



# Shedding light on vitamin D: the shared mechanistic and pathophysiological role between hypovitaminosis D and COVID-19 risk factors and complications

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## Abstract

Severe acute respiratory syndrome coronavirus (SARS-COV-2) is the culprit of the Coronavirus Disease (COVID-19), which has infected approximately 173 million people and killed more than 3.73 million. At risk groups including diabetic and obese patients are more vulnerable to COVID-19-related complications and poor outcomes. Substantial evidence points to hypovitaminosis D as a risk factor for severe disease, the need for ICU, and mortality. 1,25(OH)D, a key regulator of calcium homeostasis, is believed to have various immune-regulatory roles including; promoting anti-inflammatory cytokines, down regulating pro-inflammatory cytokines, dampening entry and replication of SARS-COV-2, and the production of antimicrobial peptides. In addition, there are strong connections which suggest that dysregulated 1,25(OH)D levels play a mechanistic and pathophysiologic role in several disease processes that are shared with COVID-19 including: diabetes, obesity, acute respiratory distress syndrome (ARDS), cytokine storm, and even hypercoagulable states. With evidence continuing to grow for the case that low vitamin D status is a risk factor for COVID-19 disease and poor outcomes, there is a need now to address the public health efforts set in place to minimize infection, such as lock down orders, which may have inadvertently increased hypovitaminosis D in the general population and those already at risk (elderly, obese, and disabled). Moreover, there is a need to address the implications of this evidence and how we may apply the use of cheaply available supplementation, which has yet to overcome the near global concern of hypovitaminosis D. In our review, we exhaustively scope these shared pathophysiologic connections between COVID-19 and hypovitaminosis D.

**Keywords** Vitamin D · COVID-19 · Immunomodulator · Hypovitaminosis D · Vitamin D receptor

## Abbreviations

ACE	Angiotensin Converting Enzyme	HCAEC	Human Coronary Arterial Endothelial Cells
ARDS	Acute Respiratory Distress Syndrome	ICU	Intensive Care Unit
APS	Antiphospholipid Syndrome	IU	International Units
COVID-19	Coronavirus Disease 2019	IL	Interleukin
DM	Diabetes Mellitus	KD	Kawasaki Disease
		MERS	Middle Eastern Respiratory Syndrome
		Nsp	Non-structural Protein
		SARS-COV-2	Severe Acute Respiratory Syndrome
		TNF	Tumor Necrosis Factor
		VDR	Vitamin D Receptor
		WHO	World Health Organization

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## Introduction

Severe acute respiratory syndrome coronavirus (SARS-COV-2), the culprit of Coronavirus Disease (COVID-19), is one of the most deadly pandemics after the Spanish flu of

1918, with approximately 173 million confirmed cases and more than 3.73 million deaths as of June 7th, 2021 (Dong and Du 2020). The virus was initially found in the city of Wuhan, China in December 2019, and in March of 2020, the World Health Organization (WHO) declared COVID-19 a pandemic of international concern (Organization 2020).

COVID-19 is primarily a respiratory disease that is transmitted via droplets or contact contamination with droplets of infected personnel Pereira et al. 2020. The incubation period for SARS-COV-2 ranges from 2 to 14 days (Organization 2020; Pereira et al. 2020). Viral particles have been detected in blood, serum, ocular fluid, nasopharyngeal secretions, urine, breast milk, placental membranes, and fecal matter (Organization 2020; Heller et al. 2020; Hindson 2020). Infection may be asymptomatic or present with varying clinical pictures that range from mild to severe. Symptoms include; low-grade fever, sore throat, cough, malaise, diarrhea, headache, anosmia, respiratory distress, as well as thromboembolic disorders (pulmonary embolism, myocardial infarctions, and stroke) (Rothan and Byrareddy 2020; García 1441). High-risk groups include patients with: cardiovascular disease, hypertension, diabetes mellitus, obesity, chronic kidney and pulmonary disease, cancer, as well as the elderly.

Recent evidence suggested that hypovitaminosis D is a risk factor for severe disease in the COVID-19 setting (Biesalski 2020; Bilezikian et al. 2020). Vit D status in northern latitudes in Non-Scandinavian European countries showed a significant inverse correlation with COVID-19 mortality rate (Biesalski 2020). Other countries which do not fall within the latitude have also demonstrated a high number of cases (Latitude and respiratory infection susceptibility). In another report, Vit D deficiency was associated with a near four-fold increase in the odds of dying from COVID-19. Severe Vit D deficiency has been observed in patients with COVID-19 acute respiratory failure, warranting the suggestion that it may be used as a marker for poor prognosis (Becky 2020). Currently, there are approximately 40 ongoing trials involving Vit D worldwide (Clinicaltrials. Gov. 2021). In this review, we summarize the role of Vit D as an immunomodulator and its potential as an adjuvant in COVID-19 therapy, as well as elaborate the role of Vit D among high-risk COVID-19 groups (diabetics and obese) and various body system complications.

