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Is Vitamin D Supplementation Protective against Coronavirus Disease 2019 (COVID-19)?

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ABSTRACT

Vitamin D, through various mechanisms, affects the immune system, resulting in antiviral effects. Recent studies have also shown that it is effective and safe in the prevention of acute respiratory infections. For this reason, in the era of Coronavirus Disease 2019 pandemic (COVID-19), it is speculated whether vitamin D may also have a positive effect in the course of COVID-19. However, the results of available studies are contradictory, although due to the safety of vitamin D, as well as the information known so far, its regular supplementation in people at risk of deficiency seems to be reasonable.

Keywords: vitamin D, coronavirus disease 2019, COVID-19, SARS-CoV-2, acute respiratory infections

INTRODUCTION

In recent years there have been a number of publications suggesting that vitamin D supplementation may prevent acute respiratory infections (ARIs) [1]. This was thought to be related, among other things, to the fact that during the winter seasons when vitamin D levels are reduced in the population there is an increased frequency of viral infections [2]. Potential mechanisms that would explain these beneficial effects of vitamin D would include, for instance, its ability to activate peptides secreted on the surface of mucous membranes, which consequently show antiviral and antibacterial properties [3]. However, the results of further studies on the importance of vitamin D supplementation in the prevention of ARIs were contradictory [1]. Afterwards, however, a large meta-analysis was able to show that regular vitamin D supplementation (but not large bolus doses of vitamin D) does indeed show a prophylactic effect against ARIs, and yet is safe [4]. Due to this, it has been speculated that vitamin D supplementation may also protect against Coronavirus Disease 2019 (COVID-19).

Mechanisms of the Hypothetical Prophylactic Effect of Vitamin D

It is important to outline the mechanisms of vitamin D action that may support this hypothesis. Vitamin D strengthens the first line of defense of the human organism which is the innate immune system. This is done through induction of antimicrobial peptides such as cathelicidin, which in turn leads to destruction and removal of viruses, stimulation of recruitment of neutrophils, monocytes/macrophages and dendritic cells, which also kill and remove pathogens, and through initiation of adaptive immune responses [5-13]. This phenomenon was first observed when it was shown that, under the influence of an intracellular infection (Mycobacterium tuberculosis), there was intracellular synthesis by monocytes or macrophages of the active form of vitamin D ($1,25\ (OH)_2D$), which ultimately resulted precisely in the synthesis of cathelicidin, and consequently in the intracellular killing of microorganisms [5,9,14-15]. Importantly, the ability of macrophages to synthesize cathelicidin has been shown to be related to plasma 25-OHD levels [5,15-16]. A similar phenomenon was also observed in epithelial tissue [5-7]. Cathelicidin exerts its numerous effects through induction of pro-inflammatory cytokines, stimulation of chemotaxis and promotion of removal of respiratory pathogens by induction of apoptosis and autophagy of infected epithelial cells [5-7].

Vitamin D has its beneficial effect on the innate immune system also through other mechanisms, as through stimulation of β-defensin2 synthesis, whose profile of action is similar to that presented by cathelicidin [9,17-18]. In general, it can be put that the presented antimicrobial mechanisms are largely related to the induction of autophagy [5,7]. Antimicrobial effects are also induced by reducing intracellular iron levels in a hepcidin-dependent mechanism [19-20]. Although this information explains why low vitamin D levels are associated with more frequent respiratory infections, the mechanisms described are rather those related to antibacterial protection [21]. Nevertheless, vitamin D may exert a number of strictly viral effects that overlap to some extent with antimicrobial mechanisms [5,22]. Both the mechanism through cathelicidin and β-defensin2 involve inhibition of the ability of the virus to enter cells and replicate [11-12]. The most key effect in this process, however, seems to be the induction of autophagy, as it has been shown that this is how the vitamin can reduce infection with influenza A, HIV-1, rotavirus and hepatitis C (**Figure 1**) [5,10,13,23-29].

