Are Adequate Vitamin D Levels Helpful in Fighting COVID-19? A Look at the Evidence

Authors
Caroline Wei Shan Hoong[1*], Koh Huilin[1*], Sanda Cho[2], Veeraraghavan Meyyur Aravamudan[1**], Jaime Hui Xian Lin[1**]

Affiliations
1 Woodlands Health Campus, National Healthcare Group, Singapore
2 Warrington and Halton Hospitals NHS Foundation Trust, Warrington, United Kingdom

Key words
Vitamin D, bone/calcium homeostasis, COVID-19, SARS-CoV-2, ACE2, immunity, respiratory tract infections

received 27.05.2020
accepted after revision 14.08.2020
Published online: 2020

Bibliography
Horm Metab Res
DOI 10.1055/a-1243-5462
ISSN 0018-5043

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence
Caroline Wei Shan Hoong
National Healthcare Group Woodlands Health Campus – Endocrinology
90 Yishun Central
768828 Singapore
Singapore
caroline_hoong@whc.sg

ABSTRACT

COVID-19 is a global pandemic with high mortality in vulnerable groups. Given the current lack of definitive treatment or vaccine that significantly reduces mortality rate, governments, researchers and healthcare providers are racing to find possible solutions to the crisis. Vitamin D and its analogues have been previously studied for their non-skeletal benefits. In particular, questions regarding their role in the modulation of immunity have re-surfaced, in view of possible epidemiological links observed between COVID-19 and vitamin D levels in selected populations. In this review, we highlight potential mechanisms and summarise the evidence for and against the potential role of vitamin D supplementation in our fight against COVID-19.

Introduction

The global COVID-19 pandemic has triggered the hunt for an effective anti-viral treatment, as well as a race against time in the development of a vaccine. Given the current lack of specific treatment protocols and the high mortality in certain vulnerable groups, researchers are mainly focused on the repurposing of available drugs to develop quick and cost-effective therapeutic strategies, in particular, targeting the hospitalised and critically ill cases. Public health preventative strategies center mainly on social distancing, as well as rapid isolation and containment of identified disease carriers. The individual is encouraged to practice good personal hygiene, be socially responsible, while maintaining health and well-being. Many have sought and tested the spectrum of alternative therapies and dietary modifications available on the market. In this review, we look at the evidence of serum vitamin D levels in relation to COVID-19 infections in retrospective studies, examine the use of vitamin D supplementation in other respiratory tract infections, and describe the anti-viral/microbial and immune-modulatory effects of vitamin D as well as potential adjunctive role in targeting SARS-CoV2.

Vitamin D and the Immune System

The main role of vitamin D in the human body is in calcium homeostasis. However, the vitamin D receptor (VDR) is ubiquitously expressed throughout the body, including on immune cells [1]. The

* These co-first authors contributed equally to this work.
** These co-principal investigators contributed equally to this work.

main form of oral vitamin D supplementation is in the form of 25-hydroxyvitamin D3 [25(OH)D], which is an inactive form of vitamin D. 1α-Hydroxylase converts 25(OH)D to the active form of 1,25-hydroxyvitamin D [$1,25(OH)_2D$]. In calcium homeostasis, the parathyroid hormone (PTH) controls the activity of renal 1α-hydroxylase. Extra-renally among immune cells, 1α-hydroxylase is expressed by peripheral blood monocytes, macrophages, B-cells, T-cells as well as dendritic cells [2]. As such, immune cells possessing both VDR and 1α-hydroxylase, control the synthesis of $1,25(OH)_2D$ in an autocrine fashion. This in turn begs the question of the role of vitamin D in modulating the immune system.

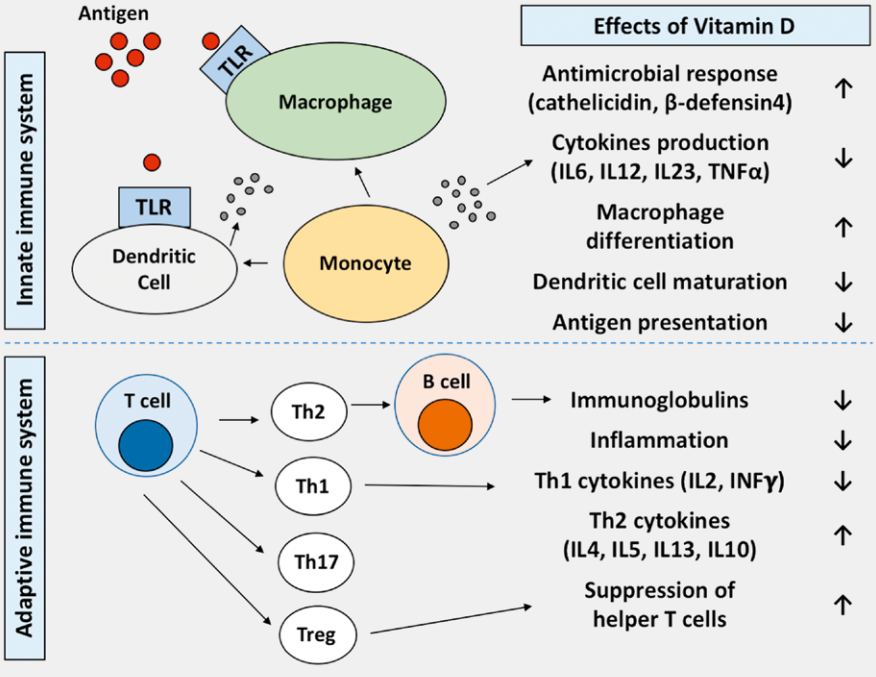
Vitamin D exerts its effects in both the innate and adaptive immune response [3]. In the event of microbial infection, macrophages recognize the lipopolysaccharide (LPS) particles through Toll-like receptors (TLR), hence triggering a cascade of peptide syntheses (cathelocidin and β-defensin4) with potent bactericidal activity [4] (▶ **Fig. 1**). TLR binding stimulates expression of 1α-hydroxylase and VDR [4]. The binding of $1,25(OH)_2D$ to VDR is needed for the transcription of cathelocidin and β-defensin-4 [4]. In particular, Liu et al found that the transcription of cathelocidin is dependent on sufficient 25(OH)D levels [4]. In addition, $1,25(OH)_2D$ inhibits monocyte production of the inflammatory cytokines IL-1, IL-6, IL-8, IL-12, and TNFα (▶ **Fig. 1**) [5], the fundamental players which build up to a cytokine storm in severe SARS-CoV-2 infection resulting in acute respiratory distress syndrome (ARDS) as well as multi-organ failure.

