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REVIEW

The evident and the hidden factors of vitamin D status in older people during COVID-19 pandemic

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Abstract

Purpose Considering the COVID-19 pandemic, vitamin D is a target of research and speculation. Lockdown or home isolation reduces sunlight exposition and increases the risk of vitamin D deficiency. Special attention is needed for older people at risk of both severe forms of COVID-19 and vitamin D deficiency. This review aims to highlight the association of vitamin D and COVID-19 in two instances, the direct influence of vitamin D on the immune system, and the indirect risks for other vitamin D deficiency-related diseases, such as musculoskeletal properties in older persons.

Methods We performed a narrative review.

Results Whether vitamin D deficiency is associated with COVID-19 poor prognosis, and if vitamin D supplementation may improve the post-infection outcomes is still unclear. In any case, the pandemic generates indirect burden, such as the sequence: home isolation, low sunlight exposition, vitamin D deficiency, and fragility fractures.

Conclusion Therefore, it is time to debate how to optimize vitamin D status in older people, especially during the COVID-19 pandemic.

Keywords Vitamin D · Older people · Care homes · COVID-19 · Frailty

Introduction

Vitamin D deficiency and supplementation have been topics of most considerable interest among researchers in various fields. Considering the pandemic's time due to the coronavirus, the subjects of vitamin D deficiency and supplementation and respiratory infections are now a target of attention and studies—along with much speculation. Regarding the need for home isolation, older people are now at greater risk of developing vitamin D deficiency.

The most significant vitamin D source is cutaneous production after exposure of the skin to solar radiation (290 to 315 nm UVB radiation). [1, 2] Vitamin D metabolically active form is the 1,25-dihydroxyvitamin D (1,25(OH)2D), produced from 25-hydroxyvitamin D [25(OH)D] (the first hydroxylation product of vitamin D) mainly in the kidney, but also different extra-renal tissue. Thus, non-exposure to the sun, a common phenomenon in our modern lives, is a decisive risk factor for this deficiency. [1] Unsurprisingly, countries with a lower incidence of sunlight are likely to have a higher prevalence of vitamin D deficiency. European data showed a general prevalence of vitamin D deficiency (25(OH)D < 50 nmol/L or 20 ng/mL), ranging from 6.6 to 33.6% in Northern Europe, from 27.2 to 61.4% in Western Europe, and from 40.5 to 62.4% in Southern Europe. [3] However, data in tropical countries are more scarce. In Brazil, despite being a tropical country, it was observed that all age groups might have vitamin D insufficiency or deficiency. [4] In a 2019 meta-analysis including 72 Brazilian studies and 340,476 individuals from 2000 to 2017, the average vitamin D serum

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concentration was 67.65 nmol/L (95% CI: 65.91, 69.38 nmol/L) and the prevalence of deficiency (< 50 nmol/L) was 28.16%. [4] However, these numbers could be overestimated because most of the studies included were carried out among at-risk populations, such as older people, menopausal women, and pregnant women, mainly in the south and southeast regions. Regarding at-risk populations, including people with diabetes, postmenopausal women, individuals with dark skin, people who are obese, and those exposed to lower sun levels, this review will focus on older adults. [2, 5, 6]

Considering the dwelling-living older people, the *Survey in Europe on Nutrition and the Elderly* (*SENECA*) evidenced that 37% of men and 45% of women had vitamin D serum concentration below 30 nmol/L (12 ng/mL). [7–9] The *Longitudinal Ageing Study Amsterdam* (*LASA*) showed 45% of men and 56% of women with serum concentration lower than 50 nmol/L. [7, 8, 10] In Brazil, an average serum concentration at 52.85 nmol/L (95% CI 45.0, 60.7 nmol/L) and 28.5% prevalence of vitamin D deficiency (< 50 nmol/L) were previously reported. [4]

The prevalence of vitamin D deficiency is more frequent in frail older people than in non-frail. Indeed, some observational studies have found an association between vitamin D deficiency and the incidence of frailty. [11] However, it is impossible to establish whether vitamin D deficiency is a cause of frailty or a consequence of these individuals' less-frequent exposure to the sun. [5] In this context, the lower serum concentration of vitamin D is reported in older people who live in care homes. In Europe, vitamin D serum concentration below 50 nmol/L may affect 80–100% of nursing home residents. [1, 8, 12] Similarly, in Brazil's southern region, vitamin D deficiency was seen in 86.5% of the residents of one care home included in the above-mentioned meta-analysis [4, 13].

