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REVIEW ARTICLE

Effects of Vitamin D in the Prophylaxis and Treatment of COVID-19: A Systematic Review

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ABSTRACT

Despite the possible effects of Vitamin D (VD) in decreasing the risk of infections and mortality in some viral diseases, the role of therapeutic VD supplementation in individuals infected with COVID is still obscure. This article reviews the possible effects of VD on COVID-19 severity. MEDLINE–PubMed, EMBASE, and Cochran were searched following PRISMA guidelines. Some studies have reported that VD does not seem to augment the immunogenicity of seasonal vaccines, nor does it significantly reduce the incidence or duration of upper respiratory tract infection, although others have. The reason for not getting a positive or significant difference may be due to inadequate VD treatment levels, and VD may not be that important in immunized individuals with adaptive immunity. VD deficiency is most prevalent in the elderly, obese, men, ethnic minorities with darker skin, people with diabetes, hypertension, and in nursing homes or institutionalized. These are individuals that are at increased risk of severe consequences of COVID-19 such as acute respiratory distress syndrome with the need for mechanical ventilation and death. Perhaps supplementation of VD to adequate VD levels will improve the inflammatory reaction and modulate a faster patient recovery with decreased morbidity and mortality.

Key-words: COVID-19, SARS-CoV-2; Vitamin D, cholecalciferol.

1. Introduction

The novel coronavirus (2019-nCoV) was detected in December 2019 in a cluster of patients with acute respiratory illness in the Chinese Province of Wuhan [1]. Officially, on January 7, 2020, Chinese health authorities confirmed that 2019-nCoV was present in these patients [2]. Since then, the world saw a rapid spread of this virus infection with pandemic consequences that are causing alarming concerns for health systems worldwide as well as a sense of insecurity and uncertainty in populations from both rich and poor countries, with robust or not health systems [3,4].

At the beginning of February 2020, more than 20,000 cases were confirmed, and the International Committee on Taxonomy of Viruses designated the condition as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the World Health Organization (WHO) officially named the disease as Coronavirus Disease 2019 (COVID-19) [5,6].

COVID-19 belongs to the beta Coronavirus family (Nidovirales order), and is a single-stranded RNA-enveloped virus. Its whole-genome is aligned with the genome of Bat-CoV and Bat-CoV RaTG13 in the bat species *Rhinolophus affinis*. This virus can be transmitted through the conjunctiva, respiratory system, and oral route, by the passage of saliva, respiratory droplets, feces, and urine. Patients may spread the infection before the presentation of the symptoms, during the symptomatic course of the infection, and during the clinical recovery phase. The clinical presentation may vary from asymptomatic to the presence of fever, tiredness, dry cough, dyspnea, muscle or bone ache, headache, loss of taste and smell, to severe pneumonia and severe acute respiratory syndrome (SARS). A worrying fact is that it has a very high transmissibility [7-9] (Figure 1).