Furthermore, vitamin D modulates adaptive immunity by inhibiting B cell proliferation, differentiation and secretion of antibodies [6] (▶ **Fig. 1**). Vitamin D also inhibits T cell proliferation and modulates the T cell phenotype (▶ **Fig. 1**). It stimulates the development of the suppressive T regulatory cells but inhibits the development of pro-inflammatory Th17 cells [7]. This results in the production of anti-inflammatory cytokines such as IL-10 but decreases the production of inflammatory cytokines such as IL-17 and IL-21 [7]. Hence, possessing adequate levels of $1,25(OH)_2D$ may have a protective effect against COVID-19 in relation to the immune suppression of cytokine response and possibly reduced severity or risk of ARDS and multi-organ failure. To the best of our knowledge, no randomized controlled study has yet reported vitamin D status and cytokine levels in patients with COVID-19 infection. As the inflammatory marker C-reactive protein (CRP) is a good surrogate of IL-6 [8], we propose to use CRP as a cost-effective marker to estimate the association between vitamin D status and severe COVID-19 infection.

Vitamin D and its association with respiratory infection

Multiple studies have demonstrated an association between low serum 25(OH)D concentrations and susceptibility to acute respiratory tract infection (RTI) [9–15]. There are also reports suggesting a reduction in chronic obstructive pulmonary disease [16–18] and asthma [19, 20] exacerbation. These findings however are not consistently demonstrated [21–24]. Research on vitamin D concentration and its association with infections are methodically challenging. The severity of vitamin D deficiency, extent of infection, variation in vitamin D replacement regimens, patient characteristics and coexisting morbidities are some factors that may contribute to the heterogeneity of effect between studies.

To limit potential confounders, meta-analysis of primary randomized controlled trials (RCTs) has been conducted in more recent



▶ **Fig. 1** Schematic diagram of the effects of vitamin D on the immune system.

▶ **Table 1** Meta-analyses on the efficacy of vitamin D in the prevention of respiratory tract infection.

Authors	Publication year	Number of trials	Number of participants	Adjusted Odds Ratio (95 % CI)	Test for heterogeneity
Charan J et al. [11]	2012	5	1868	0.582 (0.417–0.812), p = 0.001	I^2 = 24.7 %
Bergman P et al. [10]	2013	11	5660	0.64 (0.49–0.84), p = 0.0014	I^2 = 72 %
Zittermann A et al. [25]	2016	16	7421	0.65 (0.50–0.85), p = 0.005	I^2 = 74 %
Martineau AR et al. [9]	2017	25	11 321	0.88 (0.81–0.96), p = 0.003 NNT 33 (20–101)	p <0.001

CI: Confidence interval; NNT: Number needed to treat. In all 4 studies, vitamin D was shown to be protective against RTI. There was, however, significant heterogeneity in 2 of the 4 studies.

years (▶ **Table 1**) [9–11]. One such meta-analysis consisting of 5 clinical trials demonstrated an overall significant reduction in the incidence of RTI in the vitamin D group as compared to the control group [11]. Two of its clinical trials were conducted on the pediatric age group and the remaining three were conducted on adults. Further analysis based on age groups did not yield a significant result in the adult group [11]. Test for heterogeneity was mild [11], however, there were only few studies involved.

Another meta-analysis of 11 RCT performed by Bergman et al. demonstrated a protective effect of vitamin D against RTI. There was, however, significant heterogeneity among studies [10]. Furthermore, the authors acknowledged that publication bias might have influenced the results. The findings of a larger meta-analysis of 16 studies yielded similar results. Significant risk reduction of RTI with vitamin D supplementation was demonstrated [25]. Again, significant heterogeneity was found among studies [25].

To identify factors that could explain the observed heterogeneity among studies, Martineau et al. undertook a meta-analysis on 25 RCTs with 10 933 individual participant data that studied vitamin D supplementation for prevention of acute respiratory tract infection. They too have shown that overall vitamin D supplementation reduced the risk of acute RTI among all participants [9]. Subgroup analysis, however, showed that this risk reduction was greater among participants with lower baseline of circulating 25(OH)D levels of less than 25 nmol/l [9], and only with daily or weekly vitamin D supplementation without additional bolus doses [9]. No risk reduction was seen among participants who received at least one bolus dose of vitamin D [9]. Vitamin D supplementation did not induce risk of serious adverse events or death of any cause [9].

Vitamin D supplementation for the prevention of RTI remains controversial. Patients with low vitamin D levels, however should be supplemented orally for skeletal benefit, which may also offer protective effects against RTI.