## Vitamin D physiology

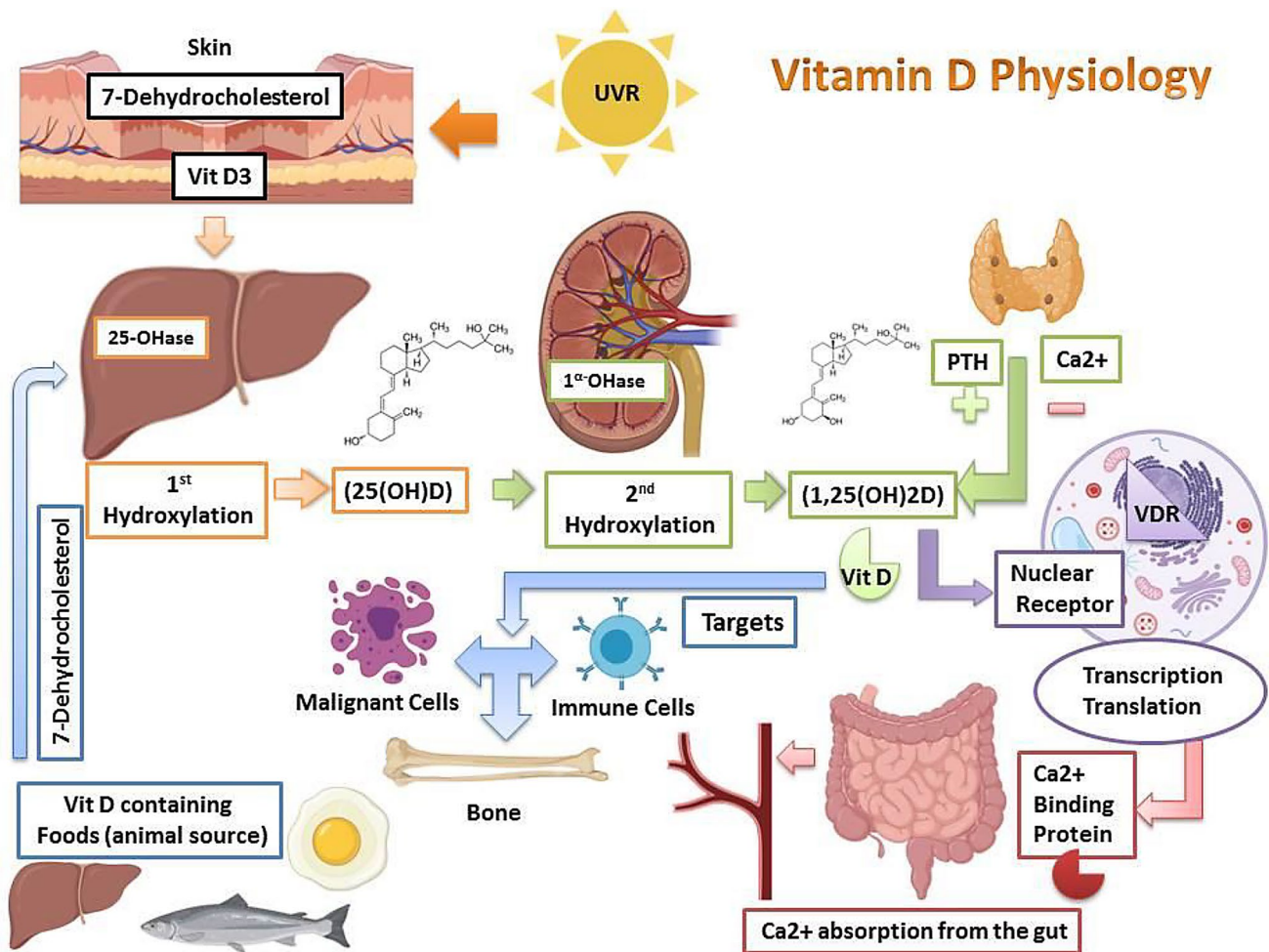
Vit D consists of two linked fat-soluble components: cholecalciferol (Vit D3) and ergocalciferol (Vit D2) (Haussler et al. 2013; Jones et al. 2014). Although Vit D3 has a longer  $t_{1/2}$  and higher affinity for Vit D binding protein (Vit BP), the total concentration of both D2+D3 are used to assess

Vit D functional status. Figure 1 (Haussler et al. 2013; Jones et al. 2014) demonstrates the physiology of Vit D. Vit D3 is synthesized in the skin using ultraviolet rays from the sun, or obtained from ingesting Vit D containing foods (fish, mushrooms, fortified foods, etc.). Hydroxylation occurs in the liver and then again in the kidney to form 1, 25-dihydroxyvitamin D [1, 25(OH) 2D], the active metabolite which functions as a nuclear hormone through its affinity for the transcription factor Vit D receptor (VDR) (Lips 2006). VDR is expressed in the vast majority of human cells extending the role of Vit D beyond just calcium homeostasis and bone formation (Lips 2006).

## Vitamin D and its effect on the immune system

1,25(OH)D affects both the innate and adaptive immune system (Aranow 2011). VDRs are present in activated macrophages, T-lymphocytes, and thymus tissue (Tsalamandris et al. 2019). 1,25(OH)D has been shown to modulate the immune system in the following ways: (1) promoting the differentiation of monocytes into macrophages (increasing cytotoxicity); (2) reducing antigen-presenting activity of macrophages; (3) preventing the maturation of dendritic cells; (4) inhibiting delayed-type hypersensitivity reactions; (5) inhibiting T lymphocyte-mediated immunoglobulin synthesis; (6) suppressing the activity and generation of new natural killer cells; (7) decreasing pro-inflammatory type I cytokines [interferon (IFN)- $\gamma$ , tumor necrosis factor (TNF)- $\beta$ , interleukin (IL)-2, IL-6, IL-8, and IL-12] (Tsalamandris et al. 2019); and (8) increasing anti-inflammatory type II cytokines (IL-4,5,10, and regulatory T cells) (Zdrenghea et al. 2017).

When looking at the relationship between 1,25(OH)D and viral immunity, Teymoori-Rad et al. points out that hypovitaminosis D is associated with an increased CD4/CD8 ratio, which would result in the decreased ability of the immune system to produce activated T lymphocytes (CD8+ T), which predominately target virally infected B cells (Teymoori-Rad et al. 2019). Vit D also promotes the production of human  $\beta$  defensins (HBDs), which facilitate the antiviral state against infection (Teymoori-Rad et al. 2019). Viral infections up-regulate CYP27B1, a cationic host defense peptide involved in the innate immunity of intracellular pathogens (Teymoori-Rad et al. 2019). CYP27B1 (mainly expressed in respiratory epithelial cells) along with Vit D induce cathelicidin (an antimicrobial peptide) at the site of infection (Teymoori-Rad et al. 2019). Elevated levels of CYP27B1 promote the expression of Vit D-regulated genes, particularly those with immuno-modulatory actions, which proves to be beneficial in response to respiratory viruses (Teymoori-Rad et al.



**Fig. 1** Vitamin D physiology. Under the effect of ultraviolet rays (sun), 7-dehydrocholesterol (skin) is converted to vitamin D<sub>3</sub> (which is also present in food sources demonstrated at the bottom left corner). Vitamin D<sub>3</sub> in the liver undergoes its first hydroxylation (25-hydroxylase) to form 25-(OH) D. In the kidneys, 25-(OH) D undergoes a second hydroxylation (1- $\alpha$  hydroxylase) to form 1,

25-(OH) D, which enters into the cell via vitamin D nuclear receptor (VDR). This promotes the formation of calcium binding protein which allows for calcium absorption from the gut and into the bloodstream. Vitamin D targets multiple bodily cells including; bone, malignant, and immune cells

2019). Hansdottri and colleagues found that 1,25(OH)<sub>2</sub>D stimulates I $\kappa$ B $\alpha$ , a nuclear factor-kappa B (NF- $\kappa$ B) inhibitor located within airway epithelium, which reduces the induction of NF- $\kappa$ B in response to the respiratory syncytial virus (RSV) (Hansdottr et al. 2010). They also demonstrated that despite the activation of I $\kappa$ B $\alpha$  and the dampening of chemokines, there was no further increase in viral proteins, mRNA, or replication (Hansdottr et al. 2010). With normal levels of serum 1,25(OH)<sub>2</sub>D, there is optimal stimulation of cathelicidin and defensins, which not only promote antimicrobial activity of the immune system, but have been found to destroy the influenza virus. Greiller et al. found that 1,25(OH)<sub>2</sub>D has a direct effect on T-cells, which is independent of dendritic cell activity (Greiller and Martineau 2015).

