# Vitamin D and COVID-19: a glimmer of hope in the storm?

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As with many recent pathologies, COVID-19 (CORONAVIRUS Disease-2019) has biological characteristics as well as clinical and medical imaging manifestations which are truly unique. In some subjects, COVID-19 is the result of infection by Severe Acute Respiratory Syndrome Corona-VIRUS-2 (SARS-CoV-2), the seventh type of coronavirus able to infect humans thus far [1]. The infection spread rapidly throughout the world, beginning from China [2]. The virus is highly transmissible, mainly by means of droplets emitted when speaking or breathing, or by direct contact (even if the virus is also detectable in feces in more advanced stages of the infection, which suggests the possibility of infection by an oral-fecal route) [1].

The incubation period of COVID-19 ranges from one day to two weeks, attaining a peak between the third and seventh day. Clinical expressions vary considerably, from total asymptomaticity to severe conditions, such as Acute Respiratory Distress Syndrome (ARDS). The most common symptoms in mild to moderate forms are fever, asthenia and dry cough, which can be followed or accompanied by headache, nasal congestion, pharyngodynia, myalgia and arthralgia. In rare cases the gastro-intestinal system is involved (especially in children), with nausea, vomiting and diarrhea [1]. A variable proportion of infected subjects develops respiratory difficulties, hypoxia, desaturation and tachypnea, especially during the second week of illness. These are the typical signs of severe pulmonary infection, which can develop into bilateral interstitial pneumonia. The latter condition can in turn unfortunately evolve into ARDS, which is characterized by significant levels of morbidity and mortality [1]. The emergence of disorders in the coagulative system is also frequent, with thrombocytopenia potentially increasing the risk of hemorrhages, whether or not these are associated with other hematological conditions, such as peripheral thrombosis, deep vein thrombosis, pulmonary embolism and disseminated intravascular coagulation (DIC) [1]. Given the current lack of antiviral treatments, clinic management of the illness is essentially based on controlling the abnormal inflammatory response and sustaining respiration in a hospital environment. These limitations explain why the pandemic has been able to upset even the most developed economic and health care systems, forcing authorities to develop new plans for the allocation of efforts and resources. It goes without saying that in such a moment of crisis attention is diverted from all situations that are not considered "essential". Yet are we absolutely certain that this is the correct strategy? An interesting editorial, which focuses in particular on the problem of osteoporosis, has been recently published on this question [3]. The authors quote a maxim of Jawaharlal Nehru (Gandhi's spiritual heir), who once said, "Every little thing counts in a crisis." These words are food for thought, especially as until now we have been in possession of limited data on truly effective treatments and on the factors able to condition our susceptibility to the infection and to determine its seriousness.

Undoubtedly, a vitamin is a "little thing", although vitamin D in particular (or its deficiency, to be precise) can play a significant role, including with regard to its much debated extra skeletal effects. Even though we are in full agreement with the European Society for Clinical and Osteoarthritis (ESCEO) that at the moment we do not possess sufficient evidence to recommend the use of vitamin D supplementation to prevent and/or treat extra skeletal pathologies [4], still we must also keep in mind that it was this very position paper that underlined the growing amount of available data (especially indirect, though also direct) which uphold the extra skeletal effects of vitamin D [4].

At present, infection from SARS-CoV-2 seems to occur more frequently and aggressively (in terms of mortality) in the countries of Southern Europe (Italy and Spain in particular), the

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***Conflict of interest***
Davide Gatti has received professional fees from: UCB, Celgene, Eli Lilly, MSD Italia, and Novartis.
Angelo Fassio has received professional fees from: Abiogen, Novartis, and Neopharmed.

