

EDITORIAL

Evidences for a protective role of
vitamin D in COVID-19Maurizio Cutolo ,^{1,2} Sabrina Paolino,¹ Vanessa Smith^{3,4}

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INTRODUCTION Vitamin D and COVID-19

A growing number of concordant reports support a protective role for vitamin D in reducing at least the risk/severity of respiratory tract infections (RTIs), especially in the influenza and COVID-19 context.^{1–5}

Major clinical reports show that vitamin D deficiency contribute to acute respiratory distress syndrome (ARDS) SARS-CoV-2 and that case-fatality rates increase with age and the highest SARS-CoV-2 serum concentrations.^{6,7}

In addition, the outbreak of COVID-19 seems to occur mainly in the cold winter time, when serum 25-hydroxyvitamin D (25(OH)D—calcidiol or calcifediol) concentrations are the lowest, as well as the ultraviolet B (UVB) doses, whereas the number of cases in the Southern Hemisphere near the end of summer are lower.⁸

Targeted 25(OH)D serum concentration measurements and vitamin D supplementation is strongly suggested have important patient and public health benefits.⁹ The positive role of vitamin D replacement therapy (vDRT) in reducing risk and severity in COVID-19 patients is supported by several clinical evidences and RCTs are undergoing, however, previous experiences of RCT related to vDRT are available from other lung viral infection studies and even in mechanically ventilated adult intensive care unit (ICU) patients.^{10–14}

These important observations are corroborated by several biological/molecular mechanisms through vitamin D can generally reduce risk of infections and downregulate the immune/inflammatory reaction. Indeed, functional vitamin D receptors (VDR) are highly-expressed in B-lymphocytes and T-lymphocytes and mainly in monocytes/macrophages, justifying a role in modulating both innate and adaptive immune responses^{15–18} (figure 1).

We will analyse and discuss such available clinical evidences on the light of vitamin D molecular actions and the need to supplementation in COVID-19 patients.

Vitamin D is a steroidal hormone (D hormone) and may influence the immune response in COVID-19

Vitamin D enters the body through dietary consumption (about 20% of vitamin D₃) or is synthesised by the skin (80%) from 7-dihydro-cholesterol (provitamin D or cholecalciferol) after exposure to type B ultraviolet (UVB) which varies seasonally (figure 1).

The discovered presence of the VDR in activated T cells and monocytes, first suggested in 1983 that vitamin D may have a role in the function of the immune system.¹⁹

As matter of fact, vitamin D has received increased worldwide attention for its involvement in reducing risk for several chronic diseases, besides infectious diseases, including type 1 diabetes and notably autoimmune rheumatic diseases for the reason that may interfere with the immune system.²⁰

The biological/molecular evidence for the interactions of vitamin D with the immune response is that its final active metabolite, namely calcitriol (1,25(OH)₂D₃), due to its structural origin from cholesterol, is molecularly considered a steroid hormone (D-hormone) like others (ie, sex hormones, cortisol) and analogously to glucocorticoids (and sex hormones) can exerts immunomodulatory/anti-inflammatory activities through functional cell steroid receptors^{21–23} (figure 1).

Furthermore, the intensity and quality of the host immune/inflammatory response seems to influence the clinical severity and mortality risk associated with viral diseases (such as influenza and COVID-19) rather than the viral pathogen itself.^{24,25}

Consequently, it is biologically plausible that 1,25(OH)₂D₃ may exert immunomodulatory effects also in COVID-19 patients,