### Cytokine storm, acute respiratory distress syndrome, and vitamin D

Cytokine storm encompasses a set of immune deregulatory conditions that are characterized by non-specific systemic inflammation, constitutional symptoms, and multi-organ dysfunction, which may be due to infection, malignancy, autoimmune disorders, and certain therapies (Fajgenbaum and June 2020). It is characterized by the hyperactivity and proliferation of macrophages, natural killer cells, T cells, as well as the over production of more than 150 inflammatory mediators and cytokines, which may be released by immune or non-immune cells/components (Sun et al. 2020).

Acute respiratory distress syndrome (ARDS) is an alarming condition which results from lung tissue damage caused by platelet and neutrophil dependent injury to the protective barriers of the respiratory tract (epithelial and endothelial) (Matthay and Zemans 2011). The damaged epithelial barrier will deprive the lung of optimal surfactant levels resulting in alveolar edema and collapse (Matthay and Zemans 2011). The clinical presentation of ARDS can also be demonstrated in cytokine storm, seeing that hypercytokinemia directly injures the lung using the same mechanisms (Fajgenbaum and June 2020; Matthay and Zemans 2011).

The highlight of severe COVID-19 infection is cytokine storm syndrome (Sun et al. 2020). Many COVID-19 patients present with an exaggerated inflammatory reaction, which results in the release of large amounts of pro-inflammatory cytokines, leading to multi-system failure, and lung injury. Human coronaviruses include SARS, MERS, and COVID-19 are associated with hypercytokinemia, which may result in ARDS and direct lung injury via lung epithelium/endothelium apoptosis causing micro-vascular damage, vascular leakage, alveolar edema, followed by hypoxia (Fajgenbaum and June 2020; Matthay and Zemans 2011). Numerous clinical publications have pointed out that, the highlight of severe COVID-19 infection is viral pneumonia induced ARDS (Torres Acosta and Singer 2020).

There is an interesting connection between the development of cytokine storm and ARDS to serum 1,25(OH)D levels. Dancer et al., found that: (1) 100% of the ARDS patients had low serum 1,25(OH)D levels (< 50 nmol/L); (2) patients with serum Vit D < 20 nmol/L were more likely to present with ARDS ( $P$  0.040) by a 3.5 fold compared to patients with Vit D > 20 nmol/L; and (3) hypovitaminosis D directly contributed to the pathogenesis of ARDS (Dancer et al. 2015). Similarly, Bajwa et al. found that: hypovitaminosis D was prevalent in 90% of ARDS patients, and these patients were more likely to have longer mechanical ventilation time (Bajwa et al. 2016). With regards to cytokine storm syndrome, Daneshkhah et al. noted an inverse correlation between C-reactive protein (CRP) (alternative cytokine storm marker) and serum 1,25(OH)D levels (Daneshkhah et al. 2020). As mentioned earlier, Vit D modulates the immune system by promoting a balance between pro and anti-inflammatory responses, which may prove beneficial in the setting of ARDS and cytokine storm.

Until now, there is limited research regarding the impact of 1,25(OH)D on cytokine storm but substantial evidence regarding its effect on ARDS. More clinical studies are needed to clearly identify this connection, and how we can benefit from 1,25(OH)D in the setting of severe COVID-19, which presents with both cytokine storm and ARDS.

## Current connections between vitamin D, COVID-19, respiratory viral infections, and latitude

### Vitamin D and COVID-19

Currently, there is a shortage of data about the mechanisms and virulent factors of SARS-COV-2. Our understanding of the mechanisms of this virus originally comes from what we know about other coronaviruses; Middle Eastern Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), which shares 79% of the genomic map with SARS-COV-2 (Zhou et al. 2020; Andersen et al. 2020).

Evidence suggests a protective role of Vit D against the development of SARS-COV-2 infection and severity of COVID-19 (McCartney et al. 1971). In a systematic review and meta-analyses on the impact of hypovitaminosis D on COVID-19 patients, Pereira et al. reported that in terms of disease severity, patients with severe COVID-19 presented with hypovitaminosis D 65% more than patients with mild disease. Although, low serum 1,25(OH)D was more likely found in COVID-19 patients (regardless of the severity) compared to healthy individuals (Pereira et al. 2020), it was noted that vitamin D deficiency was not associated with a higher rates of infection by SARS-COV-2. Similarly, Alguwaihes et al. found that in the hospital settings, hypovitaminosis D was not associated with SARS-COV-2 infection, but was associated with increased risk of mortality, especially in severely deficient cases (Alguwaihes et al. 2021). In a randomized controlled trial done by Murai et al., it was concluded that even after patients received a high dose of Vit D (200,000 IU), there was no significant reduction in hospital or ICU stay compared to patients who received placebo (Murai et al. 2021). These evidences are very conflicting and warrant more robust research.

Hernandez and colleagues found that hypovitaminosis D was present in 82.2% of COVID-19 cases compared to the control group (47.2%) (Hernández, 2020). They also demonstrated that 1,25(OH)D and serum ferritin are inversely correlated ( $P$  = 0.013), which suggests that in an active COVID-19 infection, there is both a state of hypovitaminosis D and hyperferritinemia (Menshawey et al. 2020). In addition, COVID-19 patients with Vit D deficiency had a greater prevalence of cardiovascular disease, hypertension, and longer ICU stays (Hernández et al. 2020). Meltzer et al. in a cohort of 489 patients concluded that individuals with insufficient levels of 1,25(OH)D were at a greater risk (1.77 times) of developing COVID-19 infection than those with sufficient serum Vit D (Meltzer et al. 2020). Table 1 (Rastogi et al. 2020; Miroliaee





et al. 2017; Elbers et al. 2018; Sahay and Sahay 2013; Bahreynian et al. 2018; Yusupov et al. 2010; Pourbagheri-Sigaroodi et al. 2020) demonstrates specific laboratory profiles of COVID-19 and hypovitaminosis D, as well as the effect of correcting 1,25(OH)D levels (via supplementation) on these profiles (in any pathological state). It can be seen that the inflammatory derangements in immunity are nearly identical in COVID-19 and hypovitaminosis D, which are resolved upon normalization.