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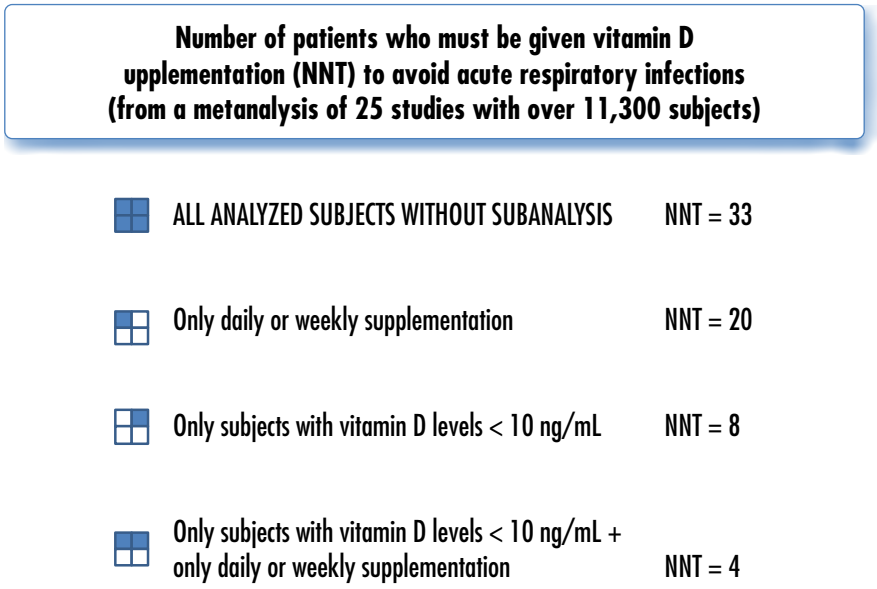


**FIGURE 1.**
Data from this wide-ranging metanalysis show that vitamin D supplementation is able to significantly reduce the risk of acute respiratory infections. Protection (in terms of NNT) is more evident in subjects with serious deficiency and appears particularly relevant when administration occurs daily or weekly (from da Martineau et al., 2017, with modifications) [6].

same ones whose populations show greater rates of hypovitaminosis D [5]. In Italy, the most affected regions are in the north, which have less sun exposure compared to those of the south, especially during winter. The elderly, and in particular those in long-stay care facilities, in whom hypovitaminosis D is effectively endemic, are those who have suffered the most dramatic consequences of this illness. The same holds true for obese subjects, who also have a high risk of vitamin D deficiency. As we have seen, COVID-19 is for the most part an infective respiratory disease, while the bulk of data supporting the claim that vitamin D has a significant effect in preventing and mitigating respiratory infections has become more substantial in recent years.

An interesting metanalysis published in 2019 analyzed data of over 11,300 patients from 25 randomized trials, showing a protective effect from vitamin D supplementation with regard to acute respiratory infections; this effect was not only statistically but also clinically significant, with a number needed to treat (NNT) of 33. Obviously, the effectiveness of supplementation was greater in subjects with severe deficiency (NNT = 8) (Fig. 1). Nonetheless, this protective action on the part of vitamin D was not apparent in the sub-analysis of 15 studies which administered supplementation by means of bolus treatments, suggesting that the shielding effect was mainly achieved by daily or weekly supplements (10 studies), in which cases the findings are particularly interesting (Fig. 1) [6].

Another metanalysis focused on patients with COPD (chronic obstructive pulmonary disease), demonstrating once again that vitamin D supplementation is able to effectively reduce by half the number of moderate/severe respiratory exacerbations in patients with baseline deficiency (<10 ng/mL) [7]. This latter observation seems significant, given the great number of negative clinical studies with regard to vitamin D that have been published recently, which, unfortunately, all share the shortcoming of enlisting a majority of subjects whose vitamin D levels are adequate or even well above the ideal maximum [8]. Indeed, we must consider vitamin D a micronutrient rather than a pharmacological agent. As a result, supplementation is recommended and effective only in conditions of deficiency.

The immunomodulatory role of vitamin D has been known for some time. It is able to support innate immunity by the production of antimicrobial peptides, such as cathelicidins, defensines and IL-37. In addition, through the modulation of the main pro-inflammatory cytokine, including IL-6, TNF-$\alpha$, and interferon gamma, it is able to act on adaptive immunity by controlling the response mediated by Th1 lymphocytes [9]. Clearly this control begins to falter at deficient levels of vitamin D, whose action is nonetheless restored following adequate supplementation. A recent study on cells of the respiratory epithelium has shown that pretreatment with physiological concentrations of vitamin D metabolites (calcifediol or calcitriol) can produce temporary resistance to the rhinovirus infection (Rv-16) and attenuate this virus's production of adhesion molecules required by both rhinovirus and *Streptococcus pneumoniae*. This process accompanies activation of the gene for cathelicidin and the modulation of NF-kB, which represent further possible mechanisms at the base of vitamin D's protective effects with regard to the rhinovirus infection and bacterial superinfection [10].

