ACTA CLINICA BELGICA
https://doi.org/10.1080/17843286.2021.2018832

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REVIEW



# Vitamin D in patients with COVID-19: is there a room for it?

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**ABSTRACT**

Vitamin-D receptors are found in a variety of cells with the potential to regulate many cellular functions. Higher COVID-19 severity has been reported in individuals, which are known to have lower vitamin-D levels. The relation between vitamin-D and COVID-19 has been analysed with a number of studies but only few met high standards. Studies revealed discordant findings. There is no data from interventional trials clearly indicating that vitamin-D supplementation may prevent against COVID-19. An increasing number of observational studies put forward the preventive feature of adequate vitamin-D status for COVID-19 mortality. Yet, there are again conflicting findings. This narrative review summarizes the current evidence and provides a practical advice to lessen the impact of COVID-19 by ensuring recommended vitamin-D intakes. This approach would not be harmful, but potentially useful. Vitamin-D is safe especially if it does not exceed the upper-tolerable-limit. Daily doses are recommended over the weekly or monthly higher doses. Mega-doses are not recommended because of its potential to lead adverse events. The target level of vitamin-D is proposed above 30 ng/mL in majority of the studies. Nonetheless, one should consider that the benefit is foreseen to be small, and some time (months) may be needed for such effect.

**KEYWORDS**

Vitamin D; COVID-19; prevention; benefit; prognosis; mortality; dose

## Background

The low vitamin D status represents a global health problem both in younger age groups and older individuals [1,2]. Adequate vitamin D levels are known to be important in preventing and counteracting osteoporosis and sarcopenia, which are prevalent conditions in older adults [3,4]. Vitamin D receptors are found in a variety of cells in the human body, nearly universally expressed in nucleated cells [1,3]. While classically kidneys are known to convert vitamin D to its active form 1,25-dihydroxy vitamin D by the enzyme 1-alpha-hydroxylase, this enzyme has been detected in several other tissues, pointing to the autocrine and paracrine effects of vitamin D in addition to its endocrine effects [1,3]. Vitamin D binding protein (DBP) is a major plasma carrier for vitamin D and its metabolites. About 85% of the total circulating 25(OH) D is coupled to DBP, whereas 15% is bound to albumin. In free form, around 0.04%-3% of 25(OH)D circulates [5]. DBP is made in the liver and is regulated by estrogen, glucocorticoids, and inflammatory cytokines, but not by vitamin D. DBP is a polymorphic protein, and it controls total and circulating free vitamin D metabolite levels in a variety of clinical settings. It is suggested that the variations in the prevalence of COVID-19 and its mortality rates among countries may be explained by vitamin D metabolism differed by the DBP polymorphisms [6]. The reported studies as we discussed below didn't give any information regarding the DBP levels. Clinical tests do not discriminate between fractions bound to carrier proteins and measure total 25-hydroxyvitamin D levels. Levels of DBP can be lower in some race or population, probably because of the high prevalence of a common genetic variant. Lower levels of vitamin D does not translate to lower levels of bioavailable 25-hydroxyvitamin D, since DBP level may be lower than standard levels. Therefore, some studies may not have found a relationship between vitamin D level and the severity of Covid infection.

Vitamin D has the potential to regulate many cellular functions. Considering its expression in many cell types and its common deficiency, the role of vitamin D in different prevalent health problems, besides those related to musculoskeletal system, has been investigated including infections, auto-immunity, cardiovascular diseases, insulin resistance, obesity, and malignancies [1,7–10]. In addition, respiratory diseases are shown to be associated with dysregulated vitamin D metabolism raising the possibility that vitamin D deficiency might be a consequence of pulmonary inflammation [11]. Various reviews underlined the association between hypovitaminosis D and many respiratory, enteric, and urinary tract infections, vaginosis, sepsis, flu-syndrome, dengue, and hepatitis [12]. Epidemiologic data, to date, suggest that the risk of infections might be higher when 25-hydroxyvitamin D [25(OH)D] levels are <20 ng/mL (50 nmol/L) while decreasing with higher levels [3].

