a regulatory role during viral infections by suppressing adaptive immune responses in respiratory epithelial cells.⁹ Lower levels of Vitamin D are usually correlated with increase in inflammatory cytokines and upper respiratory tract infections.¹⁰

Vitamin D receptor complex enhances the transcription of cathelicidin by acting on its gene promoter.¹¹ Cathelicidin is involved in clearing respiratory pathogens by activating the proinflammatory cytokines, stimulating the chemotaxis of neutrophils, monocytes, macrophages, and T cells at the site of infection.^{12,13} Another mechanism by which the vitamin provokes antimicrobial action is by regulating iron metabolism. Iron is required by the microbes for its survival. The vitamin inhibits hepcidin, thereby reducing intracellular iron, suppressing microbial growth.¹⁴

The defence mechanism in the lung includes innate and adaptive immunity. The principal cells in the airway epithelia, alveolar macrophages, and dendritic cells express CYP27B1, which have the potential to synthesize 1,25 dihydroxy vitamin D (1,25 (OH)₂D).¹⁵ These cells also express pattern recognition receptors (PRRs) that recognise the viral RNAs.¹⁶

2. Vitamin D and Corona Virus Disease

Vitamin D deficiency is regarded as a potential risk factor for coronavirus infection as suggested by many researchers.¹⁷ The evidence of association between vitamin

D deficiency and COVID-19 was first pictured by Italy, the country which was severely affected by the pandemic due to its higher deficiency prevalence rate.¹⁸

Some of the mechanisms exerted by vitamin D in controlling COVID-19 include:

1. Reduces the expression of pro-inflammatory cytokines and increases the production of antiviral proteins thereby, inhibiting viral replication.¹⁰
2. Hindering zinc metabolism thereby decreasing viral replication.^{19,20}
3. Immunomodulatory role of vitamin D by dendritic cells and T cells promotes anti-inflammatory action and viral clearance.²¹
4. D vitamin adequacy is said to correlate with lower interleukin 6 levels, thereby controlling cytokine storm in severe COVID-19 infections.^{22,23}

However, the mild deficiency of vitamin D seem to have no effect on the corona virus disease which was shown by an UK study with 580 positive patients and 723 negative controls.²⁴

3. Vitamin D levels in Disease Progression and Severity

The patients with severe COVID-19 infection requiring ICU care were vitamin D deficient as reported by Alipo M. His retrospective study with 212 covid positive cases expressed that the raise in vitamin D level to 1.63 times than the baseline would improve the clinical outcome of the critically ill patients.²⁵ De Smet et al. in his observational study observed increasing rate of deficiency correlated with the increasing radiological evidence of disease worsening especially in covid positive male patients. This sexual dimorphism might be due to the estrogen/androgen-dependent immune differences in both genders.²⁶ Another retrospective study reported a mortality rate of 98.9% in vitamin deficient covid cases.²⁷

Patients with COVID-19 are also at risk for a number of thrombotic complications and coagulopathy which is related to poor prognosis and increased mortality.²⁸ Their serum levels of cytokines are highly increased which is associated with morbidity and mortality. Activation of innate immunity leads to increased local production of 1,25(OH)₂D that amplifies viral neutralization and clearance.

Rhodes and colleagues' review states that vitamin D deficiency correlates with severity of COVID-19 infection.²⁹ Biesalski in his study quoted that deficiency of D vitamin is associated with comorbidities in covid patients and it increases the severity of illness in these patients.³⁰ Severe vitamin deficiency with 25(OH)D levels below 10 ng/mL is associated with increased mortality.³¹ The probability of death in patients with vitamin D deficiency was 34.6% compared with 6.4% in patients with adequate vitamin D levels as shown by Alizera Abrishormi et al.³² When covid positive patients were followed up by