In a study assessing 25(OH) D concentrations among asymptomatic and severely ill COVID-19 patients ( $n = 154$ ), Jain et al. found that: (1) there was a significantly lower level of 25(OH) D in the severely ill patient group, (2) serum inflammatory makers (TNF alpha and IL-6) were elevated in the vitamin deficient group; and (3) fatality rate was significantly increased in the low Vit D group, which suggests an increased risk of COVID-19-related mortality if associated with hypovitaminosis D. They recommended that a mass administration of Vit D supplementation be provided to the general public, especially those at risk of contracting COVID-19 (Jain et al. 2020). Nurshad Ali pointed out that mechanisms, including: papain-like protease-mediated replication and dipeptidyl peptidase-4 receptor (DPP4/CD26) binding are required to elucidate virulence mechanisms of COVID-19 (Ali 2020). Human DPP4/CD26 connects with the S1 domain of the spike protein of SARS-COV-2, which suggests that this substance may be a virulence factor for COVID-19 (Ali 2020). In vivo studies have shown that upon correction of hypovitaminosis D, the DPP4/CD26 receptor is significantly reduced (Ali 2020).

Although non-structural proteins (Nsp) allow for viral replication, assembly, and evasion of host immune sensors, their exact mechanisms are unclear. A classical feature of the Coronavirus genus is the Nsp15-like endoribonucleases, which was hypothesized to be the proofreader, but was later found to regulate the length of viral RNA (number of polyuridine found at the 5' end of the negative strand) to evade the hosts' response to foreign nucleic acid (innate response). Shalayel et al. (2020) concluded that Vit D may be a potential drug against COVID-19 compared to other repurposed medications seeing that it has the strongest interaction against the Nsp 15 of COVID-19 binding sites (Shalayel et al. 2020). These data requires more clarification, but raises an important question; can Vit D enhance the hosts' immunity against COVID-19 by targeting the endoribonuclease (responsible for evading the hosts' immunity during the incubation period) to limit the number of viral particles that result in cytokine storm and subsequent immune-mediated tissue destruction? More robust research is needed to determine the exact effects of Vit D in the setting of COVID-19 infection, and its potentially protective role in limiting transmission, pathogenesis, and severity of the infection. Figure 2

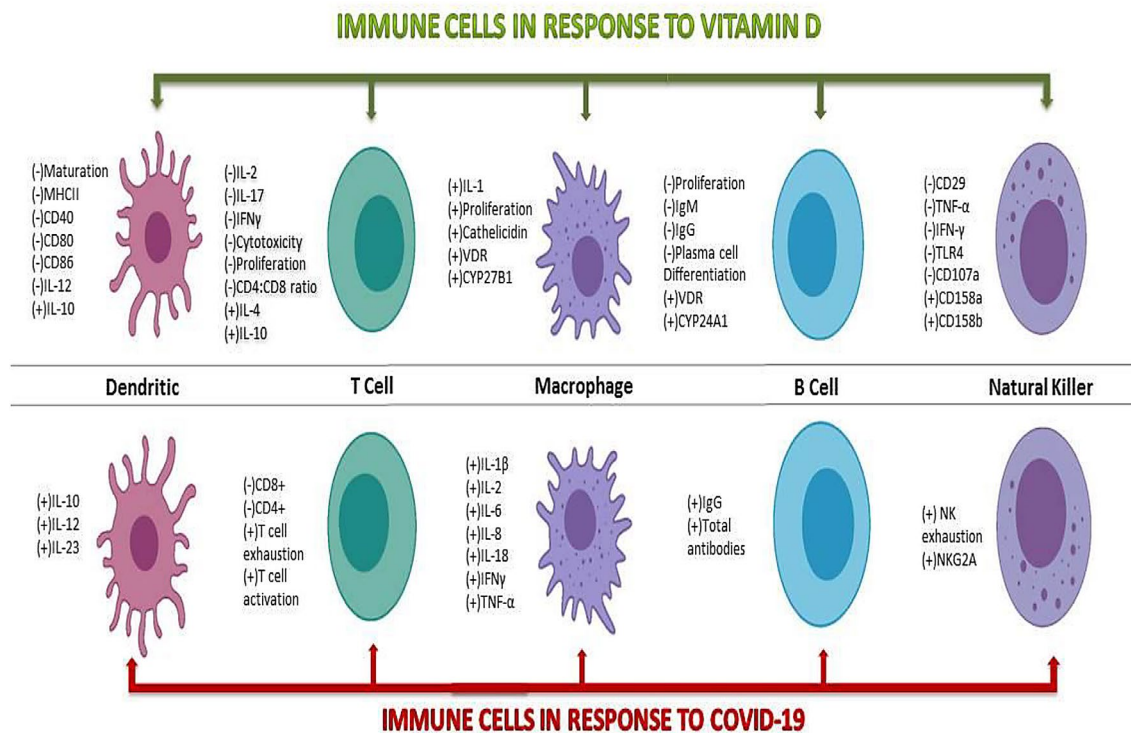
demonstrates the effect of Vit D and COVID-19 on specific immune cells.

## Respiratory viral infections

Viral pathogens associated with acute respiratory infections include the following; influenza A, B, C, rhinovirus A, B, C, enteroviruses A to D, Para-influenza, RSV, coronaviruses, and adenoviruses (Greiller and Martineau 2015). These viruses are divided into numerous families which are antigenically and genetically distinct (Nichols et al. 2008).

Trujillo et al. in a study investigating the effects of absent Vit D-binding protein (DBP) on leukocyte recruitment in alveolitis models of lung inflammation in mice found that DBP null mice had a significantly less neutrophil recruitment (~50%) to the lungs than their DBP + counterparts (Trujillo et al. 2013). They concluded that, in vivo, DBP enhances the activity of chemo-attractants (Trujillo et al. 2013). Vit D when co-administered with the trivalent influenza vaccine has been shown to enhance the anti-hemagglutinin antibody and mucosal immunity (Gruber-Bzura 2018). Urashima et al. found that, children who were not given Vit D supplementation were significantly at a greater risk of contracting influenza A virus than those who were given Vit D (Urashima et al. 2010). They also found that supplemented children were less likely to get an asthma attack compared to those who were not supplemented ( $P = 0.006$ ) (Urashima et al. 2010).