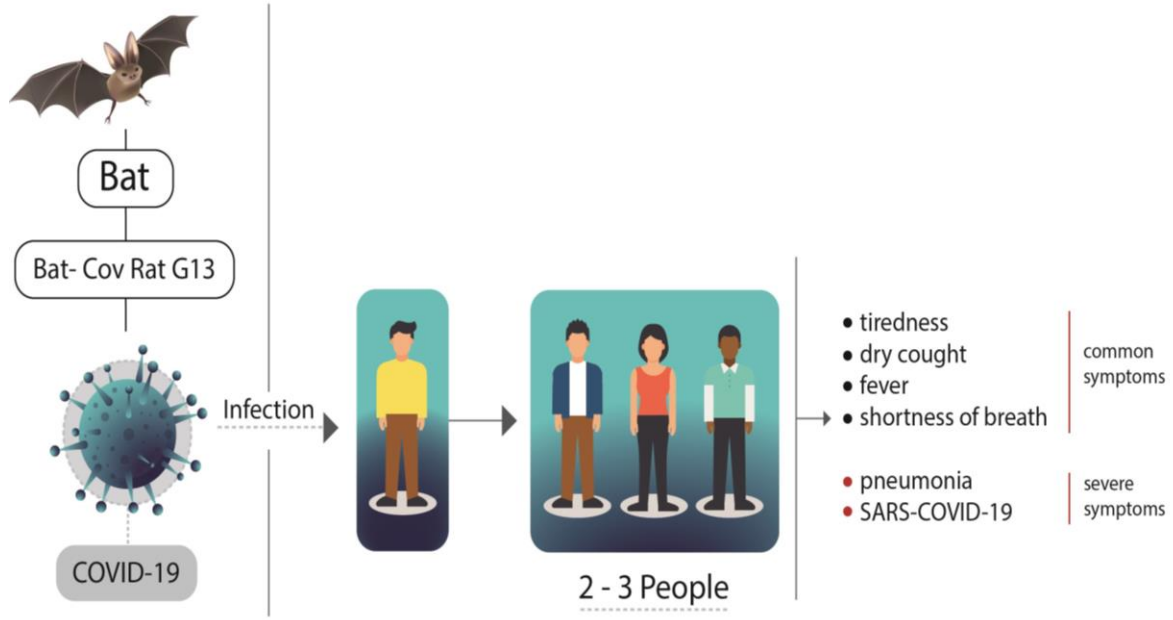

Figure 1. Infection of human beings with COVID-19 and the common and severe symptoms that can be observed.

Vitamin D is a fat-soluble sterol that can be obtained from the diet (ergocalciferol from plant sterols) or can be produced due to direct exposure to sunlight (cholecalciferol). It is linked not just with skeletal and muscle health, but with the modulation of immunity, chronic diseases, and erythropoiesis in bone marrow cells [10-14]

Many authors have considered Vitamin D (VD) to reduce the risk of viral infections and death, possibly due to its actions on the physical barrier, adaptive immunity, and natural cellular immunity. Furthermore, it plays a role in the maintenance of gap, tight, and adherents junctions[7,15]. Vitamin D plays a role as an essential immunologic mediator and low levels of Vitamin D have been associated with autoimmune diseases, cardiovascular diseases and infectious diseases [16,17].

VD also reduces lipopolysaccharide-induced lung injury in mice by blocking effects on the Ang-2-Tie-2 and renin-angiotensin pathways that are highly relevant to Severe Acute Respiratory Syndrome coronavirus2 pathogenicity [18]. A sufficient VD serum level is linked to a switch from a pro to anti-inflammatory profiles in older adults [19]. Heightened immune response in people who are VD deficient may therefore increase the potential for cytokine storm and consequent ARDS [20]. This article reviews the possible effects of VD on COVID-19 infections.

2. Methods

2.1. Focal question

This review was ~~built to~~ carried out to answer the question: *Can vitamin D exert beneficial effects on COVID-19 infections?*

2.2. Language

We included only trials published in English.

2.3. Databases

We consulted databases such as MEDLINE–PubMed (National Library of Medicine, National Institutes of Health), EMBASE, Cochrane, GOOGLE SCHOLAR, and ClinicalTrials.gov. The descriptors used were "*Vitamin D* or *calcitriol* or *25(OH)D3* or *1,25(OH)2D3* and *SARS-CoV-2* or *COVID-19*". These mesh terms enabled the authors to search and identify clinical studies that were related to the objective of this review. PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines [21,22] were followed.

2.4. Study selection

The inclusion criteria were Cohort observational Randomized Clinical Trials (RCTs) and interventional studies. The exclusion criteria were reviews, case reports, editorials, and poster presentations. The eligibility criteria for this review followed the PICO (Population, Intervention, Comparison, and Outcomes) format. (Figure 2 and Table 1).