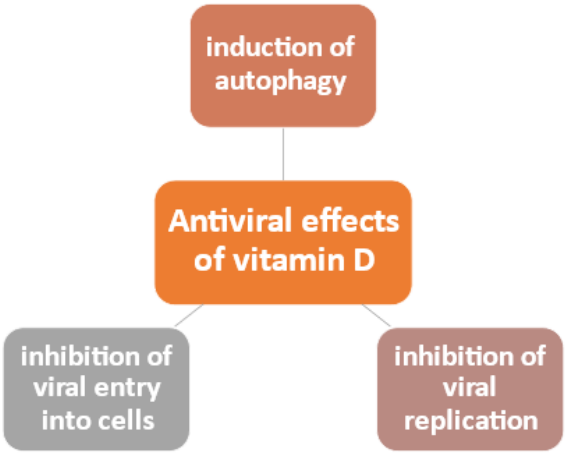

Figure 1. Basic antiviral effects of vitamin D

This induction of autophagy may be dependent on plasma 25-OHD levels [5,22]. Both 25-OHD and the active form of vitamin D increase the expression of the autophagy marker LC3 [5,7,22,29]. The enhancement of autophagy and consequently the antiviral effect by vitamin D is the effect of increasing the synthesis of Beklin-1 and PI3KC3, which are essential enzymes in increasing autophagy, and is also the effect of inhibiting the mTOR pathway, which suppresses autophagy [5,30-32]. Vitamin D may also promote autophagy by stimulating the formation of autophagosomes, and also to maximize the antiviral effect play an important role in maintaining an appropriate balance between apoptosis and autophagy [5,7,25]. It is worth mentioning that in acute conditions, activation of the innate immune response is beneficial, however, if this activation is chronic it can be the cause of a cytokine storm (and as is known, the cytokine storm is devastating aspect in the pathophysiology of COVID-19) [5]. An active form of vitamin D counteracts this chronic activation of the innate immune response, which is done by down-regulating toll-like receptors (TLR) and also by inhibiting interferon**γ** (INF-γ) and TNF/NF-κB signaling pathways [5]. Vitamin D, in addition to initiating an adaptive immune response, also prevents an uncontrolled immune response, which could also be harmful. In this case, 1,25 $(OH)_2D$ exerts this effect by, among other things, inhibiting the maturation of dendritic cells and also by altering the profile of T lymphocytes from pro-inflammatory Th1 and Th17 to anti-inflammatory Th2 and Treg, in effect again helping to prevent a cytokine storm [5,33-36].

State of Current Research

It is therefore already known that hypothetically vitamin D could have a prophylactic effect against COVID-19 (**Figure 2**). In any case, at the moment we lack cohort and clinical studies that could clearly define the role of the vitamin in the prevention of COVID-19, but there are retrospective studies. D'Avolio et al. demonstrated that patients with PCR-confirmed SARS-CoV-2 infection have significantly lower plasma 25(OH)D levels than those with negative results [37]. Rhodes et al. in their study shows an indirect relationship between vitamin D levels and COVID-19 severity [38]. Namely, it was shown that there is a 4.4% increase in COVID-19 mortality for every 1 degree north of latitude 28 degrees, and these results were adjusted for age [38]. Also in another study, a similar relationship was shown by observing that the northern states of the United States, i.e. above Latitude 40, have a higher mortality rate due to COVID-19 than the southern states [39]. This may therefore suggest that UV radiation shows a protective effect against COVID-19, potentially indirectly by increasing vitamin D synthesis. Nevertheless, it should be kept in mind that UV radiation has many vitamin D-independent effects that could potentially explain such a relationship, for example, suppression of T-lymphocyte activation in the skin [1,40]. As mentioned before, only preliminary and retrospective information is available. However, the available studies, although contradictory, often indicate that the course of COVID-19 may be related to vitamin D deficiency, and the fact that vitamin D deficiency hypothetically could be a risk factor for COVID-19 and its unfavorable outcomes may explain the extraskeletal effects of vitamin D on the immune system [5,41]. For example, a cohort observation by Tan et al. indicates that patients receiving vitamin D (as well as magnesium and vitamin

