INFECTIOUS DISEASES   **HYPOTHESIS**

ROLE OF VITAMIN D SUPPLEMENTATION IN THE PREVENTION OF INFECTION AND SEVERE COURSE IN COVID-19: TESTING THE HYPOTHESIS

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has disrupted the normal activities of various settings, including clinics, laboratories, and libraries. As the world deals with the fast-mutating causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), apart from the search for the best vaccine candidate, efforts towards repurposing existing molecules to save lives must continue. Considerable interest has centered around the implications of vitamin D deficiency and its supplementation on the outcomes in patients with COVID-19. We hypothesize that vitamin D supplementation has the potential to confer protection against SARS-CoV-2 infection and a severe COVID-19 course. Various animal, human observational as well as interventional studies have shown a protective role of vitamin D in COVID-19. More robustly designed studies where vitamin D is supplemented prophylactically and administered to those already infected are needed to determine the precise contribution of this supplementation in preventing SARS-CoV-2 infection and modifying the course of COVID-19.

INTRODUCTION

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutates, we now know of variants that are more transmissible than their predecessors [1,2]. Most vaccines have shown impressive efficacy in various phases of the trials, but their efficacy against the mutant strains remains to be established [2–4]. While efforts towards vaccination must continue, an eye should remain on repurposing existing drugs towards minimizing the damage caused by coronavirus disease 2019 (COVID-19).

There have historically been studies that have implicated vitamin D deficiency (VDD) as a factor influencing the development or worsening of infections, inflammation and allergies. Studies have identified VDD as a risk factor for community-acquired pneumonia and it has also

been associated with worse outcomes, including higher mortality in respiratory infections and sepsis [5,6]. Researchers have observed that patients with tuberculosis have significantly lower vitamin D levels, and higher levels reduced time to sputum and culture conversions, thus vitamin D supplementation should be considered along with anti-tubercular therapy [7–9]. Evidence has emerged that vitamin D supplementation potentially mitigates SARS-CoV-2 infection and reduces the severity of COVID-19. Observational data have indicated a protective role for vitamin D with regard to SARS-CoV-2 infection and COVID-19 [10,11]. The pandemic restrictions and stay-at-home orders have increased the prevalence of VDD [12]. Furthermore, observational data suggest a higher rate of infections and poorer prognosis in those with VDD [13].

HYPOTHESIS

Our understanding of this vitamin, in-vitro models, and recent research suggest that vitamin D supplementation may have roles from preventing SARS-CoV-2 infection to reducing COVID-19 severity, as well as in mitigating the inflammation induced in the later phase of the disease. We hypothesize that vitamin D supplementation has the potential to confer protection against SARS-CoV-2 infection and severe COVID-19.

HYPOTHESIS TESTING

Experimental models have revealed that 1,25-dihydroxycholecalciferol (calcitriol), the active form of vitamin D, downregulates the expression of angiotensin-converting enzyme 2 [14]. Therefore, it can reduce the entry of SARS-CoV-2 into the cells and is thus likely to be of enhanced benefit in those with diabetes. This means that vitamin D is likely to have a role before a person contracts SARS-CoV-2 infection, and also after one contracts the infection and before they develop COVID-19. Cathelicidin antimicrobial peptide (CAMP) has an antioxidant activity, besides its role in destroying microbial membranes. It has been shown to reduce the severity of lung injury. In infections, vitamin D is converted to the active form in the alveolar epithelial cells, which then upregulates the production of CAMP [15]. It also reduces vascular permeability and cell apoptosis [16]. Calcitriol downregulates Th1 cells, tumor necrosis factor-alpha, nuclear factor-κB, and interferon-gamma [17–20]. It also reduces the production of interleukins, thus it has a potential role in dampening the cytokine release syndrome [21]. The various possible mechanisms through which vitamin D can provide protection in COVID-19 are shown in figure 1.

Ecological studies found a higher incidence of SARS-CoV-2 positivity in countries with a lower national average 25-hydroxyvitamin D (25-OHD) levels [10]. Researchers also attempted to find the relation between the latitudinal position of countries and the number of SARS-COV-2 cases [22]. A Swiss study published as early as May 2020 revealed that subjects who had tested positive for SARS-CoV-2 had comparatively lower 25-OHD levels [13]. A few months later, a larger study from the US found that SARS-CoV-2 positivity was inversely related to circulating 25-OHD levels [11]. A study of over 80,000 subjects in the North West of England who had a documented 25-OHD level in the preceding 12 months found that VDD was associated with an increased risk of hospitalization [23]. The initial human studies were mostly retrospective, which by their very nature have certain limitations [24].