Likewise, in a study done by Laaski and colleagues, regarding the association between Vit D levels and upper respiratory tract infections (URTI) in military recruits, it was found that those with hypovitaminosis D lost significantly more days from active duty as a result of URTI, than those with higher Vit D levels above 40 nmol (Laaski et al. 2007). Evidence supports the antiviral activity of cathelicidin during influenza A and RSV via binding to the virus and disrupting its envelope while modulating the response of cytokines and toll-like receptor (TLR) 3. Defensin was seen to inhibit RSV by destabilizing its envelope with subsequent inhibition of viral entry (Zdrenghea et al. 2017). As mentioned before, both defensin and cathelicidin are affected by Vit D. Zdrenghea and colleagues reported that in experimental conditions, human alveolar epithelial cells (line A549) treated with Vit D prior to H1N1 exposure lowered the levels of H1N1-induced pro-inflammatory cytokines (Zdrenghea et al. 2017). Jolliffe et al. in a review concluded that patients with hypovitaminosis D had an increased risk of developing both upper and lower respiratory tract infections (Jolliffe et al. 2013). Contradicting to this data, Vuichard Gysin et al. in a systematic review and meta-analysis of 15 trials found that, in previously healthy individuals, Vit D supplementation did not reduce the risk of clinical respiratory infections (Vuichard Gysin, 2016). However, they suggested that this



**Fig. 2** Immune cells in response to vitamin D and COVID-19. The main highlight for severe COVID-19 infection is Cytokine Storm Syndrome, which is manifested by excessive production of immune cells and immune cell products such as cytokines. Vitamin D regulates both the innate and adaptive immune response by modulating

immune cells to inhibit the production of pro-inflammatory substances and stimulating the production of anti-inflammatory cytokines, which is demonstrated by the few cells in this figure (dendritic, T lymphocytes, B lymphocytes, macrophages, and natural killer cells)

conclusion is based on a group of studies that varied with respect to, baseline levels of Vit D, the population, and the length of the study (Vuichard Gysin et al. 2016).

### Latitude and respiratory infection susceptibility

Cannell et al. reviewed the effects of Vit D and the Influenza virus. In England, a significant inverse correlation is seen between the incidence of influenza and temperature, which is strongly associated with solar radiation (Cannell et al. 2006). They also pointed out that, at a latitude of 52°N (the latitude of London), no Vit D is formed in the skin, especially during October to March, since the atmospheric zone filters out most of the ultraviolet radiation (Cannell et al. 2006). In addition, during these months in particular, influenza associated mortality peaks, not only in the UK, but in other Western/European countries (Cannell et al. 2006). This may be one of the factors which could explain why currently, there is an exponential growth in COVID-19 infections and mortality during the winter season. Rhodes et al. found that countries in the northern hemisphere (during May 2020) had higher rates of COVID-19 mortality (Rhodes et al. 2021). For every

increase in latitude degree north (above 23° N), there was an increase in mortality by 4.4% ( $P$  0.031) (Rhodes et al. 2021).

It should be noted that certain geographical areas with a latitude less than 45° may also present with higher prevalence hypovitaminosis D that may be due to race (darker skin pigmentation), ethnicity (fully dressed garments that limits the skin surface area exposed to ultraviolet rays), and cultural/religious backgrounds (through social practices, or special diets) and, therefore, may have influenced the increasing number of COVID-19 cases in these areas as well. Interestingly, there is also a rise in COVID-19 cases and associated mortality in countries that do not fall within the latitude of Non-Scandinavian European countries. For example, in Brazil, the number of cases has risen by over 70,000 just within the first week of June 2021 (Organization 2020). This does not directly correlate with the latitude or the amount of sun exposure, but may actually be linked to the fact that Vit D deficiency is highly prevalent, according to a study which consisted of 80,000 Brazilian people (Leão et al. 2021). Similarly, India has seen world record COVID-19 cases which have not been linked to latitude, but they too, have a high prevalence of Vit D deficiency irrespective

of sunlight exposure, according to a systematic review by Selvarajan et al. 2017.

## High-risk COVID-19 groups and vitamin D

### Obesity

Obese individuals are more prone to developing infections. The connection between COVID-19 and obesity has been demonstrated by multiple studies (Fakhry AbdelMassih et al. 2020; Cai et al. 1392; Popkin et al. 2020; Yang et al. 2020). Evidence suggests that obese individuals have both a greater susceptibility to testing positive for COVID-19, as well as an increased risk of COVID-19 associated mortality (number one predicting factor) (Fakhry AbdelMassih et al. 2020).

Cai et al., in a multi-center study done across 383 hospitals found that, compared to normal weight individuals, obese patients were not only more likely to develop severe COVID-19 by a 3.40 fold, but had greater odds of developing symptoms such as cough and fever (Cai et al. 1392). In a systematic review by Popkin et al., pooled analysis demonstrated that obese individuals were more likely to; (1) test positive for COVID-19; (2) become hospitalized; (3) were more likely to be admitted to the ICU by 74%; and (4) had a mortality rate 48% higher than non-obese individuals ( $P < 0.001$ ) (Popkin et al. 2020). In another systematic review, Yang et al. concluded the similar results (Yang et al. 2020).

Kassir mentioned multiple reasons as to why obese individuals have a greater risk of developing COVID-19, one of which involves the expression of the angiotensin converting enzyme 2 (ACE2) (Kassir 2020). SARS-COV-2 enters the cells via the ACE2 receptor (virulence factor). Tissue expression of the ACE2 receptor varies among different body cells, with the highest expression found in adipose tissue (Kassir 2020). The same study also mentions that adipose tissue can function as a storage unit for many viral infections including influenza virus, and possibly COVID-19 (Kassir 2020). From this evidence, it can be concluded that obese individuals are at a greater risk of developing COVID-19 infection and complications.

Metabolic functions of Vit D include: inhibition of accumulating lipids and adipose stimulating transcription factors during the process of adipocyte differentiation, which affects the total body fat composition in healthy and obese individuals (Slusher et al. 2015; Wong et al. 2009). Vit D effects lipogenesis via the sterol regulatory element binding protein-1 (SREBP-1) found in the liver, as well as the peroxisome proliferator activated receptor gamma (PPAR $\gamma$ ) in adipose tissue (Wong et al. 2009). Calcitriol, is a key regulator of genes associated with thermogenesis, lipid production (fatty acid synthase), and destruction

(hormone sensitive lipase) (Wong et al. 2009; Ding et al. 2012). Elevated levels of calcitriol via stimulation of cortisol can redistribute adipose tissue towards the anterior abdominal area (Wong et al. 2009; Ding et al. 2012).

It should be noted that there is significant evidence proving that both Vit D and its receptor are involved in the regulation of de novo adipogenesis (Slusher et al. 2015; Wong et al. 2009). Evidence confirms that the VDR is expressed within preadipocytes. During the differentiation of adipocytes, 1,25(OH)D inhibits C/EBP $\beta$  mRNA and C/EBP $\beta$  (CCAAT-enhancer binding proteins which are a family of transcription factors), which are involved with lipogenic enzymatic activity of specific enzymes like fatty acid synthase, a strong precursor of lipid synthesis (Wong et al. 2009). The inhibitory effect of 1,25(OH)D on preadipocyte differentiation may be more prevalent with higher intakes of 1,25(OH)D, which would imply that Vit D plays a pivotal role in adipocyte differentiation in vivo. Interestingly, the Vit D binding protein (Calbindin-D<sub>28K</sub>), which functions as a transporter for Vit D metabolites and is required for its endocytosis and metabolism, also affects the binding of globular actin and fatty acid immunomodulation (Tsalamandris et al. 2019). These evidences suggest the potential role of Vit D in the pathogenesis of obesity.

