Republic of Iraq
Ministry of Higher Education
And Scientific Research
University of Diyala
College of Medicine

Role of Vit D supplementation in COVID-19

A project submitted to the council of College of Medicine / University of Diyala in Partial fulfillment of the Requirements for the Degree of bachelor

Done By

Jenan Loay Abd-al Jalil

Supervised By

Dr.Rana Abd-al Salam Majeed

2020-2021

بسم الله الرحمن الرحيم

(نَرْفَعُ دَرَجَاتٍ مَّن نَّشَاءُ وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ..)

صدق الله العظيم

سورة يوسف آية (76)

الاهداء

الاهداء اولآ الى وجه الله تعالى

في جميع مراحل الحياة يوجد أناس يستحقون منا الشكر والتقدير واولى الناس بالشكر

والدي العزيز الذي جرع الكأس فارغآ ليسقيني قطرة حب

والدتي العزيزة التي وضعتني على طريق الحياة وكان لها الفضل الكبير لنجاحي

والى جميع من وقفوا بجانبي وساعدوني وبالخصوص

الى أصدقائي والى جميع اساتذتي الكرام بوجه عام والى إلدكتورة

"رنا عبد السلام " المشرفة على البحث بوجه خاص التي كان لها دور كبير في اعطائي المعلومات القيمة اهدي لكم بحث تخرجي المتواضع وأتمنى ان تحوز على رضاكم .

ألشكر والتقدير

الحمدلله ألذي هدانا وأعدنا وأمدنا والهمنا الصبر على المشاق ووفقنا لما نحن عليه

فله الحمد والشكر ابتداءاً وانتهاءاً

وارفع كلمة الشكر الى الدكتورة **رنا عبد السلام**

وفقها الله فقد كانت سندا لي على طول الطريق

والى كل من مد يد العون لي من قريب او بعيد

وقبل ان امضي اقدم اسمى ايات الشكر والامتنان والتقدير والمحبة

الى الذين مهدوا لي طريق العلم والمعرفة

Abstract

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

Introduction

The occurrence of respiratory tract infections (RTI) is more common in winter, especially in the northern regions, than in the summer months [1].This also applies to the rapidly spreading in the winter period around the world of the infectious Coronavirus disease 2019 (COVID-19) which became a pandemic, since the virus is more easily transmitted at low temperatures[2]. This raises the possibility that insufficient intake of vitamin D3 may have a role in the development and severity of COVID-19. Thus, in order to curb the current pandemic of COVID-19, it is opined that the administration of an adequate amounts of vitamin D3 may stem the current situation till an effective therapy, chemoprophylaxis, and vaccination is developed.

Deficiency of vitamin D3 in all age groups is a public health problem [3] that is well recognized. It is estimated that more than one billion people suffer from vitamin D3 deficiency [4]. Several previous studies suggested that there is an independent association between low plasma concentrations of 25-hydroxyvitamin D3 and susceptibility to acute respiratory infections [5]. Vitamin D3 deficiency has been associated with many diseases including but not limited to type 2 diabetes mellitus, heart disease, stroke, autoimmune diseases, asthma and RTIs [6]. The relation between low levels of vitamin D3 and infection with bovine diarrhea virus in calves has been well established [7]. It is evident that in winter due to the shorter time spent in the sun, the plasma levels of vitamin D3 is likely to be low[8]. This is especially evident in countries such as the United States of America (USA), United Kingdom (UK), Switzerland, Italy, Spain, Iran, France, Turkey, etc. It is rather interesting that COVID-19 pandemic and its high mortality has been reported in these countries. According to the US National Center for Health Statistics, approximately 70% of the population may be deficient in vitamin D3 and surprisingly while the

United States is presently the most affected by COVID-19. This is in line with the current proposalthat severe acute respiratory syndrome due to SARS-CoV-2 and its associated high mortality rate may be as a result of vitamin D3 deficiency. Furthermore, vitamin D3 deficiency is known to elevate with increasing age and comorbidities that are associated with lower vitamin D3 levels [9].

