Effect of Vitamin-D on Covid-19: A narrative review

Abstract:

Vitamin-D deficiency is a common yet understated problem. A number of people are at a risk of its deficiency while many others go undetected. The novel corona virus, an RNA virus, has run its rampant course across the globe affecting millions for the worse. COVID-19 a disease caused as a result of the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has shown to produce severe lower respiratory symptoms, so far resulting into a reported death count of more than 4.9 million worldwide and more than 4.5 lakhs in India. It affects numerous other organs such as the liver, brain, kidney and heart as well. Dosage of Vitamin D regularly, during the treatment and as a pre-emptive measure have all shown to work to reduce respiratory tract inflammation. Low plasma 25(OH)D levels appear to be an independent risk factor for COVID- 19 infection and hospitalization. Administration of a large dose of Calcifediol or what is also known as 25-hydroxyvitamin D, a main metabolite of the vitamin D endocrine system, noticeably lessened the need for ICU treatment of patients requiring hospitalization after being tested positive for COVID-19. Elevated levels of Vitamin-D in body could decrease the length of hospital stays and reduce the intensity of the COVID 19 infection. In many COVID 19 patients these T regulatory lymphocytes (Tregs) levels are found to be low. These low levels which can be elevated by Vitamin D supplementation. Low levels of vitamin D have also been connected to increased inflammatory cytokines and a noticeably increased risk of pneumonia and viral upper respiratory tract infections. While further large-scale studies are required to provide concrete answers, the severity of the disease has been shown to be reduced and Vitamin D can potentially be used as a supplementary treatment against Covid-19 and also as a precaution against the same. These results are significant and should not be ignored.

Keywords: COVID 19, Vitamin D, Calcifediol, Vitamin-D deficiency.

Introduction:

World Health Organization (WHO) declared COVID-19 as a global pandemic in March of 2020. Since then, the novel corona virus, an RNA virus, has run its rampant course across the globe affecting millions for the worse. COVID-19 a disease caused as a result of the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has shown to produce severe lower respiratory symptoms, so far resulting into a reported death count of more than 4.9 million worldwide and more than 4.5 lakhs in India. It's a disease that affects a number of organs including the liver, brain, kidney, heart, and lungs. The main cause of these deaths is the resulting inflammation in COVID-19 patients, particularly in the lungs leading to acute respiratory distress syndrome (ARDS). A specific treatment to cure COVID-19 has not been found yet, which is one of the biggest hurdles against stopping the spread of the virus. Antimalarial drug (chloroquine and hydroxychloroquine), as well as antiviral drugs

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(remdesivir), and also dexamethasone (corticosteroid) are all being used clinically for the treatment of COVID-19 patients. Due to this lack of concrete solution, various treatments are being tried, one of which is the application of Vitamin D. It has been proposed that the deficiency of Vitamin-D may be a risk factor for various respiratory illnesses, one of which is the SARS CoV-2 infection. It has been suggested that Vitamin- D may perform immunomodulatory functions, keeping aside its known effects on mineral metabolism. Vitamin D, which is a steroid hormone also plays a key role in phosphorus–calcium metabolism. It also plays a crucial role in the immune systems of not only humans but also animals. Various studies have ended up revealing a plethora of pharmacological as well as physiological functions of vitamin D, some being anti-inflammatory and antioxidant, and also antiviral effects. It also plays a part in regulating the adaptive and innate systems of defence. In light of fresh cases every day and a growing pile of evidence in favour of administration of Vitamin-D being an effective treatment against the virus, taking a closer look at how it relates to covid is imperative.

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Objectives

- Vitamin-D and its physiological significance.
- Vitamin-D and its deficiency.
- Level of Vitamin-D and the associated risk of developing COVID-19.
- Vitamin-D deficiency and its relation to COVID-19 positivity.
- Vitamin-D status prior to the testing of COVID-19 and its association with the test results.