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***Vitamin D and the immune system***: It is long known that immune system function is impaired in older adults which often have a deficiency in vitamins, including vitamin D [2]. Vitamin D receptors are present in almost all immune system cells including antigen-presenting cells, such as dendritic cells, macrophages, and T and B cells [3]. 1,25-dihydroxy vitamin D acts as an immune system modulator, modulating both innate and adaptive immunity [13,14]. It is a stimulator for the innate immune system [3,13] that supports innate antiviral effector mechanisms [15]. It increases the oxidative burst potential of macrophages, stimulates the expression of potent anti-microbial peptides, which exist in neutrophils, monocytes, natural killer cells, and epithelial cells lining the respiratory tract where they play a major role in protecting the lung from infection [13]. It keeps the integrity of the tight junctions and the pulmonary barrier, provides immunoregulatory activity, and modulates the renin-angiotensin system (RAS), all factors of potential relevance to acute pneumonia and hyper-inflammation observed in patients with COVID-19 [12,16,17]. Vitamin D acts as a potent negative endocrine regulator of the RAS and decreased serum levels of vitamin D have been correlated with increased activity of RAS [17]. This finding is important as overactivation of RAS is associated with poor prognosis in COVID-19. Vitamin D has also anti-inflammatory effects, it inhibits dendritic cell maturation and prevents excessive expression of inflammatory cytokines induced by the viral infection, including IL6, TNF-α and IFN-β [13,14] and modulate macrophage chemotactic protein1, interleukin 8, type 1 interferon, and lower or counteract reactive oxygen species [2,14]. Vitamin D reduces the activation of the adaptive immune system [3]. It acts on T cells down-regulating T-helper-1 (TH1)-cell cytokines, particularly IFNγ, and stimulate TH2-cell responses [2]. TH1-cell response shifts to a T regulatory type 1 (TR1) cell response. Vitamin D also counteracts TH17-cell responses and the differentiation of naive TH-0 cells into a TH-17 type and promotes the reciprocal differentiation and proliferation of regulatory T (TReg) cells [2]. It decreases B-cell expansion, plasma cell development and IgG secretion [18]. We summarized these effects in Figure 1. These findings and results emerging from experimental studies in patients with autoimmune diseases have provided the rationale for the use of 1,25-dihydroxy vitamin D in association with other drugs in these diseases [19]. SARS-CoV-2 may promote a shift of the immune response towards a Th17 proinflammatory phenotype, causing the development of an unfavourable clinical evolution of the disease [2], a pathway similar in autoimmune diseases. It has been suggested that the promotion of an anti-inflammatory response, mediated by the induction of a prevalent T-regulatory-cell phenotype which may be through the effect of vitamin D, may represent a very promising strategy for the treatment of patients suffering from COVID-19 [2].

Regarding upper respiratory infections, the results from randomized controlled trials were not conclusive, with some showing beneficial effects and some not [20–22]. However, a meta-analysis including almost 11,000 patients from 25 randomized clinical trials showed that vitamin D supplementation reduced the incidence of acute respiratory infections. The proportion of patients experiencing one acute respiratory tract infection were lower especially in those with vitamin D levels <10 ng/mL (25 nmol/L) who were given daily or weekly vitamin D replacement, rather than bolus doses [23,24].

***The relation between vitamin D and COVID-19***: Higher COVID-19 severity and mortality rates have been reported in older adults, patients with diabetes, individuals suffering from chronic lung and cardiovascular diseases, and in African Americans, which are all known to have lower vitamin D levels. In line with these, ecological studies revealed that higher latitudes and winter season, which are also known risk factors for low vitamin D levels, were associated with higher COVID-19 related mortality rates [14,15]. Therefore, association between vitamin D and COVID-19 deserves further studies. A possible explanation or contributor in this documented relationship between vitamin D and COVID-19 may be the healthy user effect. A healthy lifestyle includes physical activity and better eating habits and this may explain the association between lower vitamin D levels and more severe COVID-19. Apparently, a healthier life-style would be associated with both higher vitamin D levels and better reacting immune system against infections. On the other hand, vitamin D deficiency may be a risk factor for COVID-19 and its severity. Accordingly, it may be a potential therapeutic, which is cheap, safe and already globally available. The latter is currently under extensive investigation.

There is a high number of studies in this field but only few of them meet high methodological standards. So far, studies have revealed discordant findings on vitamin D levels and risk for COVID-19 infection [25]. We have summarized an overview of the included studies in Table 1. Clear support for causality between serum 25(OH) D levels and COVID-19 remains undetermined [14].