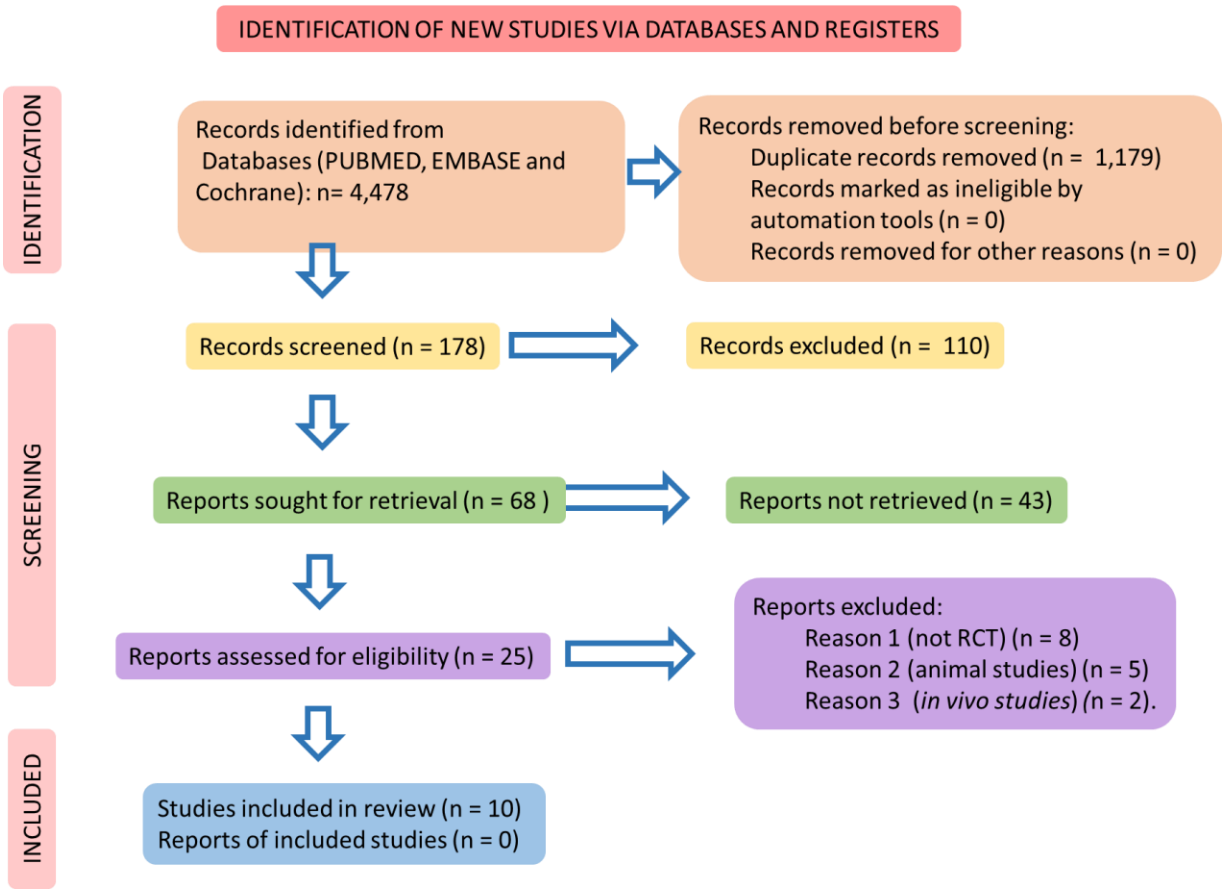

Figure 2. PRISMA flowchart showing the studies selection (Page et al. [12]).

Table 1. Randomized Clinical Trails showing the effects of Vitamin D in Influenza and COVID-19.