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Discussion:

Coronavirus disease (COVID-19) identifies as a infectious disease which is caused by the SARS-CoV-2 virus. [1] Many months ago it was first detected in Wuhan district of China and from there spread to all continents. Once infected, most will end up experiencing moderate to mile respiratory illness in body and recovery can happen without any special treatment. However, some people unfortunately enough will become seriously ill and will need medical attention. The most common symptoms of the virus are cough, fever, tiredness, loss of smell and taste. Older persons and those with pre-existing medical conditions like cardiovascular disease, diabetes, chronic respiratory disease, or cancer have a much greater chance of developing a serious illness. However, as it stands, anyone can come out positive for COVID-19 and become seriously ill and in worst cases even die at any age. The spread of the virus can be from an infected person's mouth or nose in small liquid particles when they cough, sneeze, speak, sing or breathe. Less commonly found symptoms include sore throat, headaches, aches and pain, diarrhoea, rash on skin, discolouration of toes or fingers, red or irritated eyes. More serious symptoms include difficulty breathing or shortness of breath loss of speech or mobility, confusion, chest pain. It is advised that persons showing mild symptoms should handle their symptoms at home and call their doctor before seeking medical attention. On average, symptoms present themselves in 5-6 days but can also at times take up to 14 days.[2]

Comment [a8]: Include both direct and indirect modes of transmission

These expelled particles may range anywhere from being larger respiratory droplets to also smaller aerosols. It is therefore extremely necessary to be cautious and practice respiratory etiquette, such as coughing into a flexed elbow, and be aware enough to stay home and self-isolate until one recovers if they feel unwell.[2]

Vitamin D is inert in nature and needs two hydroxylations before it can be activated. The first of these two occurs in the liver to produce “calcidiol” while the subsequent one occurs in the kidney and forms “calcitriol”. The latter of the two is the physiologically active form. The primary functions of this vitamin include promoting the absorption of calcium in gut and regulating serum calcium and phosphate concentrations to adequate levels. This ensures the normal growth i.e. mineralization of bones while preventing hypocalcemic tetany. Other secondary functions modulation of processes like cell growth, immune function, glucose metabolism and neuromuscular function. It also in part modulates numerous genes responsible for encoding proteins that further help regulate cell proliferation, differentiation, and apoptosis.[3]

The required levels of Vitamin-D a person required varies based on their age. From birth up to the age of 12 months the required level is 400 IU in infants. Then from the age of 1 to 13 years, it increases to 600 IU. This level then stays more or less the same in teens between the age of 14 to 18 years and is similarly 600 IU for adults under the age group 19 to 70 years. Women who are pregnant or are breastfeeding similarly require a minimum of 600 IU of Vitamin-D in their diet regularly. The demand of vitamin D however increases in adults above the age of 71 and above and is a minimum of 800 IU. This is because the skin stops synthesising Vitamin-D as efficiently once a person is old and also their kidneys are unable to convert as much Vitamin-D to its active for. However, these are tentative and ideal levels which vary for people who are at a risk of Vitamin-D deficiency.[4]

This vulnerable sector of the population includes children who are being breast fed. Infants who are being breast fed should be given an additional supplement of 400 IU everyday of Vitamin-D. Interesting enough, Vitamin-D requires the help of fat to be absorbed and thus people who suffer from disorders like Crohn’s disease or celiac disease are also at a risk of being deficient in Vitamin-D as their body is unable to handle fat properly. While on the flip side people who are obese have excess fat which then binds to some Vitamin-D and prevents its passage into blood. Those who have had gastric bypass surgery, suffer from osteoporosis or chronic kidney disease or chronic liver disease are all at a risk of being deficient in Vitamin-D as well. Also, people who have been diagnosed with hyperparathyroidism (which is a hormone whose job is to control the level of blood calcium level). Granulomatous diseases (Sarcoidosis, Tuberculosis, Histoplasmosis, to name a few) are diseases that result into a collection of cells or granulomas because of chronic inflammation. They also result in Vitamin-D deficiency. A type of cancer called lymphomas also reduces a person’s blood calcium level. Medicines which adversely affect vitamin D metabolism like cholestyramine, anti-seizure drugs, glucocorticoids, antifungal drugs, and HIV/AIDS medicine all put their consumer at a risk of having low Vitamin-D levels in their blood. [4]