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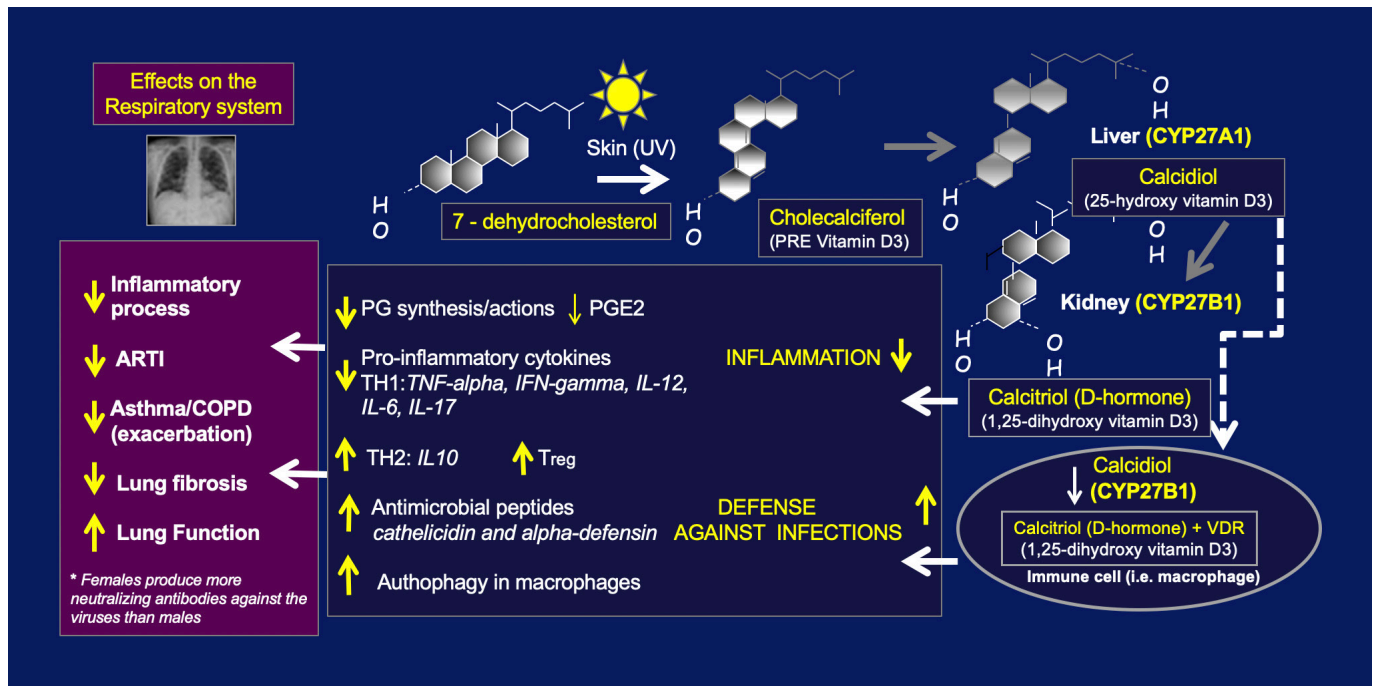


Figure 1 Proposed mechanism whereby 1,25(OH)₂D-VDR (D-hormone) signalling acts on the respiratory system during the COVID-19 infection. 1,25(OH)₂D, 1,25-hydroxyvitamin D; ARTI, acute respiratory tract infection; IFN-gamma, interferon gamma; IL-6, interleukin 6; IL10, interleukin; IL-12, interleukin 12; IL-17, interleukin 17; Treg, T regulatory cells; TNF, tumour necrosis factor; UV, ultraviolet; VDR, vitamin D receptor.

playing a role in the regulation of both innate and adaptive immunity.²⁶

The intracellular conversion of 25(OH)D (calcidiol or calcifediol) into the active metabolite 1,25(OH)₂D₃ (calcitriol), through the intracrine actions of the enzyme 1- α -hydroxylase (CYP27B1), is distinct from the 1,25(OH)₂D₃ produced in kidneys and released into the systemic circulation; however, both have autocrine and paracrine functions that enhance host immunity, for example, by upregulating the antimicrobial peptides cathelicidin and alpha-defensin²⁶ (figure 1).

In addition, the lung epithelium also expresses the VDR and CYP27B1 and may be an important target tissue for the vitamin D endocrine system.²⁷

Innate immunity is the first line of defence against bacteria and viruses and is activated within hours of exposure to the pathogen.

Calcitriol (1,25(OH)₂D₃) can inhibit inflammatory T cell cytokines such as interleukin (IL)-2 and IL-17 and toll-like receptors present on monocytes^{28 29} (figure 1).