Vitamin D deficiency and possible links with COVID-19

There have been several associations observed that may link vitamin D deficiency to the occurrence and severity of COVID-19 infections. The geographical distribution of COVID-19 cases worldwide has led to hypotheses regarding vitamin D status and number and severity of infection. A study has linked increasing latitude above 35 degrees North to higher mortality, suggesting vitamin D deficiency over winter could be linked to SARS-CoV-2 becoming rampant [26]. Seeming to be outliers, Nordic countries have relatively low rates of COVID-19 infections and mortality despite having low sunlight exposure during winter. However, the prevalence of vitamin D deficiency is low in Nordic countries due to the widespread use of cod liver oil and supplementation [27], leading one to speculate about the role of vitamin D supplementation in the outcome of COVID-19 infections.

A negative correlation was found between mean vitamin D levels in each country versus their number of COVID-19 cases and mortality rates (▶ **Table 2** and ▶ **Fig. 2**), which corresponds to that found in another study [28]. Notably there is significant scatter, as other factors such as government policies and availability of healthcare services may significantly influence outcome as well, however an interesting pattern is observed.

There is also growing evidence that COVID-19 tends to disproportionately affect African Americans in the United States [29, 30], and that those of black and ethnic minority origins have more severe disease [31]. Due to reduced vitamin D production from skin pigmentation, there is a higher prevalence of vitamin D deficiency in dark-skin individuals [32].

Many proposed confounders that link ethnic minority groups to increased COVID-19 infections such as socioeconomic status, access to healthcare and comorbidities are insufficient to explain the disparity in COVID-19 cases and death rates. In models accounting for socioeconomic factors and significant comorbidities, Black race still remained an independent factor for COVID-19 cases and deaths in the United States [33]. These findings are mirrored in a British cohort: after correcting for population density, deprivation level, socioeconomic status, education, self-reported health and occupational exposure, increased COVID-19 mortality remained significant in Black, Indian, Bangladeshi and Pakistani populations as compared to a White cohort [34]. Biological and genetic factors may play a role in the ethnic disparity observed, nonetheless the possible effect of low vitamin D status in these ethnic groups cannot be excluded. The effect of confounding variables particularly socio-economic status on vitamin D levels was reported using data from the UK Biobank, where vitamin D levels and presence of vita-

▶ **Table 2** Vitamin D status of populations worldwide and their corresponding COVID-19 case numbers and mortality.

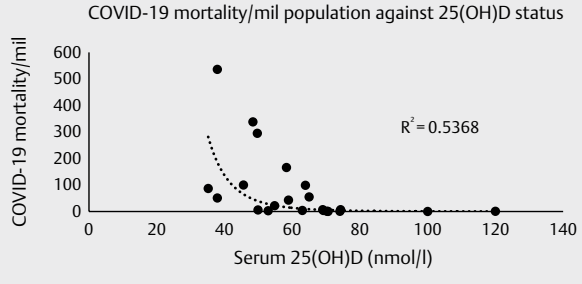
Country	COVID-19 cases/ mil	COVID-19 deaths/mil	Vit D/nmol/l*	Population, years	n	Reference
Americas						
USA	4974	295	49.7 ± 21.2	Age > 20	4495	Forrest et al. 2011 [81]
Canada	2187	166	58.3 ± 0.9	Age 3–79	11 336	Sarafin et al. 2015 [82]
Brazil	1565	99	63.9 ± 28.6	Age 2–95	39 004	Eloi et al. 2016 [83]
Europe						
Russia	2237	22	54.8 ± 0.7	Age 18–75	1544	Karonova et al. 2016 [84]
UK	3747	536	Men 37.0 (95 % CI 36.8–37.2), Women 38.7 (95 % CI 38.6–38.8)	Age > 18	210 502	Crowe et al. 2019 [36]
Germany	2146	100	45.6	Age 18–79	6995	Rabenberg et al. 2015 [85]
Netherlands	2620	338	48.4	Age 0–98, winter	2503	Boonman-de Winter et al. (2015) [86]
Norway	1538	43	58.9 ± 23.1	Age 19–55	2505	Larose et al. 2014 [87]
Finland	1180	55	65 (95 % CI 65–66)	Age > 30	4051	Jääskeläinen et al. 2017 [27]
Asia						
Japan	131	6	49.9 ± 18.4	Age 40–74	9084	Nakamura et al. 2015 [88]
Hong Kong	142	0.5	70.6 ± 27.0	Age > 50	382	Wat et al. 2007 [89]
China	58	3	Median 52.9 (IQ 42.4–62.4)	Age 20–89	2588	Lu et al. 2012 [90]
Oceania						
Australia	279	4	69.2 ± 26.4	Age > 24	2413	Gill et al. 2014 [91]
New Zealand	312	4	63 ± 1.5	Age > 15	4721	NZ Ministry of Health, 2012 [92]
Africa						
South Africa	340	7	69.0 ± 23.8	Age 0–90	3112	Mogire et al. 2020 [93]
Egypt	155	7	74.3 ± 24.7	Age 0–90	1851	Mogire et al. 2020 [93]
Zimbabwe	3	0.3	100 ± 27.1	Age 0–90	63	Mogire et al. 2020 [93]
Kenya	22	0.9	70.3 ± 92.1	Age 0–90	385	Mogire et al. 2020 [93]
Ghana	209	1	74.1 ± 8.5	Age 0–90	595	Mogire et al. 2020 [93]
Middle East						
Iran	1570	87	Median 35.2 (IQ 24.0–72.4)	Age > 30	251	Hosseinpanah et al. 2011 [94]
Turkey	1834	51	37.9 ± 22.0	All ages	35 667	Solak et al. 2018 [95]
Jordan	69	0.9	Men 183 ± 73.1 Women 99.3 ± 51.7	Age > 19	4590	Batieha et al. 2011 [96]

