# Possible preventive and therapeutic role of vitamin D in the management of the COVID-19 pandemic

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With reference to the useful measures to combat the effects of the Coronavirus pandemic, we believe it appropriate to recall the attention to an aspect of prevention, less known to the general public, **Hypovitaminosis D** , whose compensation, in association with the well-known general prevention measures, could help overcome this difficult moment. On the basis of numerous scientific evidences and epidemiological considerations, it seems that the achievement of adequate plasma levels of Vitamin D is necessary first of all to prevent the numerous chronic pathologies that can reduce life expectancy in the elderly, but also to determine a greater resistance. COVID-19 infection which, although with less scientific evidence, can be considered likely. This compensation can be achieved first with the adequate exposure to sunlight, then feeding with foods rich in Vitamin D (Figure 1 shows the ten foods in which it is most present), and lastly with the intake of specific pharmaceutical preparations , always under medical supervision. This recommendation is useful for the general population, but it is particularly meaningful for those already infected, their relatives, healthcare personnel, frail elderly people, guests of care homes, pregnant women, people in a cloistered regime and all those who for various reasons do not expose themselves adequately to sunlight. Furthermore, the acute administration of calcitriol by IV route in patients with COVID-19 with particularly impaired respiratory function could be considered.

**Vitamin D**

Even if there is no full agreement between the different Scientific Societies, we can consider as acceptable values in the general population above 20 ng / ml, while in the elderly it would be advisable to reach at least 30 ng / ml. Vitamin D can be synthesized by the skin, due to the effect of ultraviolet radiation emitted by sunlight, which determines the conversion of 7-dehydrocholesterol to Cholecalciferol, or it can be taken with food. Once produced from the skin, or taken with food, Cholecalciferol accumulates in the adipose tissue to be gradually released and to undergo two successive hydroxylations, the first in the liver (25 OHD) and the second in the kidney, with the production of its active form (1-25 $OH_2$ $D_3$ or calcitriol) which then, by binding to specific receptors, acts on different tissues with a hormone-like mechanism. During the winter, the levels of cholecalciferol drop significantly, both due to the lower solar radiation and the exhaustion of the reserves accumulated during the summer: for this reason, in the months of February / March there is a greater risk of its shortages.

**Scientific reasons to support the anti-infective effects of Vitamin D**

1) Reduced concentrations of 25 (OH) D increase the risk of osteoporosis and falls in the elderly https://doi.org/10.1016/S2213-8587(18)30347- 4, but are also associated with tumors, cardiovascular diseases, autoimmune diseases, chronic respiratory infections, diabetes mellitus, neurological diseases and hypertension. These pathologies cause higher mortality, especially if these patients fall ill with COVID-19

2) The immunomodulatory role of Vitamin D has long been known and also its antagonistic effect on viral replication in the respiratory tract https: //www.ncbi.nlm. nih.gov/pmc/articles/PMC3308600/

3) A 2014 review, "Vitamin D: a new anti-infective agent?", examined the interactions between Vitamin D, the immune system and infectious diseases, emphasizing the association between hypovitaminosis D and respiratory and enteric infections, otitis media, Clostridium infections, vaginosis, urinary tract infections, sepsis, influenza, dengue, hepatitis to be attributed to the ability of the vitamin D to increase antimicrobial peptides (catelicidine and beta-defensins) with antiviral and immunomodulatory activity (www.ncbi.nlm.nih.gov/pubmed/24593793).

4) A study conducted in South Korea www.ncbi.nlm.nih.gov/pubmed/25946368 showed values reducedof 25 (OH) D (14 ± 8 ng / ml) in patients with community-acquired acute pneumonia.

5) In patients with inflammatory bowel disease www.ncbi.nlm.nih.gov/pubmed/30601999 it has been shown that, in the presence of levels of 25 (OH) D <20 ng / ml, the administration of vitamin D3 (500 U / day) reduces the incidence of upper respiratory tract infections by two thirds.