Vitamin-D, also called as the “sunshine vitamin” is synthesised endogenously in our skin when exposed to sunlight. The UV rays of the sun kickstart the synthesis of Vitamin D in the body. It is a fat-soluble vitamin. Despite this vitamin-D deficiency is not uncommon. Up to 42% of the adult American population is deficient in Vitamin-D. While in India it ranges from 50% to around 94%. Occasional exposure to strong sunlight may be enough to fulfil the required vitamin D requirements if the sunlight remains strong all throughout the year.[5]

Yet in places that are far north or south of the equator, vitamin D levels can fluctuate as the seasons vary. In winters, the levels may go down due to a lack of sufficient sunlight. In this case one will have to rely on supplements or diet to balance the falling vitamin D levels. The

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deficiency for it is common, with varied greater rates among people whose skin tone is darker or reduced sun exposure. The latter includes people residing in high latitudes during the winter, nursing home residents, and health care workers. COVID-19 is also more prevalent in African American people, those who live through late winters in northern cities, older adults, health care workers and individuals living in nursing homes. These are populations who also are more likely to be deficient in Vitamin D. Pregnant women, children and people living in Japan, all who have their Vitamin D deficiency rates as lower, have shown to be less affected by Covid-19. Shelters-in-place orders to lessen the spread may also end up providing decreased skin exposure and increase the need for Vitamin D supplementation. [5]

Keeping in mind the low cost of Vitamin D treatment and the benefit it provides, studies have suggested to scale its usage to treat Covid 19 patients, as well as using it as a precaution to fortify the immune system against the virus.

A parallel pilot randomized open label, double-masked clinical trial in Spain (Reina Sofia University Hospital, Córdoba) gave results that favoured the notion that early Calcifediol treatment helps reduce severity of Covid-19. In this study, 76 people hospitalised with Covid-19 were provided best available therapy with the only difference being the application of calcifediol in 50 of them. Of these 50, one required admission to the ICU (2%) and of the 26 untreated patients, 13 required admissions i.e 50% ($P < 0.001$). [6]

Of the patients treated with calcifediol, none died and all were discharged, without complications. Of the patients not treated, 2 died. [6]

This pilot study worked to demonstrate how the administration of a large dose of Calcifediol, also known as 25-hydroxyvitamin D, which is a main metabolite of vitamin D endocrine system, noticeably lessened the need for ICU treatment of patients requiring hospitalization after being tested positive for COVID-19. [6]

Relationship between a positive PCR (polymerase chain reaction) test and clinical results of vitamin D levels measured during a duration of 6 months before the PCR test in patients who were suffering from coronavirus disease 2019 (COVID-19), was examined by a retrospective cohort study. Here 227 patients who had COVID-19 and 260 patients who did not have COVID-19 were distributed into 4 groups in accordance of their vitamin D levels: [7]

Table 1. Vitamin D levels in different groups

Groups	**Vitamin D levels**
Group I	0–10 ng/ml
Group II	10–20 ng/ml
Group III	20–30 ng/ml
Group IV	> 30 ng/ml

The result was 260 patients who had their vitamin D levels tested. [7]

In 94.27% of 227 patients who tested positive for COVID-19 the vitamin D levels were found to be below 30 ng/ml, while 93.07% of 260 non-COVID-19 found their vitamin D levels to be below 30 ng/ml. Regardless, significant vitamin D deficiency (<10 ng/ml) ended up being considerably more frequent in COVID-19 patients (44%) as opposed to in non-COVID-19

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ones (31%). Amongst the patients who came out positive for COVID-19, those who had vitamin-D levels greater than a measurement of 30 ng/ml had evidently lower D-dimer and C-reactive protein (CRP) levels, number levels, as well as number of affected segements of lung and much shorter hospital stays. It again showed that increased levels of Vitamin-D in the human body could decrease the extent of hospital stays as well as reduce the intensity of what has ended up being known as the COVID 19 infection. [7]