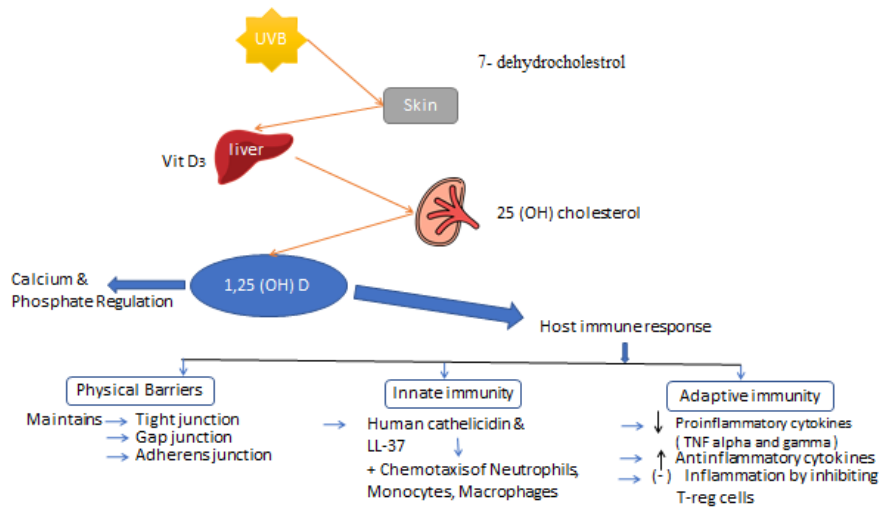


Fig. 1: Vitamin D role in antimicrobial action

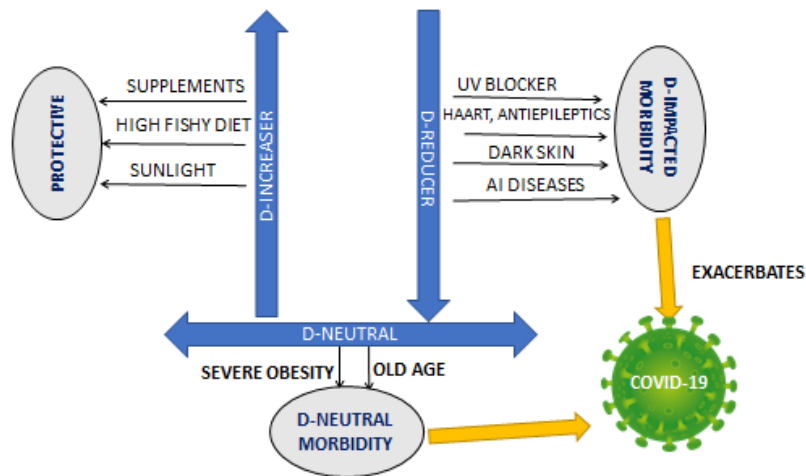


Fig. 2: Exploring the link between Vitamin D and COVID-19

Radujkovic et al. for a median period of 66 days, showed that Vitamin D deficiency was associated with a 6-fold higher risk for severity of disease and a 15-fold higher risk of mortality with increased oxygen requirement and requirement of intermittent ventilation.³³

(HAART – Highly active anti-retroviral therapy, PM 10 – Particulate matter 10 micro meters, PM 2.5 - Particulate matter 2.5 micro meters, COPD – Chronic obstructive pulmonary disease, CVD – Cardiovascular disease, DM – Diabetes mellitus, HTN - Hypertension)

Confounding factors are those which exert an influence over both exposure and outcome in an epidemiological study. In light to COVID-19, Vitamin D deficiency cannot

be held responsible solely for increased susceptibility of the disease. Along with the deficiency, the following factors also contribute to the COVID-19 disease:

1. Age and sex
2. Social factors
3. Health risk factors
4. Medical variables (comorbidities and number of medications)
5. Environmental factors

These are described briefly in pictorial representation. (Figure 3)