In late 2020, a randomized, placebo-controlled study was conducted on SARS-CoV-2 positive, asymptomatic or mildly symptomatic individuals in India. The authors found that a significantly higher percentage of those who received 60,000 IU of cholecalciferol daily for 7 days (versus those who received placebo) tested negative on day 14 and also had lower fibrinogen levels [25]. A pilot randomized trial in Spain on patients hospitalized with COVID-19 compared those who received the best available treatment with those who additionally received calcifediol on days 0, 3, and 7, and then weekly. Two percent (n = 1) in the calcifediol group versus 50% (n = 13) required transfer to the intensive care unit (ICU) [26]. A recently published study on 103 COVID-19 in-patients in North Italy found that the severely ill had a mean 25-OHD level of 18.2 ± 11.4 ng/mL versus 30.3 ± 8.5 ng/mL in those who remained mildly symptomatic. The levels correlated inversely with interleukin-6 levels, need for transfer to the ICU, and mortality [27]. Multivariate analysis of an Israeli cohort found that 25-OHD levels were independent risk factors for COVID-19 and hospitalization [28]. A quasi-experimental study on the frail elderly in France found that bolus doses of vitamin D given regularly resulted in less severe disease and improved survival [29]. At the same time, there have been some studies, including a randomized trial that failed to show benefit with vitamin D supplementation in COVID-19 [30].

Ongoing trials and studies in the coming days are likely to shed more light on the role of vitamin D in the context of COVID-19. COVIDENCE UK is a large prospective study that plans to recruit over 12,000 subjects. Those who join the study would fill a vitamin D status and other risks assessment questionnaire, and will then be followed up to document the development of SARS-CoV-

2 infection and COVID-19 [31]. There are ongoing trials on asymptomatic, mildly symptomatic, and non-hospitalized patients who have tested positive for SARS-CoV-2. While one such trial is studying the role of a single bolus dose in reducing the time taken to test negative after a positive test, another trial is testing the efficacy of smaller doses given daily for 28 days in reducing hospitalisations and mortality [32,33]. Ongoing clinical trials are also looking at the role of vitamin D supplementation in reducing the risk of SARS-CoV-2 infection in healthcare workers [34,35]. Then there are ongoing studies on hospitalized patients who have developed pneumonia, and researchers are studying the role of vitamin D supplementation in reducing mortality [36]. In France, CoVitTrial, designed to compare a single dose of 400,000 IU vitamin D with a single dose of 50,000 IU vitamin D in patients with high-risk features has finished recruiting [37]. A study (CORONAVIT) on a large cohort in the UK aims to compare the effect of high dose versus low dose supplementation of vitamin D on the risk of SARS-CoV-2 infection as well as severe COVID-19 [38].

Community-based, as well as hospital-based studies, are needed to precisely delineate the place and impact of vitamin D supplementation on SARS-CoV-2 infection and COVID-19. Studies for determining the prevalence of vitamin D deficiency, estimation of serum levels, and meticulous registries of SARS-CoV-2 infections will help determine the precise nature of the association of vitamin D levels and risk of infection. A negative correlation would imply a role of vitamin D supplementation in SARS-CoV-2 prophylaxis. Case-control studies comparing COVID-19 hospitalized patients with and without VDD will help determine its influence on the course of the disease. Similarly, randomized trials recruiting patients admitted with COVID-19 will help determine the impact of vitamin D supplementation on outcomes in COVID-19.

The role of VDD in COVID-19 is of particular interest to the countries of the region as studies have shown that VDD is far more prevalent in Central Asia [39,40].

Researchers have also noted a dearth of studies on the subject from this region, highlighting the relative lack of concern and awareness [41].

