

Can Vitamin D Positively Impact COVID-19 Risk and Severity Among Older Adults: A Review of the Evidence

Ray Marks^{1,*}

¹Department of Health and Behavior Studies, Teachers College, Columbia University, New York, NY 10027, USA

Abstract:

Background: The coronavirus Covid-19 strain that emerged in December 2019, continues to produce a widespread and seemingly intractable negative impact on health and longevity in all parts of the world, especially, among older adults, and those with chronic health conditions.

Aim: The first aim of this review article was to examine, summarize, synthesize, and report on the research base concerning the possible use of vitamin-D supplementation for reducing both Covid-19 risk and severity, especially among older adults at high risk for Covid-19 infections. A second was to provide directives for researchers or professionals who work or are likely to work in this realm in the future.

Methods: All English language relevant publications detailing the possible efficacy of vitamin D as an intervention strategy for minimizing Covid-19 infection risk published in 2020 were systematically sought. Key words used were: *Vitamin D*, *Covid-19*, and *Coronavirus*. Databases used were PubMed, Scopus, and Web of Science. All relevant articles were carefully examined and those meeting the review criteria were carefully read, and described in narrative form.

Results: Collectively, these data reveal vitamin D is a powerful steroid like compound that is required by the body to help many life affirming physiological functions, including immune processes, but its deficiency may seriously impact the health status and well being of the older adult and others. Since vitamin D is not manufactured by the body directly, ensuring those who are deficient in vitamin D may prove a helpful overall preventive measure as well as a helpful treatment measure among older adults at high risk for severe Covid-19 disease outcomes.

Conclusions: Older individuals with chronic health conditions, as well as healthy older adults at risk for vitamin D deficiency are likely to benefit physically as well as mentally, from efforts to foster adequate vitamin D levels. Geriatric clinicians can expect this form of intervention to reduce infection severity in the presence of Covid-19 infection, regardless of health status, and subject to careful study, researchers can make a highly notable impact in this regard.

Corresponding author: Ray Marks, Department of Health and Behavior Studies, Teachers College, Columbia University, New York, NY 10027, USA, Tel: +1-212-678-3445, Fax: +1-212-678-8259, Email: rm226@columbia.edu

Keywords: Coronavirus, Covid-19, infection, immunity, older adults; prevention, therapeutic use of vitamin D

Received: Dec 05, 2020

Accepted: Dec 05, 2020

Published: Dec 10, 2020

Introduction

The COVID-19 or pandemic remains an intractable problem despite months of study and investigation of the many possible causes, as well as strategies for amelioration or prevention. At the same time, adults with a variety of chronic health conditions may not be able to either access or receive optimal care due to many travel and other social restrictions. This narrative report focuses on vitamin D as a possible antidote to the widespread risk of severe illness on acquiring this virus, as well as for mediating its severity, and fostering a more rapid return to health. Since vitamin D may prove helpful for ameliorating or preventing Covid-19, and sunlight is one source of vitamin D that may be challenging to harness by many who are home bound or live in northern countries, or who are bound by a variety of cultural norms, work situations indoors or underground, or living in regions where the potency of ultraviolet light is diminished as a result of global warming, can a case be made for vitamin D supplementation among older at risk adults and others? Indeed, older adults, especially those who now have restrictions placed on their movements due to the Covid-19 pandemic may not only be highly vulnerable to the consequences of vitamin D deficiency, but may not understand the implications of their situation in this respect, even if they personally follow legal Covid-19 rulings in all respects.

Discussed is the evidence base in favor of efforts to ensure all citizens, including older adults, and especially those with chronic health conditions associated with a deficiency of vitamin D, such as diabetes, one of four main disease correlates found among Covid-19 cases. Some information on the past use of vitamin D in other infectious diseases such as influenza is discussed as well.

Drawn largely from the PUBMED database, the overview should provide the interested reader a general view of past work as well as current trends in this regard that might be worthy of further consideration and study, as well as applications in the health care field.