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

Vitamin D synthesis and sources

Vitamin D is derived from 7-dehydrocholesterol in the skin by the action of ultraviolet B (UVB, wavelength 280–315 nm) splitting a carbon to carbon bond (C9–C10) thus opening up its B ring—it is structurally related to other cholesterol-derived hormones such as cortisol, testosterone and oestrogen. Formation of the active hormonal form of vitamin D, 1,25 dihydroxyvitamin D (1,25(OH)2D), requires25-hydroxylation, performed in the liver, and 1-hydroxylation, performed in the kidneys but also in many immune cells and epithelial cells by the action of the enzyme 1- hydroxylase also referred to as CYP27B1 [10].

Vitamin D exists in two forms, D2 and D3. Vitamin D2 (ergocalciferol) derives from UVB irradiation of the yeast and plant sterol ergosterol, and vitamin D3 (cholecalciferol) is found in oily fish and cod liver oil and is also made in the human skin. It is very hard to obtain sufficient vitamin D from food. Oily fish is the only substantial dietary source. Other sources that include liver, eggs and mushrooms (the latter only if they have been UV irradiated) provide only

modest amounts of vitamin D. The main source of vitamin D is its generation by the action of UVB on the skin [11].

Vitamin D and mechanisms to decrease viral infections

Some recent reviews demonstrated some pathways by which vitamin D decreases the risk of microbial infections [12]. Vitamin D follows different mechanisms in reducing the risk of viral infection and mortality. To reduce the risk of common cold, vitamin D uses three pathways: physical barrier, cellular natural immunity, and adaptive immunity [13]. A recent review also supported the possible role of vitamin D in decreasing the risk of COVID19 infections and mortality [14]. These comprise maintaining of cell junctions, and gap junctions, increasing cellular immunity by decreasing the cytokine storm with influence on interferon and tumor necrosis factor [14] and regulating adaptive immunity through inhibiting T helper cell type 1 responses and stimulating of T cells induction [15]. Vitamin D supplementation was also found to enhance CD4+ T cell count in HIV infection [16]. One of the major manifestations of severe SARS-CoV-2 infection is lymphopenia [17]. In both the mouse models and in human cell lines, vitamin D exerted activity in lung tissue and played protective effects on experimental interstitial pneumonitis [18]. Several in vitro

Studies demonstrated that vitamin D plays a significant role in local “respiratory homeostasis” either by stimulating the exhibition of antimicrobial peptides or by directly interfering with the replication of respiratory viruses [19]. Vitamin D insufficiency can, therefore, be involved in ARDS and heart failure and these are the manifestations of severely ill COVID-19 subjects. Therefore, vitamin D deficiency promotes the renin-angiotensin system (RAS), which may lead to chronic cardiovascular disease (CVD) and reduced lung function [20]. People with such comorbidities account for a higher percentage of severe ill cases in COVID-19 [21]. Although, many studies supported the immunomodulatory characteristics of vitamin D and its significant role in the maintenance of

immune homeostasis; well-designed randomized controlled trials are required to elucidate the plausible role of vitamin D in protective immune responses against respiratory microbes and in preventing various types of acute respiratory tract infections.