6) A concentration of 25 (OH) D above 38 ng / ml is associated with halving the risk of infections acute respiratoryof the respiratory system https://www.ncbi.nlm.nih.gov/pubmed/20559424

7) A The 2017 meta-analysis considered 25 randomized studies, highlighting that Vitamin D supplementation reduces the incidence of acute respiratory infections by two thirds in subjects with 25 (OH) D levels below 16 ng / ml: https: // www. ncbi.nlm.nih.gov/pubmed/28202713

8) Calcitriol has proven effective in rats in reducing acute lung injury induced in rats by lipopolysaccharides through an effect on the renin-angiotensin system: https: //www.ncbi.nlm .nih.gov / pubmed / 28944831

9) The contents of a preprint of March 15, 2020,seem particularly current and important https://www.preprints.org/manuscript/202003.0235/v1 “**Vitamin D Supplementation Could Prevent and Treat Influenza,Coronavirus, and Pneumonia Infections**”which emphasizes a little sensitive role of vitamin D in the prevention and treatment also of coronavirus disease. It states that Vitamin D

reduces the risk of respiratory infections through three mechanisms:

➢ Maintenance of tight junctions, and of the lung barrier:
https://www.ncbi.nlm.nih.gov/pubmed/30409076

➢ Increase in expression of antimicrobial peptides such as catelicidine and beta-defensins:
www.ncbi.nlm.nih.gov/pubmed/16497887 www.ncbi.nlm.nih.gov/pubmed/15322146
Note that these peptides are equipped with antiviral activity: www.ncbi.nlm.nih.gov/pubmed/25909853 www.ncbi.nlm.nih.gov/pubmed/29310427

➢ Stimulation of immunoregulatory activity, potentially relevant to the risk of storm cytokine and pneumonia, observed in patients with COVID-19 : https://www.ncbi.nlm.nih.gov/pubmed/31986264

Here are some passages of the text that seem particularly significant to us:

➢ *A high-dose (250,000 or 500,000 IU) vitamin D3 trial in ventilated intensive care unit patients with mean baseline 25 (OH) D concentration of 20–22 ng / ml reported that hospital length of stay was reduced from 36 days in the control group to 25 days in the 250,000-IU group and 18 days in the 500,000-IU group*

➢ *In a pilot trial involving 30 mechanically ventilated critically ill patients, 500,000 IU of vitamin D3 supplementation significantly increased hemoglobin concentrations and lowered hepcidin concentrations, improving iron metabolism and the blood's ability to transport oxygen*

➢ *During the COVID-19 epidemic, all people in the hospital, including patients and staff, should take vitamin D supplements to raise 25 (OH) D concentrations as an important step in preventing infection and spread. A trial on that hypothesis would be worth conducting*.

10) A recent work ("Pulmonary activation of vitamin D3 and preventive effect against interstitial pneumonia", https://www.ncbi.nlm.nih.gov/pubmed/31777427) has shown that:

➢ Calcitriol, produced by fibroblasts lung, has an anti-inflammatory preventive effect diseaseon experimentally induced interstitial pneumonia in mice;

➢ A diet rich in Vitamin D was able to mitigate the symptoms ofpneumonia interstitialin mouse models;

➢ Vitamin D deficiency has been correlated with the severity ofinterstitial pneumonia experimentally induced.

11) Particularly significant are the recommendations of the *British Dietetic Association* of 16 March 2020 https://www.bda.uk.com/resource/covid-19-corona-virus-advice-for-the-general-public.html)

of which we report some significant passages:

➢ *Sunshine, not food, is where most of your vitamin D comes from. During autumn and winter months when we spend more time indoors and the sun is weaker; if you are not able to get enough sun, even a healthy, well-balanced diet, that provides all the other vitamins and nutrients you need, is unlikely to provide enough vitamin D. Vitamin D works with calcium and phosphorus for healthy bones, muscles and teeth. It is also important in protecting muscle strength and preventing rickets, osteomalacia and falls.*

➢ *In spring, if you can, you should seek to spend some time outdoors in the sunshine (eg your garden or balcony). However, if you are having to self-isolate or if you are unable to go outside, you should consider taking a daily supplement to ensure a healthy vitamin D status.*

**Epidemiological considerations**

1) Italy is one of the European countries (together with Spain and Greece) with the highest prevalence of hypovitaminosis D. In Northern Europe the prevalence is lower due to the ancient custom of adding commonly consumed foods (milk, cheese, yoghurt etc.) with Vitamin D (www.ncbi.nlm.nih.gov/pubmed/10197176).

2) In Italy, it has been shown (https://www.ncbi.nlm.nih.gov/pubmed/12856111) that 76% of older women have marked vitamin D deficiency, without however significant regional differences.

3) The reduced incidence of COVID-19 in children could be attributed to the lower prevalence of Hypovitaminosis D following the rickets prevention campaigns activated all over the world since the end of the nineteenth century.

4) The onset of an outbreak in Piedmont in a convent of cloistered nuns, a population at higher risk of Hypovitaminosis D, constitutes another suggestive element on the possible protective role of Vitamin D on viral infections.

5) The geographical distribution of the pandemic seems to be more evident in countries located above the tropic of cancer, with relative protection of subtropical ones (Figure 2).