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Point of view: Should COVID-19 patients be supplemented with vitamin D?

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ABSTRACT

Using Hill's methodology for exploring causality, we aimed to determine in early May 2020 whether evidence supports vitamin D as a biological determinant of COVID-19 outcomes. Vitamin D is a secosteroid hormone theoretically able to reduce COVID-19 risk through regulation of (i) the renin-angiotensin system, (ii) cellular innate and adaptive immunity, and (iii) physical barriers. Inverse associations were found between 25-hydroxyvitamin D concentrations and COVID-19 incidence and mortality. Randomized controlled trials testing vitamin D supplementation in the treatment of COVID-19 are in progress. Positive results in such studies would encourage the use of vitamin D supplements as an adjuvant treatment in COVID-19.

1. Introduction

As of June 4, 2020, the COVID-19 pandemic caused by the SARS-CoV-2 virus has seen the infection of more than 6,300,000 people in 194 countries around the world, leaving more than 380,000 dead [1]. Symptoms include fever, marked asthenia and dry cough, which may gradually progress to severe manifestations such as lethal acute respiratory disease syndrome (ARDS) [2]. With the lack of scientifically-validated treatment, chemoprevention and vaccination, the immediate repurposing of existing drugs gives hope of curbing the pandemic. Importantly, a recent unbiased genomics-guided tracing of the SARS-CoV-2 targets in human cells identified vitamin D among the three top-scoring molecules manifesting potential infection mitigation patterns [3]. We aimed to determine whether preclinical and epidemiological evidence supports vitamin D as a central biological determinant of COVID-19 outcomes.

2. Methods

To assess the value of this natural drug candidate as objectively and consensually as possible, literature from Medline and preprint databases was critically reviewed in early May 2020. Evidence is summarized in Table 1 using Hill's criteria for causality in a biological system [4].

3. Results

3.1. Preclinical findings

Vitamin D is a secosteroid hormone, the active form of which (125-dihydroxyvitamin D) binds to vitamin D receptor (VDR) [5]. The latter complex is then translocated into the cell nucleus, where it combines with retinoid X receptor (RXR). The RXR-VDR heterodimer finally interacts with DNA at sites referred to as Vitamin D Response Elements (VDRE) located in the promoter regions of genes, and expression is either activated or repressed [5]. This is the way vitamin D may theoretically reduce the risks of COVID-19 infection and mortality through, at least, three mechanisms: (i) regulation of the renin-angiotensin system (RAS), (ii) cellular innate and adaptive immunity, and (iii) physical barriers [6].

First, vitamin D reduces lung permeability in animal models of ARDS by modulating RAS activity and angiotensin-converting enzyme-2 (ACE2) expression [7]. This action is crucial since the SARS-CoV-2 reportedly uses ACE2 as the main receptor to infect host cells and downregulates ACE2 expression [1]. ACE2 is expressed in many organs, notably in lung alveolar epithelial cells, where it exerts some protective

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Table 1
Evidence that vitamin D is causally linked to COVID-19 outcomes using consensual Hill's criteria for causality in a biological system.

Criterion	Evidence
Temporality	Hypovitaminosis D being a chronic condition, it precedes COVID-19 outcomes, which evolution is rapid over a few days.
Strength of association	Mortality associated to hypovitaminosis D with OR = 7.6 (P < 0.001), meaning that death risk in COVID-19 is multiplied by more than 7 in the case of hypovitaminosis D [20].
Dose-response relationship	For each standard deviation increase in serum 25(OH)D among COVID-19 patients, the odds of having a mild clinical outcome rather than a critical outcome were 19.6 times (OR = 0.05, P < 0.001) [21].
Consistency of findings	Only observational data available at the moment; the results of which consistently showed associations between vitamin D status and COVID-19 outcomes [17,18,19,20,21].
Plausibility (e.g. mechanisms)	Regulation of the renin-angiotensin system and of cellular innate and adaptive immunity, and stabilization of physical barriers [6,7,8,9,10,11].
Alternate explanations	i) Reverse causation (i.e. COVID-19 precipitates hypovitaminosis D) is made unlikely by the temporality of both conditions. ii) Association between hypovitaminosis D and COVID-19 mortality still significant after adjustment for potential confounders including age, gender and comorbidities [20].
Experiment	Prophylactic vitamin D supplementation reduced the risk of developing acute respiratory tract infections (OR = 0.88 [95 %CI: 0.81 − 0.96], P < 0.001) [22]. RCTs dedicated to COVID-19 are in progress.
Specificity	Although particularly severe among COVID-19 patients [17,18,19,20,21], the prevalence of hypovitaminosis D is too high in the general population to be considered specific to COVID-19 and COVID-19 serious forms.
Coherence with known facts	More COVID-19 cases and deaths in locations with lower ultraviolet-B irradiance and following lower irradiance days [13]. BAME individuals disproportionately impacted by COVID-19 mortality [15].