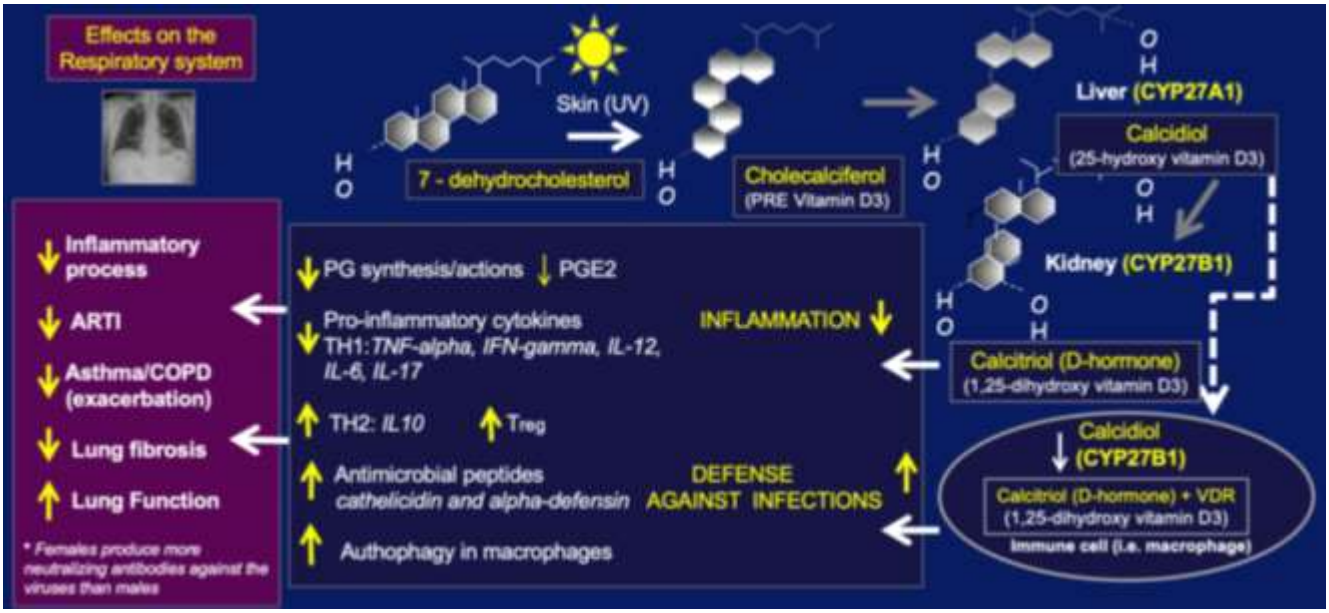

Figure 1 Proposed mechanism whereby 1,25(OH) D -VDR (D-hormone) signalling acts on the respiratory system during the COVID-19 infection. 1,25(OH) D, 1,25-hydroxyvitamin D; ARTI, acute respiratory tract infection; IFN-gamma, inteferon gamma; IL-6, inteleukin 6; IL10, interleukin; IL -12, interleukin 12; IL-17, interleukin 17; Treg, T regulatory cells; TNF, tumour necrosis factor; UV, ultraviolet; VDR, vitamin D receptor.

The relevance of vitamin D to COVID-19

Yet, it is important to fully elucidate the virulence mechanisms of COVID-19, several cellular mechanisms including Papain-like protease (PLpro)-mediated replication, dipeptidyl peptidase-4 receptor (DPP-4/CD26) binding, disruption of M-protein mediated type-1 IFN induction and MDA5 and RIG-I host-recognition evasion have been recognized in the closely-related COVID-MERS virus [22,23]. Of the above processal, human DPP-4/CD26 has been exhibited to connect with the S1 domain of the COVID-19 spike glycoprotein, suggesting that it could also be a salient virulence factor in Covid-19 infection [24]. The expression of the DPP-4/CD26 receptor is reduced significantly in vivo upon the

correctness of vitamin D insufficiency [25]. There is also an indication that maintaining of vitamin D may reduce some of the unfavorable downstream immunological sequelae thought to extract poorer clinical outcome in Covid-19 infection, such as interleukin 6 elevation, delayed interferon-gamma response, and, a negative prognostic marker in subjects with acutely-ill pneumonia [26], including those having Covid-19 [27].