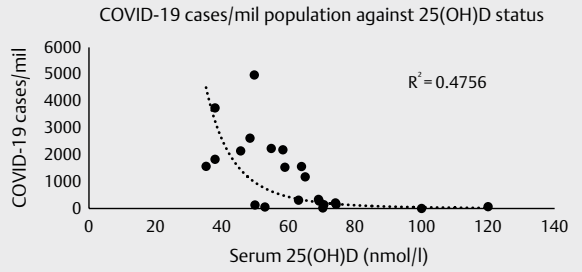
Cumulative COVID-19 data as of 23rd May 2020 [37]. * Vitamin D is represented as mean levels ± standard deviation, unless otherwise stated. IQ: Interquartile range, CI: Confidence interval. Vitamin D population data were limited in Latin America, Asia, and Africa. Studies in selected groups, e. g., pregnancy, infants, elderly and the institutionalised were avoided as they were deemed to be not representative of the overall population.

min D deficiency were significant risk factors for COVID-19 infection, however this significance was negated when adjusted for confounders such as comorbidities, deprivation status and disability [35]. In interpreting data from the UK Biobank, we are mindful that vitamin D levels were collected more than a decade ago, and evidence suggests that an increasing awareness of vitamin D deficiency particularly among ethnic groups has led to an increase in testing and supplementation in the UK in recent years [36]. Due to conflicting evidence from retrospective studies, data from randomised controlled trials are urgently needed to elucidate the role of vitamin D supplementation in COVID-19 infections.

Other poor prognostic factors for COVID-19 include older age and underlying comorbidities such as hypertension, diabetes, obesity, and ischemic heart disease [38–40], which are also risk factors for vitamin D deficiency [41–45]. Indeed, two retrospective preprint studies have found that serum 25(OH)D levels were lowest in critical cases and highest in mild cases of COVID-19 [46, 47], and was significantly correlated with positivity for SARS-CoV-2 [48]. A retrospective cohort study which explored the role of combined vitamin D, vitamin B12, and magnesium supplementation in COVID-19 hospitalised patients found a significant protective effect against clinical deterioration after correction for age and hy-

pertension [49]. Although the contribution from individual components of supplementation are unclear and the mechanism of a rapid clinical response within days of supplementation is not specified, it provides a promising base for future controlled trials.



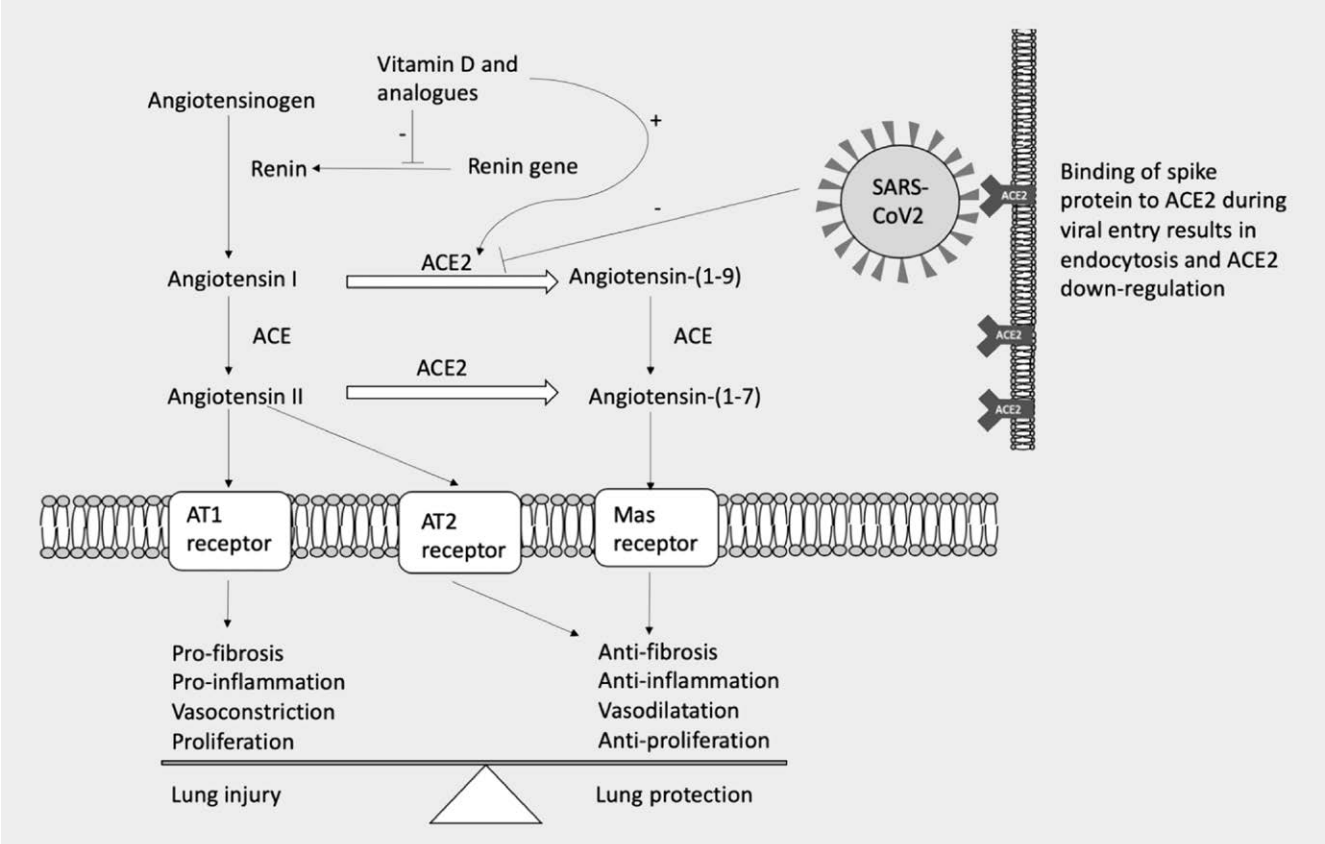


▶ **Fig. 2** Cumulative number of COVID-19 cases and mortality per million population as of 23 May 2020 [37] are higher in countries with lower vitamin D levels. Refer to data from studies in ▶ **Table 2**.

