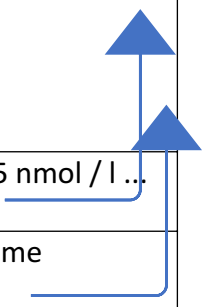
# Recommendations for the replacement of cholecalciferol (vitamin D3) in periods of respiratory infection and for the replacement of cholecalciferol in individuals with COVID-19

| | **PREVENTION** | **DOSAGE** | | |
|---|---|---|---|---|
| ADULTS | Helathy | 800‡-2.000 IU#/day<br>From beginning of October until end of April | | |
| ENDANGERED | • Chronic patients<br>• Over 70 years<br>• Healthcare professionals<br>• Relatives of patients in the same Household<br>• Risky contacts with Covid-19 positive patients<br>• Pregnant women | 1.000-2.000 IU/day or 10.000-14.000 IU/week<br>1.500-2000IE*/day | All year round<br>At least one month or from October to April<br>whole pregnancy | **The daily dose is increased:** up to 4,000 IU / day at low measured conc. vit D3 (less than 50 nmol / l) to a measured end of at least 75 nmol / l<br>at 2,000-4,000 IU / day **for all with a BMI> 25 kg / m2** |
| CHILDREN | 0-1 years<br>1-18 years | 400-1.000* IU/day<br>600-1.000* IU/day | | |
| **SICK** | **TREATMENT** | **DOSAGE** | | |
| Covid 19 | ALL as soon as possible after confirmation SARS-CoV-2 infections (asymptomatic or mild clinical picture) | 14,000 IU / day for 4 consecutive days if not previously taken (sufficient) vitamin D, then 2000 IU / day or 14,000 IU / week | | |
| | Hospitalized | Determination of 25 (OH) D3 ... if <75 nmol / l ... | | |
| | Hospitalized, transfer to EIT | Proceed according to the above scheme | | |



# IU - International Units, 1000 IU = 25mcg of colecalciferol
‡ Reference values for the intake of Vitamins and minerals - tabular recommendations for children, adolescents, adults and the elderly, NIJZ (National Health research Institute in Ljubljana), 2013; summarized after D-A-CH: New Reference Values for Vitamin D. Ann Nutr Metab 2012; 60: 241-246.
*Holick M et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline, J Clin Endocrinol Metab 2011; 96: 1911–1930

**2,000 IU cholecalciferol = Plivit D3 10 drops OR Oleovit 5 drops**
**14,000 IU cholecalciferol = Plivit D3 70 drops OR Oleovit 35 drops**
(expl. Oleovit and Plivit are vitamin D drops, registered as medicines and commonly used in Vitamin D deficiency or in babies... etc. (Oleovit, producer Fresenius Kabi Austria GmbH, Plivit drops, MAH Pliva Ljubljana d.o.o. )

| **Vitamin D supply limits** | | |
|---|---|---|
| **Optimal level 25 (OH) D:** | **>75 nmol/L** | **>30 ng/ml** |
| **Limit values 25 (OH) D:** | **50-75 nmol/L** | **20-30 ng /ml** |
| **Deficiency of 25 (OH) D:** | **<50 nmol/L** | **<20 ng/ml** |
| **Severe shortage** | **<30 nmol/L** | **<12 ng/ml** |

Note: [a] 25 (OH) D: serum concentration of 25-hydroxy-vitamin D.

## EXPLANATION OF INSTRUCTIONS IN TABLES

1. Prevention
    - In all healthy individuals during the period of respiratory infections from October to April we advise providing a daily intake of vitamin D3 at a dose of 800-2,000 IU / day.
    - In all individuals who belong to the high-risk group for vitamin D deficiency and at the same time to the group at high risk for higher morbidity and mortality due to COVID-19, we advise to ensure the intake of vitamin D3 in all seasons at a dose of 1,000-2,000 IU per day or 10,000-14,000 IU once a week.

