COVID-19 Disease and Vitamin D: A Mini-Review

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Novel coronavirus disease (COVID-19) pandemic caused by SARS-CoV-2, for which there is no effective treatment except employing prevention strategies, has already instituted significant number of deaths. In this review, we provide a scientific view on the potential role of vitamin D in SARS-CoV-2 virus/COVID-19 disease. Vitamin D is well-known to play a significant role in maintaining the immune health of an individual. Moreover, it induces antimicrobial peptide expression that can decrease viral replication and regulate the levels of pro-inflammatory/anti-inflammatory cytokines. Therefore, supplementation of vitamin D has the potential to reduce the incidence, severity and the risk of death from pneumonia resulting from the cytokine storm of many viral infections including COVID-19. We suggest that supplementation of subjects at high risk of COVID-19 with vitamin D (1.000 to 3.000 IU) to maintain its optimum serum concentrations may be of significant benefit for both in the prevention and treatment of the COVID-19.

Keywords: SARS-CoV-2, COVID 19, respiratory tract infection, vitamin D3, vitamin D3 receptor

INTRODUCTION

The occurrence of respiratory tract infections (RTI) is more common in winter, especially in the northern regions, than in the summer months (Hope-Simpson, 1981). This also applies to the rapidly spreading in the winter period around the world of the infectious Coronavirus disease 2019 (COVID-19) which became a pandemic, since the virus is more easily transmitted at low temperatures (Qu et al., 2020; Sajadi et al., 2020). This rises the possibility that insufficient intake of vitamin D3 may have a role in the development and severity of COVID-19. Thus, in order to curb the current pandemic of COVID-19, it is opined that the administration of an adequate amounts of vitamin D3 may stem the current situation till an effective therapy, chemoprophylaxis, and vaccination is developed.

Deficiency of vitamin D3 in all age groups is a public health problem (Palacios and Gonzalez, 2014) that is well recognized. It is estimated that more than one billion people suffer from vitamin D3 deficiency (Van Schoor and Lips, 2011). Several previous studies suggested that there is an independent association between low plasma concentrations of 25-hydroxyvitamin D3 and susceptibility to acute respiratory infections (Cannell et al., 2006). Vitamin D3 deficiency has been associated with many diseases including but not limited to type 2 diabetes mellitus, heart disease, stroke, autoimmune diseases, asthma and RTIs (Hollick, 2007; Hollick, 2017). The relation...
between low levels of vitamin D₃ and infection with bovine diarrhea virus in calves has been well established (Nonnecke et al., 2014). It is evident that in winter due to the shorter time spent in the sun, the plasma levels of vitamin D₃ is likely to be low (Berardi and Newton, 2009; https://www.medlineplus.gov/vitaminD.html). This is especially evident in countries such as the United States of America (USA), United Kingdom (UK), Switzerland, Italy, Spain, Iran, France, Turkey, etc. It is rather interesting that COVID-19 pandemic and its high mortality (Pharmacy Times, 2020; https://www.pharmacytimes.com/publications/issue/2010/february2010/ofcfocusvitamind-0210) has been reported in these countries. According to the US National Center for Health Statistics, approximately 70% of the population may be deficient in vitamin D₃ and surprisingly while the United States is presently the most affected by COVID-19 (Kmieć et al., 2014). This is in line with the current proposal that severe acute respiratory syndrome due to SARS-CoV-2 and its associated high mortality rate may be as a result of vitamin D₃ deficiency. Furthermore, vitamin D₃ deficiency is known to elevate with increasing age and comorbidities that are associated with lower vitamin D₃ levels.

In the current review, we present a scientific rationale on the potential relationship between vitamin D₃ content and higher incidence of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) virus infection. Moreover, our review also summarizes the current understanding of the link among vitamin D₃, the immune system, and respiratory infections.

**VITAMIN D AND IMMUNE SYSTEM**

Vitamin D is a pluripotent hormone that modulates the innate and adaptive immune responses (Rezaei, 2018). Vitamin D could play a decisive role in the proliferation and immunomodulation of cells, affecting several immune pathways enhancing the protective properties of the mucous membranes of the body and inhibiting excessive inflammation (D’Ambrosio et al., 1998; Khare et al., 2013; Parlak et al., 2015). Immunocytes such as macrophages, B and T lymphocytes, neutrophils and dendritic cells express Vitamin D₃ receptors (VDRs) that is enable to the actions of vitamin D (Di Rosa et al., 2011). The active metabolite of vitamin D lead to the activation of VDRs that can form Retinoid X Receptor (RXR) heterodimer that, in turn, influences the proteins of the innate and adaptive immune system (the regulatory T cells, defensins, cytokines, pattern recognition receptors, etc.) (Chun et al., 2014).