Concerning the SARS-CoV-2 virus, data are still limited at present, although a preliminary report of a study that assessed the antiviral potential of various molecules points to the inhibitory effect of calcitriol on nasal epithelia that have been infected by the virus [11]. This datum is of particular interest if we consider an Israeli study on 14,000 subjects tested for infection by SARS-CoV-2 who had previously received at least one serum dose of 25-hydroxyvitamin D [25(OH) D]. The findings show that suboptimal vitamin D levels (< 30 ng/mL) constitute a potential risk factor for infection by SARS-CoV-2, for contracting the COVID-19 illness as a result, and in particular for the need for hospitalization [12]. These results appear in line with those of an American study on a sample of 489 subjects whose vitamin D status had been measured the previous year. Of this cohort, 71 subjects tested positive for the SARS-CoV-2 infection. The study reported that the state of being "probably" deficient (circulating levels of 25(OH)D < 20 ng/mL, or 1,25(OH)2D < 18 pg/mL) was associated with a 1.77-time greater risk of testing positive [13].

On the other hand, a similar study conducted in the U.K. did not reproduce these results [14], even if the "anamnestic" values of vitamin D metabolites were perhaps not representative of real conditions at the time of infection; this circumstance constitutes a

limitation of this type of scientific research, one which is by no means insignificant. An interesting finding from the above mentioned American study [13] is that of the 48 subjects who were initially deficient and who then achieved adequate levels from vitamin D supplementation, the risk of testing positive for SARS-CoV-2 overlapped with the same risk in subjects who had sufficient levels from the start. This result indeed seems to support the claim for the protective effect of vitamin D supplementation when it is possible to normalize a subject's vitamin D status. The limited number of cases, however, results in a confidence level that is too wide to provide certain substantiation of this hypothesis.
Meanwhile, a Swiss study used a different study design to evaluate a cohort of patients with suspected COVID-19 symptoms at an interval of several weeks following testing. Findings showed that vitamin D levels were significantly lower (median ca. 11 ng/mL) in subjects who tested positive compared to those testing negative [15]. This finding seems of interest, although we cannot exclude the possibility that the viral infection itself was responsible for the vitamin D deficiency. The relatively short duration of the infection (only a few weeks), however, makes this hypothesis less likely.
In addition to playing a potentially protective role vis-à-vis the infection, vitamin D may also affect the evolution of its severity, as is suggested by the data concerning hospitalizations in the above mentioned Israeli study [12]. The modulating/suppressing action of a possible excessive Th1 response on the part of vitamin D may in fact constitute a contributing factor in counteracting the cytokine storm at the base of lung damage and progression toward ARDS [9]. Indeed, vitamin D deficiency has been shown to be associated with greater risk of developing ARDS [16]. In addition, achieving adequate levels could aid in reducing the alveolar-capillary damage that occurs in deficient subjects [16]. This protective capacity of vitamin D seems to be secondary with respect to the local action of the active metabolite calcitriol on the renin-angiotensin system, which is generated by means of a direct effect on the expression of ACE enzymes [17]. This finding is of especial significance if we bear in mind that ACE-2 is believed to be the key receptor for SARS- CoV-2 infections. As is well known, the virus binds by means of a spike protein at the ACE-2 receptor, enabling it to then penetrate pulmonary cells; it later acts by downregulating both the activity and expression of this enzyme [9].

In conclusion, available data in our view lends credence to a connection between vitamin D deficiency and susceptibility to and severity of infection by SARS-CoV-2. Following this reasoning, various interventional studies have been conducted on patients diagnosed with severe infections. This virus represents a challenge that many experts, ourselves included, believe will be difficult to overcome [18]. In these patients, in fact, the abnormal inflammatory response is probably too far developed in order to hypothesize a significant benefit from vitamin D supplementation, even in subjects with high levels of deficiency. In addition, the steroid drugs or immunosuppressants used in these cases produce effects which mask the potential action of vitamin D, which, after all, is a micronutrient. In any case, we believe that in light of the prevalence of vitamin D deficiency these patients should be given supplementation.
A more promising perspective is rather offered by research on the benefits of supplementation (daily or weekly) in reducing susceptibility to infection and progression toward more severe forms. In this light, we continue to fear the impact that AIFA's "nota 96" may have had on the prevalence of vitamin D deficiency, not only in subjects with compromised bone health but also in those most at risk of contracting COVID-19. We therefore wish to emphasize the need for forceful and prompt advocacy along these lines, before the onset of winter and a possible new wave of the pandemic, above all if we believe that "every little thing counts in a crisis."