ETHICAL CONSIDERATIONS

There has been a lack of awareness and due attention to vitamin D levels, and their correction has not been accorded. The role of vitamin D in health outside of the musculoskeletal system remains a not-so-widely known subject. While the stay-at-home orders are being enforced to limit the spread of infection, they lead to a decline in the serum levels of 25-OHD, and necessary awareness needs to be raised and steps taken to prevent VDD. Further studies may also provide the rationale for checking the serum levels of 25-OHD in those admitted for COVID-19, and for making corrections.

CONCLUSION

While the jury is still out on the role of vitamin D supplementation in preventing SARS-CoV-2 infection and a severe COVID-19 course, it might be pragmatic to supplement this vitamin as per the national guidelines. At such doses, there does not appear to be a significant risk of adverse effects or toxicity and are outweighed by the potential benefits.

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AUTHOR CONTRIBUTIONS

MG generated the hypothesis and drafted and revised the manuscript. NG performed the literature search, revised the manuscript. MG and NG approved the final manuscript and take full responsibility for the integrity of all aspects of the work.

CONFLICTS OF INTEREST

Both authors have completed the ICMJE Disclosure Form (http://www.icmje.org/disclosure-of-interest/ ; available on request). The authors declare that there are no potential conflicts of interest.
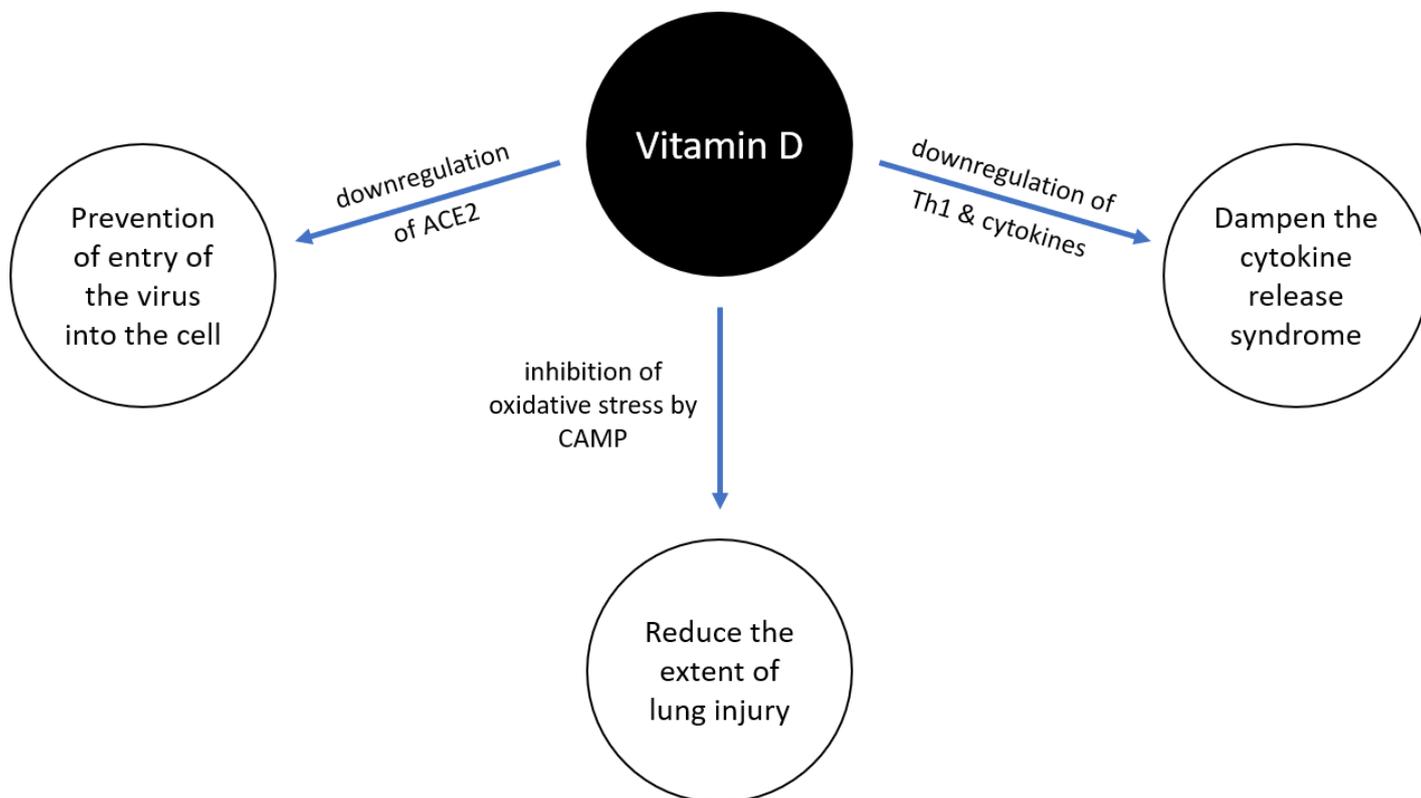
Figure 1. Possible mechanisms for the protective role of vitamin D in coronavirus disease 2019 (ACE2, angiotensin-converting enzyme 2; CAMP, Cathelicidin antimicrobial peptide)