Reference	Country	Population	Intervention / Comparison	Outcomes/ estimated study completion
31	India	Asymptomatic or mildly symptomatic COVID-19 VD deficient individuals (36-51y).	Intervention group (n=16) received 60000 IU of VD daily for 7 days and control (n=24) received placebo.	A greater proportion of VD-deficient COVID-19 affected individuals turned negative to the disease. These patients had a significant decrease in fibrinogen due to VD supplementation.
32	USA	Hospitalized patients by COVID-19 infection	Intervention group (n=25) received calcitriol 0.5 µg daily for 14 days or hospital discharge and the control group (n=25) received no treatment.	The VD supplementation significantly improved the oxygenation among treated COVID-19 hospitalized individuals compared to those that received no treatment.
33	Spain	Patients (>18y) with moderate or severe COVID-19 infection that required hospitalization.	Intervention group (n=277) received an oral bolus of VD 100,000 IU at hospital admission and the control group (n=271) received no treatment.	VD bolus of 100,000 IU at hospital admission did not improve the COVID-19 outcomes among the included participants that received this treatment.
34	Russia	Health-care workers (18–65y) under risk of getting COVID-19 infection.	Intervention group I (n=45) received VD 50000 IU twice weekly for two weeks (followed by 5000 IU/day for the rest of the study) and intervention group II (n=46) received VD 2000 IU daily for two weeks.	Neither VD sufficiency nor VD deficiency were associated with SARS-CoV-2 morbidity protection. Participants that received higher doses of VD supplementation had more number of asymptomatic cases.
35	Saudi Arabia	Mild to moderate COVID-19 patients (20-75y) with sub-optimal VD levels.	Patients received 5000 IU/d (n=36) or 1000 UI/d (n=33) of oral VD supplementation / 2 weeks.	Doses of 5000 UI/d of VD supplementation for 2 weeks were more effective to reduce recovery time for cough and gustatory sensory loss among mild to moderate COVID-19 patients with sub-optimal VD levels.
36	Brazil	Patients (56.2±14.4y) that were hospitalized with COVID-19 infection who had moderate to severe illness.	Patients received a single high dose of VD 200000 IU (n=120) or placebo (n=120).	Compared to a placebo, one single dose of 200000 IU of VD did not significantly affect the length of stay at the hospital.
38	India	Confirmed COVID-19 patients (>18y) with hypovitaminosis D and mild to moderate illness were included.	Patients received VD pulse therapy (n=65, 60000 IU daily) or not (n=65) for 8 to 10 days depending on their BMI.	Pulse therapy with VD could effectively reduce inflammatory biomarkers (IL-6 and ferritin) of COVID-19 patients significantly when compared with those who did not receive VD.
39	Mexico	Asymptomatic or mildly symptomatic COVID-19 patients.	Patients received 10000 IU of VD (n=22) or not (n=20) for 14 days.	On the seventh and fourteenth days of supplementation, the supplemented patients had fewer symptoms compared to those non-supplemented.
41	Iran	Patients hospitalized by COVID-19 (≥18y) VD deficiency (<30 ng/mL).	Patients received VD (n=53, 25 µg administered orally) or placebo once daily for 60 days.	VD supplementation was able to improve VD deficiency of the included patients. Additionally, the lymphocytes presentation in the blood of the patients was augmented, categorizing a better immune function.

40	Spain	Patients hospitalized by COVID-19 infection (53±10y).	Patients received VD in higher (n=50, 0.266mg) or not (n=26) in a ratio of 2:1 on days 3 and 7, and then daily until discharge from hospitalization.	The intervention with VD significantly reduced the need for ICU interventions during the hospitalization of the COVID-19 treated patients.

VD: Vitamin D; IBD: Inflammatory Bowel Disease; CRP: C Reactive Protein; GINA: Global Initiative for Asthma (GINA); CACT: Childhood asthma control test; COVID-19: Coronavirus Disease 2019; ICU: Intensive Care Unit; BMI: Body Mass Index; IL-6: Interleukin 6;

2.5. Data extraction

The search included studies published in the past ten years. These studies can all be seen in Table 1.

2.6. Quality assessment

The risk of bias evaluation was performed for each included RCT (detection, selection of the trial, and reporting of bias) according to the Cochrane Handbook for Systematic Reviews of Interventions for quality assessment [23]. Biases can all be seen in Table 2.

3. COVID-19 in a nutshell

Although most patients with COVID-19 infection have mild symptoms, some individuals evolve to a severe condition that can result in death. Most of these patients did not show severe clinical symptoms in the early stages of the infection. These patients suddenly developed a deterioration of their overall health condition that can include acute respiratory failure (viral pneumonitis), acute respiratory distress syndrome (ARDS), and a thrombotic state leading to fast multiple-organ failure and death within a short period of time. Cytokine storm (Figure 3) has been considered to be responsible for this [24-27].

Table 2. Descriptive table showing the biases of the selected randomized clinical trials.

Reference	Question Focus	Appropriate Randomization	Allocation Blinding	Double-blind	Losses (<20%)	Prognostic and Demographic Characteristics	Outcomes	Intention to Treat Analysis	Sample Calculation	Adequate Follow-up
31	Yes	NR	No	No	Yes	Yes	Yes	Yes	Yes	No
32	Yes	Yes	No	No	Yes	Yes	Yes	NR	NR	No
33	Yes	No	No	No	Yes	Yes	Yes	No	NR	No
34	Yes	No	No	No	Yes	Yes	Yes	NR	Yes	No
35	Yes	No	No	No	No	Yes	Yes	Yes	Yes	No
36	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No
38	Yes	NR	No	No	No	Yes	Yes	No	Yes	No
39	Yes	NR	NR	No	NR	Yes	Yes	NR	NR	No
40	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR
41	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	NR	Yes