Covid-19, which may occur independently as a separate health condition, or in conjunction with one or more chronic health conditions, may well be life

threatening, and even if not, may induce the presence of other illnesses, while heightening prevailing adverse life events and functional losses, including immense life quality and socioeconomic losses. While the world waits for a possible Covid-19 antidote, other remedies to offset excess risk of Covid-19 and its consequences must be sought as argued by Simonson [1]. In this regard, mounting evidence points to a possible role for vitamin D in explaining infection risk, as well possible benefits of intervening in this regard to offset or minimize this risk.

Although research in this realm is clearly in its infancy, and based largely on observational studies, Covid-19 infection and death rates do appear to be notably higher in the elderly than any other sub group, and this may be mediated in part, by the presence of a prevailing vitamin D deficiency. Since many adults suffer from this particular deficiency, it can be argued that a proportion of Covid-19 cases may be preventable. Since vitamin D sources are several, potential efforts to attain adequate sunlight exposure, exposure to foods or beverages containing vitamin D, and/or supplementation of vitamin D in vulnerable adults may be more beneficial than not.

Indeed, if found to be influential in any way, intervention in this regard may provide one avenue that is reasonably practical for purposes of securing the well-being of the aging person, especially in the case of the chronically ill older adult that alone can heighten risk of infection due to its overall potentially debilitating effect on immune, musculoskeletal and cognitive health. Others may be given medications that render them more prone to Covid-19, and less likely to be 'good' surgical candidates or ventilator candidates if they have severe disabling chronic health conditions, especially those who may also be vitamin D deficient.

This work is significant because the ability to minimize Covid-19 risk and severity is currently of the highest importance, especially among the elderly confined to their homes in isolation, as well as nursing homes, or to situations that limit sunlight and nutrient based vitamin D exposure. As discussed by Mok et al. [2], the Covid-19 pandemic proceeds unabated, despite considerable public health efforts to mitigate this spread. The development of a vaccine is still awaiting

confirmation, and even then vaccinations may be only part of the solution. However, other compounds with antiviral properties may be helpful to consider not only in the interim, but in the future.

Aims

This narrative review aimed to specifically examine the value of vitamin D therapy for or minimizing the risk of acquiring Covid-19 infections in the older population, especially those with preexisting vitamin D deficits. Its second aim was to offer recommendations for future consideration by clinicians and researchers in the field based on these findings.

Materials and Methods

To obtain the data for this review, the electronic data sources PUBMED, Scopus, and Web of Science were searched. The time period searched ranged from January 1 2020- December 2, 2020 and the key words included *Covid-19, vitamin D, coronavirus, older adults*. All forms of study or analysis were deemed acceptable. However, because most empirical studies are in process, and unpublished, and no consistent intervention approach could be identified among these trials, a narrative summary of all available data including case studies, and uncontrolled observational studies was implemented. Selected material had to focus on vitamin D related facts relevant to infection risk and recovery, as well as symptoms of infection in the older adult. Excluded were articles that did not focus specifically on this set of issues and non English based articles. Preprints were used to highlight the possible scope and updated findings concerning this present topic, rather than for prescribing clinical guidelines.

Results

Of the more than 60,000 publications on Covid-19, published as of December 2 2020, a total of 307 articles potentially relevant to the current topic were listed on PUBMED. Very few additional articles were found on the additional web sites. In terms of the topic of interest to this report, however, only 75 articles were deemed relevant as more publications than not did not meet criteria for this review, for example, they discussed vitamin D in children, or were letters to the editor. Even when the topic of the listed publication was relevant, it was clear that the prevailing reports were predominantly

literature reviews, rather than actual studies. These were not uniform however, and tended to discuss studies with considerable variation in the samples studied, as well as types of vitamin D and modes of usage, with no consistency in reviewed content or overall approach. Most too, focused on the role of vitamin D as deduced from past studies on acute respiratory infections, or alternately on currently recorded medical records or observations on Covid-19 hospitalized cases made on a single occasion, rather than any observed prospective follow up studies. In particular, among the available publications related to Covid-19, and vitamin D the majority do not currently focus on vitamin D as a possible primary or secondary prevention approach. Indeed, very few have examined the possible role of vitamin D as an important biological determinant in mediating risk and outcomes of Covid-19 as experienced by older adults, even though vitamin D tends to meet Hill's criteria for infection causality as detailed by Annweiler et al. [3].