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COVID-19 КЕЗІНДЕ ЖҰҚПАНЫҢ ТАРАЛУЫН ЖӘНЕ АУРУДЫҢ АУЫР АҒЫМЫН БОЛДЫРМАУДА D ДӘРУМЕНІНІҢ РӨЛІ: ГИПОТЕЗАНЫ ТЕКСЕРУ

Түйіндеме

2019 жылғы коронавирустық ауру пандемиясы (COVID-19) клиникада, зертханада және кітапханада медициналық қауымдастықты қамтыды. Әлем тез мутацияға ұшырайтын бұл вируспен күресіп жатқандықтан, вакцинаның ең жақсы кандидатын табумен қатар, адам өмірін құтқару үшін қолданыстағы молекулаларды қайта орналастыруды жалғастыруды күшейту қажет. Д дәруменінің жетіспеушілігі мен COVID-19 шалдыққан науқастарының нәтижелері үшін бұл дәріменнің қоспаларын қабылдау үлкен қызығушылық тудырды. Біз D дәруменінің қоспасы коронавирус 2 (SARS-CoV-2) мен ауыр COVID-19 туындайтын жіті респираторлық синдромнан қорғауды қамтамасыз етуі мүмкін деп болжаймыз. Жануарлар мен адамдарға жүргізілген әр түрлі зерттеулер, сондай-ақ интервенциялық зерттеулер COVID-19 кезінде Д дәруменінің қорғаныш рөлін көрсетті. Бұл қоспаның инфекцияны алдын алуда және COVID-19 барысын өзгертуде қосатын нақты үлесін анықтау үшін Д дәрумені алдын алу мақсатында енгізілген және жұқтырғандарға енгізілетін мұқият ойластырылған зерттеулер қажет.

Түйінді сөздер: 2019 коронавирус ауруы, ауыр жіті респираторлық синдром, коронавирус 2, пандемия, холекальциферол, кальцитриол, клиникалық сынақтар

РОЛЬ ВИТАМИНА D В ПРОФИЛАКТИКЕ РАСПРОСТРАНЕНИЯ ИНФЕКЦИИ И ТЯЖЕЛОГО ТЕЧЕНИЯ ЗАБОЛЕВАНИЯ ПРИ COVID-19: ПРОВЕРКА ГИПОТЕЗЫ

Резюме

Пандемия коронавирусного заболевания 2019 года (COVID-19) поглотила медицинское сообщество в клинике, лаборатории и библиотеке. Поскольку мир имеет дело с этим быстро мутирующим вирусом, помимо поиска лучшего кандидата на вакцину, необходимо продолжить усилия по перепрофилированию существующих молекул для спасения жизней. Большой интерес вызвали последствия дефицита витамина D и приема добавок этого витамина для исходов у пациентов с COVID-19. Мы предполагаем, что добавка витамина D может обеспечить защиту от тяжелого острого респираторного синдрома, вызванного коронавирусом 2 (SARS-CoV-2), и тяжелого COVID-19. Различные исследования на животных и людях, а также интервенционные исследования показали защитную роль витамина D при COVID-19. Чтобы определить точный вклад этой добавки в предотвращение инфекции и изменение течения COVID-19, необходимы более тщательно продуманные исследования, в которых витамин D вводится с профилактической целью и вводится тем, кто уже инфицирован.

Ключевые слова: коронавирусная болезнь 2019, тяжелый острый респираторный синдром, коронавирус 2, пандемия, холекальциферол, кальцитриол, клинические испытания