A preprint study noted an inhibitory effect of the active 1,25-dihydroxy vitamin D in human nasal epithelial cells infected with SARS-CoV-2 [26]. In a single-centre retrospective study including 489 participants who had a 25(OH) D level measured within one year of testing for COVID-19, seventy-one participants were reported COVID-19 positive. In multivariate analysis, the risk of a positive COVID-19 test was higher in patients likely to have deficient 25(OH) D level (<20 ng/mL) than in those who were likely sufficient. Predicted COVID-19 rates in the deficient group were 21.6% vs. 12.2% in the sufficient group [27]. In a study

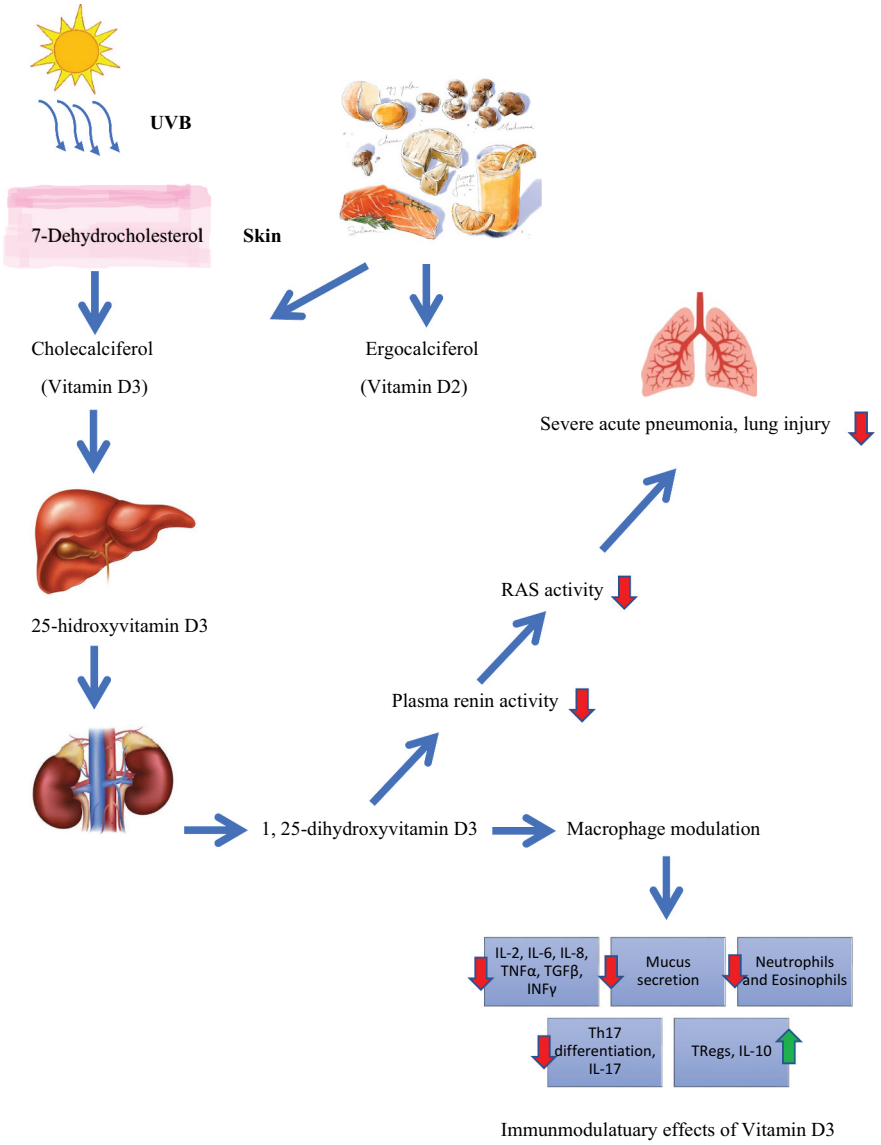


**Figure 1.** Potential working mechanisms of vitamin D against COVID-19 owing to immunomodulatory actions of vitamin D. Vitamin D may suppress RAS activity through inhibition of renin. IL: interleukin; TNF: Tumor necrosis factor; IFN: Interferon; Th: T-Helper; 7-DHC: 7-Dehydrocholesterol; PGE2: Prostaglandin E2.