The immune system is influenced in various ways by both vitamin D₃ and its metabolite 1,25-hydroxy-vitamin D₃, 1,25-hydroxy-vitamin D₃ rigorously regulates antimicrobial peptides such as defensin and cathelicidin (Adams et al., 2009). Cathelicidin possesses an antimicrobial function against mycobacteria, Gram-positive and Gram-negative bacteria due to its ability to destroy cell membranes. 1,25-hydroxy-vitamin D₃ has antiviral effect against adenovirus, herpes simplex virus, enveloped and non-enveloped retroviruses, and fungi (Herr et al., 2007). By damaging cell membranes, these peptides penetrate infected cells and neutralize the action of endotoxins (Agier et al., 2015). For instance, the IL-37, antimicrobe peptide, has antibacterial and antifungal properties by virtue of its ability to disrupt the integrity of the cell membrane and proton gradient (Bals and Wilson, 2003) by vitamin D₃ (Howell et al., 2004; Leikina et al., 2005; Steinstraesser et al., 2005; Bergman et al., 2007). In addition, vitamin D₃ inhibits the production of pro-inflammatory cytokines and augments that of anti-inflammatory cytokines (Gombart et al., 2020). Thus, vitamin D₃ influences the incidence and severity of viral infections by altering the production of pro-inflammatory cytokines. There is reasonable evidence to suggest that vitamin D₃ can inhibit the transcription induced by tumor-necrosis-factor-α (TNF-α) in latently infected cells by human immunodeficiency viruses (HIV) (Nunnari et al., 2016). These and other results suggest that vitamin D₃ can inhibit the production of inflammatory cytokines and chemokines such as TNF-α, interferon-β (IFN-β), interleukine (IL)-8, IL-6 and Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted (RANTES) (Hansdottir et al., 2010; Khare et al., 2013). Increase in mortality in those with COVID-19 is due to acute respiratory distress syndrome (ARDS) due to unantagonized production of pro-inflammatory cytokines IL-6 and TNF-α. Vitamin D₃ has a decisive role in the regulation of the innate and adaptive immune responses implying that adequate intake of vitamin D₃ may protect patients with COVID-19 at least, in part by inhibiting the excess production of IL-6 and TNF-α (Daneshkhah et al., 2020). Vitamin D₃ can also contribute to the modification of the antiviral response by enhancing the secretion of pro-inflammatory chemokines (C-X-C Motif Chemokine Ligand 8, CXCL8 and C-X-C Motif Chemokine Ligand 10, CXCL10) (Brockman-Schneider et al., 2014). Lytic phase of cytomegalovirus (CMV) replication can be induced by vitamin D₃ in vitro (Wu and Miller, 2015).

Vitamin D₃ promotes immunoglobulin and complement-mediated phagocytosis by stimulating the maturation of monocytes to macrophages. In addition, vitamin D₃ maintains self-tolerance by reducing a hyperactive adaptive immune system (Bowie and Unterholzner, 2008). Vitamin D₃ reduces the replication of influenza A (Barlow et al., 2011), rotavirus (Zhao et al., 2019) and dengue microbes (Martínez-Moreno et al., 2019). These results imply that excess innate immune response induced by viral and other microbial infections seen in patients with SARS-CoV-2 and associated cytokine storm can be effectively reduced by vitamin D₃ (Huang et al., 2020). The immunomodulatory effect of vitamin D₃ on viral infections appears to be temporary and at least, this in part could be attributed to its immunomodulatory role in viral infections is rather complex and depends on the nature of the pathogen and the type of immune function that is needed to resolve the disease process (Sacco et al., 2012; Gotlieb et al., 2018).

There is reasonable evidence to suggest that vitamin D₃ modulates adaptive immune responses by inhibiting the Th1 cell function that leads to a reduction in the production of TNF-α, IL-2, granulocyte macrophage colony-stimulating factor and IFN-β 1,25-(OH)₂-Vitamin D₃ enhances the action of Th2 cells and production of their anti-inflammatory cytokines, IL-
4, IL-5, and IL-10 (Hughes and Norton, 2009). In addition, supplementation of vitamin D3 increases the number of regulatory T cells (Treg cells), suppresses IgG production and differentiation of dendritic cells (Kamen and Tangpricha, 2010; Aranow, 2011; Rondanelli et al., 2018). 1,25-(OH)2-Vitamin D3 inhibits the proliferation and activation of T cells and T and B lymphocytes (Martineau et al., 2017). Thus, vitamin D3 suppresses T-cell-mediated inflammation and promote the proliferation of Treg cells that results in an increase in the production of IL-10 that leads to suppression of inappropriate inflammation (Adorini and Penna, 2009; Chun et al., 2014). Vitamin D3 can also increase the expression of glutathione reductase and glutamate–cysteine ligase modifier subunit (Lei et al., 2017) that may lead to a decrease in oxidative stress. These results led to the proposal that (Biancatelli et al., 2019; Mousavi et al., 2019; Wimalawansa, 2020) vitamin D3 may be of benefit to combat SARS-CoV-2 infection (Grant et al., 2020a).