While evidence from retrospective studies and associations cannot prove causality, there are plausible mechanisms regarding the role of vitamin D deficiency and its modulation of the renin-angiotensin system (RAS) and immune response that may influence the outcome of COVID-19 infection. Together, they give sufficient grounds to investigate the role of vitamin D deficiency further with prospective randomised trials.

Severe COVID-19 results in ARDS, mediated by a cytokine storm, which can cause multi-organ failure and death. Several pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, IFN-γ, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, and TNF-α have been implicated in the pathogenesis of cytokine storm in COVID-19, favouring a Th1 and Th-17 cytokine profile [50–52]. 1,25-Dihydroxyvitamin D3 was able to suppress the pro-inflammatory Th1 and Th17 cytokine profile in mice and human trophoblasts [53, 54]. A meta-analysis found that vitamin D supplementation significantly reduced hs-CRP but not TNF-α and IL-6 levels in type 2 diabetes mellitus [55]. The negative results about suppression of chronic inflammation in chronic disease may not be generalizable to the possible effects of vitamin D on a cytokine storm induced by acute illness. More evidence is needed in critically ill patients.

Besides its effects on blood pressure and sodium retention, activation of the RAS has more recently been linked to autocrine and paracrine effects that are involved in tissue remodelling and fibro-



▶ **Fig. 3** Mechanism of possible lung protective effect of vitamin D and its analogues in COVID-19 infection via upregulation of ACE2-Ang-(1–7)-Mas axis.

sis in the lung [56], and vitamin D has been shown to regulate the RAS. Angiotensin converting enzyme (ACE) and ACE2 have opposing actions to up and downregulate angiotensin II, respectively [57]. Angiotensin II, in addition its hypertensive effects, mediates pro-inflammatory responses via an increased production of reactive oxygen species and leukocyte recruitment, and induces a fibro-proliferative response in the lungs [58, 59].

ACE2 is the entry receptor via which SARS-CoV-2 infects human host [60], and is expressed in endothelial cells and arterial smooth muscle cells in almost all organs, including lung alveolar epithelial cells [61, 62]. While increased ACE2 acting as viral entry points may theoretically be a risk factor for infection of SARS-CoV-2, there is currently no evidence for this. Diabetes and hypertension are risk factors for COVID-19 infection, even though ACE2 levels are reduced in these conditions [63, 64]. On the contrary, upregulation of the ACE2-Ang-1(1–7)-Mas axis appears to have an anti-inflammatory role and is protective against acute lung injury [65, 66], while blocking ACE2 can exacerbate SARS-CoV-induced pulmonary injury [65, 67]. Binding of the viral spike protein to ACE2 downregulates ACE2 and increases angiotensin II-mediated lung inflammation [67]. In mice and in vitro studies, vitamin D suppresses renin synthesis and is a negative regulator of the RAS via inhibition of cAMP response element in the renin gene promoter [68, 69]. Calcitriol increased ACE2, Ang-(1–7) and Mas levels and reduced ACE/ACE2 ratio [69, 70]. Conversely, vitamin D deficiency is associated with downregulation of the ACE2 pathway, activation of the RAS and higher circulating angiotensin II levels [71]. A schematic diagram is illustrated in ▶ **Fig. 3**.

Vitamin D deficiency has been described to be associated with the development of acute respiratory failure [72, 73], with type II alveolar cells displaying an upregulation of multiple genes associated with cell growth, differentiation and response to wounding in response to vitamin D treatment [72]. In critically ill patients with severe vitamin D deficiency, administration of high dose vitamin D was found to reduce hospital mortality [74] and increase ventilator-free days among mechanically-ventilated patients [75]. Besides its role in modulating the RAS and suppressing cytokine storm in ARDS, calcitriol has also been thought to attenuate lung injury by increasing surfactant production, stimulating epithelial repair, and inhibiting alveolar cell apoptosis [76, 77]. We await the results from the VITADLIZE study about the effect of high dose vitamin D3 supplementation in critically ill patients with severe vitamin D deficiency [78]. Similarly, prospective studies are needed to evaluate if vitamin D administration will be beneficial to reduce the development of ARDS induced by SARS-CoV-2.

Vitamin D supplementation is cheap and safe, with low risk of toxicity [79]. Target levels for optimal immune function is unknown, although experts suggest higher levels of 25(OH)D above 75 nmol/l (30 ng/ml) may be required for non-skeletal benefits [80], which is greater than what is frequently defined for bone health of levels above 50 nmol/l (20 ng/ml). Practically, given that it can take weeks to months to raise serum 25(OH)D levels, a population-based preventive strategy can be undertaken for at-risk groups. Its use can be seen as an adjunctive role for reducing overall population risk rather than an acute treatment strategy.