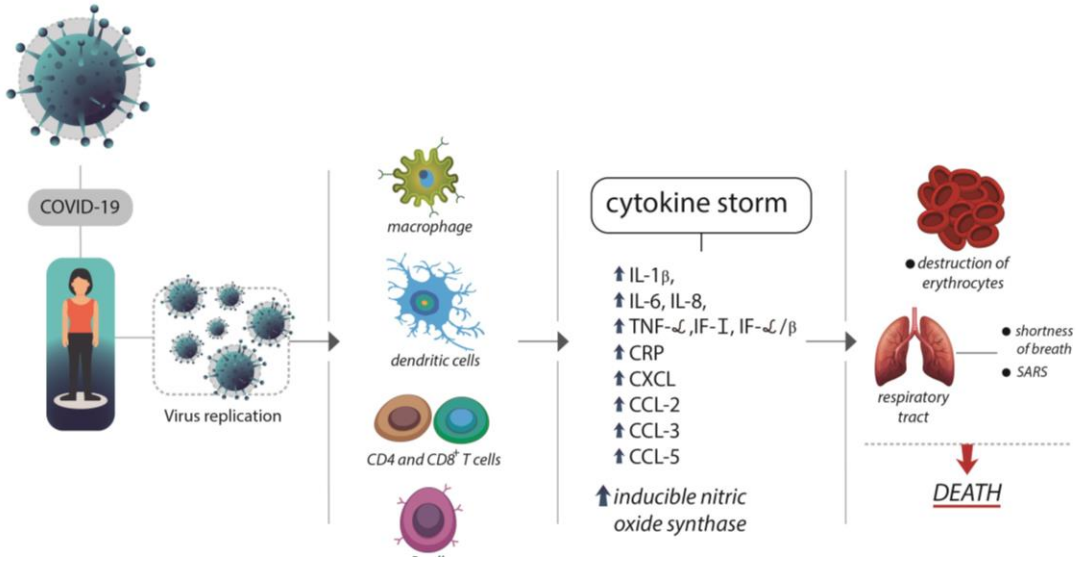

Figure 3. Main aspects of the pathophysiology of COVID-19 and the cytokine storm scenario. CCL: C-C Motif Chemokines Ligand; CRP: C Reactive Protein; IFN-γ, interferon gamma; IL, interleukin; TNF-α: Tumor Necrosis Factor-α.

It is well known that cytokines play a crucial role in the immune response to viral infections. The first line of defense against viral infections is a fast and well-coordinated innate immune response. However, in some circumstances, there is an excessive and unbalanced response of the defense systems leading to an exacerbated release of pro-inflammatory cytokines. This scenario can lead to the immune response of the body responsible for the organ damage and death of COVID-19 infection [28,29].

The renin-angiotensin-aldosterone system (RAAS) plays a role in virus entry to the lungs. SARS-CoV-2 Spike Protein binds with Angiotensin Converting Enzyme 2 (ACE2), on type II pneumocytes, resulting in endocytosis of the virus. After this step, ACE2 is down regulated resulting in accumulation of angiotensin II, since ACE2 metabolizes angiotensin II. In addition to being expressed in type II pneumocytes, the ACE2 molecule is also expressed in other cells, endothelial cells, small intestinal enterocytes, smooth muscle cells, myocardial cells, and proximal renal tubule epithelial cells. Therefore, the receptor for SARS-CoV2 is present in several systems, such as respiratory, gastrointestinal, renal and cardiovascular, thus showing that there may be tropism for different organs. This fact is probably associated with the systemic compromise seen in severe cases of COVID-19 and the possible protective effects of vitamin D may not be restricted to a single system or organ. [30]

4. Vitamin D and COVID infection

We found ten completed Randomized Clinical Trials that showed the effects of VD on COVID-19 in the selected databases (Table 1).