There are some reasons to explain why older people are at risk of vitamin D deficiency. Studies have suggested that the skin of the elderly is less able to synthesize vitamin D, possibly reaching only 30% of the capacity of younger adults. [5, 14] Importantly, the decrease in vitamin D synthesis is related to reduced mobility, less access to sun exposure, and chronic kidney disease than to factors intrinsic to the skin. [5] At this time of social isolation, older adults and those who live in care homes face an increased risk of vitamin D deficiency.

Known and unknown benefits of vitamin D

1,25(OH)2D binds to the vitamin D receptor (VDR) present in all the body tissues. VDR forms a heterodimer complex with the retinoid-X receptor (RXR). Further, 1,25(OH)2D activates VDR/RXR, bound to DNA sequences named vitamin D response elements (VDREs). This interaction modulates the expression of many genes, such as the ones related to calcium, phosphate, parathormone and bone metabolism, hormone secretion (for example, insulin), cell differentiation and proliferation, and immune function. [15]

Vitamin D deficiency is known to be associated with bone health. Lifestyle factors, such as adequate daily vitamin D and calcium intake, physical activity, not smoking, and low alcohol intake, are fundamental to improve bone health. [16] In this sense, studies have shown that vitamin D supplementation, especially when combined with calcium, is integral to strategies to prevent and treat osteoporosis, reducing the number of fractures and possibly falls. [17–19]

Regarding extra-bony effects, most observational studies have shown an association between lower serum concentration of vitamin D and cardiovascular disease, diabetes, cancer, respiratory infection, mortality, amid others. [20, 21] However, the cause-effect relationship between a deficiency and vitamin D supplementation for extra-bony causes is considered controversial, mainly because large, well-designed trials have failed to prove the cause-effect relationship. [17, 18, 22, 23]

Vitamin D and the immune system

In the context of the COVID-19 pandemic, interest in the effects of vitamin D on the immune system has increased. Data from experimental studies have shown an influence of vitamin D in different phases of immune response. However, the association between vitamin D and immune response is far from being fully understood and involves a massive complexity of pathways at different stages. We will highlight here some previously studied pathways that figure as examples of the immunomodulatory action of vitamin D.

First, the detection of vitamin D receptors (VDR) in large amounts throughout the immune system and the observation that the immune system can regulate the VDR suggest a connection between them. Another relevant feature is that the immune response can regulate the hydroxylation of 25(OH)D in 1,25 $(OH)_2D$. [24] For example, when a virus enters the body, it binds to adhesion molecules, such as ICAM-1. After binding, the virus is internalized and can be replicated or transcribed into new viruses that will infect other cells. However, the moment a cell is infected, it is recognized by receptors such as toll-like receptors (TLR). The TLR, when activated by some pathogen, increases the expression of extra-renal CYP27B1, which in turn is an enzyme that hydroxylates 25(OH)D in 1,25 $(OH)_2D$. Therefore, viral infections may demand more active vitamin D. [24]

The active form of vitamin D binds to its receptor VDR by regulating the transcription of several genes that modulate the immune system, supporting its response against the invading pathogen. For example, in the innate immune response, vitamin D stimulates monocytes to produce LL-37, β-defensins, and cathelicidins, which are antimicrobial peptides, to act as the first line of defense for the organism against the invasion of pathogens. [1, 25] Additionally, there is a more effective differentiation

of monocytes into macrophages, increasing their capacity for phagocytosis and chemotaxis. There is also the modulation of oxidative stress and cytokine secretion, mainly the anti-inflammatory interleukins. Then, vitamin D acts as a critical mediator between the innate and adaptive response, due to its influence on the presentation of the antigen. Finally, the adaptive response is observed stimulating the Th2 and Treg profile to the detriment of Th1, Th17, and B cells. In this phase, the stimulus to apoptosis and the production of anti-inflammatory cytokines is observed as well. [1, 25]