Vitamin D deficiency is common in patients with HIV (Herr et al., 2007). The antiviral action of vitamin D3 can also be attributed to its ability to increase the production of cathelicidin and defensins (Herr et al., 2007; Hughes and Norton, 2009; Beard et al., 2011). Furthermore, 1,25-dihydroxy-cholecalciferol is known to regulate more than 200 genes including those responsible for cell proliferation, differentiation, and apoptosis (Umar and Sastry, 2018) including those involved in immune homeostasis (Van Herwegen et al., 2017). Recent meta-analysis of randomized controlled trials (RCTs) showed that vitamin D deficiency increases the overall mortality (Bjelakovic et al., 2014; Keum et al., 2019; Manson et al., 2019; Scragg, 2020). All above-mentioned effects of Vitamin D3 are presented in Table 1.

### RELEVANCE OF VITAMIN D REGARDING TO RESPIRATORY TRACT INFECTIONS AND INFLUENZA

There is a provided evidence given by many reviewed studies to support the hypothesis that higher serum level of vitamin D3 is associated with a low risk of microbial infections and deaths from RTIs caused by pneumonia and influenza. In addition, SARS-CoV-2 infection and decrease the severity and mortality may be avoided by a normal serum vitamin D3 levels (Wimalawansa, 2020). Unfortunately, there are no standard recommendations regarding the dose and the desired optimal concentration of vitamin D3 required to protect people from RTI during the winter season.

Epidemiological studies revealed that vitamin D3 plays a critical role in viral RTIs and associated acute lung injury (Hansdottir and Monick, 2011). In a recent meta-analysis, it has been shown that a daily or weekly vitamin D3 dose between 20 and 50 μg resulted in a significant reduction of RTIs (Martineau et al., 2017). A high-dose, isolated, or added bolus of (2.5 mg once or monthly) did not reduce the risk. One study supplemented for one-year high risk individual for ARDS with a 100 μg/daily (Bergman et al., 2012). The overall infection score was significantly reduced in the treated groups, and those with vitamin D3 deficiency showed the greatest benefit of the supplementation.

In addition, it is observed that the degree of protection generally increases when the concentration of vitamin D3 reaches its optimal range of 40 to 60 ng/ml. To reach this level, an individual must take between 2,000 and 5,000 IU/day of vitamin D3 (Heaney et al., 2003). Calcitriol protects against acute lung injury by modulating the expression of the renin–angiotensin system including angiotensin-converting enzyme 2 (ACE2) in lung tissue (Xu et al., 2017). There seems to be a direct relationship between plasma 25-(OH)-Vitamin D3 concentrations and severity of COVID-19 (Huang et al., 2020; Wang et al., 2020; Zhou et al., 2020). It is noteworthy that the expression of the DPP-4/CD26 receptor is significantly reduced as a result of vitamin D3 deficiency (Komolmit et al., 2017). Furthermore, adequate provision of vitamin D3 seems to attenuate immunological events that may lead to prolonged interferon-gamma response (Zdrenghe et al., 2017), and persistent interleukin six elevation that are negative prognostic value indicators in those with severe COVID-19 (Mirolaee et al., 2018).

VDRs are very widely distributed in respiratory epithelial cells and immune cells (B cells, T cells, macrophages and monocytes). VDRs are in the epithelium of the bronchi and immune cells (Pfeiffer and Hawrylowicz, 2012). The enzyme, 1α-hydroxylase (CYP27B1), required for vitamin D activation, is induced by diverse stimuli, including cytokines and toll-like receptor ligands in the respiratory tract. Nevertheless, adequate serum levels of 25-(OH)-vitamin D3 is required to increase levels of 1,25-(OH)2-vitamin D3 and to improve the immune response to respiratory virus infections (Greiller and Martineau, 2015). The development

| Immune cell type | Effect of vitamin D | References |
|------------------|---------------------|------------|
| Airway epithelium | Increases CD14 and cathelicidin, dampens IFN-γ and chemokine response during viral infection | Hansdottir et al. (2010) |
| Alveolar macrophages | Increases the antimicrobial peptide cathelicidin | Liu et al. (2007) |
| Dendritic cells | Inhibits dendritic cell differentiation, maturation and function, decreases IL-12 and increases IL-10, alters T cell activation | Penna and Adorini (2000); Piemonti et al. (2000); Fritsche et al. (2003); Sigmundsdottir et al. (2007) |
| T lymphocytes | Inhibits proliferation, modulates cytokine production - inhibits Th1 and Th17 cytokines but induces Tregs | Lemire et al. (1995); Penna and Adorini (2000); Sigmundsdottir et al. (2007); Daniel et al. (2008); Mora et al. (2008) |
| B lymphocytes | Inhibits proliferation of activated B cells and generation of plasma cells | Chen et al. (2007) |
of ARDS shows typical changes in membrane permeability of the alveolar capillary, progressive edema, severe arterial hypoxemia and pulmonary hypertension (Matthay et al., 2012). In animal studies, vitamin D₃ significantly attenuated lung damage caused by lipopolysaccharides (LPS) (Xu et al., 2017). This is noteworthy since LPS increase the pulmonary expression of renin and angiotensin 2 (Ang 2) that promotes inflammation. Vitamin D₃ reduces the increased renin and Ang 2 expression and thus significantly lowers lung injury. It has been suggested that vitamin D₃ promotes ACE2/Ang 1–7 activity. This is supported by the observation that calcitriol treatment significantly increased the expression of VDR mRNA and ACE2 mRNA that leads to a reduction in angiotensin II, ACE2 expression resulting in suppression of inflammation (Yang et al., 2016). VDRs are not only a negative regulator of renin, but also of NF-κB (Li et al., 2004), leading to an increase in Ang 2 formation, which promotes inflammation and vascular permeability, reduced lung function) and associated RAS dysregulation leads to increased inflammation, unfavorable pregnancy and birth outcomes and type 2 diabetes mellitus (Grant et al., 2020b). From another analysis it is suggested that optimal vitamin D₃ standard should be 40–60 ng/ml for prevention of breast and colorectal cancer (Garland et al., 2009).