2. Replacement of vitamin D3 is recommended in all individuals with newly diagnosed SARS-CoV-2 infection vitamin D3 according to the following scheme:
    - 4 days 14,000 IU (350 mcg) of cholecalciferol to normalize 25 (OH) D3 levels - "Loading": Plivit D3 70 drops or Oleovit 35 drops.
    - Then 2,000 IU (50 mcg) of cholecalciferol / day: Plivit D3 10 drops or Oleovit 5 drops or once a week 14,000 E cholecalciferol: Plivit D3 70 drops or Oleovit 35 drops
3. Patients with COVID-19 who require hospitalization should have their serum determined

at admission level 25 (OH) D, if below 75 nmol / l, correction and follow-up of the regimen referred to in point 2 are advised.

**NOTE: All overweight and obese (BMI> 25 kg / m2) require double or even triple doses of cholecalciferol.**

## JUSTIFICATION

**High prevalence of vitamin D deficiency in the Slovenian population**

A recent national Nutrihealth survey conducted on a representative sample of healthy Slovenes aged 18 to 74 found that in the autumn-winter period (between November and April) about **80%** of adult Slovenes **are deficient in vitamin D** - level 25 (OH) D <50 nmol / L) and **40%** of healthy Slovenes **severe vitamin D deficiency** - level 25 (OH) D <30 nmol / L (1). The same group of researchers did a pilot study of Senior Citizens living in DSOs (*expl.: Centre for Elderly – usually older people living in Centre usually cannot take care of themselves, have some health issues, which are chronic and do not need to be administered in hospitals. They usually have relatives, but they cannot take care of them…*) who did not add vitamin D. Study found out that **84% of elderly suffer severe lack of** (25 (OH) D - levels below 30 nmol / L) in winter .(not yet published data from the Institute of Nutrition).
Our country is therefore one of those with an extremely high prevalence of vitamin D deficiency.

## Vitamin D has been shown to reduce the incidence of acute respiratory infections

A meta-analysis of individual data from participants published in 2019 in 25 double-blind, randomized, placebo-controlled studies (10,900 subjects aged 0 to 95 years) examining the effects of vitamin D replacement on the incidence of acute respiratory infections (ARIs). At participants who had a 25 (OH) D level below 25 nmol / L before replacement and received vitamin D once daily or once a week, found 70% less ARI than in the placebo group (RR 0.30), in those with a concentration of 25 (OH) ) D greater than 25 nmol / L, a 25% reduction in the incidence of ARI with the same vitamin D3 regimen (RR 0.75) (2). The vitamin D replacement regimen with doses greater than 30,000 IU given to subjects at intervals of one or more months was not effective.

## Mechanisms of action of vitamin D on the immune system

Vitamin D increases the natural resistance (innate immunity) to infections. It is known that cells of the immune system can activate inactive 25 (OH) D into active steroid hormone D (1.25 (OH) 2D - calcitriol) because they have inducible 1 alpha-hydroxylase (3). In macrophages attacked by the virus, under the influence of the hormone D, endogenous antimicrobial peptides cathelicidin and defensin beta are formed, which accelerate the autophagy of viruses and their destruction. The efficacy of macrophages to form cathelicidin

depends on level 25 (OH) D (3). Respiratory epithelial cells have constitutively active 1-alpha-hydroxylase and can also activate 25 (OH) D into the hormone D, which similarly destroys viruses (3) and maintains close, intermittent and adjacent contacts between epithelial cells, including alveolar ones, and thereby increasing the antimicrobial barrier.

Vitamin D is known as an immunomodulator of acquired immunity. It calms the excessive activation of the immune system with antigens and the inflammatory response by inhibiting the maturation of dendritic cells and the transfer of antigens to lymphocytes, regulates the balance between T lymphocytes (increases the cohort of anti-inflammatory Th2 and Treg and inhibits proinflammatory Th1 and ThT17). ) and inhibits the secretion of pro-inflammatory cyto- and chemokines (TNF-alpha, IL 1, IL 6, IF-gamma ...) (3).