Numerous studies concluded that in obese patients, the level of serum Vit D is significantly lower than that of non-obese individuals. Buffington et al., in a study that included 60 morbidly obese females, found that 62% of them presented with hypovitaminosis D (16–74 ng/ml) (Buffington et al. 1993). Wortsman et al. also demonstrated similar findings (Wortsman et al. 2000). Parikh et al. found a negative correlation between vitamin D and BMI ( $P < 0.0001$ ) (Parikh et al. 2004). Although the exogenous intake of Vit D is not blunted in obese patients, the bio-availability has been shown to become inhibited, thereby resulting in hypovitaminosis D even when the patient is on Vit D supplementation (Parikh et al. 2004); this may have current implications on the suggested use of vitamin D as a therapy for COVID-19 if obesity is a potential effect modifier and may warrant the additional need for weight loss in these patients. Zhu et al. reported that elevated serum Vit D is linked to lower adiposity and metabolic health (Zhu et al. 2013).

In their study, which included 176 elderly obese COVID-19 patients, Gonçalves and colleagues found that 94.2% of the patients had hypovitaminosis D of  $< 30$  ng/ml (Gonçalves et al. 2020). They also concluded that there was a negative and significant bivariate correlation between serum 25(OH)D and BMI. Majority of these patients required extended ICU stay and presented with COVID-19-associated complications (Gonçalves et al. 2020). Thus, Gonçalves and colleagues concluded that testing for serum 25(OH)D should be essential for COVID-19 patients, especially the obese



population, as it may prove to be beneficial in determining the prognosis of the infection (Gonçalves et al. 2020).

These evidences suggest the need for the use of 25(OH)D levels assessment as a prognostic marker for COVID-19 disease, and the need for supplementation of Vit D and its inclusion in treatment protocols in this at risk group, which should be the target of diligent clinical trials to prove.

## Diabetes

Diabetes mellitus (DM), characterized by defective insulin function and/or secretion, results in a state of chronic hyperglycemia which affects multi-organ systems particularly the; peripheral nervous system, cardiovascular system, kidneys, and eyes. Diabetics are at risk of developing COVID-19 complications and mortality. There is evidence that supports the use of Vit D supplementation for diabetics.

Pittas et al. suggest that Vit D may directly (via the VDR) or indirectly (via regulation of calcium homeostasis) affect the pathophysiology of diabetes, as well as the  $\beta$  islet pancreatic cells (Pittas and Dawson-Hughes 2010). Few observational case controlled studies demonstrated that supplementation of Vit D during pregnancy and early childhood are associated with decreased incidence of type I diabetes (Pittas and Dawson-Hughes 2010). Hypovitaminosis D has been found to decrease the secretion of insulin as well as its sensitivity in both animals and humans (Palomer et al. 2008). There are many factors that explain the involvement of Vit D in the pathogenesis of this metabolic syndrome including: (1) allelic variations in the VDR and Vit DBP may influence glucose tolerance and secretion; (2) Vit D modulates the expression of the insulin receptor and secretion; (3) the presence of Vit D-dependent calcium binding proteins on  $\beta$  cells of the pancreas which suggest a non-classical alternative mechanism of action; (4) alterations of serum Vit D levels result in the decreased secretion of insulin without altering the secretion of glucagon; (5) Vit D increases the levels of intracellular calcium via non-selective voltage gated channels, which may directly affect the levels of calcium dependent endopeptidases, enzymes which are required for the cleavage of pro-insulin to insulin; and (6) the chromosome region that codes for the Vit DBP is located on chromosome 4q11-13 was found to be linked to fasting insulin within the genome of some type II diabetics (Palomer et al. 2008).

In a systematic review which included 8 observational cohorts and 11 randomized control trials, Mitri et al. found that subjects who were given Vit D supplementation (> 500 international units (IU)) per day, decreased the risks of developing type II diabetes by 13% when compared to those who were given <200 IU per day (Mitri et al. 2011). Individuals who had the highest (> 25 ng/ml) levels of serum 25(OH)D were 43% less likely to develop DM than those

who received the lowest dose of Vit D supplements (< 14 ng/ml) (Mitri et al. 2011). Furthermore, in a double blinded cohort assessing the effect of serum 25(OH)D levels on endothelial function in diabetic patients, Sugden et al. found that, the use of Vit D supplementation for patients with type II diabetes improved endothelial function significantly by 2.3% ( $P=0.048$ ) (Sugden et al. 2008). They also performed a post-hoc analysis which showed that, insulin sensitivity was improved in individuals who received Vit D supplementation compared to those who did not ( $P=0.003$ ) (Sugden et al. 2008). It should be noted that endothelial function is dramatically affected in patients with COVID-19 due to the fact that the cytokine storm (the main pathogenesis for COVID-19) causes vasculature damage as a result of endothelial leukocyte recruitment, also the high expression of ACE2 on endothelium makes it more susceptible to direct viral damage. This explains why COVID-19 can present with cardiovascular complications (thromboembolism, DIC, etc.) (Evans et al. 2020).

In a study with a 22 year follow-up period, Knekt et al. concluded that not only did those who have higher serum 25(OH)D concentrations have a lower incidence of developing diabetes, but also 1,25(OH)D served as a protective factor against type II DM complications (Knekt et al. 2008). Similar results have been noted by multiple studies, which concluded that, optimal serum 25(OH)D levels, whether obtained exogenously (via supplementation) or endogenously will decrease the susceptibility to developing type I and II diabetes, and may be used as a preventative measure to decrease the likelihood of developing the complications associated with diabetes (Pittas and Dawson-Hughes 2010; Pittas et al. 2019).