The U.S. Institute of Medicine noted that no research observed negative consequences of supplementation of vitamin D₃ of less than 10,000 IU/daily, but set the upper consumption limit at 4,000 IU/daily, partially owing to retrospective tests that found U-shaped 25-(OH)-vitamin D₃ concentration/health outcome relationships. However, further findings indicate that most observations of J- or U-shapes relationships came from observational studies that did not test serum 25-(OH)-vitamin D₃ concentrations, and that the likely explanation for these relationships was the presence of some participants who started taking vitamin D₃ complementation shortly before registration (Grant et al., 2016). Particularly in winter, supplementation with vitamin D₃ is required for many individuals to reach concentrations of 25-(OH)-vitamin D₃ above 30 ng/ml (Pludowski et al., 2018). However, vitamin D₃ fortification of basic foods such as dairy and flour products may increase serum 25(OH)D concentrations by a few ng/ml among those members of different populations with the lowest concentrations (Pilz et al., 2018; Grant and Boucher 2019).

Table 2 describes the findings from meta-analyses that vitamin D₃ is protective against acute RTI, particularly in patients with vitamin D₃ deficiency.

HYPOTHESIS OF THE CORRELATION ON VITAMIN D₃ LEVELS AND CORONAVIRUS DISEASE-19 CASES/SEVERITY

Still there is a lack of a cohort studies and clinical trials in determining the role of vitamin D₃ in the prevention of COVID-19 infections and/or severity. Some retrospective studies have demonstrated the relationships between vitamin D₃ levels and COVID-19 cases and severity (Table 3). For example, a preliminary information study from Philippines on 212 reported COVID-19 patients, found that the severity of the infection is a highly correlated to the
vitamin D₃ levels (Alipio, 2020). Authors have found that 85.5% of patients with an adequate status of vitamin D₃ (>30 ng/ml) showed a moderate disease, while a 72.8% of patients with vitamin D₃ deficiency (<20 ng/ml) had the serious disease symptoms (Alipio, 2020). The correlation between vitamin D₃ and COVID-19 have extensively investigated in a group of 178 Indonesians (Raharusun et al., 2020). According to this study, the patients with vitamin D₃ levels in the categories, 20–30 and <20 ng/ml, were 12.55 times and 19.12 times more likely to die from COVID-19, respectively, as compared with COVID-19 patients with sufficient levels of vitamin D₃. The main conclusion is that, even after controlling for age, sex and comorbidities, deaths were 10.12 times more likely in patients with vitamin D₃ deficiency than in patients with normal vitamin D₃ levels (Raharusun et al., 2020). A limited cohort observational study with 43 cases in Singapore have found that a treatment of COVID-19 patients with an oral doses of vitamin D₃ (1,000 IU), Mg (150 mg), and vitamin B₁₂ (500 μg) significantly reduced the application of the subsequent oxygen therapy compared to controls (3/17 vs. 16/26, p = 0.006) (Tan et al., 2020). Furthermore, such drugs combination have protected against the clinical deterioration (p = 0.041) even after adjustment of confounders (age, sex and comorbidity) (Tan et al., 2020). Severe COVID-19 patients and patients with pre-existing medical conditions were reported to have low levels of vitamin D₃ (Glicio et al., 2020; Lau et al., 2020). A retrospective observational study with 186 positive cases and 2,717 negative controls in Belgium have demonstrated a low median for vitamin D₃ in the COVID-19 patients compared to the control subjects (p = 0.0016) (De Smet et al., 2020). A retrospective cohort study with 780 cases in Indonesia showed that below-normal vitamin D₃ levels and the pre-existing medical conditions in the older and male cases have higher odds of death. Moreover, the vitamin D₃ status has a strong relationship with COVID-19 mortality if it adjusted for age, sex and comorbidities (Raharusun et al., 2020). The similar retrospective study in the USA with many cases have showed that the reduced risks for both COVID-19 cases and the mortality are possibly associated with the sunlight and vitamin D₃, as well with the latitude as an indicator (Li et al., 2020).