Epidemiological and clinical observations regarding COVID-19

Some clinical and epidemiological studies support to outline the hypothesis regarding COVID-19 and its relationship with vitamin D status. Recent studies indicated that COVID-19 is associated with the increased generation of pro-inflammatory cytokines, Creative protein (CRP), ARDS, pneumonia, and heart failure [28, 29]. In China, chronic fatality rates were 6-10% for people with chronic respiratory tract disease, cardiovascular disease, hypertension, and diabetes [12, 30]. In other studies, serum concentrations of 25(OH) D were inversely associated with pro-inflammatory cytokines, IL-6, increased CRP, and increased risk of pneumonia, ARDS, diabetes and heart failure [31]. In randomized control trials, vitamin D supplementation has been shown to reduce the risk of respiratory diseases [32, 33]. A placebo-controlled trial with 5660 subjects showed that vitamin D supplementation significantly reduces the risk of respiratory tract infections [34]. A review included five clinical studies reported that respiratory tract infections were significantly lower in the vitamin D supplementation group than the control group [35]. Another study included 25 randomized controlled trials, with 10,933 participants in total from 14 different countries indicated the beneficial effects of vitamin D supplementation in reducing the risk of at least one acute respiratory tract infection [36].

How to supplement vitamin D in COVID-19

Patients with deficiency Although the degree of protection generally increases as 25(OH)D serum concentration increases, the optimal range is considered to be in the range of 40–60ng/mL (100–150nmol/L). In order achieve those levels; approximately half the population should take at least 2000– 5000IU/day of vitamin D [37]. The supplementation with calcidiol (25(OH)D) may present some advantages over the native vitamin D (cholecalciferol), in fact, calcidiol has a more reliable intestinal absorption (close to 100%) and its administration can rapidly restore serum concentrations of 25OHD as it does not require hepatic 25-hydroxylation (CYP27A1) . This is especially relevant in clinical situations whereby rapid restoration of serum 25OHD is desirable and expression is compromised. Such impaired hepatic vitamin D hydroxylation by cytochrome p450 2R1 (CYP2R1) activity has been well demonstrated in several animal models of obesity, diabetes or glucocorticoid excess and in patients with COPD or asthma [38]. Various loading doses have been studied for achieving a 25(OH)D concentration of 30ng/mL. For example, one study used a weekly or fortnightly dose totaling 100000–200000IU over 8 weeks (1800 or 3600IU/ day) [39]. Clinical data suggest that daily or weekly doses offer better results than bolus in the protection against acute pulmonary infections and supplementation with extremely high doses of vitamin D could be harmful and toxic, especially to elderly individuals [40,41]. Some reports just speculated on single high vitamin D doses and mechanisms for prevention and treatment of COVID-19 patients [42]. Therefore, the supplementation of vitamin D by bolus or extremely high doses (ie, 600000 UI single dose oral dose) should be avoided since can increase the risk of intoxication without evidence of benefits at least in COVID-19 patients [43]. In addition, from the literature, for healthy individuals, it is suggested taking 10000IU/day for a month, which is effective in rapidly

increasing serum concentrations of 25(OH) D into the optimal range of 40–60ng/mL [44]. To maintain that level after that first month, the dose can be decreased to almost 2000–3000IU/day. However, measuring serum 25(OH)D concentration would be useful to determine baseline and the achieved 25(OH)D concentrations. Patients hospitalised with COVID-19 should have baseline serum 25(OH)D concentrations measured and must be supplemented at least to a level ≥30ng/mL (optimal 40–60), especially when the baseline level is <10ng/mL and such deficiency is significantly more present in male patients [45]. In conclusion, we might suggest in COVID-19 patients with 25(OH)D serum levels under 20ng/mL that the usual recommended dose for correction of deficiency should be 6000–7000 oral IU/day for the first 6–8 weeks. For maintenance, the dose should varies from 2000 to 3000 oral IU/day depending on the age and clinical condition of the patient up to achieve the suggested concentrations [46].