25(OH)D: 25-hydroxyvitamin D; ACE2: angiotensin-converting enzyme 2; BAME: Black, Asian and Minority Ethnic; CI: confidence interval; COVID-19: coronavirus disease 2019; OR = odds ratio; RCT: randomized controlled trials.

effects against inflammatory damages. In COVID-19, ACE2 down-regulation leads to unopposed inflammatory chain-reaction, cytokine storm (i.e. generation of both pro-inflammatory and anti-inflammatory cytokines by innate immune system) and lethal ARDS [1]. In contrast, a study in rats with chemically-induced ARDS reported that vitamin D administration increased the mRNA and proteins levels of ACE2 [8]. The rats supplemented with vitamin D exhibited milder symptoms of ARDS and moderate lung changes as compared to controls [8].

Second, numerous studies have described the antiviral effects of vitamin D, which acts either by induction of antimicrobial peptides with direct antiviral activities against enveloped and nonenveloped viruses or through immunomodulatory and anti-inflammatory effects [9,10]. The latter may be important in COVID-19 to minimize the cytokine storm [11]. Vitamin D may prevent ARDS [12] by reducing the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor α and interferon γ [9,10]. It also increases the expression of anti-inflammatory cytokines by macrophages [9,10].

Third, vitamin D stabilizes physical barriers. They consist of cells that are tightly joined to prevent invaders (such as viruses) from reaching tissues that are sensitive to infection. Although viruses are altering cell junction integrity, which favors virus-to-cell infection, vitamin D contributes to the maintenance of functional tight junctions, gap junctions, and adherens junctions via E-cadherin [6].

3.2. Epidemiological findings

Vitamin D is naturally synthesized in the skin after exposure to solar ultraviolet-B rays when the sun's elevation angle is above about 45 degrees [13]. Hypovitaminosis D in humans is therefore more common in winter from October to March at northern latitudes (above 20 degrees) [5], which correspond precisely to the latitudes where some high lethality rates of COVID-19 were observed during the first months of winter 2020 [1] but exceptions have also occurred. For example, Norway and Finland suffered a relatively mild epidemic compared to Italy and Spain [14]. Moreover, it is noticeable that COVID-19 mortality disproportionately impacts BAME (Black, Asian and Minority Ethnic) individuals [15], whose melanin levels are reducing the potential of vitamin D synthesis by the skin.

Consistently, the first reports in COVID-19 patients indicate that hypovitaminosis D is highly prevalent in this population, reaching 85 % [16], and that serum 25-hydroxyvitamin D (25(OH)D) concentrations are lower in COVID-19 patients than in controls [17]. However, lower vitamin D concentrations are usually found in older individuals and those in poor health [5]. Similarly, significant inverse correlations were reported in 20 European countries between the mean serum 25(OH)D concentrations and the number of COVID-19 cases/1 M, as well as with mortality/1 M [18]. In another study, this association, although significant in the univariate model (P = 0.013), disappeared after adjustment for several confounders (P = 0.208) in younger and middle-aged adults [19]. Also, besides the risk of infection, the severity of hypovitaminosis D appeared to relate to the prognosis of the infection since the mortality rate, in a study with 780 COVID-19 patients, was multiplied by 7.6 in the case of 25(OH)D < 75 nmol/L (mean age, 46.6years) after adjustment for age, gender and comorbidities (P < 0.001), although 25(OH)D < 50 nmol/L (mean age, 66.9years) was associated to greater mortality rate with adjusted odds ratio of 10.1 (P < 0.001) [20]. Another observational study in 212 cases showed that, for each standard deviation increase in serum 25(OH)D, the probability of mild rather than severe COVID-19 was multiplied by 7.9 (P < 0.001), while the probability of mild rather than critical COVID-19 was multiplied by 19.6 (P < 0.001) [21]. These results suggest that increasing serum 25(OH)D concentrations might improve the prognosis of COVID-19.