Conclusion

We have discussed the role of vitamin D and its analogues in the modulation of the innate and adaptive immunity which may protect against several respiratory tract pathogens, suppression of cytokine storm in ARDS and modulation of the renin-angiotensin system favouring the ACE2 axis. There are some epidemiological associations between vitamin D deficiency and the prevalence and severity of COVID-19 infection which may be explored further. Prospective interventional studies are necessary to establish whether population-based vitamin D supplementation as an adjunct to other anti-viral therapies will be helpful in reducing severity and risk of COVID-19 infection.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor? Arch Biochem Biophys 2012; 523: 123–133

[2] Townsend K, Evans KN, Campbell MJ et al. Biological actions of extra-renal 25-hydroxyvitamin D-1alpha-hydroxylase and implications for chemoprevention and treatment. J Steroid Biochem Mol Biol 2005; 97: 103–109

[3] Aranow C. Vitamin D and the Immune System. J Investig Med 2011; 59: 881–886

[4] Liu PT, Stenger S, Li H et al. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 2006; 311 (5768): 1770–1773

[5] Almerighi C, Sinistro A, Cavazza A et al. 1Alpha,25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immunomodulatory activity in human monocytes. Cytokine 2009; 45: 190–197

[6] Chen S, Sims GP, Chen XX et al. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J Immunol 2007; 179: 1634–1647

[7] Daniel C, Sartory NA, Zahn N et al. Immune modulatory treatment of trinitrobenzene 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 Ther 2008; 324: 23–33

[8] Slaats J, ten Oever J, van de Veerdonk FL et al. IL-1b/IL-6/CRP and IL-18/ferritin: Distinct Inflammatory Programs in Infections. PLoS Pathog 2016; 12: e1005973

[9] Martineau AR, Jolliffe DA, Hooper RL et al. Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. BMJ 2017; 356: i6583

[10] Bergman P, Lindh AU, Björkhem-Bergman L et al. Vitamin D and respiratory tract infections: A systematic review and meta-analysis of randomized controlled trials. PLoS One 2013; 8: e65835

[11] Charan J, Goyal JP, Saxena D et al. Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis. J Pharmacol Pharmacother 2012; 3: 300–303

[12] Camargo CA, Ganmaa D, Frazier AL et al. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. Pediatrics 2012; 130: e561–e567

[13] Sabetta JR, DePetrillo P, Cipriani RJ. Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. PLoS One 2010; 5: e11088

[14] Bergman P, Norlin A-C, Hansen S et al. Vitamin D3 supplementation in patients with frequent respiratory tract infections: A randomised and double-blind intervention study. BMJ Open 2012; 2: e001663. doi: 10.1136/bmjopen-2012-001663

[15] Urashima M, Segawa T, Okazaki M et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr 2010; 91: 1255–1260

[16] Martineau AR, James WY, Hooper RL et al. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): A multicentre, double-blind, randomised controlled trial. Lancet Respir Med 2015; 3: 120–130

[17] Kim C, Ko Y, Jung JY et al. Severe vitamin D deficiency is associated with emphysema progression in male patients with COPD. Respir Med 2020; 163: 105890

[18] Burkes RM, Ceppe AS, Doerschuk CM et al. Associations among 25-hydroxyvitamin d levels, lung function, and exacerbation outcomes in COPD: An analysis of the SPIROMICS cohort. Chest 2020; 157: 856–865

[19] Tachimoto H, Mezawa H, Segawa T et al. Improved control of childhood asthma with low-dose, short-term vitamin D supplementation: a randomized, double-blind, placebo-controlled trial. Allergy 2016; 71: 1001–1009

[20] Martineau AR, Cates CJ, Urashima M et al. Vitamin D for the management of asthma. Cochrane Database Syst Rev 2016; 9: CD011511

[21] Mao S, Huang S. Vitamin D supplementation and risk of respiratory tract infections: a meta-analysis of randomized controlled trials. Scand J Infect Dis 2013; 45: 696–702

[22] Xiao L, Xing C, Yang Z et al. Vitamin D supplementation for the prevention of childhood acute respiratory infections: A systematic review of randomised controlled trials. Br J Nutr 2015; 114: 1026–1034

[23] Vuichard Gysin D, Dao D, Gysin CM et al. Effect of Vitamin D3 supplementation on respiratory tract infections in healthy individuals: A systematic review and meta-analysis of randomized controlled trials. PLoS One 2016; 11: e0162996

[24] Lehouck A, Mathieu C, Carremans C et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med 2012; 156: 105–114

[25] Zittermann A, Pilz S, Hoffmann H et al. Vitamin D and airway infections: a European perspective. Eur J Med Res 2016; 21: 14

[26] Rhodes JM, Subramanian S, Laird E et al. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. Aliment Pharmacol Ther 2020; 51: 1434–1437

[27] Jääskeläinen T, Itkonen ST, Lundqvist A et al. The positive impact of general vitamin D food fortification policy on vitamin D status in a representative adult Finnish population: evidence from an 11-y follow-up based on standardized 25-hydroxyvitamin D data. Am J Clin Nutr 2017; 105: 1512–1520

[28] Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res 2020; May 6: 1–4

[29] Gold JAW, Wong KK, Szablewski CM et al. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19 - Georgia, March 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 545–550

[30] State Testing Data by Race [Internet]. Johns Hopkins Coronavirus Resource Center.[cited 2020 May 25] Available from https://coronavirus.jhu.edu/data/us-state-data-availability

[31] Coronavirus (COVID-19) related deaths by ethnic group, England and Wales - Office for National Statistics [Internet] [cited 2020 May 26] Available from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/coronavirusrelateddeathsbyethnicgroupenglandandwales/2march2020to10april2020

[32] Martin CA, Gowda U, Renzaho AMN. The prevalence of vitamin D deficiency among dark-skinned populations according to their stage of migration and region of birth: A meta-analysis. Nutrition 2016; 32: 21–32