Public Health and Clinical Implications

Vitamin D insufficiency and deficiency are widespread in many countries, in particular among the elderly, calling for public health action even before the COVID-19 pandemic [47]. Randomized controlled trials (RCTs) have shown efficacy and safety of vitamin D supplementation

in preventing various adverse health outcomes, such as hip fractures, acute respiratory infections, or deaths from cancer [48]. Widespread vitamin D supplementation, at least for the elderly and the high risk groups, thus seems to be prudent even in the absence of the COVID-19 pandemic and is recommended or practiced to some extent in a few countries [49]. Nevertheless, vitamin D levels have remained inadequate in most countries, with prevalence of vitamin D deficiency remaining highest among nursing home residents [50], the group at highest risk for COVID-19 infection and death. The ongoing COVID-19 pandemic, globally accounting for more than 10 million new cases

and 200,000 deaths per month in the second half of 2020, calls for immediate efforts to enhance vitamin D status of populations at risk and of those infected with COVID-19 even before results of the ongoing large trials become available, which will not be before spring to summer of 2021. Besides the recent epidemiological evidence outlined above, a major protective impact of vitamin D supplementation on risk and course of COVID 19 infections is strongly supported by long known and well established molecular mechanisms of vitamin D, such as its immunomodulatory effects, as outlined in detail elsewhere [51]. Vitamin D supplementation could thus be a most cost-effective, readily available tool that could potentially prevent millions of COVID-19 infections and tens if not hundreds of thousands COVID-19 deaths, and at the same time, prevent overstretching of health care
systems, beyond its established beneficial effects on other health outcomes. Obviously, vitamin D supplementation should complement, not replace established and other efforts to cope with the COVID-19 pandemic, such as social distancing, wearing of masks, and hygiene measures with which it shares protective effects not only against COVID-19 infections, but also other infections, such as other acute respiratory infections including influenza. Although there is hope that widespread vaccination will finally end or at least widely control the current COVID-19 pandemic, its long-term safety and effectiveness are yet to be demonstrated. In the meantime, but also in the long run, vitamin D supplementation, for which safety and effectiveness with respect to acute respiratory infections has long been established, and which is a very low-cost measure, should be widely applied. Even a minor effect on protection from infection that might turn the COVID-19 effective reproduction number from slightly above one (as estimated for many countries shortly before or during lockdown measures of varying intensity during most of the second half of 2020) to slightly below one could make the difference between further exponential growth or regression of the pandemic. In the absence of specific

contraindications, supplementation with safe, but sufficient doses (e.g., ranging from 800 to4000 IU/day for older adults depending on individual factors, such as age and sex [52], body mass index, or comorbidity) should thus be strongly promoted for the population at large and the high-risk population in particular, not only to those with already manifest COVID-19 infection. Despite remaining uncertainties with respect to optimal dosing, evidence from vitamin D trials with other endpoints suggests supplementation should preferably be done on a regular basis rather than by occasional high-dose bolus therapy. For patients with manifest COVID-19 infection, initiation of high-dose supplementation as early as possible after diagnosis should be strongly considered whenever there are no specific contraindications against such treatment. At the very least, such strategies would help to reduce the burden of established adverse consequences of widespread vitamin D insufficiency and deficiency, which would be a great achievement by itself. In the best case, they might add to this the even greater achievement of curbing the ongoing COVID-19 pandemic with all its adverse consequences even prior to and beyond widespread availability of vaccination. Immediate action is warranted [53].

CONCLUSIONS

Given the evidence supporting the role of vitamin D in modulating immune function, and the impact of vitamin D supplementation on vitamin D-deficient patients with COVID-19, as well as the favourable safety profile(and low cost) of vitamin D, practical recommendations should be synthesized as follows:

► Current public health guidelines for optimising vitamin D status should be followed always and clinical data from systematic reviews and meta-analyses show benefits in the prevention of respiratory infections and improvement of pulmonary function when vitamin D-deficient patients are supplemented.

►The optimal vitamin D status of the host may contribute key immunoregulatory functions in settings of viral respiratory infection and overall the altered immune-inflammatory COVID-19 reactivity at least by downregulating overly exuberant cytokine responses (pathological cytokine storm, in fact higher vitamin D levels correlate with lower IL-6 levels).