In a new systematic review and meta-analysis with an ecological approach, they found a high percentage of COVID-19 patients who suffer from vitamin D₃ deficiency or insufficiency. Much more important its ecological investigation resulted in the substantial direct and reverse correlations between the recovery and mortality rates in COVID-19 patients with vitamin D₃ deficiency at the different countries. A small reverse correlation between vitamin D₃ status and the mortality rate have found globally. The populations with a lower levels of vitamin D₃ might be more susceptible to the novel coronavirus infection (Ghasemian et al., 2020). Recently, a cohort study of 489 patients who had a vitamin D₃ levels detected in the year before COVID-19 testing was 1.77 times greater for patients with vitamin D₃ deficiency compared to the patients with a normal vitamin D₃ status. These findings appear to support a role of vitamin D₃ status for the COVID-19 risk (Meltzer et al., 2020).

The hypothesis that supplementation with vitamin D₃ may reduce the risk of influenza and COVID-19 disease, as well the death should be examined in the trials to evaluate the correct doses, the serum 25-(OH)-vitamin D₃ concentrations and the existence of any health concerns. There are a good model from Atlanta and Georgia in which have done the RCT on vitamin D₃ supplementation for the ventilated ICU patients (Han et al., 2016). There is a recommendation to take a vitamin D₃ at 10,000 IU/day as an acceptable dose to raise circulatory concentration of vitamin D₃ to the optimum range of 40–60 ng/ml; after 1 month this dose should be lowered to 5,000 IU/day to the sustain serum rate (Ekwaru et al., 2014; Shirvani et al., 2019). A recent study have suggested a loading doses of 200,000–300,000 IU of vitamin D₃ to reach the optimum serum range, thereby the reducing of the risk/severity for COVID-19 (Wimalawansa, 2020).

The observation that normal vitamin D₃ status is important for the immune system as well as for the regulation of SAR should lead to a correction of vitamin D₃ status if a deficiency has been detected. There is no experience with the use of vitamin D₃ in COVID-19. In addition, it should be noted that a very high doses of the upper limit of 4,000 IU (100 μg) per day of vitamin D₃ still have the risks and may be dangerous. Since such doses might result in to the improvements in the VDR competency and could have an inhibitory impact on the immune function (Mangin et al., 2014).

**CONCLUSION**

It is evident from the preceding discussion that vitamin D₃ may be of benefit in COVID-19. Since the higher plasma concentrations of vitamin D₃ is better for the protection from
| Country | Population type | n   | Study design          | Vitamin D<sub>3</sub> doses | Outcomes                                                                                                                                                                                                 | Reference            |
|---------|-----------------|-----|-----------------------|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Singapore (a tertiary academic hospital) | Adults, age ≥50 years | 43  | Cohort observational  | Vitamin D<sub>3</sub> 1,000 IU, Mg 150 mg, and vitamin B<sub>12</sub> 500 μg (oral)                                                                 | i) A fewer patients who received vitamin D<sub>3</sub>, Mg and vitamin B<sub>12</sub> required the subsequent oxygen therapy compared to controls (3/17 vs. 16/26, p = 0.006)  
ii) in multivariate analysis, the patients treatment with vitamin D<sub>3</sub>, Mg and vitamin B<sub>12</sub> have showed a significant protective effects against clinical deterioration (p = 0.041) after adjusting for age, gender and comorbidities | Tan et al., 2020      |
| 20 European countries | Adults | Cases and death/1 M population | Retrospective | NA | A significant negative correlation was observed for the serum 25-(OH)-vitamin D<sub>3</sub> levels with COVID-19 cases (p = 0.033) but not with a death (p = 0.123) per million of population | Present study         |
| 20 European countries | Adults | Cases and death/1 M population | Retrospective (as of 8 April 2020) | NA | A negative correlation was observed between the serum 25-(OH)-vitamin D<sub>3</sub> levels and COVID-19 cases (p = 0.050) and a death (p = 0.053) per million of population  
i) The differences in the levels of vitamin D<sub>3</sub> mean were significant within the mild, ordinary, severe and critical cases of COVID-19 (p < 0.001)  
ii) Vitamin D<sub>3</sub> status showed a significant association with clinical outcomes (p < 0.001) | Ilie et al. (2020)     |
| Southern Asian countries | NA | 222 | Retrospective multicentral study | NA | i) Severe patients had a low level of vitamin D than mild patients  
ii) Subjects with the pre-existing medical conditions had a low level of vitamin D<sub>3</sub> | Alpio (2020)          |
| USA (a single tertiary academic medical center) | Adults, mean age 65.2 years | 20  | Retrospective observational study | NA | A high vitamin D<sub>3</sub> insufficiency was observed in ICU patients (84.6%) than in the floor patients (57.1%) (p = 0.29) | Lau et al. (2020)     |
| South Asia (two tertiary medical centers) | Adults, age ≥60 years | 176 | Retrospective | NA | i) Vitamin D<sub>3</sub> levels showed a significant association with COVID-19 infection in an univariate analysis (p = 0.013) but not after an adjustment for confounders (p = 0.208)  
ii) Ethnicity showed a significant association with COVID-19 infection univariably | Glicio et al. (2020)  |
| UK (UK Biobank data 2006–2010 for vitamin D<sub>3</sub> and ethnicity) | Adults, age 37–73 years | 449 | Cross-sectional (16 March–14 April 2020) | NA | (Continued on following page) | Hastie et al. (2020)  |