Currently, there is evidence that suggests that DM patients have an increased susceptibility to developing COVID-19 and its associated complications. Diabetic patients who had SARS and MERS not only presented with more complications, but also had increased chances of getting infected than those without diabetes. Diabetics are more likely to develop COVID-19 as a result of: (1) higher affinity cellular binding and efficient viral entry; (2) decreased viral clearance; (3) low T cell function; and (4) diabetics are more prone to hyperinflammation and cytokine storm syndrome (Muniyappa and Gubbi 2020). In a cohort involving 174 positive COVID-19 patients, Guo et al. found that, patients with DM were: (1) at risk for developing severe pneumonia; (2) had an hyperactive uncontrolled inflammatory response as well as a hypercoagulable state; (3) presented with elevated tissue-injury-related enzymes; and (4) had significantly elevated IL-6, CRP, serum ferritin, and D-dimer ( $P<0.01$ ) when compared to those without diabetes (Guo et al. 2020). Barron and colleagues, in a nation-wide study in England reported that, of the 3,170,250 diabetic individuals, 33.4% of them died of COVID-19, and the remaining majority

presented with COVID-19-associated complications. The study concluded that in England, diabetes was independently associated with significantly increased odds of in-hospital COVID-19-associated mortality (Barron et al. 2020).

Vit D has been found to play an important role in the pathogenesis of diabetes. Diabetes is one of the main predictors of COVID-19-associated complications and mortality. Optimal serum 25(OH)D levels increase insulin sensitivity and reduce the complications associated with diabetes, thus suggesting the need for Vit D supplementation for diabetics to reduce their likelihood of developing COVID-19 and its associated complication (Singh et al. 2020). There is no definitive data that clearly defines the link between serum 25(OH)D, diabetes, and COVID-19. Vit D supplementation may benefit this patient group but requires more convincing data; there is evidence of a shared “pathophysiologic and mechanistic link” between COVID-19 and diabetes that is evident in the setting of hypovitaminosis.

## COVID-19 complications and the overarching connection to vitamin D

### Kawasaki-like disease

Kawasaki disease (KD) is an acute febrile vasculitis of unknown etiology, which typically affects children less than 5 years of age (Burns et al. 1996). Although there is no definitive method for diagnosing KD, there are some criteria that are used to differentiate it from other differentials, which includes fever (5 or more days), and at least four of the following signs; lip and oral cavity changes, extremity changes, polymorphous rash, cervical lymphadenopathy, bilateral conjunctival injection, and typically supersedes a viral infection.

Current reports have demonstrated that younger individuals who test positive for COVID-19 will present with symptoms that typically match the criteria of KD rather than the clinical picture seen in adults. This Kawasaki like disease seen in young COVID-19 patients, also known as MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN (MIS-C) was demonstrated in several studies (Acharyya et al. 2020; Jones et al. 2014; Rivera-Figueroa et al. 2020; Ouldali et al. 2020). Acharyya et al. in a case report noted that a 4-month-old baby who tested positive for COVID-19 and presented with the clinical features of KD (Acharyya et al. 2020). An echocardiogram was performed which showed diffuse ectasia of the coronary arteries, and after administering intravenous immunoglobulins (IVIG), a therapy used in the setting of KD, the new born recovered (Acharyya et al. 2020). Many other case reports reported similar findings and outcomes (Jones et al. 2014; Rivera-Figueroa et al. 2020). Unfortunately, there is still no solid

explanation as to why KD or Kawasaki-like disease occurs, and whether or not the patient originally had KD, thus making them more susceptible to COVID-19 or vice versa. More research is needed to further clarify the association between KD and COVID-19.

Interestingly, Vit D modulates the inflammatory effect of KD, and any alterations in its serum levels may affect the prognosis and progression of KD. Suzuki et al. demonstrated that there is mRNA and protein expression of the VDR in human coronary arterial endothelial cells (HCAEC) (Suzuki et al. 2009). They also examined whether or not Vit D inhibits TNF- $\alpha$ -induced activation of NF- $\kappa$ B, an essential factor needed for the expression of pro-inflammatory cytokines in HCAEC (Suzuki et al. 2009). The results of their study were as follows: (1) Vit D inhibits TNF- $\alpha$  and its consequent expression of E-selectin on HCAEC and (2) Vit D significantly inhibits TNF- $\alpha$ -induced activation of NF- $\kappa$ B, both of which play a vital role in the pathogenesis of KD vasculitis (Suzuki et al. 2009). In a study assessing the relationship between 25(OH)D serum levels in KD children and the occurrence of KD-associated vascular abnormalities, Stagi et al. reported the following; 98.7% of the patients presented with hypovitaminosis D, and those who presented with severe deficiency developed coronary artery abnormalities significantly ( $P < 0.0001$ ) (Stagi et al. 2016). Sung Jun et al. also noted that patients with KD who presented with severe hypovitaminosis D ( $P = 0.023$ ) were resistant to IVIG therapy than those who did not, thus concluding that low 1,25(OH)D levels may be a risk factor for immunoglobulin resistance (Jun et al. 2017). Falcini et al. concluded that Vit D may contribute to the course and severity of coronary aneurysms present in the setting of KD (Falcini et al. 2015).

There is definitely a correlation between Vit D and the pathogenesis of KD, but until now, it is not fully understood. The connection between COVID-19 and KD is demonstrated in not only children, but adults as well. Whether or not KD makes the individual more susceptible to developing COVID-19 infection or vice versa requires robust research. From these data, it can be concluded that COVID-19 predominately affects children in the form of a Kawasaki-like clinical presentation, and both the pathogenesis and disease progression of COVID-19 and KD are influenced by the levels of serum Vit D.

### Hypercoagulability and thrombosis

There is substantial evidence regarding the effect of hypovitaminosis D, fibrinolysis, and coagulation in animals and human studies (Targher et al. 2012). Agmon-Levin et al. documented that: (1) there is a significantly higher prevalence of hypovitaminosis D among antiphospholipid syndrome (APS)-hypercoagulable state patients ( $P < 0.05$ ); (2) an inverse relationship between thrombotic manifestations

and Vit D levels in APS patients ( $P < 0.05$ ); (3) Vit D supplements aid in preventing thrombosis mediated by APS; and (4) there is a 50% increased risk of developing arterial and venous thrombosis during winter (lack of sun exposure) compared to other seasons (Agmon-Levin et al. 2013). The mechanism by which 1,25(OH)D exerts an anticoagulant effect is by; up regulating the anticoagulant glycoprotein (thrombomodulin), and down regulating the expression of some coagulation and tissue factors (García-Carrasco et al. 2018). In a 6538 cohort study investigating the association between Vit D levels and seasonal variations of plasma hemostatic markers (fibrinogen, D-dimer, tissue plasminogen activator (tPA), and Von Wille-brand factor), Hyppönen et al. reported the following: (1) serum 25(OH)D levels were inversely correlated with tPA antigen as well as D-dimer and fibrinogen but to a lesser extent and (2) all three of these hemostatic factors varied by season which was correlated with the seasonal fluctuations of Vit D (Hyppönen et al. 2010). In addition, hypovitaminosis D is associated with elevated levels of asymmetric dimethyl-arginine, which is a marker for endothelial dysfunction (Targher et al. 2012). Beer et al. noticed a significant reduction of thrombotic adverse events (pulmonary embolism, deep vein thrombosis, arterial thrombosis, myocardial infarction, and ischemic cerebrovascular accident) in cancer patients receiving Vit D along with their cancer therapy compared to those receiving placebo (Beer et al. 2006). Although these data may suggest that Vit D has a non-classical coagulation associated mechanism of action, more clinical studies are needed to better understand the impact that Vit D has on the coagulation process and coagulopathies.