In fact, the behavior of the immune response is different according to the type of pathogen. Therefore, specifically concerning respiratory viral infection, studies have shown the influence of vitamin D in recruiting macrophages, neutrophils, and T cells, inducing apoptosis and autophagy in addition to reducing viral replication, and in turn, increasing viral inactivation and clearance. [24, 26] Although from a pathophysiological point of view, evidence for the relationship between vitamin D and the immune system is strong, clinical studies in this area are heterogeneous and controversial. [6, 17, 18] The most recent research is promising regarding vitamin D supplementation and the prevention of respiratory infections. In a meta-analysis involving 10,933 patients in 25 randomized clinical trials, it was observed that daily vitamin D supplementation, with 1000 to 2000 IU or equivalent to a weekly dose, reduces acute respiratory infection incidence. Those with lower concentrations < 25 nmol/L who did not receive additional bolus doses showed more significant benefits. [27]

A preprint meta-analysis analyzed the data from 29,841 participants (from 0 to 95 years) in 39 randomized clinical trials. The authors observed that vitamin D (400–1000 IU/day for up to 12 months) against placebo protected from an acute respiratory infection. Despite the heterogeneity and bias found in some trials, the data suggests the benefits of lower doses of vitamin D within the prevention of respiratory disease. [27, 28]

Another potential effect of vitamin D is its ability to boost the immune response to vaccines. Studies have suggested an association between vitamin D deficiency and lower response to vaccine immunization. [29–31] They have also found that adding vitamin D to vaccine preparations could improve the response to some pathogens' vaccination. [29–31] The immune response phenotype to vitamin D status may differ according to the target pathogens and with the vaccine type. However, the available data are controversial and unclear. [29] For example, recently, meta-analysis failed to prove the association of vitamin D deficiency with the response to influenza virus vaccination. [32]

Vitamin D and COVID-19

The effects of vitamin D on coronavirus (*SARS*-CoV-2) infections are so far unknown. [26, 33] One reason older people may be at greater risk of severe COVID-19 is their weak immune innate capacity, leading to a higher virus overload and an exacerbated adaptative response that includes cytokine overproduction. [34] It favors the SARS-CoV-2 to replicate more intensively and to spread rapidly to the lung alveoli, leading to pneumonia. [30] As aforementioned, vitamin D can improve the innate immune response and attenuate the cytokine storm and adaptative immune response. [34] Lower vitamin D serum concentration, in combination with aging, may result in a synergic condition for the most critical outcomes.

In addition, SARS-CoV-2 also causes damage to the myocardium. The mechanisms of cardiac damage induced by COVID-19 are still not conclusive but are probably related to cytokine storm, angiotensin-converting enzyme 2 (ACE-2), and hypoxemia. ACE-2 is an enzyme highly expressed in the heart and lungs. [35] SARS-CoV-2 interacts with ACE-2 that facilitates cell infection. Unsurprisingly, people with hypertension, diabetes mellitus, and older ages present an unbalance of the renin-angiotensin system (RAS) are at significant risk of COVID-19. [35, 36] Considering the potential role of vitamin D in balancing the renin-angiotensin system and its immunomodulatory effects, the cardiac target might also be affected by vitamin D status.

Observational studies investigating the association of vitamin D status and COVID-19 disease have been published. However, they are heterogeneous and show different conclusions.