Rastogi et al [31] in a randomized, placebo-controlled study evaluated the short-term supplementation with high doses of VD on asymptomatic or mildly symptomatic COVID-19 VD deficient individuals. The sample comprised 40 individuals that were randomized to receive 60,000 IU of cholecalciferol (oral nano-liquid droplets) with therapeutic target 25(OH)D>50 ng/ml (intervention group) or placebo (control group). This dose led a greater proportion of VD-deficient COVID-19 affected individuals to turn negative to the disease with a significant decrease in fibrinogen level. This was the first study to document the role of therapeutic high dose of daily oral vitamin D supplementation to reach the 25(OH)D >50 ng/ml levels and its effects on COVID-19; however, it carried limitations for only enrolling mildly symptomatic or asymptomatic COVID-19 patients, decreasing its generalizability for severe or moderate symptomatic cases. In addition, it was not double-blinded and the placebo droplet forms were not exactly matched to the VD ones.

Elamir et al [32] evaluated in an open-label, randomized clinical trial the effects of calcitriol supplementation among hospitalized COVID-19 patients. The sample comprised 25 treated (0.5 µg daily for 14 days or hospital discharge, 69 ± 18y) and 25 untreated participants. The results showed

that the supplementation with VD significantly improved oxygenation between the treated participants in comparison with the untreated. However, this study presents limitations such as the absence of a control group that received a placebo. Finally, the patients in the control group had significantly more age (65y) in comparison with the intervention group, which can decrease the study's generalizability as patients above 65 years have more comorbidities than younger patients.

Cannata-Andía et al [33] conducted an open-label, randomized clinical trial to evaluate if only one bolus of VD 100,000 IU could be effective in decreasing COVID-19 outcomes among moderate-severe diseased patients. The results showed that this dose was not effective in improving the disease outcomes. The limitations of this study include: high prevalence of diabetes, hypertension, and obesity comorbidities among the treated patients, which can decrease the study's generalizability. This study has also methodological bias mainly driven by the fact that the VD supplementation and its relationship with the onset of COVID-19 symptoms were not analyzed. The open-label characteristics of this study can also be considered a bias because this study protocol does not carry the aspects of being double-blinded, adding bias to its results.

Karonova et al [34] evaluate the VD supplementation effects among healthcare workers at risk of COVID-19 infection. This study included two groups that were only interventional; the first received VD 50000 IU twice weekly for two weeks (followed by 5000 IU daily for the rest of the study) and the second received VD 2000 IU daily for two weeks. The results showed no significant effects of VD in protecting against COVID-19 morbidity, although higher VD supplemented individuals exhibited more number of asymptomatic cases in comparison with the participants that received lower doses. As possible limitation is the small sample size and the absence of lab baseline data of VD serum levels before randomization. Added to this, this study was open-label and not double-blinded, which can decrease its generatability and increase its biases.

Sabico et al [35] conducted a randomized study comparing the effectiveness of two different doses of VD supplementation on treating mild to moderate COVID-19 patients. A total of 69 patients with confirmed infection by SARS-CoV-2 were randomly divided into two groups to receive once daily either 5,000 IU or 1,000 UI of oral vitamin D3 supplementation for 2 weeks. The dose of 5,000 IU daily showed better results compared to 1,000 IU bringing recovery of COVID-19 symptoms quickly, such as for cough and gustatory sensory loss among patients with sub-optimal VD status. The duration of the intervention and the open label design of the study (absence of a placebo group) represent some of the limitations of the study.

Murai et al [36] in a multicenter, double-blind, randomized, placebo-controlled trial with 120 moderately to severely ill hospitalized COVID-19 patients evaluated the effects of a single high dose of oral dose of 200,000 IU of vitamin D3 or placebo on hospital length of stay. The results showed that, compared to placebo, this intervention with high dose of VD did not significantly affect the length of stay at the hospital. The sample size and the heterogeneity of the sample were some of limitations of this study. A post-hoc analysis [37] of this same research group revealed that in moderate to severe COVID-19 infection a single oral dose of VD 200 000 IU was not able to improve cytokines, chemokines, and growth factors secretion among 101 treated patients. Although it is a post-hoc study, it is derived from a larger multicenter, double-blind, placebo-controlled, randomized, registered clinical trial.

Lakkireddy et al [38] studied the effects of VD supplementation by pulse D therapy in COVID-19 patients with hypovitaminosis D with mild to moderate illness. This study aimed to assess if VD supplementation could effectively reduce inflammatory biomarkers among the treated individuals (60,000 IU daily for 8 to 10 days depending upon their BMI). The results showed significant reductions of inflammatory biomarkers (such as IL-6 and ferritin) among the participants that received VD supplementation and improved their VD serum level to 80-100 ng/ml. The study was performed in a single center and this could represent a limitation of the study.