On the other hands, in response to calcitriol administration, Th cells in an inflammatory environment they exhibit an enhanced potential for Th2 polarisation along with a decreased potential for Th17 polarisation.³⁰

High doses of calcitriol supplementation in healthy human subjects (1 μ g two times per day for 7 days) leads to a dramatic reduction in the levels of proinflammatory cytokine IL-6, secreted by peripheral mononuclear cells.³¹

All these effects likely combine and translate in the induction of potential regulatory T cells, which are

important for regulating immune responses and for the development of autoreactivity³² (figure 1).

Adaptive immunity is the immune process by which immunological memory to a specific antigen is established and requires a timeline much slower than innate immunity. Adaptive immunity is further mediated through two types of lymphocytic cells: T cells for cell-mediated immunity and B cells that are responsible for humoral immunity. Activated B cells produce specific antibodies to the pathogen and neutralise or destroy it through a variety of mechanisms.

Calcitriol has been shown to suppress adaptive immunity in animal models, however, recent data are not yet sufficient to prove a real role for vitamin D in the modulation of adaptive immune system in humans,³³

Lastly, the 'cytokine storm' is a term used to describe a hyperactive immune response to COVID-19. Although much yet to learnt about the pathophysiology of 'cytokine storm', it is considered to be mediated by the activation of the innate immune system and with an overly increased activation of the adaptive immunity.^{34 35}

The clinical manifestations of this acute reaction include critical lung injury, wide-spread tissue damage, multiorgan failure and frequently death.

Regarding vitamin D and gender, it is known that mortality is higher in COVID-19 male than female patients, possibly because, due to androgens, the adaptive immune response in men is less efficient to mount an antibody response (against SARS-CoV-2), with the result that their disease further evolves severely³⁶ (figure 1).

On the contrary, female COVID-19 patients react immunologically better due to enhancing estrogenic effects on adaptive immunity, with the result to produce specific antibodies that may neutralise earlier the virus, like what happen with other infections and after vaccinations.³⁷

Interestingly, it has been reported that in severe COVID-19 patients, the average of SARS-CoV-2 IgG antibody serum concentrations in women tended to be higher and the generation of IgG antibody was stronger in female than male patients.³⁸

Therefore, vitamin D deficiency, seems to add further risks to the male COVID-19 patients, in fact concentrations of 25(OH)D, have been found significantly lower only in male patients COVID-19 vs women and controls ($p=0.0006$) and were not confounded by vitamin D-impacted comorbidities and seasonality. Conclusion, vitamin D deficiency seems a prevalent and further risk factor for severe COVID-19 male patients.³⁹

Vitamin D and RTIs: lesson from the recent experience

The seasonality of viral RTIs such as those caused by influenza virus and rhinovirus has been recognised from long time and is even considered to be one of the major contributor to seasonal variations in human mortality.⁴⁰

As matter of fact, a recent large study found that sunlight UV radiation dose is negatively correlated with the percent positive patients for SARS-CoV-2 and for four other common human coronaviruses in the USA, and this association is season-related with lowest vitamin D serum concentrations.⁴¹

In a large population survey (6789 participants), the prevalence of RTIs and altered lung function showed a strong seasonal pattern and linear association in the opposite direction to the vitamin D serum concentrations.⁴²

A more detailed study evaluating the link between vitamin D concentrations and ARDS, patients with 25(OH)D₃ <20 ng/mL showed a significantly higher odds of ARDS compared with patients with 25(OH)D >20 ng/mL after adjustment for age, gender, diagnostic category, staging and degree of cigarette consumption, ($p=0.032$).⁷

Interestingly, when 25(OH)D concentrations were analysed with logistic regression as a continuous exposure in 0.4 ng/mL increments, the odds of ARDS decreased by 17% for every 0.4 ng/mL increase in 25(OH)D (OR 0.83 (95% CI 0.69 to 0.98; $p=0.033$)).⁷