Some studies used vitamin D status before the pandemic, using previous individual dosage or population means. A retrospective study evaluated the COVID-19 case mortality rate in 10 different countries from February to April 2020, using a mathematical model. [34] The authors found an inverse association between reported vitamin D serum concentration in older persons in countries with similar screening approaches and C reactive protein levels, a well-known marker of higher inflammation and overproduction of cytokines, especially interleukin 6. This finding was more evident among older people than in the younger ones. The reported lower serum concentration of vitamin D was associated with higher COVID-19 mortality as well. The authors emphasized that the results may infer a possible association between vitamin D deficiency and COVID-19 severity. However, this association was indirect, and vitamin D and cytokine serum concentration in individual patients were not assessed. [34]

A further study investigated 191,779 individuals, from the District of Columbia, USA, with vitamin dosage within the last year. Vitamin D levels are associated inversely with SARS-CoV-2 positivity, even when adjusted by age, gender, ethnicity, zip-code, and latitude. Interestingly, older people (≥ 60 years old) presented with higher vitamin D serum levels and lowered SARS-CoV-2 positivity than the younger ones. [37] In addition, in a retrospective unicentric study, the deficiency of vitamin D detected within 1 year before the positive test was associated with increased COVID-19 risk. [38] This study brings up the necessity for more research on vitamin D

deficiency prevention as a potential benefit approach to reduce the risk for the COVID-19. [38]

Yet, the correlation of world meters for COVID-19 in late May and the vitamin D concentration in 20 European countries, published by Lips et al., showed an inversion correlation between vitamin D serum concentration and the number of COVID-19 cases. However, vitamin D deficiency was not correlated with the number of deaths. [3, 39]

Another study utilized vitamin D dosages from the United Kingdom Biobank, collected from 2006 to 2010. The authors found no association regarding vitamin D status and SARS-CoV-2 infection of disease severity. [40, 41]

Considering the assessment of vitamin D during COVID-19, there are also some interesting results. In an observational study that included 105 patients older than 65 years old, 70 were SARS-CoV-2 positive. Vitamin D was collected at the beginning of the disease. Vitamin D deficiency (≤ 30 nmol/L) was associated with higher D-dimer levels and invasive mechanical ventilation. [42] In another retrospective observational study that included 185 patients (93 inpatient and 92 outpatients), vitamin D insufficiency (< 50 nmol/L) at admission was associated with invasive mechanical ventilation and mortality. Even when adjusted by gender, age, and comorbidities, individuals older than 60 years old had an independently higher risk for disease severity and mortality. [43]

On the other hand, although it is still controversial whether vitamin D circulates freely or bind to proteins, lower levels of vitamin D binding protein (VDP), induced by inflammation, might be reflected in lower concentrations of 25(OH)D and 1,25 (OH)2D. [44] Therefore, it is not possible to confirm whether inflammation leads to the lower serum concentration of vitamin D or lower serum concentration of vitamin D yields higher inflammation.

In fact, by now, some trials of vitamin D supplementation (for prevention and treatment) for COVID-19 have been carried on, though none of them is published yet. [45, 46] Only one pilot open label randomized study included 77 patients that showed a potential benefit of calcifediol in reducing the need for ICU hospitalization. [47] While the controlled trial evidence has already been pending, the observational studies have inferred the association of lower vitamin D serum concentration as a biomarker of SARS-CoV-2 infection and disease severity.

Martineau and Forouhi commented about the upcoming trials involving in-hospital vitamin D supplementation that will face a challenge because it might be too late to start supplementation. This opinion may be corroborated by a previous study that failed to prove the benefits of vitamin D to improve critically ill patients' outcomes. [46] Besides, it might be too hard to show the benefit of a micronutrient over the hyperinflammatory state and the concomitant use of corticoid in COVID-19. Again, the authors highlight that the role of vitamin D within the scenario of respiratory infection prevention might be more promising than the treatment. [46, 48]

Therefore, at the moment, there is no evidence that vitamin D supplementation could prevent or treat COVID-19. However, the European Society for Clinical Nutrition and Metabolism (ESPEN) has recommended that malnourished people at risk for or have COVID-19 should intake the daily recommendation ingestion (DRI) micronutrients to optimize the general anti-infection response. [33]