Vitamin D inhibits renin formation and renin-angiotensin system activity. Angiotensin II is greatly increased in SARS-CoV2 infection in the lungs, as the virus reduces the expression of ACE2 on the cells it attacks, thus dominating ACE, which converts angiotensin I to angiotensin II. ACE2 reduces the production and proinflammatory and vasoconstrictor action of angiotensin II via AT1 receptors because it catalyzes the conversion of angiotensin I to angiotensin 1-7. The latter has completely opposite effects as angiotensin II, binds to ATR2 and has an anti-inflammatory effect, promoting NO production and vasodilation. Vitamin D increases ACE2 expression and angiotensin 1-7 production (4).

Vitamin D deficiency also increases the risk of developing acute respiratory distress syndrome (ARDS) (5), and calcitriol alleviates the pathogenetic process (4,5).

## Vit D deficiency is associated with an increased risk for COVID-19

In principle, in countries with lower average levels of 25 (OH) D, they have a higher incidence of SARS CoV2 infections and higher mortality (Italy, France, Spain, Switzerland) (6). At the COVID-19 test in Chicago, those with 25 (OH) D levels below 50 nmol / L had a 1.77-fold higher risk of a positive test - infection. Vitamin D was determined in them for up to one year before they became ill or. were tested (7). A similar difference in level 25 (OH) D between positive and negative subjects was also found in a Swiss study, where those with a positive test had an average level of 25 (OH) D of only 27 nmol / L (8), and those with a negative test 61 nmol / L. Also in Israel, lower levels of vitamin D have been shown to increase the risk of SARS CoV2 infection (9).

## Vitamin D deficiency is associated with poorer COVID-19 outcomes

Several observational studies during the new pandemic found an association between low levels of 25 (OH) D and more frequent illness and a more severe course. poor COVID-19 results, but the causal relationship between low vitamin D levels and disease has not yet been demonstrated by this study.

In observational studies in Iran (10), Germany and Italy, those patients with COVID who had lower levels of 25 (OH) D had poorer outcomes. In Bari, 42 patients at the EIT were studied.

After ten days, the mortality rate for those with 25 (OH) D below 25 nmol / L (the level of most DSO patients in Slovenia if vitamin D is not added) was 50%, and for those with higher levels 5% (11 ). In Heidelberg, the association between 25 (OH) D levels and COVID outcomes was studied in 185 patients. After weighting by age, sex, and comorbidities, those with 25 (OH) D levels below 30 nmol / L had a six-fold higher risk (HR 6.12; 95% CI 2.79–13.42 ;, p <0.001 ) for mechanical ventilation and death together and almost 15 times higher risk (HR 14.73; 95% CI 4.16–5.29; p <0.001) for death compared to those with higher vitamin D levels; similar ratios were also evident when the 25 (OH) D limit was set at 50 nmol / L (12).

## A high-dose 25 (OH) D intervention study dramatically improved outcomes in patients with COVID-19 pneumonia

Recently, the results of an interventional randomized study were published, where 50 patients with confirmed COVID pneumonia were given relatively high doses of vitamin D (25 (OH) D - calcifediol) and 26 patients were not. Half of the latter required artificial respiration in the intensive care unit, two died. In the group receiving 25 (OH) D, however, only one patient needed to be transferred to the intensive care unit, and no one died (13). The results are convincing, although the groups were not equal in the presence of arterial hypertension. After balancing against hypertension and diabetes, the remaining results were still statistically strongly significant. The downside of the study was that it was not double-blind and placebo-controlled, and that vitamin D levels were not measured.

The favorable outcome of this intervention study with vitamin D can be explained by the knowledge that vitamin D in patients with viral respiratory infections soothes excessive pneumonia (cytokine storm), which is so devastating for some patients with COVID-19. Many other interventional studies with vitamin D are still ongoing, with no results yet.