Randomized controlled trials (RCTs) are warranted to investigate the role of vitamin D supplementation on COVID-19 outcomes. Interestingly, previous RCT meta-analyses found that prophylactic vitamin D supplementation was able to reduce the risk of acute respiratory tract infections [22]. The optimal dose ranged between 1,000–4,000IU/day, suggesting benefits of high-dose vitamin D supplementation; just as did a previous study in intensive care that reported 17 % mortality rate reduction among patients having received high-dose vitamin D compared to a placebo [23]. Based on these observations, an RCT dedicated to COVID-19 is testing the effect on 14-day mortality of high-dose vitamin D versus standard dose in COVID-19 older patients (https://clinicaltrials.gov/ct2/show/NCT04344041).

3.3. Causality inference

Hill's criteria for causality were used to evaluate whether vitamin D may be considered causally linked to COVID-19 outcomes (Table 1). Not all Hill's criteria need to be satisfied to claim causality, but the more that are, the stronger the claim. All criteria were satisfied here, with the exception of specificity, which is a minor criterion generally not used for vitamin D [24]. RCTs dedicated to COVID-19 are in progress. It should be acknowledged that the quality of some evidence assigned to Hill's criteria was not very strong here, e.g. relying on a small number of non-peer-reviewed preprints rapidly released in the COVID-19 era and complete absence of high-quality RCTs. Also, an alternate explanation could be that vitamin D level accounts for general

health and that vitamin D supplementation improves the clinical picture and frailty of the host, rather than directly combating the infection and its complications. However, both hypotheses encourage the examination of supplementation of COVID-19 cases with vitamin D [25].

4. Conclusions

Suggestive evidence was gathered that serum vitamin D may be considered a biological determinant of COVID-19 outcomes according to Hill's criteria for causality. Given the lack of specific treatment for COVID-19, the urgency of the pandemic, and the safety of vitamin D supplementation, these observations provide an argument for testing vitamin D as an adjuvant treatment to improve the clinical presentation of COVID-19 and its prognosis, just as recently recommended in prophylaxis by some scientific societies [26].

Contributors

Cédric Annweiler was responsible for study conception and design, analysis and interpretation of data, and drafting of the manuscript,

Zhijian Cao contributed to analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

Jean-Marc Sabatier contributed to analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

All authors read and approved the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

[1] D.G. Ahn, H.J. Shin, M.H. Kim, S. Lee, H.S. Kim, J. Myoung, et al., Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19), J. Microbiol. Biotechnol. 30 (2020) 313–324.

[2] G. Sacco, O. Brière, M. Asfar, O. Guérin, G. Berrut, C. Annweiler, Symptoms of COVID-19 among older adults: systematic review of biomedical literature, Geriatr. Psychol. Neuropsychiatr. Vieil. (2020) in press.

[3] G. Glinsky, D. Vitamin, Quercetin, and Estradiol manifest properties of candidate medicinal agents for mitigation of the severity of pandemic COVID-19 defined by genomics-guided tracing of SARS-CoV-2 targets in human cells, ChemRxiv (2020), https://doi.org/10.26434/chemrxiv.12052512.v7 Preprint.

[4] A.B. Hill, The environment and disease: association or causation? Proc. R. Soc. Med. 58 (1965) 295–300.

[5] A. Hossein-nezhad, M.F. Holick, Vitamin D for health: a global perspective, Mayo Clin. Proc. 88 (2013) 720–755.

[6] W.B. Grant, H. Lahore, S.L. McDonnell, C.A. Baggerly, C.B. French, J.L. Aliano, H.P. Bhattoa, Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths, Nutrients. 12 (2020) 988.

[7] W. Yuan, W. Pan, J. Kong, W. Zheng, F.L. Szeto, W.E. Wong, 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. 282 (2007) 29821–29830.

[8] J. Yang, H. Zhang, J. Xu, Effect of Vitamin D on ACE2 and Vitamin D receptor expression in rats with LPS-induced acute lung injury, Chinese. J. Emerg. Med. 25 (2016) 1284–1289.