Management of vitamin D status in older people

The COVID-19 pandemic may increase the burden of healthcare systems directly or indirectly. For instance, when all efforts are focused on coping with the pandemic, other common diseases may be neglected. Furthermore, lockdowns and home isolation reduce exposure to sunlight, which could aggravate vitamin D deficiency, increasing the risk for osteoporotic fractures. Fragility fractures are more frequent than the combination of stroke, myocardial infarction, and breast cancer cases. [49] Within the osteoporotic fracture scenario, it is relevant to highlight the burden of hip fracture, which is associated with high morbidity and high mortality. Hip fracture is associated with a decline in mobility, independence, and quality of life. Notably, the 1-year mortality after hip fracture is around 30% compared with the mortality for the same age population that would be 10%. [50]

The Brazilian Society of endocrinology recommends the target of vitamin D serum concentrations above 75 nmol/L (30 ng/mL) for older people. [51] Nevertheless, the health care professional should draw attention to the potential toxicity risk, maintaining the concentration up to 150 nmol/L (60 ng/L) and avoiding the serum concentration above 250 nmol/L (100 ng/mL). The intake of higher doses, especially in a bolus, should be discouraged because it does not help older people. In a previous clinical trial, the two groups treated with 60,000 IU/month or 24,000 IU + calcidiol presented the higher percentage of fallers and had no improvement in lower extremity function, when compared with the control group, which received 24,000 IU/month (the equivalent of 800 IU/day). In another trial, the bolus of 500,000 IU annually also increased the risk of falling. [51–53]

Screening for vitamin D deficiency in a non-risk bone disease population is not recommended, as it is not cost-effective. [6, 19, 54] However, there is no consensus regarding the prescription of vitamin D guided by deficiency level or standard supplementation in the groups at risk. [7] Some of the osteoporosis guidelines recommend that all at-risk populations have their vitamin D serum concentration assessed before supplementation. [6, 19, 55] On the other hand, supplementation of physiological doses that meet the DRI without previous dosage is a strategy to prevent vitamin D deficiency, especially in European countries. [8, 54, 56]

In 2017, a systematic review of universal vitamin D supplementation's economic aspects to prevent deficiency, versus screening and treatment according to the vitamin concentration, was inconclusive. [57] In 2019, Aguiar et al. proposed a model to estimate population strategies' cost-effectiveness to prevent vitamin D deficiency. The authors simulated the model using the entire population of England and Wales for 90 years. The model suggested that wheat fortification alone would reduce 25%, and wheat flour fortification plus supplementation would reduce 33% of vitamin D deficiency. [58]

Necessary to clarify the difference between treating a vitamin D deficiency already detected from the strategies to prevent the deficiency. The treatment of hypovitaminosis D for the population at risk aged over 70 years may include the maintenance doses of 1500–2000 IU/day to maintain 25(OH)D > 30 ng/mL. [18] However, the strategies to prevent the deficiency, without previous screening, involve the supplementation of a dose around DRI. [3]

The DRI of nutrients can be defined using the estimated average requirement (EAR) and/or the recommended dietary allowance (RDA), which indicates intake that meets the needs of 50% and 97.5% of the population. [59, 60] Regarding bone health, to achieve a vitamin D serum concentration above 50 nmol/L, the Institute of Medicine (IOM) in 2011 reviewed the recommendations and suggested setting the vitamin D EAR at 400 IU/day for people 1 to 70 years old and 600 IU/day for those older than 70 years old. Similarly, the vitamin D RDA was set at 600 IU for adults and 800 IU for older than 70 years old. [59, 60] It is important to highlight that is not necessary to exceed the RDA; otherwise, the supplementation can reach the upper limits, increasing the risk of adverse effects. [59]

The current recommendation for daily vitamin D intake to achieve deficiency prevention varies according to the country, latitude, vitamin D consumption, and politics for food fortification. Therefore, European countries' dietary reference values regarding older people range from 200 to 800 IU/day. [8]

In the UK, the British Dietitian Association (BDA) and the National Institute for Health and Care Excellence (NICE) suggest 400 IU/day for adults during autumn and winter and the entire year for those older than 65 years old. [54] Despite these recommendations, in observational studies performed in the UK, it was observed that in some studies, few people are receiving vitamin D. [2, 60] It was observed, for example, in some care homes, that only 20% of the residents were prescribed vitamin D. [2, 61] The Dutch recommendation reviewed in 2012 suggests that all people older than 70 should intake 800 IU of vitamin D daily.