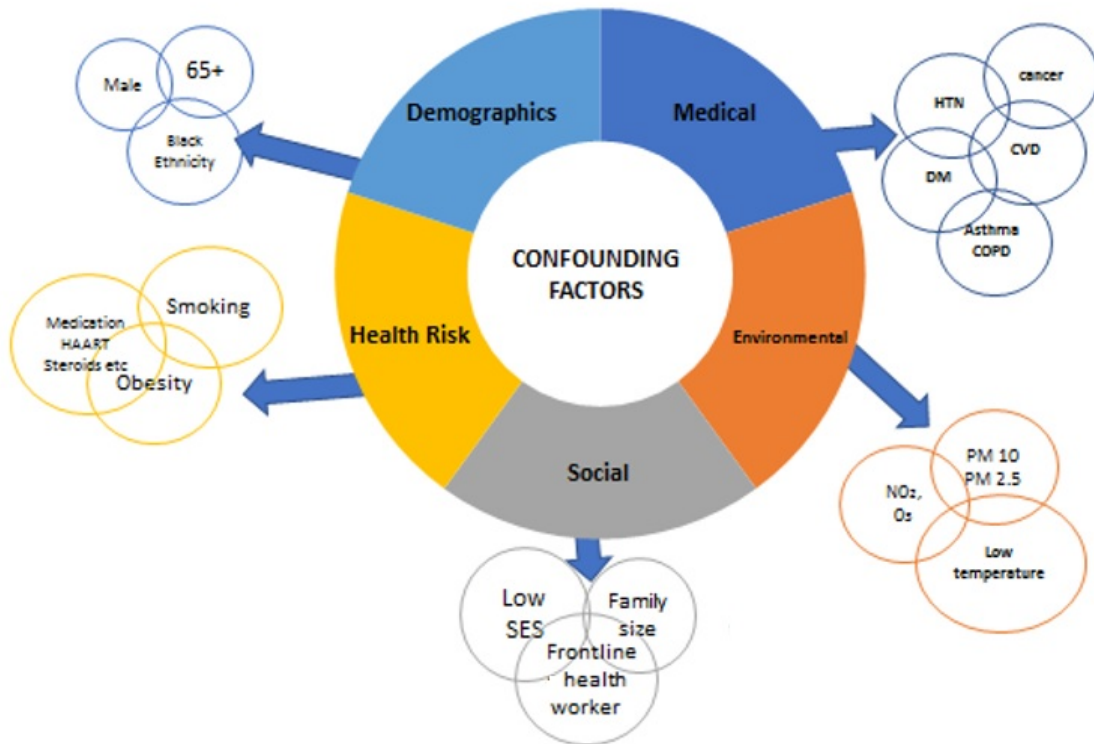


Fig. 3: Confounding factors

Table 1: Vitamin D and COVID-19 related studies

S. No	Author	Place of study	No. of Covid Patients	Inference
01	Meltzer et al ³⁴	USA	489	Vitamin deficiency is associated with increased COVID risk
02	Pinzon et al ³⁵	Indonesia	10	Hypovitaminosis D is reported in 90% of the covid patients in the study
03	Jain et al ³⁶	India	154	Vitamin D deficiency is related to high fatality rate in corona affected patients
04	L. Hernandez ³⁷	Spain	216	Vitamin D deficient COVID-19 patients had increased prevalence of hypertension and cardiovascular diseases, raised serum ferritin and troponin levels and prolonged hospital stay
05	Alex Pizzini ³¹	Austria	109	Severe COVID infection displays disturbed vitamin D – PTH axis
06	Antonio D Avolio ³⁸	Switzerland	27	Low Vitamin D3 concentrations are noted in SARS CoV2 patients
07	Alizera Abrishormi ³²	Iran	73	High levels of vitamin D is associated with lesser extent of lung involvement and low levels are associated with mortality
08	Alexandar Radujkovic ³³	Germany	185	Vitamin D deficiency and its association between severity and mortality of COVID-19 patients
09	Vadir Baktash ³⁹	UK	105	Increased mortality in older adults with vitamin D deficiency.
10	Faul et al ⁴⁰	Ireland	33	Patients with (Acute Respiratory Distress Syndrome) ARDS had low vitamin D levels