[33] Li AY, Hannah TC, Durbin JR et al. Multivariate Analysis of Black Race and Environmental Temperature on COVID-19 In the US. Am J Med Sci. 2020; doi: 10.1016/j.amjms.2020.06.015 [Epub ahead of print]

[34] Model estimates of deaths involving the coronavirus (COVID-19) by ethnic group, England and Wales - Office for National Statistics [Internet] [cited 2020 Jun 25] Available from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/modelestimatesofdeathsinvolvingthecoronaviruscovid-19byethnicgroupenglandandwales

[35] Hastie CE, Mackay DF, Ho F et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes Metab Syndr 2020; 14: 561–565

[36] Crowe FL, Jolly K, MacArthur C et al. Trends in the incidence of testing for vitamin D deficiency in primary care in the UK: A retrospective analysis of The Health Improvement Network (THIN), 2005-2015. BMJ Open 2019; 9: e028355

[37] Cases and Deaths from COVID-19 Virus Pandemic - Worldometer [Internet] [cited 2020 May 23] Available from https://www.worldometers.info/coronavirus/

[38] Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020; 28: 395 (10229) 1054–1062

[39] Li X, Xu S, Yu M et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol 2020; Apr 12 S0091-6749: 30495–4

[40] Peng YD, Meng K, Guan HQ et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. Zhonghua Xin Xue Guan Bing Za Zhi 2020; 48: E004

[41] Vanlint S. Vitamin D and Obesity. Nutrients 2013; 5: 949–956

[42] Scragg R, Sowers M, Bell C et al. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004; 27: 2813–2818

[43] Kunutsor SK, Apekey TA, Steur M. Vitamin D and risk of future hypertension: Meta-analysis of 283,537 participants. Eur J Epidemiol 2013; 28: 205–221

[44] Brøndum-Jacobsen P, Benn M, Jensen GB et al. 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. Arterioscler Thromb Vasc Biol 2012; 32: 2794–2802

[45] Daly RM, Gagnon C, Lu ZX et al. Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. Clin Endocrinol (Oxf) 2012; 77: 26–35

[46] Alipio M. Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19) [Internet].Rochester, NY: Social Science Research Network; 2020 ;Apr [cited 2020 May 26]. Report No.: ID 3571484. Available from https://papers.ssrn.com/abstract=3571484

[47] Raharusun P, Priambada S, Budiarti C et al. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study [Internet].Rochester, NY: Social Science Research Network; 2020Apr [cited 2020 May 26] Report No.: ID 3585561.Available from https://papers.ssrn.com/abstract=3585561

[48] D'Avolio A, Avataneo V, Manca A et al. 25-Hydroxyvitamin D Concentrations Are Lower in Patients with Positive PCR for SARS-CoV-2. Nutrients 2020; 12: 1359

[49] Tan CW, Ho LP, Kalimuddin S et al. A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients. medRxiv. 2020; 2020.06.01.20112334

[50] Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor Fedratinib. J Microbiol Immunol Infect 2020; 53: 368–370

[51] Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: (10223) 497–506

[52] Tay MZ, Poh CM, Rénia L et al. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020; 20: 363–374

[53] Xie Z, Chen J, Zheng C et al. 1,25-dihydroxyvitamin D3 -induced dendritic cells suppress experimental autoimmune encephalomyelitis by increasing proportions of the regulatory lymphocytes and reducing T helper type 1 and type 17 cells. Immunology 2017; 152: 414–424

[54] Díaz L, Noyola-Martínez N, Barrera D et al. Calcitriol inhibits TNF-alpha-induced inflammatory cytokines in human trophoblasts. J Reprod Immunol 2009; 81: 17–24

[55] Yu Y, Tian L, Xiao Y et al. Effect of vitamin D supplementation on some inflammatory biomarkers in type 2 diabetes mellitus subjects: A systematic review and meta-analysis of randomized controlled trials. Ann Nutr Metab 2018; 73: 62–73

[56] Marshall RP. The pulmonary renin-angiotensin system. Curr Pharm Des 2003; 9: 715–722

[57] Lambert DW, Hooper NM, Turner AJ. Angiotensin-converting enzyme 2 and new insights into the renin-angiotensin system. Biochem Pharmacol 2008; 75: 781–786

[58] Bernstein KE, Khan Z, Giani JF et al. Angiotensin-converting enzyme in innate and adaptive immunity. Nat Rev Nephrol 2018; 14: 325–336

[59] Marshall RP, Gohlke P, Chambers RC et al. Angiotensin II and the fibroproliferative response to acute lung injury. Am J Physiol Lung Cell Mol Physiol 2004; 286: L156–L164

[60] Yan R, Zhang Y, Li Y et al. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science 2020; 367: (6485) 1444–1448

[61] Sungnak W, Huang N, Bécavin C et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020; 26: 681–687

[62] Hamming I, Timens W, Bulthuis MLC et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004; 203: 631–637

[63] Koka V, Huang XR, Chung ACK et al. Angiotensin II Up-Regulates Angiotensin I-Converting Enzyme (ACE), but Down-Regulates ACE2 via the AT1-ERK/p38 MAP Kinase Pathway. Am J Pathol 2008; May 172: 1174–1183

[64] Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. Int J Pept 2012; 256294

[65] Imai Y, Kuba K, Rao S et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 2005; 436: (7047) 112–116

[66] Wösten-van Asperen RM, Lutter R, Specht PA et al. Acute respiratory distress syndrome leads to reduced ratio of ACE/ACE2 activities and is prevented by angiotensin-(1-7) or an angiotensin II receptor antagonist. J Pathol 2011; 225: 618–627