In 2019, the Working Group on Vitamin D of the European Calcified Tissue Society stated for all European countries and the Middle East region: "vitamin D supplement of 10–20 μg/day (400–800 IU/day) is advised to all older institutionalized subjects and should be considered for all older persons above 70 years old." [3].

Another strategy to avoid vitamin D deficiency is exposure to sunlight. The advantages for older people would be less toxic levels of oral supplements, polypharmacy prevention, and beneficial effects on health and well-being. [62] The Brazilian Society of Dermatology suggests that 10-min exposure without sunscreen from 10:00 a.m. to 3:00 p.m. is enough for people to produce sufficient serum concentration of vitamin D and is safe in terms of the risk of developing skin cancer. [63] In the Netherlands, exposure to sunlight for 15–30 min, from 11:00 a.m. to 3:00 p.m. from March to November, before the skin becomes burned, is one strategy to produce vitamin D. [64] We must weigh the risks for skin cancer, however. Undoubtedly, people must avoid long-term sun exposure without sunscreen. However, lower sunlight exposure may be beneficial for vitamin D production and also people's well-being. In a Dutch study carried out on care homes residents, exposure to 50% of the minimal erythema dose (MED) in a UVB sunbed once a week improved vitamin D serum concentration in all participants, from a median baseline 26.5 to 43.5 nmol/L. [62]

In Brazil, a tropical country, there is no recommendation for prophylactic supplementation for people, at-risk or not, unless an insufficiency or deficiency is detected. In other words, universal vitamin D supplementation is not recommended unless subjects have a proven deficiency. However, presently, people are isolated, reducing their sun exposure. Thus, older people will experience a double challenge: being a population at major risk and experiencing more intensive isolation. Therefore, we should provoke the debate on strategies to optimize vitamin D serum concentration and avoid deficiency, especially among older populations, in Brazil.

Conclusion

Whether vitamin D will protect against coronavirus infection or be influential in reaching the best outcome in viral infection, we have no assurance. Regardless, older adults and care home residents are at risk of falls and fractures beyond the infectious disease and will benefit from maintaining the vitamin D status. [65]. Falls in care facilities and hospitals are everyday events that cause considerable morbidity and mortality for older people, independently of the current pandemic. [21] Therefore, at the moment, while this high-risk population is not allowed to have their blood test for vitamin D, we would like to provoke the debate over providing a vitamin D daily allowance of 400 IU to 800 IU for all socially isolated older people in Brazil, especially for those who live in care homes. We also outstand the possibility of incentivizing the sun exposure from 10 to 30 min, regarding the information aforementioned. Finally, all the countries with previous standard recommendation shall double-check if the older people get vitamin D as a standard recommendation.

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Abbreviation $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ACE-2, Angiotensin-converting enzyme 2; BDA, British Dietitian Association; COVID-19, Coronavirus disease; CYP27B1, Cytochrome P450 family 27 subfamily B member 1; DRI, Daily recommendation ingestion; EAR, Estimated average requirement; ESPEN, European Society for Clinical Nutrition and Metabolism; ICAM-1, Intercellular adhesion molecule 1; ICU, Intensive care unit; IOM, Institute of Medicine; LASA, Longitudinal Ageing Study Amsterdam; LL-37, Antibacterial peptide LL-37; MED, Minimal erythema dose; NICE, National Institute for Health and Care Excellence (NICE); RAS, Renin-angiotensin system; RDA, Recommended dietary allowance; RXR, Retinoid-X receptor; SARS-CoV-2, Coronavirus; SENECA, Survey in Europe on Nutrition and the Elderly; Th, T helper cells; TLR, Toll-like receptors; Treg, Regulatory T cells; UVB, Ultraviolet B radiation; VDR, Vitamin D receptors; VDREs, Vitamin D response elements

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