that searched the literature for the mean levels of vitamin D in 20 European countries, negative correlations between mean levels of vitamin D and the number of COVID-19 cases and mortality per one million population were observed, both at borderline significance ($p = 0.05$) [28]. In another recent study that also involved 20 European countries, a significant negative correlation has been observed between mean vitamin D levels and COVID-19 cases per one million population [25]. However, the correlation of vitamin D with COVID-19 deaths in that study was not significant. In a study from Switzerland, 107 patients (median age, 73 years) were included and 27 were SARS-CoV-2 PCR-positive. Vitamin D levels were significantly lower in positive patients (median, 11.1 ng/mL vs. 24.6 ng/mL) [29]. However, results were not adjusted for predictors other than age. An Italian questionnaire-based study of 1486 patients with Parkinson's disease reported that those taking vitamin D supplements were less likely to have COVID-19 [30]. On the other hand, a large cohort study from the United Kingdom (UK) Biobank that included 348,598 participants of whom 499 were positive for COVID-19, after adjustment for confounders, reported no association between 25(OH)D levels and risk of COVID-19 [31]. Considering the associations between mortality/severity of COVID-19 and vitamin D, some retrospective studies demonstrated a correlation between vitamin D status and COVID-19 severity or mortality, while other studies did not when confounding variables were adjusted [25]. In a study involving 134 COVID-19 inpatients reported from UK, lower circulating 25(OH)D concentrations have been reported to associate with COVID-19 severity as indicated by intensive care unit admission [32]. Similarly, in a study including 149 COVID-19 patients from Turkey, mean serum 25(OH) vitamin D level was significantly lower in patients with severe-critical COVID-19 compared to that of patients with moderate COVID-19

Table 1. Summary characteristics of included studies.

| Study | Design/study type | Number of participants | Finding |
|---|---|---|---|
| Bergman et al. [21] | A randomized and double-blind intervention study | 140 | Supplementation with vitamin $D_3$ may reduce disease burden in patients with frequent respiratory tract infections. |
| Murdoch et al. [22] | Randomized, double-blind, placebo-controlled trial | 322 | Monthly administration of 100,000 IU of vitamin D did not reduce the incidence or severity of upper respiratory tract infections in healthy adults. |
| Meltzer et al. [27] | A single-center retrospective study | 489 | In multivariate analysis, the risk of a positive COVID-19 test was higher in patients likely to have deficient 25(OH) D level (<20 ng/mL) than in those who were likely sufficient. |
| Ilie et al. [28] | Short communication | 24,527 | Significant crude relationships between vitamin D levels and the number COVID-19 cases and especially the mortality caused by this infection. |
| Fasano et al. [30] | Case-controlled study | 2693 | Reported that those taking vitamin D supplements were less likely to have COVID-19 |
| Hastie et al. [31] | Cohort study | 348,598 | Do not support a potential link between vitamin D concentrations and risk of COVID-19 infection, nor that vitamin D concentration may explain ethnic differences in COVID-19 infection. |
| Panagiotou et al. [32] | A single-center retrospective study | 134 | Higher prevalence of Vitamin D deficiency was observed in patients requiring intensive care unit admission compared to patients managed on medical wards |
| Karahan et al. [33] | Retrospective observational study | 149 | Serum 25(OH) vitamin D was independently associated with mortality in COVID-19 patients. |
| Cereda et al. [36] | Single-center cohort study | 129 | Low 25(OH)vitamin D levels were not associated with outcome variables |
| Murai et al. [38] | Multicenter, double-blind, randomized, placebo-controlled trial | 240 | Among hospitalized patients with COVID-19, a single high dose of vitamin $D_3$, compared with placebo, did not significantly reduce hospital length of stay |
| Entrenas Castillo et al. [39] | Parallel pilot randomized open label, double-masked clinical trial | 76 | Administration of a high dose of Calcifediol or 25-hydroxyvitamin D, significantly reduced the need for intensive care unit treatment of patients requiring hospitalization due to proven COVID-19 |
| Tan et al. [40] | Cohort observational study | 43 | A vitamin D/magnesium/vitamin $B_{12}$ combination in older COVID-19 patients was associated with a significant reduction in the proportion of patients with clinical deterioration requiring oxygen support, intensive care support, or both |
| Rastogi et al. [41] | Randomized, placebo-controlled study | 40 | Greater proportion of vitamin D-deficient individuals with SARS-CoV-2 infection turned SARS-CoV-2 RNA negative with a significant decrease in fibrinogen on high-dose cholecalciferol supplementation |
| Sabico et al. [42] | Multi-center randomized clinical trial | 69 | A 5000 IU daily oral vitamin D3 supplementation for 2 weeks reduces the time to recovery for cough and gustatory sensory loss among patients with sub-optimal vitamin D status and mild to moderate COVID-19 symptoms |