Sánchez-Zuno et al [39] evaluated the effects of VD supplementation among 42 individuals asymptomatic or mildly symptomatic affected by COVID-19. The results showed that 10,000 IU of daily VD supplementation for fourteen days were significant to raise VD serum concentrations and to decrease symptoms associated with the disease when compared to the placebo group. Information on the adequate concentrations of VD supplementation in the Mexican population is scarce and this was the first study to report baseline VD status in COVID-19 outpatients in Mexico. Some of the limitations to this study are related to the sample

size, short intervention period, and the design of the study (not a double-blinded study).

In a randomized, open-label clinical trial, Entrenas Castillo et al [40] evaluated the effects of VD supplementation among 76 individuals hospitalized with COVID-19 that were receiving the best available therapy in the intensive care unit (ICU) in the year 2020. Patients were randomized in two groups. The treatment group received soft capsule of calciferol (0.532mg) on the day of admission and continued with oral supplementation (0.266mg) on day 3 and 7 and then weekly until discharge or ICU admission. The results demonstrated that calciferol supplementation in patients hospitalized with COVID-19 was effective in reducing the severity of the disease and the need for ICU treatment. However, this study has some limitations related to the study design (not double-blinded placebo controlled), the variability of the period of supplementation, and not considering obesity as a risk factor for COVID-19 severity.

In a randomized, double-blind, placebo-controlled clinical trial, Maghbooli et al [41] evaluated if VD supplementation among 53 COVID-19 infected and hospitalized individuals could improve lymphocyte presence in the blood samples of the participants. All the 106 participants had VD deficiency and were randomized into two groups: intervention and control. The intervention group received orally 25 µg of VD administered once daily and the control group received a placebo for two months. The results demonstrated that VD supplementation did not only improved VD deficiency but also increased lymphocytes percentage in the blood samples of the analyzed patients, contributing to a better immune function. However, this study has some limitations related to its sample size, such as a high number of follow-up losses and age disparities between the groups (control and intervention) and intra-groups (males and female participants).

Other studies have been designed to assess COVID-19 infection severity in comparison with baseline VD statuses [42]. Dror et al [43] demonstrated that lower VD status was more commonly associated with the severe or critical disease among patients with COVID-19. These authors assessed data from more than 250 medical records. Maghbooli et al [44] analyzing medical records from 235 patients assessed that VD levels of at least 30ng/mL were associated with reduced risk for adverse outcomes among individuals with COVID-19. These results, in addition to the results of Jolliffe's et al [45] meta-analysis, confirm the idea that VD supplementation against viral diseases can be safe. Jain et al [46] also showed that VD levels were markedly low in severe COVID-19 patients and that in these initials the inflammatory response against the virus is more prominent, causing more damage and being more associated with higher mortality rates.

A recent large cross-sectional clinical trial, case control studies, and meta- analysis have all shown higher respiratory infection rates in individuals with low VD levels [47-50]. These studies have also shown that VD supplementation seems to help reduce the symptoms and antibiotic use [51,52]. This suggests that VD deficiency may have a small impact on the development of viral upper respiratory infections, but its impact on modulating the immune system to have a healthier immune response may lead to decreased lung injury, death, and the length of illness

It is noteworthy to say that concentrations of VD tend to be reduced with age due to the reduction of time spent in the sun, reduced levels of 7-dehydrocholesterol in the skin, decreased gastrointestinal absorption and intake. In addition, many drugs typically used by older people can reduce the serum levels of the VD. This may be a relevant factor since there is an increased mortality rate seen in the elderly with COVID-19, particularly in those that are ill who tend to be on multiple medications and spend less time outdoors [27,53,54].

There is also increased mortality seen in darker skin individuals with COVID-19, African Americans and Latinos, who tend to have lower VD levels due to their skin pigmentation blocking UVB light needed to synthesize cholecalciferol [55] and darker skin individuals and the elderly are also more likely to have hypertension and diabetes, a risk factor for increased morbidity and mortality from COVID-19 [56]. Individuals with diabetes, hypertension and visceral insulin resistant adiposity syndrome (VIRAS/Metabolic Syndrome) are also more likely to have decreased serum VD levels.