► Patients hospitalized with COVID-19 should have baseline serum 25(OH)D concentrations measured and should be supplemented to a level >30 ng/mL(optimal 40–60 ng/mL), especially when the baseline level is <10 ng/mL.

► In COVID-19 patients with 25(OH)D serum concentrations under 20 ng/mL the recommended dose for correction of deficiency is 6000–7000 oral IU/ day for 6–8 weeks. For maintenance, the dose varies from 2000 to 3000 oral IU/day depending on the age and clinical condition of the individual up to reach optimal concentrations.

► When it is not possible to measure baseline 25(OH)D concentrations in COVID-19 patients, it seems essential supplementing with 2000–3000 oral IU per day up to the suggested optimal serum concentrations (40–60 ng/mL).

A final message based on all the practical issues discussed: keep the vitamin D serum concentrations during all the year between 40 and 60 ng/mL (100–150 nmol/L), it is one of the fundamental care to reduce, at least the risk of RTIs, COVID-19 included.

References

1. Hope-Simpson, R. E. (1981). The role of season in the epidemiology of influenza. *J. Hyg*. 86, 35–47. doi:10.1017/S0022172400068728
2. Sajadi, M. M., Habibzadeh, P., Vintzileos, A., Shokouhi, S., Miralles-Wilhelm, F., and Amoroso, A. (2020). Temperature, humidity and latitude analysis to predict potential spread and seasonality for COVID-19. Available at: https://ssrn.com/abstract=3550308
3. Palacios, C., and Gonzalez, L. (2014). Is vitamin D deficiency a major global public health problem? *J. Steroid Biochem. Mol. Biol.* 144 (Pt A), 138–145. doi:10.1016/j.jsbmb.2013.11.003
4. Van Schoor, N. M., and Lips, P. (2011). Worldwide vitamin D status. *Best Pract. Res. Clin. Endocrinol. Metab*. 25, 671–680. doi:10.1016/j.beem.2011.06.007
5. Cannell, J. J., Vieth, R., Umtau, J. C., Hollick, M. F., Grant, W. B., Madronich, S., et al. (2006). Epidemic influenza and vitamin D. *Epid. Infect.* 134, 1129–1140. doi:10.1017/S0950268806007175
6. Hollick, M. F. (2007). Vitamin D deficiency. *N. Engl. J. Med*. 357, 266–281. doi:10.1056/NEJMra070553
7. Nonnecke, B. J., McGill, J. L., Ridpath, J. F., Sacco, R. E., Lippolis, J. D., and Reinhardt, T. A. (2014). Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. *J. Dairy Sci.* 97, 5566. doi:10.3168/jds.2014-8293
8. Berardi, R., and Newton, G. (2009). *Handbook of nonprescription drugs*. 16th Edition. Washington DC: American Pharmacists Association, 1050
9. Kmiec, P., Zmijewski, M., Waszak, P., Sworczak, K., and Lizakowska-Kmieć, M. (2014). Vitamin D deficiency during winter months among an

adult, predominantly urban, population in Northern Poland. *Endokrynol. Pol.* 65, 105–113. doi:10.5603/EP.2014.0015

10. Bishop E, Ismailova A, Dimeloe SK, Hewison M, White JH. 2020 Vitamin D and immune regulation: antibacterial, antiviral, antiinflammatory. JBMR Plus e10405. (doi:10.1002/ jbm4.10405)
11. Wacker M, Holick MF. 2013 Sunlight and Vitamin D: a global perspective for health. Dermatoendocrinology 5, 51–108. (doi:10.4161/ derm.24494)
12. Coussens AK. The role of UV radiation and vitamin D in the seasonality and outcomes of infectious disease. Photochem Photobiol Sci 2017;16:314–38.
13. Rondanelli M, Miccono A, Lamburghini S, Avanzato I, Riva A, Allegrini P, et al. Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and Echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds—practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. Evid-Based Complement Altern Med 2018;2018
14. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020;12:988.
15. Cantorna MT, Snyder L, Lin Y-D, Yang L. Vitamin D and 1, 25 (OH) 2D regulation of T cells. Nutrients 2015;7:3011–21.
16. Alvarez N, Aguilar-Jimenez W, Rugeles MT. The potential protective role of vitamin D supplementation on HIV-1 infection. Front Immunol 2019;10:2291
17. Tian Y, Rong L. Covid-19 and vitamin D-authors' reply. Aliment Pharmacol Ther 2020.
18. Tsujino I, Ushikoshi-Nakayama R, Yamazaki T, Matsumoto N, Saito I. Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia. J Clin Biochem Nutr 2019;65:245–51.

19. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol 2017;27:e1909.
20. Shi Y, Liu T, Yao L, Xing Y, Zhao X, Fu J, et al. Chronic vitamin D deficiency induces lung fibrosis through activation of the renin–angiotensin system. Sci Rep 2017;7:1–10.
21. Tian Y, Rong L. Covid-19 and vitamin D-authors' reply. Aliment Pharmacol Ther 2020
22. Skariyachan S, Challapilli SB, Packirisamy S,Kumargowda ST, SridharVS.
23. Recent aspects on the pathogenesis mechanism, animal models and novel therapeutic interventions for Middle East respiratory syndrome coronavirus infections. Front Microbiol 2019;10.
24. McCartney DM, Byrne DG. Optimisation of vitamin D status for enhanced immuno-protection against Covid-19. Irish Med J 2020;113:58
25. Vankadari N,Wilce JA. EmergingWuHan(COVID-19) coronavirus: glycanshield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microb Infect 2020;9:601–4
26. Komolmit P, Charoensuk K, Thanapirom K, Suksawatamnuay S, Thaimai P, Chirathaworn C, et al. Correction of vitamin D deficiency facilitated suppression of IP-10 and DPP IV levels in patients with chronic hepatitis C: a randomised double-blinded, placebo-control trial. PLoS ONE 2017;12.
27. Miroliaee AE, Salamzadeh J, Shokouhi S, Sahraei Z. The study of vitamin D administration effect on CRP and Interleukin-6 as prognostic biomarkers of ventilator associated pneumonia. J Crit Care 2018;44:300–5.
28. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
29. Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol 2020, jmv.26097.

30. Surveillances V. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. China CDC Wkly 2020;2:113–22.
31. Poudel-Tandukar K, Poudel KC, Jimba M, Kobayashi J, Johnson CA, Palmer PH. Serum 25-hydroxyvitamin d levels and C-reactive protein in persons with human immunodeficiency virus infection. AIDS Res Hum Retroviruses 2013;29:528–34.
32. Dancer RC, Parekh D, Lax S, D'Souza V, Zheng S, Bassford CR, et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax 2015;70:617–24.
33. Rejnmark L, Bislev LS, Cashman KD, Eiríksdottir G, Gaksch M, Grübler M, et al. Non-skeletal health effects of vitamin D supplementation: a systematic review on findings from meta-analyses summarizing trial data. PLoS ONE 2017;12:e0180512.
34. Bergman P, Lindh ÅU, Björkhem-Bergman L, Lindh JD. Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials. PLoS ONE 2013;8:e65835.
35. Charan J, Goyal J, Saxena D, Yadav P. Vitamin D for prevention of respiratory tract infections: a systematic review and meta-analysis. J Pharmacol Pharmacother 2012;3:300.
36. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017:i6583.
37. Santos RND, Maeda SS, Jardim JR, Nolasco Dos Santos R, Setsuo Maeda S, et al. Reasons to avoid vitamin D deficiency during COVID-19 pandemic. Arch Endocrinol Metab 2020:S2359–39972020005006214.