## References


1 Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. Front Med 2020;14:126-35. https://doi.org/10.1007/s11684-020-0767-8

2 Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. Nature 2020;579:265-9. https://doi.org/10.1038/s41586-020-2008-3

3 Paskins Z, Crawford-Manning F, Bullock L, et al. Identifying and managing osteoporosis before and after COVID-19: rise of the remote consultation? Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA 2020;31:1629-32. https://doi.org/10.1007/s00198-020-05465-2

4 Cianferotti L, Bertoldo F, Bischoff-Ferrari HA, et al. Vitamin D supplementation in the prevention and management of major chronic diseases not related to mineral homeostasis in adults: research for evidence and a scientific statement from the European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO). Endocrine 2017;56:245-61. https://doi.org/10.1007/s12020-017-1290-9

5 Manios Y, Moschonis G, Lambrinou C-P, et al. A systematic review of vitamin D status in southern European countries. Eur J Nutr 2018;57:2001-36. https://doi.org/10.1007/s00394-017-1564-2

6 Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017;356:i6583. https://doi.org/10.1136/bmj.i6583

7 Jolliffe DA, Greenberg L, Hooper RL, et al. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. Thorax 2019;74:337-45. http://dx.doi.org/10.1136/thoraxjnl-2018-212092

8 Gatti D, Bertoldo F, Adami G, et al. Vitamin D supplementation: much ado about nothing. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol 2020;36:185-9. http://dx.doi.org/10.1080/09513590.2020.1731452

9 Chandran M, Chan Maung A, Mithal A, et al. Vitamin D in COVID-19: dousing the fire or averting the storm? – A perspective from the Asia-Pacific. Osteoporos Sarcopenia 2020 Jul 23; in press. https://doi.org/10.1016/j.afos.2020.07.003

10 Greiller CL, Suri R, Jolliffe DA, et al. Vitamin D attenuates rhinovirus-induced expression of intercellular adhesion molecule-1 (ICAM-1) and platelet-activating factor receptor (PAFR) in respiratory epithelial cells. J Steroid Biochem Mol Biol 2019;187:152-9. https://doi.org/10.1016/j.jsbmb.2018.11.013

11 Mok CK, Ng YL, Ahidjo BA, et al. Calcitriol, the active form of vitamin D, is apromising candidate for COVID-19 prophylaxis. MedRxiv 2020; published online June 22. https://doi.org/10.1101/2020.06.21.162396

12 Merzon E, Tworowski D, Gorohovski A, et al. Low plasma 25(OH) vitamin D

level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS J 2020 Jul 23. https://doi.org/10.1111/febs.15495

13 Meltzer DO, Best TJ, Zhang H, et al. Association of vitamin D status and other clinical characteristics with COVID-19 test results. JAMA Netw Open 2020;3:e2019722. https://doi.org/10.1001/jamanetworkopen.2020.19722

14 Hastie CE, Pell JP, Sattar N. Vitamin D and COVID-19 infection and mortality in UK Biobank. Eur J Nutr 2020 Aug 26. https://doi.org/10.1007/s00394-020-02372-4

15 D'Avolio A, Avataneo V, Manca A, et al. 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. Nutrients 2020;12:1359. https://doi.org/10.3390/nu12051359.

16 Dancer RCA, Parekh D, Lax S, et al. Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS). Thorax 2015;70:617-24. https://doi.org/10.1136/thoraxjnl-2014- 206680

17 Xu J, Yang J, Chen J, et al. Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. Mol Med Rep 2017;16:7432-8. https://doi.org/10.3892/mmr.2017.7546

18 Martineau AR, Forouhi NG. Vitamin D for COVID-19: a case to answer? Lancet Diabetes Endocrinol 2020;8:735-6. https://doi.org/10.1016/S2213-8587(20)30268-0