In another study, it was found that each 4 ng/mL increase in 25(OH)D was associated with a 7% lower risk of lung infection (95% CI 3% to 11%) after adjustment for lifestyle, socioeconomic factors and adiposity.⁴²

Therefore, it has been argued that vitamin D status should be taken into account as an important contributor in determining the population susceptibility to seasonal epidemic outbreaks, together with the effects of augmented indoor confinement in wintertime (ie, school) and increased circulating reservoirs of respiratory viruses.⁴³

Furthermore, another large observational study evaluating healthy adults during the fall and winter of 2009–2010, investigated the relationship between serum 25(OH)D concentrations and incidence of acute RTIs (ARTIs).⁴⁴

The result was that only 17% of patients showing serum 25(OH)D concentrations over 38 ng/mL throughout the study developed ARTIs, on the contrary 45% of those with serum concentrations less than 38 ng/mL did.

Concentrations of vitamin D over 40 ng/mL induced a significant ($p<0.0001$) twofold reduction in risk of developing ARTIs including a strong reduction in the percentage of days of illness (figure 1).

The negative correlation between seasonality (winter) of inflammatory conditions (ie, rheumatoid arthritis) and vitamin D concentrations (UV effects) has been already deeply analysed and it links the immune response with the 25(OH)D concentrations.^{45,46}

More recently, the prevalence of vitamin D insufficiency and deficiency, (serum concentrations of 12–20 and <12 ng/mL, respectively), was assessed in association with mortality from respiratory diseases during 15 years of follow-up in a cohort of 9548 adults, aged 50–75 years.⁴⁷

Overall, 41% of respiratory disease mortality was statistically attributable to vitamin D insufficiency or deficiency.

Previously, in a systematic review and meta-analysis, 25 randomised, double blind, placebo controlled trials (total 11 321 participants, aged 0–95 years) were selected in order to evaluate if supplementation of vitamin D might reduce the risk of ARTIs.⁴⁸

Interestingly, vitamin D supplementation reduced significantly the risk of ARTI among all participants ($p<0.001$) and in a subgroup analysis, protective effects against ARTIs were observed in those individuals receiving daily or weekly vitamin D without additional bolus doses, but not in those receiving one or more bolus doses ($p=0.05$). Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25(OH)D <10 ng/mL than in those with baseline 25(OH)D levels ≥ 10 ng/mL (for interaction $p=0.006$). The lesson from these recent evidences seem to confirm that vitamin D supplementation is safe and might protect at least against ARTIs overall.⁴⁹

This experience seems today replicated in COVID-19 patients.

Clinical evidences for vitamin D involvement in COVID-19 and earliest therapeutical interventions

SARS-CoV-2 is the major allmark of COVID-19, with clinical outcomes ranging from mild to severe, including death.

The most recent evidences support the clinical experience that vitamin D supplementation would be advantageous in the treatment of COVID-19 patients, in reducing the presence of SARS-CoV-2 at the level of the upper respiratory tract, in making the patients less infectious (justifying the presence of negative PCR in people

with higher 25(OH)D) and in preventing a more severe symptomatology.²

On the other hands, a very recent study, showed the first direct evidence of the association between vitamin D deficiency and potentially insufficient treatment with testing positive for COVID-19.⁵⁰

The multivariable analysis suggested that individuals with most recent vitamin D deficiency whose treatments were not increased (remained vitamin D deficient), were at higher risk of testing positive for COVID-19, than were individuals with serum concentrations that were likely to be sufficient confirming the majority of reports.⁵¹

In addition, a very recent small study showed that 84.6% of intensive treatment unit (ITU) severe COVID-19 patients had deficiency of vitamin D (<12 ng/mL) compared with only 57.1% of patients on medical ward.⁵¹

Similar results were confirmed in another study in which serum 25(OH)D concentrations were evaluated in 134 inpatients with positive SARS-CoV-2 swab or clinic-radiological diagnosis of COVID-19.² Again, ITU COVID-19 patients showed lower 25(OH)D serum concentrations compared with non-ITU patients despite being younger, (13.4 ng/mL±6.7 vs. non-ITU: 19.4 ng/mL±15.3; p=0.03).