A recent study shows that, counter intuitively, countries at lower latitudes, typically sunny countries, such as Spain and Northern Italy, had low concentrations of VD. These countries also experienced the highest infection and death rates in Europe. The northern latitude countries of Norway, Finland, and Sweden have higher VD levels despite less UVB sunlight exposure, because supplementation and fortification of foods is more common. These Nordic countries have lower COVID-19 infection and death rates. The correlation

between low VD levels and death from COVID-19 is statistically significant [56].

A cohort study conducted by Meltzer et al [57] with 489 patients who had a VD level measured in the year before COVID-19 testing showed a relative risk of 1.77 greater of ~~testing positive for~~ COVID-19 ~~in~~ patients with VD deficient status compared with patients with normal VD status. Then again, Katz et al [58] reported that patients with VD deficiency were 4.6 times more likely to have a positive COVID-19 test result than patients with no VD deficiency. In addition, other recent cohort and retrospective observational studies of COVID-19 hospitalized patients showed an inverse association between 25(OH)D levels and in-hospital mechanical ventilation and mortality (74,75).

While the benefit of VD supplementation is not very clear in critically ill patients, there is evidence to suggest that VD may suppress the inflammatory cascade that mediate severe outcomes from COVID-19 when given to adequate levels prior to infection [59].

In summary, it is known that people around the world tend to have insufficient plasma levels of VD. The modern lifestyle offers many benefits, but there is more time spent indoors leading to less VD production. Another reason for this, is that sun exposure is related to premature skin aging and skin cancer, leading people to use sun blockers frequently which prevent skin production of VD. People also tend to not consume foods with VD, particularly the elderly. The aging skin of the elderly also favors hypovitaminosis D. During the winter, there is also a significant decrease in the production of VD due to a lack of UVB exposure from the sun and decreased skin temperature. This led us to question whether the increase in some seasonal winter infectious diseases and their severity have an association with VD deficiency. Data now suggests that individuals and countries with higher VD levels are less likely to have more severe disease. Furthermore, VD deficiency is most prevalent in the elderly, obese, men, ethnic minorities with darker skin, people with diabetes, hypertension and in nursing homes or institutionalized [60]. These are the same groups of individuals that are at increased risk of severe consequences of COVID-19 such as pneumonia and ARDS which are associated with mechanical ventilation and death [61,62].

5. The other side of the coin

Despite the positive effects of VD in some of the RCT discussed above and the literature review performed by Lee [12] there is no consensus on the role of VD in the treatment of diseases produced by viral infections. For example, the use of VD failed to inhibit human cytomegalovirus replication in human foreskin fibroblasts; showed no significant reduction in mortality of HIV patients; weak association with virological characteristics in Hepatitis C; and did not show a beneficial effect in the development of acute bronchiolitis resulting from infection of respiratory syncytial virus. The full panorama of the immunomodulatory actions of VD in different viral infections is still to be determined. Unfortunately, these studies also failed to correlate the dose of VD given with an adequate blood level of 25(OH)D3, as mentioned above.

Bianconi et al 2021 [63] evaluated theprevalence of VD deficiency and its prognostic impact on patients hospitalized with COVID-19 and found that, regardless of the potential usefulness of Vit-D measurement to guide appropriate supplementation, Vit-D does not appear to provide helpful information for the stratification of in-hospital prognosis in patients with COVID-19.

6. Conclusion

Vitamin D may play an immunomodulatory role in decreasing lung damage from COVID-19. Perhaps supplementation of VD would reduce the inflammatory reaction and modulate a faster patient recovery and maybe should be considered an additional tool to fight against COVID-19. More studies using adequate VD supplementation to adequate levels will be needed to determine this.

For now, we would recommend supplementation with VD to a serum VD levels greater than 30ng/mL but preferable between 40-60 ng/mL which would require potentially higher dosages of VD supplementation than are currently stated in some guidelines (5,000 IU per day or more in adults, particularly in obese individuals). The risk of VD toxicity to this level of supplementation is low and the above stated dosage of Vitamin D3 is readily available and inexpensive over the counter.

Our results show that are necessary larger studies that could the effects of VD on SARS-CoV-2 or other viral infections such as influenza. Improvement of triage could reduce bad outcomes such as morbidity and mortality by identifying patients at increased risk to develop severe viral infection. This is critical in the current COVID-19 pandemic and seasonal influenza infection, but also essential in future pandemics or other viral infections.

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