Another retrospective cohort study was conducted to examine if a person's last taken vitamin D status prior to being tested for COVID-19 is in anyway associated with the forementioned COVID-19 test results. It included patients who had their 25-hydroxycholecalciferol or what is also known as 1,25-dihydroxycholecalciferol level measured and checked within the span of last one year before they were tested for COVID-19 from March 3 to April 10, 2020. A total of 489 patients had their vitamin D levels tested and measured in the year before COVID-19 testing. Vitamin D status before COVID-19 testing was categorized as; [8]

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Table 2. List of respondents

Likely deficient	124 participants (25%)
Likely sufficient	287 participants (59%)
Uncertain	78 participants (16%)

All in all, 71 participants (15%), ended up being tested positive for the COVID-19. [8]

In this single-center, moreover retrospective cohort study, the probably deficient status of vitamin D was associated with an increased chance of COVID-19 risk. [8]

Habitual and continual use of Vitamin-D supplements in a UK based study has shown, after having their covariates adjusted, that the continuous supplementation of Vitamin D reduces the risk of COVID-19 infection by 34%. Which is a significant reduction. All the studies described in this review article have given significant results and while admittedly more data from larger studies is required, these results cannot be ignored either. [9]

One of the biggest studies till date to investigate the role that vitamin D plays in the severity of the COVID-19 infection is a retrospective case-control study in the North West England. It's primary objective was to look into whether hospitalization with COVID-19 is more recurring in individuals who had lower vitamin D levels by evaluating associations of the levels of plasma 25 (OH)D with the chances of suffering from coronavirus disease infection as well as hospitalization. It also concluded that the low blood levels of Vitamin-D are associated with a higher likelihood of being hospitalised for COVID-19. [10]

In another Israeli based population study, between the duration of 1st February to April 30th 2020, data from 7807 people was collected. Participants had one previous blood test for the plasma 25 (OH)D level. [11]

According to them levels were marked as;

- Suboptimal' or 'low' levels of blood plasma 25(OH)D. Which were below 30 ng/mL

- Sufficiency more than 30 ng/ml. (75 nmol/L)
- Insufficiency, 20 – 29 ng/ml
- Deficiency less than 20 ng/ml (50 nmol/L)

Consistent with other studies risk by age and sex were as expected i.e., male and older persons were more at risk. While according to the study, obesity was not significantly associated with increased risk for COVID- 19 infection or hospitalization. [11]

When the control was tested of the 7807 people, 7025 tested negative for COVID 19 while 782 tested positive. After comparing with their Vitamin D levels it was found that people with low Vitamin D levels were 45% more likely to be diagnosed with Covid 19 [Odds ratio (OR) of 1.45]. While people with low Vitamin D in the case of hospitalisation were nearly twice or 95% as likely to be hospitalised [OR of 1.95]. [11]

The study concluded that low plasma 25(OH)D levels appear to be an independent risk factor for COVID- 19 infection and hospitalization. [11]

The severity of COVID-19 is determined by the presence of several issues such as pneumonia, severe acute respiratory distress syndrome (SARS-CoV-2), myocarditis, microvascular thrombosis and/or cytokine storms and all of them involve underlying inflammation. T regulatory lymphocytes (Tregs) provide defence against uncontrolled inflammation and as such against viral infection in general. In many COVID 19 patients these T regulatory lymphocytes (Tregs) levels are found to be low. These low levels which can be elevated by Vitamin D supplementation. Low levels of vitamin D have also been connected to increased inflammatory cytokines and a noticeably increased risk of pneumonia and viral upper respiratory tract infections. The deficiency of Vitamin D has also been linked to increased thrombotic episodes. Thrombotic episodes are often seen in COVID-19 patients.[12-17]

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However, there is always a potential for vitamin D toxicity and therefore any supplementation should be taken under medical advice. As it stands its efficacy in preventing acute respiratory tract infections has been shown to be better with the chronic intake of low doses, rather than bolus administration of large doses.