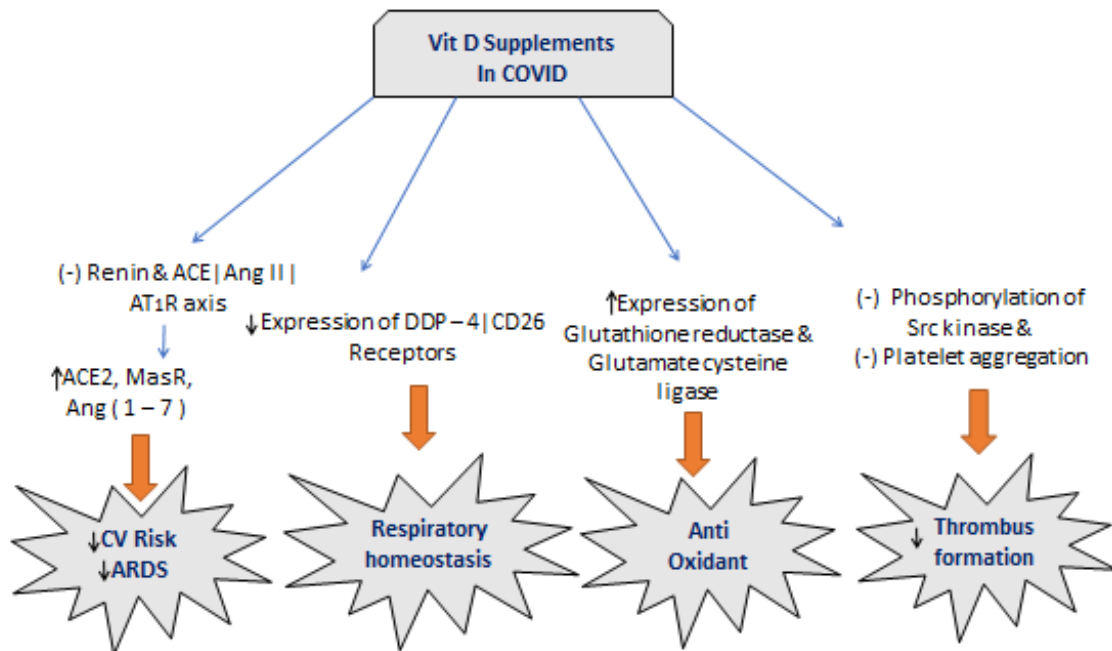


Fig. 4: Mechanism of action of Vitamin D supplements

4. Vitamin D Supplementation

For every 4 ng/mL increase in vitamin D level there is 7% chance of lowering infection.⁴¹ So, vitamin D supplementation would be useful in reducing the viral replication and in treatment of patients with corona virus disease. Daily or weekly Vitamin D dose between 20 μ g and 50 μ g showed to reduce respiratory tract infections.⁴² When supplemented with a dose of 100 μ g/daily for one year showed reduced risk of infection.⁴³ Hence, patients with Covid infection, belonging to a high risk group, should be checked for vitamin D status as it boosts immune system and regulates Renin angiotensin system. However in high doses, it is inhibitory to immune system.⁴⁴ The goal of the supplementation is to maintain the vitamin D level between 40-60 ng/ml. People at risk of COVID-19 are recommended to take 10,000 IU/day of vitamin D3 for a few weeks followed by 5000 IU/day as suggested by Gant et al.⁴⁵

Some of the limitations of the supplementation include:

1. The patients, who report late, present with severe symptoms in the hyper-inflammatory stage, making it onerous for VD3 to exert its anti-viral effect.
2. It is arduous to potentially specify the effect of a micro-nutrient over other concurrently given potent anti-inflammatory such as Dexamethasone in severe cases.⁴⁶

5. Clinical Trials

Few studies have been conducted to prove the efficacy of vitamin D3 supplementation as a therapeutic measure or as an adjuvant in COVID-19 affected patients. The purpose of these studies and their findings are summarized as follows:

A short term, randomized, placebo controlled study by Rastogi et al. was done to find the outcome of high dose, oral vitamin D supplementation on SARS-COV2 viral clearance. The results have shown that a daily supplementation of 60,000IU for 14 days helped in achieving a serum concentration of greater than 50ng/ml in 75% of the study population. High dose of supplementation, therapeutically, lead to SARS-COV2 RNA negative in 41.7% participants and was also found useful for viral clearance.⁴⁷

A quasi experimental study conducted by Cedric Annweiler et al. in France conclusively stated that regardless of all confounding factors involved, regular bolus supplementation of vitamin D was linked with less severe infection and better survival rate in hospitalized frail elderly patients.⁴⁸

To the contrary, a double blind randomized control study conducted at Sao Paula, Brazil stated that vitamin D supplementation did not confer any therapeutic gain as a measure of improvising the severe illness and thereby does not have any effect on length of stay in hospital.⁴⁹

A Pilot study done by Castillo et al. evaluated established that a high dose of Calcifediol - a metabolite

of Vitamin D, when supplemented in patients with COVID-19 significantly reduced the need for ICU treatment of patients and also the severity of infection amongst Spanish population.⁵⁰

In a clinical case series by Ohaegbulam et al., New York, Vitamin D supplementation was given to 4 COVID-19 hospitalized patients who were Vitamin D deficient. The cases displayed the following key findings- doubling levels of Vitamin D concentration in serum thereby gaining Vitamin D improvement state, lowering in CRP and ESR levels, and undetectable concentrations of IL-6; Also it has substantiated that achieving and maintaining adequate levels of Vitamin D can be looked upon as an effective strategy to decrease potential risks of secondary bacterial infection caused by interleukin inhibitors.⁵¹

6. Limitation

Majority of the study shows only the association between vitamin D and COVID-19. Only few studies show the underlying cause of the disease and deficiency.

7. Conclusion

Vitamin D' anti-inflammatory, antiviral and immunomodulatory effect makes it a safe and inexpensive therapy to combat and overcome corona virus disease. However, trials have to be conducted to set up the therapeutic levels for mild, moderate and severely affected covid patients.

8. Disclosure Statement

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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