## What doses of vitamin D are optimal

It has been established that in the absence of UVB-induced vitamin D biosynthesis, vitamin D supply in healthy adults can be maintained by a dietary intake of between 600 and 800 IU of vitamin D (14, 15). It should be noted that this does not apply to individuals who already have vitamin D deficiency, and that such doses are sufficient to reach the supply limit for skeletal and muscular functions (50 nmol / L), but not to achieve higher concentrations serum 25 (OH) D (e.g. 75 nmol / L). Several studies find that higher levels of 25 (OH) D are required for beneficial effects on the immune system and other extra-skeletonl effects of vitamin D than for skeletal and muscular effects. Thus, in the group of 198 healthy subjects, those with viral ARI were twice as likely to recover and those with 25 (OH) D levels above 95 nmol / L recovered faster than those with lower levels (p <0.0001) ( 16). In a retrospective study of 14,108 individuals (National Health and Nutrition Examination Survey), those with 25 (OH) D levels below 75 nmol / L were 58% more likely to develop ARI (17). Vitamin D replacement at daily doses of 1,000 IU resulted in an increase in levels above 50 nmol / L after two months at 88% in subjects who had between 25 and 50 nmol / L prior to vitamin D administration. 78% of them remained below the optimal level of 75 nmol / L. Those with a

higher BMI had a smaller increase in vitamin D levels than lean ones. Because we want to achieve optimal levels of 25 (OH) D as soon as possible after SARS CoV2 infection so that vitamin D inhibits an excessive inflammatory response, we suggest the four-day stocking regimen described above with doses that would otherwise be given once a week. to continue with 2,000 IU per day, in people with BMI over 25 and with 3,000 or 4,000 IU. The toxic concentration of 25 (OH) D when hypercalcemia occurs with characteristic clinical signs, nephrocalcinosis, kidney stones is at 375 nmol / L (18). This level is practically very difficult to achieve, with the doses we recommend practically never. In large multicenter intervention studies with vitamin D or placebo, where 2,000 IU of cholecalciferol per day (VITAL) was administered for 5 years, or 4,000 IU per day for two and a half years (D2d study) (19), no side effects were reported that would were due to vitamin D intake compared to the placebo group. Cholecalciferol has a very wide therapeutic window, as it is inactive until the kidneys or other cells (immune, epithelial) activate it into the hormone D to the extent they need it. Activation in the kidneys is systemically controlled by serum calcium, phosphate, parathyroid hormone, FGF-23, calcitriol levels, while activation in immune and epithelial cells in which the hormone D is produced is autocrine (not normally excreted into the bloodstream). ) depends only on level 25 (OH) D. The higher it is, the more effective the extra-annual effects of vitamin D. The target level is above 75 nmol / L, according to some findings above 100 nmol / L (19).

Routine vitamin D replacement at slightly higher doses has been introduced into COVID treatment protocols in several institutions, including Eastern Virginia Medical School - Medical Group Critical Care (20).

As the upper safe daily dose of vitamin D for healthy adults according to EFSA recommendations and all other guidelines, 100 mcg or 4,000 IU (21).

## Caution when replacing vitamin D

Granulomatosis such as tuberculosis, sarcoidosis, leprosy: Immune cells in granulomas can uncontrollably activate 25 (OH) D into hormone D, the increased concentration of which can cause hypercalcaemia and kidney stones. Some lymphoma cells can have a similar effect. Therefore, in patients with these diseases, vitamin D is replaced very carefully, safely only when the underlying disease is in remission.

## Conclusion

The COVID epidemic is on an unprecedented scale. Vitamin D has proven mechanisms of action on the immune system, with which it can improve the natural resistance to acute viral (and other) respiratory infections and alleviate their course by inhibiting the excessive inflammatory response. The first intervention study with higher doses of vitamin D in patients with COVID pneumonia showed extremely beneficial effects on the course of the disease.

In Slovenia, the prevalence of vitamin D deficiency and severe deficiency is high in autumn and winter, especially in the most endangered group for COVID, DSO patients.

Therefore, it is advisable to replace vitamin D in the form of cholecalciferol according to the above recommendations to reduce the incidence of SARS CoV2 infections and to alleviate the course of COVID disease in already infected patients, especially those with vitamin D deficiency and risk factors for more severe course and poor disease outcomes.

We prepared the document for the time of the COVID-19 pandemic due to the absence of national recommendations; we recommend that it be applied until the adoption of national guidelines in this area.

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