Conclusion:

Multiple studies have linked COVID 19 and low levels of Vitamin-D in blood together. Optimal levels of Vitamin D in body reduce the likeliness of testing positive for COVID 19, while its supplementation helps reduce the severity of the infection and has been shown to work well as a supplementary treatment in many cases.

References:

1. WHO Coronavirus (COVID-19) Dashboard.
2. WHO Coronavirus disease (COVID-19), Health Topics.
3. Vitamin D, Fact Sheet for Health Professionals, U.S. Department of Health & Human Services, National Institutes of Health.
4. Vitamin D deficiency, Health topics, medlineplus.gov.
5. Center for Systems Science and Engineering (CSSE) at Johns Hopkins University.
6. Marta Entrenas Castillo, Luis Manuel Entrenas Costa, José Manuel Vaquero Barrios, Juan Francisco Alcalá Díaz, José López Miranda, Roger Bouillon, José Manuel

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Quesada Gomez, “Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study”, The Journal of Steroid Biochemistry and Molecular Biology, Volume 203, 2020, 105751, ISSN 0960-0760.

7. Mustafa Demir,Fadime Demir,Hatice Aygun. Vitamin D deficiency is associated with COVID-19 positivity and severity of the disease.
8. Meltzer DO, Best TJ, Zhang H, Vokes T, Arora V, Solway J. Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results. *JAMA Netw Open.* 2020;3(9):e2019722.
9. Hao Ma, Tao Zhou, Yoriko Heianza, Lu Qi, Habitual use of vitamin D supplements and risk of coronavirus disease 2019 (COVID-19) infection: a prospective study in UK Biobank, *The American Journal of Clinical Nutrition*, Volume 113, Issue 5, May 2021, Pages 1275–1281,
10. Jude EB, Ling SF, Allcock R, Yeap BXY, Pappachan JM. Vitamin D Deficiency Is Associated With Higher Hospitalization Risk From COVID-19: A Retrospective Case-control Study. J Clin Endocrinol Metab. 2021 Oct 21;106(11):e4708-e4715. doi: 10.1210/clinem/dgab439. PMID: 34139758; PMCID: PMC8344535.
11. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. Eugene Merzon,Dmitry Tworowski,Alessandro Gorohovski,Shlomo Vinker,Avivit Golan Cohen,Ilan Green,Milana Frenkel-Morgenstern
12. Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19?. *Clin Med (Lond)*. 2020;20(4):e107-e108. doi:10.7861/clinmed.2020-0301
13. Acharya, Sourya, Samarth Shukla, and Neema Acharya. “Gospels of a Pandemic- A Metaphysical Commentary on the Current COVID-19 Crisis.” JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH 14, no. 6 (June 2020): OA01–2. https://doi.org/10.7860/JCDR/2020/44627.13774.
14. Arora, Devamsh, Muskan Sharma, Sourya Acharya, Samarth Shukla, and Neema Acharya. “India in ‘Flattening the Curve’ of COVID-19 Pandemic - Triumphs and Challenges Thereof.” JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 43 (October 26, 2020): 3252–55. https://doi.org/10.14260/jemds/2020/713.
15. Bawiskar, Nipun, Amol Andhale, Vidyashree Hulkoti, Sourya Acharya, and Samarth Shukla. “Haematological Manifestations of Covid-19 and Emerging Immunohaematological Therapeutic Strategies.” JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 46 (November 16, 2020): 3489–94. https://doi.org/10.14260/jemds/2020/763.
16. Burhani, Tasneem Sajjad, and Waqar M. Naqvi. “Telehealth - A Boon in the Time of COVID 19 Outbreak.” JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 29 (July 20, 2020): 2081–84. https://doi.org/10.14260/jemds/2020/454.
17. Butola, Lata Kanyal, Ranjit Ambad, Prakash Keshaorao Kute, Roshan Kumar Jha, and Amol Dattaroa Shinde. “The Pandemic of 21st Century - COVID-19.” JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS 9, no. 39 (September 28, 2020): 2913–18. https://doi.org/10.14260/jemds/2020/637.

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Try to use the same reference style throughout