Nevertheless, ITU COVID-19 patients showed a significantly higher prevalence of vitamin D deficiency, with only 19% being vitamin D replete compared with 39.1% of non-ITU patients (p=0.02). However, serum 25(OH)D concentrations were not associated with mortality (p=0.94) probably due to the short time of observation.

These results suggest the acute and follow-up assessment of serum 25(OH)D concentrations during COVID-19 admission.

Another study, among patients with vitamin D deficiency, further confirmed higher incidence of noninvasive ventilation support and high-dependency unit admission (p=0.042), with older COVID-19 adults demonstrating worse morbidity outcomes. Again the vitamin D status may be considered at least an useful prognosticator.⁵²

A number of investigations confirm that deficient/insufficient concentrations of vitamin D are associated with the hospitalisation of COVID-19 patients, and less than 16 ng/mL values of the serum vitamin D have been reported to be possibly associated even with increased risk of sepsis in critically ill patients.^{53 54}

A large Israeli studied cohort, proved that, low serum 25(OH)D concentrations almost doubled the risk for hospitalisation due to the COVID-19 infection.⁵⁵

Finally, in a very recent case-control study, the serum 25(OH)D concentration in COVID-19 patient was found the lowest in severe/critical cases, compared with mild cases. Severe/critical COVID-19 cases were significantly older and had higher percentages of comorbidity (renal failure) compared with mild cases, however, the statistically significant associations remained even after controlling for demographics and comorbidities.⁵⁶

Of course, the majority of these studies has aimed to correct the results from concomitant risk factors for

vitamin D deficiency, but a residual confounding is still always possible. In fact, factors associated with worse COVID-19 prognosis include old age, ethnicity, male sex, socioeconomic level, as well as comorbidities like obesity, diabetes and hypertension, and all of these also associate with deficiency of vitamin D.⁵⁷

Therefore, the absence of specific treatment for COVID-19 generated many trials, but so far without final guide lines, the same holds true for testing the potential benefits of vitamin D supplementation of patients with SARS-CoV-2 infections.⁵⁸

Interesting a pilot RCT published in October 2020, demonstrated that administration of a high dose of Calcifediol (25(OH)D), significantly reduced the need for ICU treatment of patients requiring hospitalisation due to proven COVID-19.⁵⁹

At the same time, in a clinical cases series report, COVID-19 patients who received a high dose of vitamin D supplementation, they achieved normalisation of vitamin D serum concentrations and improved clinical recovery, evidenced by decrease in inflammatory biomarker status, lower oxygen requirements and finally less days of hospitalisation.⁶⁰

In addition, it has been already published a pragmatic trial design that will allow parallel testing of vitamin D3 supplementation for early treatment and postexposure prophylaxis of COVID-19.⁶¹

To conclude, according to National Institute of Health (NIH) Trialnet database, several observational and intervention studies, including some RCT, are running and should provide guidelines within a few months.^{62 63}

In essence, the rationale for intervention studies with vitamin D in COVID-19 patients, is focused on the ability of 1,25(OH)2D3 to activate the native immune defence system, while reducing the proinflammatory cytokine production and tapering down the acquired immune system.⁶⁴

In addition, as discussed previously in this text, vitamin D deficiency may predispose to increased risk of infections including SARS-CoV-2, and its supplementation may decrease the risk of upper respiratory infections.

How to supplement vitamin D in COVID-19 patients with deficiency

Although the degree of protection generally increases as 25(OH)D serum concentration increases, the optimal range is considered to be in the range of 40–60 ng/mL (100–150 nmol/L). In order to achieve those levels, approximately half the population should take at least 2000–5000 IU/day of vitamin D.⁶⁵

The supplementation with calcidiol (25(OH)D) may present some advantages over the native vitamin D (cholecalciferol), in fact, calcidiol has a more reliable intestinal absorption (close to 100%) and its administration can rapidly restore serum concentrations of 25(OH)D as it does not require hepatic 25-hydroxylation (CYP27A1) (figure 1).