(10.1 ± 6.2 vs. 26.3 ± 8.4 ng/mL, respectively, $p < 0.001$) [33]. Rhodes et al. examined the mortality of COVID-19 and the latitude of different countries as an indirect estimate of vitamin D status. They reported a 4.4% increase in mortality for each degree latitude north of 28 degrees north, a link that remained after adjustment for age. This observation suggests that UV-light, and thus indirectly vitamin D, may be involved in the protection against COVID-19 [34]. On the other hand, mortality from COVID-19 was not associated with 25 (OH) D levels in some studies including the study from UK Biobank [25,35]. In an Italian study that included 129 consecutive adult COVID-19 in-patients 25 (OH) vitamin D deficiency was not associated with COVID-19 clinical features or outcomes [36]. Yet, unexpectedly, after adjusting for some major confounders, i.e. age, sex, C-reactive protein, ischemic heart disease and severe pneumonia, a significant positive association between increasing 25 (OH) vitamin D levels and in-hospital mortality was observed [36]. It should be noted that retrospective case-control studies all suffer from major methodological limitations [14,29,31]. Consequently, the results of the studies are conflicting. When we look at the studies in detail, most of them are designed retrospectively and the number of patients is low. For this reason, a large cohort study from the United Kingdom (UK) Biobank comes to the fore with high patient numbers and could not find a relationship between Vitamin D levels and risk of COVID-19 infection. Therefore, more prospective studies with a high number of patients are needed.

***The potential effect of vitamin D treatment on COVID-19***: The clinicians are curious to know if vitamin D supplements or treatment at higher pharmacological doses would have a beneficial effect on COVID-19 risk and/or severity and mortality. A strong rationale is present behind this suggestion regarding the previous publications in the field [20]. An increasing number of observational studies put forward the preventive feature of adequate vitamin D status for COVID-19 mortality [17]. Yet, there are conflicting findings [3,14,25]. A study including 324 COVID-19 cases from Lombardy, Italy aimed to evaluate whether 25(OH) D supplementation was associated with prognosis in COVID-19 patients. The use of 25 (OH) D supplements was present in only 38 (11.7%) of the participants. In accordance with supplementation, serum 25 (OH) D levels of supplemented inpatients were about 3-fold higher than those of nonusers. Of note, two (18.1%) had insufficient levels and three (27.2%)

presented a deficiency status. The authors reported that use of 25(OH) D supplements was not associated with either hospitalization or in-hospital mortality. A trend toward a 2-fold higher risk of death was found for supplement users in multivariate analysis that included age, sex, body mass index, Parkinson's disease, and number of other comorbidities or ischemic heart disease [37]. A single oral dose of 5000 µg of vitamin D3 did not influence length of stay among Brazilian patients with severe COVID-19 [38]. On the other hand, a pilot randomized open-label and double-blinded study from Spain included 76 consecutive patients (mean age, 53 years) hospitalized with COVID-19. All patients received the same standard care for COVID-19 plus oral calcifediol (0.532 mg, followed by 0.266 mg on days 3 and 7 of hospitalization, and then weekly) or no supplementation [39]. Among patients treated with calcifediol, 2% required admission to the intensive care unit (ICU), while 50% of untreated patients required ICU ($p < 0.001$), with an odds ratio for ICU in patients with calcifediol treatment versus without calcifediol treatment of 0.02. After adjustments, the odds ratio remained significant [39]. A small cohort observational study including a total of 43 patients from Singapore aimed to determine clinical outcomes of older patients (≥50 years of age) with COVID-19 who received a combination of vitamin D, magnesium, and vitamin B12 compared with those who did not [40]. Patients were administered oral 1000 IU/day vitamin D3, 150 mg/day magnesium, and 500 mcg/day vitamin B12 upon admission if they did not require oxygen therapy. Fewer treated patients than controls required initiation of oxygen therapy during hospitalization (17.6% vs 61.5%, $p = 0.006$). The active drug arm was associated with an odds ratio of 0.20 for oxygen therapy, intensive care support, or both on multivariate analyses. A one small ($n = 76$) low quality randomized control trial from Spain reported significantly reduced disease severity among patients given high dose vitamin D during their hospital admission [39]. Another small trial from India ($n = 40$) reported that patients with mild or asymptomatic disease had more likely negative testing for COVID-19 at third week after 1500 µg/d supplementation [41]. A small ($n = 69$) randomized clinical trial from Saudi Arabia reported that the differences in recovery times and revealed that the number of days to resolve cough was significantly shorter in the 5000 IU group than the 1000 IU group (6.2 ± 0.8 versus 9.1 ± 0.8; unadjusted $p = 0.007$). The same shorter period was observed for ageusia (loss of taste), again in favor of the 5000 IU group (11.4 ± 1.0 versus 16.9 ± 1.7; unadjusted $p = 0.035$) [42]. Although many of the studies that we mentioned are not high in number of patients, they are valuable because they are prospective and power analyzes have been made [38,39,41,42]. Detailed information of the studies is also given in the Table 1. Even though the relationship between vitamin D level and COVID-19 infection is controversial, there is strong evidence that vitamin D therapy reduces hospitalization due to COVID-19 infection or reduces the need for intensive care treatment. In view of these findings, we suggest that vitamin D, which has a low risk of side effects when the dose is adjusted, can be attempted in the treatment of COVID-19 infection.