[67] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11: 875–879

[68] Li YC, Kong J, Wei M et al. 1,25-Dihydroxyvitamin D3 is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 2002; 110: 229–238

[69] Yuan W, Pan W, Kong J et al. 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem 2007; 282: 29821–29830

[70] Lin M, Gao P, Zhao T et al. Calcitriol regulates angiotensin-converting enzyme and angiotensin converting-enzyme 2 in diabetic kidney disease. Mol Biol Rep 2016; 43: 397–406

[71] Forman JP, Williams JS, Fisher NDL. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertension 2010; 55: 1283–1288

[72] Dancer RCA, Parekh D, Lax S et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax 2015; 70: 617–624

[73] Thickett DR, Moromizato T, Litonjua AA et al. Association between prehospital vitamin D status and incident acute respiratory failure in critically ill patients: A retrospective cohort study. BMJ Open Respir Res 2015; 2: e000074

[74] Amrein K, Schnedl C, Holl A et al. Effect of high-dose vitamin D3 on hospital length of stay in critically ill patients with vitamin D deficiency: the VITdAL-ICU randomized clinical trial. JAMA 2014; 312: 1520–1530

[75] Leclair TR, Zakai N, Bunn JY et al. Vitamin D Supplementation in Mechanically Ventilated Patients in the Medical Intensive Care Unit. JPEN J Parenter Enteral Nutr 2019; 43: 1037–1043

[76] Zheng S, Yang J, Hu X et al. Vitamin D attenuates lung injury via stimulating epithelial repair, reducing epithelial cell apoptosis and inhibits TGF-β induced epithelial to mesenchymal transition. Biochem Pharmacol 2020; 177: 113955

[77] Sakurai R, Shin E, Fonseca S et al. 1alpha,25(OH)2D3 and its 3-epimer promote rat lung alveolar epithelial-mesenchymal interactions and inhibit lipofibroblast apoptosis. Am J Physiol Lung Cell Mol Physiol 2009; 297: L496–L505

[78] Amrein K, Parekh D, Westphal S et al. Effect of high-dose vitamin D3 on 28-day mortality in adult critically ill patients with severe vitamin D deficiency: A study protocol of a multicentre, placebo-controlled double-blind phase III RCT (the VITDALIZE study). BMJ Open 2019; 9: e031083

[79] Dudenkov DV, Yawn BP, Oberhelman SS et al. Changing incidence of serum 25-hydroxyvitamin D values above 50 ng/mL: A 10-year population-based study. Mayo Clin Proc 2015; 90: 577–586

[80] Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357: 266–281

[81] Forrest KYZ, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res 2011; 31: 48–54

[82] Sarafin K, Durazo-Arvizu R, Tian L et al. Standardizing 25-hydroxyvitamin D values from the Canadian Health Measures Survey. Am J Clin Nutr 2015; 102: 1044–1050

[83] Eloi M, Horvath DV, Szejnfeld VL et al. Vitamin D deficiency and seasonal variation over the years in São Paulo, Brazil. Osteoporos Int 2016; 27: 3449–3456

[84] Karonova T, Andreeva A, Nikitina I et al. Prevalence of Vitamin D deficiency in the North-West region of Russia: A cross-sectional study. J Steroid Biochem Mol Biol 2016; 164: 230–234

[85] Rabenberg M, Scheidt-Nave C, Busch MA et al. Vitamin D status among adults in Germany--results from the German Health Interview and Examination Survey for Adults (DEGS1). BMC Public Health 2015; 15: 641

[86] LJM Boonman-de Winter, Albersen A, Mohrmann K et al. High prevalence of vitamin D deficiency in the south-west Netherlands. Ned Tijdschr Geneeskd 2015; 159: A8167

[87] Larose TL, Chen Y, Camargo CA et al. Factors associated with vitamin D deficiency in a Norwegian population: the HUNT Study. J Epidemiol Community Health 2014; 68: 165–170

[88] Nakamura K, Kitamura K, Takachi R et al. Impact of demographic, environmental, and lifestyle factors on vitamin D sufficiency in 9084 Japanese adults. Bone 2015; 74: 10–17

[89] Wat WZM, Leung JYY, Tam S et al. Prevalence and impact of vitamin D insufficiency in southern Chinese adults. Ann Nutr Metab 2007; 51: 59–64

[90] Lu H-K, Zhang Z, Ke Y-H et al. High prevalence of vitamin D insufficiency in China: Relationship with the levels of parathyroid hormone and markers of bone turnover. PLoS One 2012; 7: e47264

[91] Gill TK, Hill CL, Shanahan EM et al. Vitamin D levels in an Australian population. BMC Public Health 2014; 14: 1001

[92] Vitamin D. Status of New Zealand Adults [Internet]. Ministry of Health NZ. [cited 2020 May 26] Available from https://www.health.govt.nz/publication/vitamin-d-status-new-zealand-adults

[93] Mogire RM, Mutua A, Kimita W et al. Prevalence of vitamin D deficiency in Africa: A systematic review and meta-analysis. Lancet Glob Health 2020; 8: e134–e142

[94] Hosseinpanah F, Yarjanli M, Sheikholeslami F et al. Associations between vitamin D and cardiovascular outcomes; Tehran Lipid and Glucose Study. Atherosclerosis 2011; 218: 238–242

[95] Solak I, Cihan FG, Mercan S et al. Evaluation of 25-Hydroxyvitamin D Levels in Central Anatolia, Turkey. Biomed Res Int 2018; 4076548

[96] Batieha A, Khader Y, Jaddou H et al. Vitamin D status in Jordan: dress style and gender discrepancies. Ann Nutr Metab 2011; 58: 10–18