[9] A. Fabbri, M. Infante, C. Ricordi, Editorial - Vitamin D status: a key modulator of innate immunity and natural defense from acute viral respiratory infections, Eur. Rev. Med. Pharmacol. Sci. 25 (2020) 4048–4052.

[10] K.C. Olson, P.M. Kulling Larkin, R. Signorelli, C.E. Hamele, T.L. Olson, M.R. Conaway, et al., Vitamin D pathway activation selectively deactivates signal transducer and activator of transcription (STAT) proteins and inflammatory cytokine production in natural killer leukemic large granular lymphocytes, Cytokine. 111 (2018) 551–562.

[11] A. Daneshkhah, V. Agrawal, A. Eshein, H. Subramanian, H.K. Roy, V. Backman, The possible role of vitamin d in suppressing cytokine storm and associated mortality in COVID-19 patients, MedRxiv (2020), https://doi.org/10.1101/2020.04.08.20058578 Preprint..

[12] R.C. Dancer, D. Parekh, S. Lax, V. D'Souza, S. Zheng, C.R. Bassford, et al., Vitamin d deficiency contributes directly to the acute respiratory distress syndrome (ARDS), Thorax. 70 (2015) 617–624.

[13] A. Bäcker, Follow the Sun: Slower COVID-19 Morbidity and Mortality Growth at Higher Irradiances, SSRN, 2020, https://doi.org/10.2139/ssrn.3567587 Preprint..

[14] E. Laird, J. Rhodes, R.A. Kenny, Vitamin D. and Inflammation: Potential Implications for Severity of Covid-19, Irish Med J. 113 (2020) P81.

[15] K. Khunti, A.K. Singh, M. Pareek, W. Hanif, Is ethnicity linked to incidence or outcomes of covid-19? BMJ 369 (2020) m1548.

[16] G. El James, Vitamin D Level of Mild and Severe Elderly Cases of COVID-19: A Preliminary Report, Preprint SSRN, 2020, https://ssrn.com/abstract=3593258.

[17] A. D'Avolio, V. Avataneo, A. Manca, J. Cusato, A. De Nicolò, R. Lucchini, F. Keller, M. Cantù, 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2, Nutrients 12 (5) (2020).

[18] P.C. Ilie, S. Stefanescu, L. Smith, The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality, Aging Clin. Exp. Res. (2020), https://doi.org/10.1007/s40520-020-01570-8.

[19] C.E. Hastie, D.F. Macka, F. Ho F, C.A. Celis-Morales, S. Vittal Katikireddi, C.L. Niedzwiedz, et al., Vitamin d concentrations and COVID-19 infection in UK Biobank, Diabetes Metab. Syndr. 14 (2020) 561–565.

[20] P. Raharusun, S. Priambada, C. Budiarti, E. Agung, C. Budi, Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study, Prepint SSRN, 2020, https://ssrn.com/abstract=3585561.

[21] M. Alipio, Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected With Coronavirus-2019 (COVID-2019), Preprint SSRN, 2020, https://ssrn.com/abstract=3571484.

[22] A.R. Martineau, D.A. Jolliffe, R.L. Hooper, L. Greenberg, J.F. Aloia, P. Bergman, et al., Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data, BMJ. 356 (2017) i6583.

[23] K. Amrein, C. Schnedl, A. Holl, R. Riedl, K.B. Christopher, C. Pachler, 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. 312 (2014) 1520–1530.

[24] W.B. Grant, Review of recent advances in understanding the role of vitamin d in reducing Cancer risk: breast, colorectal, prostate, and overall Cancer, Anticancer Res. 40 (2020) 491–499.

[25] N. Potischman, D.L. Weed, Causal criteria in nutritional epidemiology, Am. J. Clin. Nutr. 69 (1999) 1309S–1314S.

[26] J.K. Chhetri, P. Chan, H. Arai, S. Chul Park, P. Sriyani Gunaratne, S. Setiati, et al., Prevention of COVID-19 in older adults: a brief guidance from the International Association for Gerontology and Geriatrics (IAGG) Asia/Oceania Region, J. Nutr. Health Aging (2020), https://doi.org/10.1007/s12603-020-1359-7.