(Continued on following page)
| Country | Population type | n | Study design | Vitamin D3 doses | Outcomes | Reference |
|---------|----------------|---|--------------|-----------------|----------|-----------|
| United Kingdom (UK Biobank data 2006-2010 for BMI, vitamin D3 and ethnicity) | Adults, mean age 57.7 years | 580 cases and 723 control | Retrospective | NA | i) No significant difference was observed for vitamin D3 levels between COVID-19 cases and the control group  
ii) Vitamin D3 status was significantly lower in those of Asian, Black and mixed ethnicity (p < 0.0010) compared with those of White ethnicity  
iii) Vitamin D3 levels were significantly lower in those with obesity (p < 0.001). Overweight or obese person; living in London; being male and being of Asian, Black or mixed ethnicity was associated with a higher odd of positive cases  
iv) In the regression model, the interaction between BMI and vitamin D3 status did not predict the test result in the available data set | Darling et al. (2020) |
| Mainland of United States (48 states and Columbia district) | 1,609,488 cases and 51,094 deaths | - | Retrospective (22 Jan–23 May 2020) | NA | i) Latitudes were marginally associated with the cases (p = 0.0792) and the deaths (p = 0.0599)  
ii) Sunlight and vitamin D3, with latitude as an indicator, possibly associated with reduced risks for both COVID-19 cases and mortality | Li et al. (2020) |
| Belgium (central network hospital) | Adults, median age 71 years (cases), 68 years (control) | 186 cases, 2,717 controls | Retrospective observational (1 March–7 April 2020) | NA | i) Patients with COVID-19 had significantly a low median value of vitamin D3 and higher vitamin D3 deficiency compared to control subjects (p = 0.0016, p = 0.0005, respectively)  
ii) This difference were more pronounced in male COVID-19 subjects than male control subjects that increased with advancing radiological stage and were not confounded vitamin D3-impacted comorbidities | De Smet et al. (2020) |
| Hospitals and clinics from different parts of the world | Age up to 80 years | 5,000 cases | As on March 21, 2020 | NA | About 15% reduction in the number of severe COVID-19 cases given a normal vitamin D3 status within a population | Daneshkhah et al. (2020) |
| Indonesia (Government hospital) | Adults, mean age 54.5 years | 780 cases | Retrospective cohort study (2 March 2–24 April 2020) | NA | i) In univariate analysis, older and male cases with the pre-existing medical condition and below normal vitamin D3 levels were associated with the higher odds of death  
ii) After adjustment of confounders (age, sex and comorbidity), vitamin D3 levels showed a strong relationship with the COVID-19 mortality | Raharusun et al. (2020) |
various viral and respiratory infections, it is reasonable to suggest that regular supplementation of vitamin D₃ to those who are at high risk of developing various viral respiratory infections including COVID-19 need to considered seriously. To verify this proposal, double-blind placebo-controlled trials and large-scale intervention and prevention studies using vitamin D₃ are needed. If this proposal is true it leads to the development of a simple, easy implementable method of preventing the incidence of COVID-19 and reducing its serious complications by simple oral supplementation of vitamin D₃. Furthermore, vitamin D₃ has several other benefits in the form of preventing rickets, improving general health, and reducing mortality due to its deficiency (though for this exact cause for this association is not clear) add strength to the concept that its supplementation is warranted.

**AUTHOR CONTRIBUTIONS**

MB, VI, RM, DB interpreted the data from the literature. MB, VI, RM, JF, DB wrote the original draft. MB, VI, RM, JF, FD, LG, UD, AE-A reviewed, edited and drafted the manuscript, and approved the final version.

**REFERENCES**

Adams, J. S., Ren, S., Liu, P. T., Chin, R. F., Laghi Shetty, V., Gombart, A. F., et al. (2009). Vitamin D-directed rheostatic regulation of monocyte antibacterial responses. *J. Immunol.* 182, 4289–4295. doi:10.4049/jimmunol.0803736

Adorini, L., and Penna, G. (2009). Dendritic cell tolerogenicity: a key mechanism in immunomodulation by vitamin D receptor agonists. *Hum. Immunol.* 70 (5), 345–352. doi:10.1016/j.jhimmun.2009.01.016

Agier, J., Elenberger, M., and Brzezińska-Blaszcyk, E. (2015). Cathelicidin inactivation on inflammatory cells. *Cent. Eur. J. Immunol.* 40, 225–235. doi:10.5114/cej.2015.51359

Alipio, M. M. (2020). Letter-preprint vitamin D supplementation could possibly improve clinical outcomes of patients infected with coronavirus-2019 (Covid-19). Available at: https://www.ssrn.com/abstract=3571484 (Accessed 09 May, 2020).