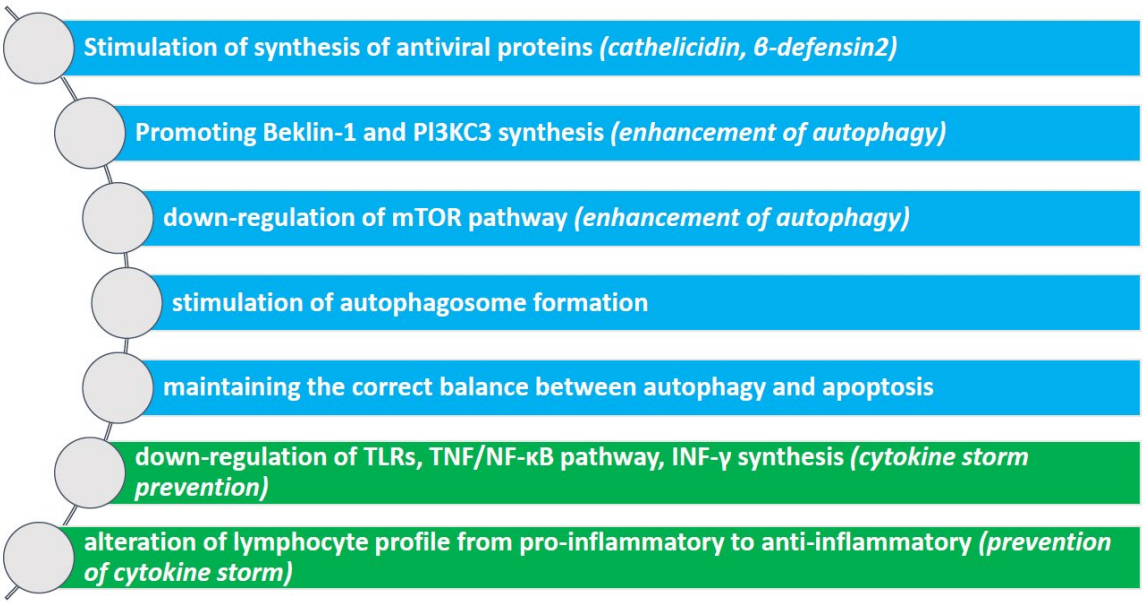

Figure 2. Summary of vitamin D effects that may be potentially beneficial against COVID-19

B12) shows a significant protective effect against clinical deterioration in the course of COVID-19, the Ilie et al. study showed a significantly negative correlation between vitamin D levels and the number of cases and deaths due to COVID-19, while the Ali study observed a similar relationship to the Ilie et al. report, but no negative correlation between vitamin D levels and deaths due to COVID-19 [41-43]. On the other hand, there are also studies that show opposite results [5,41]. Hastie et al. revealed that vitamin D has a significant association with COVID-19 infection, in a univariate analysis, although once co-variables are taken into account, such a relationship is no longer observed [44]. Also Darling et al. observed no difference in vitamin D levels between COVID-19 cases and controls [45]. Although the results presented are conflicting, recent studies have consistently shown a more common presence of reduced vitamin D levels in patients with severe forms of COVID-19 [46]. This therefore supports that patients who are at risk of COVID-19 infection and/or influenza should consider several weeks of vitamin D supplementation at a safe dose of 10,000 IU/d to quickly increase 25(OH)D levels, followed by a dose of 5000 IU/d [46-50].

CONCLUSIONS

Thus, in conclusion, it is not clear whether vitamin D can show a protective effect against COVID-19 or reduce mortality in its course. The available studies are contradictory and, at the moment, we can only state with certainty that further research on the matter is necessary. Nevertheless, it seems reasonable that, in the era of the COVID-19 pandemic, people at risk of reduced vitamin D levels should be advised to supplement it regularly, which is all the more justified in view of the results of the cited recent meta-analysis that demonstrated the efficacy and safety of vitamin D in preventing ARI.

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