38. Jolliffe DA, Stefanidis C, Wang Z, et al. Vitamin D metabolism is dysregulated in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2020;202:371–82.
39. Cipriani C, Romagnoli E, Pepe J, et al. Long-Term bioavailability after a single oral or intramuscular administration of 600,000 IU of ergocalciferol or cholecalciferol: implications for treatment and prophylaxis. J Clin Endocrinol Metab 2013;98:2709–15.
40. Martineau AR, Jolliffe DA, Greenberg L, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. Health Technol Assess 2019;23:1–44.
41. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J, et al. Vitamin D Toxicity-A clinical perspective. Front Endocrinol 2018;9:55.
42. Liu G, Hong T, Yang J. A single large dose of vitamin D could be used as a means of coronavirus disease 2019 prevention and treatment. Drug Des Devel Ther 2020;14:3429–34.
43. Santos RND, Maeda SS, Jardim JR, Nolasco Dos Santos R, Setsuo Maeda S, et al. Reasons to avoid vitamin D deficiency during COVID-19 pandemic. Arch Endocrinol Metab 2020:S2359–39972020005006214.
44. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients 2020;12:988.
45. Lewiecki EM. Vitamin D and COVID-19: is something better than nothing? Osteoporos Sarcopenia 2020;6:95–6.
46. Santos RND, Maeda SS, Jardim JR, et al. Reasons to avoid vitamin D deficiency during COVID-19 pandemic. Arch Endocrinol Metab 2020;28:S2359–39972020005006214.
47. Cashman, K.D.; Dowling, K.G.; Škrabáková, Z.; Gonzalez-Gross, M.; Valtueña, J.; De Henauw, S.; Moreon, L.; Damsgaard, C.T.; Michaelsen,

K.F.; Kiely, M.; et al. Vitamin D deficiency in Europe: Pandemic? Am. J. Clin. Nutr. **2016**, 103, 1033–1044. [CrossRef] [PubMed]

48. Weaver, C.M.; Alexander, D.D.; Boushey, C.J.; Dawson-Hughes, B.; Lappe, J.M.; LeBoff, M.S.; Liu, S.; Looker, A.C.; Wallace, T.C.; Wang, D.D.; et al. Calcium plus vitamin D supplementation and risk of fractures: An updated meta-analysis from the National Osteoporosis Foundation. Osteoporos. Int. **2016**, 27, 367–376. [CrossRef] [PubMed]
49. Rizzoli, R.; Boonen, S.; Brandi, M.L.; Bruyère, O.; Cooper, C.; Kanis, J.A.; Kaufman, J.-M.; Ringe, J.D.; Weryha, G.; Reginster, J.-Y.; et al. Vitamin D supplementation in elderly or postmenopausal women: A 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr. Med. Res. Opin. **2013**, 29, 305–313. [CrossRef]
50. Griffin, T.P.; Wall, D.; Blake, L.; Griffin, D.G.; Robinson, S.M.; Bell, M.; Mulkerrin, E.C.; O'Shea, P.M. Vitamin D Status of Adults in the Community, in Outpatient Clinics, in Hospital, and in Nursing Homes in the West of Ireland. J. Gerontol. A Biol. Sci. Med. Sci. **2020**, 75, 2418–2425. [CrossRef] [PubMed]
51. Jeffery, L.E.; Burke, F.; Mura, M.; Zheng, Y.; Qureshi, O.S.; Hewison, M.;Walker, L.S.K.; Lammas, D.A.; Raza, K.; Sansom, D.M. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J. Immunol. **2009**, 183, 5458–5467. [CrossRef] [PubMed]
52. Spanier, J.A.; Nashold, F.E.; Mayne, C.G.; Nelson, C.D.; Hayes, C.E. Vitamin D and estrogen synergy in Vdr-expressing CD4(+) T cells is essential to induce Helios(+)FoxP3(+) T cells and prevent autoimmune demyelinating disease. J. Neuroimmunol. **2015**, 286, 48–58. [CrossRef]

53. Pagano, M.T.; Peruzzu, D.; Ruggieri, A.; Ortona, E.; Gagliardi, M.C. Vitamin D and Sex Differences in COVID-19. Front. Endocrinol. **2020**, 11, 567824. [CrossRef]