This is especially relevant in clinical situations whereby rapid restoration of serum 25(OH)D is desirable and expression is compromised. Such impaired hepatic vitamin D hydroxylation by cytochrome p450 2R1 (CYP2R1) activity has been well demonstrated in several animal models of obesity, diabetes or glucocorticoid excess and in patients with COPD or asthma.⁶⁶

Various loading doses have been studied for achieving a 25(OH)D concentration of 30 ng/mL. For example, one study used a weekly or fortnightly dose totaling 100 000–200 000 IU over 8 weeks (1800 or 3600 IU/day).⁶⁷

Clinical data suggest that daily or weekly doses offer better results than bolus in the protection against acute pulmonary infections and supplementation with extremely high doses of vitamin D could be harmful and toxic, especially to elderly individuals.^{68 69}

Some reports just speculated on single high vitamin D doses and mechanisms for prevention and treatment of COVID-19 patients.⁷⁰

Therefore, the supplementation of vitamin D by bolus or extremely high doses (ie, 600 000 UI single dose oral dose) should be avoided since can increase the risk of intoxication without evidence of benefits at least in COVID-19 patients.⁶⁵

In addition, from the literature, for healthy individuals, it is suggested taking 10 000 IU/day for a month, which is effective in rapidly increasing serum concentrations of 25(OH)D into the optimal range of 40–60 ng/mL.¹⁰

To maintain that level after that first month, the dose can be decreased to almost 2000–3000 IU/day.

However, measuring serum 25(OH)D concentration would be useful to determine baseline and the achieved 25(OH)D concentrations.

Patients hospitalised with COVID-19 should have baseline serum 25(OH)D concentrations measured and must be supplemented at least to a level ≥ 30 ng/mL (optimal 40–60), especially when the baseline level is < 10 ng/mL and such deficiency is significantly more present in male patients.⁷¹

In conclusion, we might suggest in COVID-19 patients with 25(OH)D serum levels under 20 ng/mL that the usual recommended dose for correction of deficiency should be 6000–7000 oral IU/day for the first 6–8 weeks. For maintenance, the dose should varies from 2000 to 3000 oral IU/day depending on the age and clinical condition of the patient up to achieve the suggested concentrations.⁷²

CONCLUSIONS

Given the evidence supporting the role of vitamin D in modulating immune function, and the impact of vitamin D supplementation on vitamin D-deficient patients with COVID-19, as well as the favourable safety profile (and low cost) of vitamin D, practical recommendations should be synthesised as follows:

- ▶ Current public health guidelines for optimising vitamin D status should be followed always and clinical data from systematic reviews and meta-analyses show benefits in the prevention of respiratory infections and improvement of pulmonary function when vitamin D-deficient patients are supplemented.
- ▶ The optimal vitamin D status of the host may contribute key immunoregulatory functions in settings of viral respiratory infection and overall the altered immune-inflammatory COVID-19 reactivity at least by downregulating overly exuberant cytokine responses (pathological cytokine storm, in fact higher vitamin D levels correlate with lower IL-6 levels).
- ▶ Patients hospitalised with COVID-19 should have baseline serum 25(OH)D concentrations measured and should be supplemented to a level > 30 ng/mL (optimal 40–60 ng/mL), especially when the baseline level is < 10 ng/mL.
- ▶ In COVID-19 patients with 25(OH)D serum concentrations under 20 ng/mL the recommended dose for correction of deficiency is 6000–7000 oral IU/day for 6–8 weeks. For maintenance, the dose varies from 2000 to 3000 oral IU/day depending on the age and clinical condition of the individual up to reach optimal concentrations.
- ▶ When it is not possible to measure baseline 25(OH)D concentrations in COVID-19 patients, it seems essential supplementing with 2000–3000 oral IU per day up to the suggested optimal serum concentrations (40–60 ng/mL).

A final message based on all the practical issues discussed: keep the vitamin D serum concentrations during all the year between 40 and 60 ng/mL (100–150 nmol/L), it is one of the fundamental care to reduce, at least the risk of RTIs, COVID-19 included.

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