Amrein, K., Scherkl, M., Hoffmann, M., Neuwersch-Sommeregger, S., Köstenberger, M., Berisha, A. T., et al. (2020). Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur. J. Clin. Nutr.* 20, 1–16. doi:10.1038/s41430-020-0558-y

Aronow, C. (2011). Vitamin D and the immune system. *Curr. Opin. Pharmacol.* 10, 482–496. doi:10.1016/j.coph.2010.04.001

Bals, R., and Wilson, J. (2003). Cathelicidins—a family of multifunctional antimicrobial peptides. *Cell. Mol. Life Sci.* 60, 711–720. doi:10.1007/s00018-003-2186-9

Barlow, P., Svoboda, P., Mackellar, A., Nash, A., York, I., Pobl, J., et al. (2011). Antiviral activity and increased host defense against influenza infection elicited by the human cathelicidin LL-37. *PLoS One* 6, e25333. doi:10.1371/journal.pone.0025333

Berardi, R., and Newton, G. (2009). *Handbook of nonprescription drugs*. 16th Edition. Washington DC: American Pharmacists Association, 1050

Bergman, P., Walter-Jallow, L., Broliden, K., Agerberth, B., and Soderlund, J. (2007). The antimicrobial peptide LL-37 inhibits HIV-1 replication. *Curr. HIV Res.* 5:410–429. doi:10.4049/jimmunol.179.3.1634

Bergman, P., Norlin, A. C., Hansen, S., Rakha, R. S., Agerberth, B., Bjorkhem-Bergman, L., et al. (2012). Vitamin D supplementation in patients with frequent respiratory tract infections: a randomized and double-blind intervention study. *BMJ Open* 2, e000163. doi:10.1136/bmjopen-2012-001663

Biancatti, R. C., Berrill, M., and Marik, P. (2019). The antiviral properties of vitamin C. *Expert. Rev. Anti Infect. Ther.* 18, 99–101. doi:10.1080/14787210.2020.1706483

Biesalski, H. K. (2020). Vitamin D deficiency and co-morbidities in COVID-19 patients – a fatal relationship? *NFS J.* 20, 10–21. doi:10.1016/j.nfsj.2020.06.007

Bjelakovic, G., Giusu, L. L., Nikolina, D., Whitley, R., Witterslev, J., Simonetti, G. G., et al. (2014). Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst. Rev.* 1:CD007470. doi:10.1002/14651858.CD007470.pub3

Bombardini, T., and Picano, E. (2020). Angiotensin converting enzyme 2 as the molecular bridge between epidemiologic and clinical features of COVID-19. *Can. J. Cardiol.* 36 (5), 784.e1–784.e2. doi:10.1061/cjca.2020.03.026

Bowie, A., and Unterholzer, L. (2008). Viral evasion and subversion of pattern-recognition receptor signalling. *Nat. Rev. Immunol.* 8, 911–922. doi:10.1038/nri2436

Brockman-Schneider, R. A., Pickles, R. J., and Gern, J. E. (2014). Effects of vitamin D on airway epithelial cell morphology and rhinovirus replication. *PLoS One* 9 (1), e86755. doi:10.1371/journal.pone.0086755

Camargo, C. A., Jr., Garnaa, D., Frazier, A. L., Kirchberg, F. F., Stuart, J. I., Kleinman, K. et al. (2012). Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. *Pediatrics.* 130, e561–e567. doi:10.1542/peds.2011-3029

Cao, D., and Norton, R. (2009). Vitamin D and respiratory health. *Clin. Exp. Immunol.* 158, 20–25. doi:10.1111/j.1365-2499.2009.04001.x

Cannell, J. J., Vieth, R., Umtau, J. C., Hollick, M. F., Grant, W. B., Madronich, S., et al. (2006). Epidemic influenza and vitamin D. *Epid. Infect.* 134, 1129–1140. doi:10.1099/02688067-1757

Charan, J., Goyal, J., Saxena, D., and Yadav, P. (2012). Vitamin D for prevention of respiratory tract infections: a systematic review and meta-analysis. *J. Pharmocol. Pharmacother.* 3, 300–303. doi:10.4103/0976-500X.103685

Chen, S., Sims, G. P., Chen, X. X., Gu, Y. Y., Chen, S., and Lipsky, P. E. (2007). Modulatory effects of 1,25-dihydroxyvitamin D₃ on human B cell differentiation. *J. Immunol.* 179, 1634–1647. doi:10.4049/jimmunol.179.3.1634

Chun, R. F., Liu, P. T., Modlin, R. L., Adams, J. S., and Hewison, M. (2014). Impact of vitamin D on immune function: lessons learned from genome-wide analysis. *Front. Physiol.* 5, 151. doi:10.3389/fphys.2014.00151