But, there is no data from interventional trials clearly indicating that vitamin D supplementation may prevent against COVID-19 [20]. On the other hand, it is also challenging to detect a signal for vitamin D supplementation in patients with severe COVID-19 [15]. The patients with COVID-19 generally present to the hospital in the hyperinflammatory stage of the disease. In this case, the benefit from any antiviral effects induced by vitamin D supplementation could not be expected. Second, dexamethasone is the standard of care in severe disease with its potent anti-inflammatory actions, and therefore the anti-inflammatory effects of vitamin D might not be shown [15]. Large epidemiological studies are warranted to assess if vitamin D levels correlate with COVID-19 risk and its severity [20]. Moreover, randomized and placebo-controlled trials are needed to have a qualified evidence-based view. In these studies, the participants who are deficient in vitamin D should be included to maximize the potential effect [20]. At present, several larger scale, placebo-controlled trials focusing on vitamin D in COVID-19 are ongoing [3,14,43,44].

***Conclusion (Box)***: The clinicians should consider that there is a possibility to lessen the impact of COVID-19 by ensuring recommended vitamin D intakes in populations in which vitamin D deficiency is prevalent, including mainly older cardiovascular patients. More importantly, this approach would not be harmful, but potentially useful [15]. The effect of vitamin D is proposed to be prominent in extreme levels, i.e. the extreme deficiency or exposure to high 1,25-dihydroxy vitamin D [3]. It is important to consider that vitamin D is safe especially if it does not exceed the upper tolerable limit [20]. Supplementation by 600–1000 IU/day vitamin D [3], 1000–2000 IU/day [20] and daily or weekly, at daily equivalent doses of 1000–4000 IU [14] have been proposed by different authors. Of note, daily doses are recommended over the weekly or monthly higher doses [20]. Mega-doses are not recommended. Noteworthy, loading doses seem to lack an added beneficial effect on acute respiratory infections [23] but have the potential to leading increased risk for adverse events. These adverse events may be especially devastating in older adults, i.e. falls and fractures [20,45,46], and possibly other COVID-19 related respiratory outcomes [14]. National Institute for Health and Care Excellence (NICE) rapid has been published very recently,

indicating the validity of their existing advice that adults in the UK should take 400 IU/d between October-March, while certain populations at risk of vitamin D deficiency consider taking vitamin D throughout the year [47]. The target level of 25(OH) D is proposed above 20 ng/mL (50 nmol/L) [20] by some authors, however, the majority suggests 30 ng/mL (75 nmol/L) [14]. Nonetheless, one should consider that the benefit is foreseen to be small and some time (months) may be needed for a such effect [20]. On the other hand, there are currently ongoing studies in this area and our conclusions may change by the newly evolving data. We have summarized our suggestions in the Table Box below.

**Box.** Suggestions regarding use of vitamin in COVID-19 era.

| |
|---|
| Vitamin D is safe especially if it does not exceed the upper tolerable limit. |
| Supplementation by 600–1000 IU/day vitamin D, 1000–2000 IU/day and daily or weekly, at daily equivalent doses of 1000–4000 IU have been proposed. |
| In general, daily doses are recommended over the weekly or monthly higher doses. |
| Mega-doses are not recommended. |
| The target level of 25(OH)D is proposed > 20 ng/mL (50 nmol/L) by some authors, however, the majority suggests 30 ng/mL (75 nmol/L). |
| Clinicians should consider that the benefit is foreseen to be small, and some time (months) may be needed for an effect. |

## Acknowledgments

Bahat G, Petrovic M and Erbas Sacar D contributed to study design. Bahat G wrote the article and Petrovic M performed critical review.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Institutional review board statement

Not applicable

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