Vascular complications of severe COVID-19 infection include; venous/arterial thromboembolism, disseminated intravascular coagulation, and elevated levels of coagulation profiles (Gómez-Mesa et al. 2020). Gomez-Mesa et al. noted that: (1) 71.4% of COVID-19-associated mortality is caused by DIC; (2) 20–50% of hospitalized COVID-19 patients present with hematologic changes in their coagulation profiles (prolonged Prothrombin time, thrombocytopenia, elevated D-dimer, and low fibrinogen); (3) there is a pro-coagulant response to acute phase reactants (factor VIII, Von Wille-brand factor, and fibrinogen) in response to COVID-19 which are directly associated with increased risk of thrombosis; and (4) severe COVID-19 patients present with cytokine storm (IL-6) which induces the expression of tissue factor in macrophages, resulting in the activation of thrombin (Gómez-Mesa et al. 2020). These evidences suggest the potential relevance of vitamin D status to thrombotic disorders which are a devastating complication of COVID-19; normalization of Vit D values may aid in decreasing the risk of thrombotic events which requires more evidence.

## Integrating vitamin D during the current pandemic

To limit the spread of the virus, new policies have been set, which included; the closure of public parks and recreational centers, which no doubt limits the healthy exposure of sunlight, the main yielder of Vit D. In the winter seasons, there is a higher burden of hypovitaminosis D and an increased susceptibility to respiratory viral infections. More so, at risk groups such as the elderly, diabetics, and obese persons are at additional risk of low Vit D given their already abnormal Vit D profiles, which may have been exacerbated by stay at home orders. Government suggestions to adopt at home work and online home schooling (George 2021) are additional risk factors to the development of hypovitaminosis D. Paiva et al. noted that institutionalized elderly (from August to November) had significantly higher levels of hypovitaminosis D than those who were not or taking supplementation (Paiva et al. 2017), which further suggests the need for supplementation.

It is important to address the fact that hypovitaminosis D is currently an international health issue. Over 1 billion people have Vit D deficiency and 50% of the population has Vit D insufficiency worldwide (Sizar et al. 2020). The role of Vit D supplementation is many folds and includes prophylactic supplementation for at risk groups, those with hypovitaminosis D, those with severe COVID-19, and those in the ICU. Vit D is a good prognostic factor for COVID-19, so serum 25(OH) D levels of positive patients should be constantly evaluated. There is a need for optimal Vit D levels, which could be achieved by supplementation as well as ingestion of high content Vit D foods. The optimal level may vary depending on age, ethnicity, race, the presence of diseases and comorbidities.

In areas that are limited through physical or geographical factors resulting in hypovitaminosis D, the fortification of foods with vitamin D was associated with less prevalence of hypovitaminosis D (Shakur et al. 2014; Cashman and Kiely 2016). Moreover, there are several social, ethnic, religious, cultural, dietary, geographical, and vocational factors that affect Vit D status. Individuals with increased skin pigmentation are at high risk of hypovitaminosis D (Kaufman et al. 2017). Currently people of color are disproportionately affected by COVID-19 in terms of poor outcome. Ethno religious variations are another risk factor for vitamin status, for example, Muslim women are at risk of hypovitaminosis D due to adapting modest attire which covers most of their skin, in spite of living in sunny equatorial countries (Ojah and Welch 2012). Dietary concerns are another problem that should be addressed from perspectives of both personal dietary choices and economic influences on diet. Further observation would show that

food options which contain the highest available Vit D can be expensive (Hess et al. 2019). The cheapest known source of Vit D is fortified milk, and though it has contributed greatly to increasing 1,25(OH) D levels in consumers, it is still not enough. A call has been made for more biofortification of foods with 1,25(OH) D to accommodate dietary diversity (and economic diversity should be considered). Clinical patients are likely to require additional means to address their low Vit D status.

Attention must be brought to the current social attitudes to drugs or adjuvants being labeled as a “cures” for COVID-19. Recently, Vit D has been making headlines and a brief Google search (performed of 13/01/21) will show that 119,000 news articles have been made with the search inquiry “COVID-19” “Vitamin D”, and “cure”, (90 articles within the first 2 weeks of January 2021). Hypovitaminosis D is an issue of concern given the current atmosphere of social panic with regards to the pandemic, and scientific papers and news articles touting vitamin supplementation as a cure not yet backed by conclusive evidence will likely do more harm than good. While there is definitely some excitement among the scientific community regarding Vit D and COVID-19, we must focus our efforts on robust clinical evidence. Currently there are two completed and published clinical trials regarding the effect of Vit D supplementation on COVID-19 patients. One of the clinical trials (NCT04449718) (Rastogi et al. 2020) found that supplementing 200,000 IU of Vit D did not significantly reduce clinically relevant outcomes or hospital stay, while the other clinical trial (NCT04459247) Murai et al. (2020) demonstrated that positive COVID-19 patients converted to negative upon supplementation of 60,000 IU of Vit D daily. There were no adverse reactions recorded other than one individual in the first trial who presented with vomiting after administration of Vit D (Murai et al. 2020).

If at most, low Vit D status has substantial circumstantial evidence that it is risk factor for poor outcomes in COVID-19, then it offers a relatively safe and cheap adjuvant that may benefit at risk groups and those with hypovitaminosis D. While this evidence is being built upon, normalizing body levels through food choices, supplementation, and increasing day time exposure to sunlight in a safe low risk way are options to be considered. More research is required to confirm the appropriate dosages of supplementation that provide optimal benefits specific to COVID-19 patients without producing toxic adverse effects.

## Conclusion

In conclusion, there are substantial clues that suggest the pathophysiologic role of hypovitaminosis D in the COVID-19 setting along with a shared connection of deregulated Vit

D levels in the pathology of certain at risk groups (diabetics and obese) and COVID-19 complications (ARDS). Low Vit D has been pinpointed as a risk factor for COVID-19 poor outcomes. Vit D should be considered as a prognostic marker for COVID-19 patients and an elaborate plan should be developed to address the issue of low status which encompasses the various dietary, ethnic, cultural, social, vocational, and health factors that influence Vit D status.

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## Declarations

**Conflict of interest** The authors of this manuscript declare that there is no conflict of interest.

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