Daneshkiah, A., Agrawal, V., Eshein, A., Subramanian, H., Roy, H. K., and Backman, V. (2020). The possible role of vitamin D in suppressing cytokine storm and associated mortality in COVID-19 patients. *MedRxiv Preprint*. doi:10.1101/2020.04.08.2005878

Daniel, C., Sartory, N. A., Zahn, N., Radeke, H. H., and Stein, J. M. (2008). Immune modulatory treatment of trinitrobenezene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. *J. Pharmacol. Exp. Therapeut.* 324, 23–33. doi:10.1124/jpet.107.127209

Darling, A. L., Ahmadi, K. R., Ward, K. A., Harvey, N. C., Alves, A. C., Dunn-Waters, D. K., et al. (2020). Vitamin D status, body mass index, ethnicity and COVID-19: Initial analysis of the first-reported UK Biobank COVID-19 positive cases (n 580) compared with negative controls (n 723). *MedRxiv*. doi:10.1101/2020.04.29.20084277

De Smet, D., De Smet, K., Herroelen, P., Gryspeerdt, S., and Martens, G. A. (2020). Vitamin D deficiency as risk factor for severe COVID-19: a convergence of two pandemics. *MedRxiv Preprint*. doi:10.1101/2020.05.01.20079376

Di Rosa, M., Malaguarnera, M., Nicoletti, F., and Malaguarnera, L. (2011). Vitamin D₃: a helpful immuno-modulator. *Immunology* 134, 123–139. doi:10.1111/j.1365-2667.2011.03482.x

D’Ambrosio, D., Cippitelli, M., Coccio, M., Mazzeo, D., Di Lucia, P., Lang, R., et al. (1998). Inhibition of IL-12 production by 1,25-dihydroxyvitamin D₃.
Tjabringa, G. S., Rabe, K. F., and Hiemstra, P. S. (2005). The human cathelicidin LL-37: a multifunctional peptide involved in infection and inflammation in the lung. *Pulm. Pharmacol. Ther.* 18, 321–327. doi:10.1016/j.pupt.2005.01.001

Umar, M., and Sastry, K. S. (2018). Chouchane AI. Role of vitamin D beyond the skeletal function: a review of the molecular and clinical studies. *Int. J. Mol. Sci.* 19. doi:10.3390/ijms19061618

Van Herwegen, A.-S., Gysemans, C., and Mathieu, C. (2017). Vitamin D endocrinology on the cross-road between immunity and metabolism. *Mol. Cell. Endocrinol.* 453, 52–67. doi:10.1016/j.mce.2017.04.007

Van Schoor, N. M., and Lips, P. (2011). Worldwide vitamin D status. *Best Pract. Res. Clin. Endocrinol. Metab.* 25, 671–680. doi:10.1016/j.beem.2011.06.007

Veugelers, P. J., Pham, T. M., and Ekwur, J. P. (2015) Optimal vitamin D supplementation doses that minimize the risk for both low high serum 25-hydroxy vitamin D concentration in general population. *Nutrients* 7, 10189–10208. doi:10.3390/nu7125257

Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., et al. (2020). Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *J. Am. Med. Assoc.* 323, 1061–1069. doi:10.1001/jama.2020.1585

Wimalawansa, S. J. (2020). Global epidemic of coronavirus-COVID-19: what we can do to minimize risks. *Eur. J. Biomed. Pharm. Sci.* 7, 432–438. Available at: https://www.ejbps.com/ejbps/abstract_id/6656

Wu, S.-E., and Miller, W. E. (2015). The human cytomegalovirus lytic cycle is induced by 1,25-dihydroxyvitamin D3 in peripheral blood monocytes and in the THP1 monocytic cell line. *Virol.* 483, 8395. doi:10.1016/j.virol.2015.04.004

Xu, J., Yang, J., Chen, J., Luo, Q., Zhang, Q., and Zhang, H. (2017). Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Mol. Med. Rep.* 16, 7432–7438. doi:10.3892/mmr.2017.7546

Yang, I., Xu, J., and Zhang, H. (2016). Effects of vitamin D on ACE2 and vitamin D receptor expression in rats with LPS induced acute lung injury. *Chin. J. Enm. Med.* 25, 1284–1289. doi:10.3760/cma.j.issn.1671-0282.2016.12.016

Zdrenghea, M. T., Makrinioti, H., Bagacean, C., Bush, A., Johnston, S. L., and Stanciu, L. A. (2017). Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev. Med. Virol.* 27. doi:10.1002/rmv.1909

Zhao, Y., Ran, Z., Jiang, Q., Hu, N., Yu, B., Zhu, L., et al. (2019). Vitamin D alleviates rotavirus infection through a microRNA-155–5p mediated regulation of the TBK1/IRF3 signaling pathway in vivo and in vitro. *Int. J. Mol. Sci.* 20, 3562. doi:10.3390/ijms20143562

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., et al. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *Lancet* 395, 1054–1062. doi:10.1016/S0140-6736(20)30566-3

**Conflicts of Interest:** UD was employed by the company UND Life Sciences LLC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

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