To provide an overview of this quite considerable, but potentially highly relevant material in this regard, this review chose to discuss the science base and basis as regards vitamin D as a form of possible form of prevention and/or therapy relative to acute respiratory infections, such as Covid-19 among older adults. Findings regarding its specific immune related benefits and others relevant to the safety and life quality of the older adult are described. The term vitamin D is applied throughout, even though several formulae and categories of this compound exist.

Prior Studies

Past research on the value of vitamin D in the context of health status, shows this compound in its various forms has the potential to strongly influence overall health status and outcomes across the lifespan, including the elderly, as well as outcomes of infections analogous to the Covid-19 pandemic. While most of these data point to research on vitamin D deficits and how these may raise the risk of more severe infection responses in the vulnerable adult [1, 4], other data show that there is a positive benefit of vitamin D supplementation on the risk of acute respiratory infection, depending on dosage. Simonson [1] also reports on the possible linkages of chronic health conditions, as well as Northern latitudes and cold weather that can implicate vitamin D deficits in exacerbating Covid-19 morbidity rates. The link between

vitamin D and the immune system functioning has also been discussed [4].

Current Reports

Among the 75 studies and reports retrieved from the present search, Merzon et al. [5] who evaluated the degree of association between plasma vitamin D levels and the presence of Covid-19 disease and hospitalizations among 14,000 members of a Health Services unit found 10.1% to be Covid-19-positive. They also noted that the mean plasma vitamin D level among this infected group was significantly lower than that of the negative Covid-19 group. While the low vitamin D level may have been caused by the Covid-19 presence, their univariate analysis demonstrated an association between low plasma vitamin D levels and the increased likelihood of acquiring a Covid-19 infection, followed by hospitalization due to this virus. In a multivariate analyses that controlled for demographic variables as well as psychiatric and somatic disorders, the adjusted odds of acquiring Covid-19 infections, as well as hospitalization due to the virus was unchanged, implying that a low vitamin D status is a possible risk factor for acquiring or exacerbating Covid-19 infection risk and severity.

Martineaus et al. [6] who assessed the overall effect of vitamin D supplementation on risk of acquiring an acute respiratory tract infection, associated with Covid-19 by reviewing data from several electronic data bases up until 2015 that were randomized, double blind, placebo controlled trials of vitamin D supplementation of any duration showed vitamin D administration was beneficial overall. That is, of the 25 eligible randomized controlled trials housing a total of 11 321 participants up to 95 years of age, vitamin D supplementation appeared to reduce the risk of acute respiratory tract infection among all participants. In subgroup analysis, protective effects were also seen in those receiving daily or weekly vitamin D without additional bolus doses. It was concluded that vitamin D supplementation is able to safely protect against acute respiratory tract infection overall, and cases who are vitamin D deficient and receive non bolus supplements of vitamin D experience the most benefit.

Mok et al. [2] who examined a natural product library, among other sources in the search for Covid-19

prophylactic compounds, shortlisted the active form of vitamin D, termed calcitriol, as a prospective adjunctive agent in this regard. They then provided well documented background evidence that vitamin D has the potential to exhibit significant potent activity against Covid-19 or SARS-CoV-2. According to this group, their review findings pave the way for consideration of a practical host-directed therapy for helping to protect against SARS-CoV-2 or Covid-19 infection. Their arguments align to some degree at least with those of Mendy et al. [7] who sought to identify factors associated with hospitalization and disease severity in a racially and ethnically diverse cohort of COVID-19 patients and found that among the 689 Covid-19 patients in their study, a vitamin D deficiency was one factor associated with hospitalization and/or disease severity.

As well, Laird et al. [8] who specifically examined the role of vitamin D in the context of inflammation similarly support a strong plausible biological hypothesis and evolving epidemiological data as regards a favorable role for vitamin D in mitigating Covid-19 risk as proposed by Melzer et al. [9], especially in the case of any vitamin D deficiency. This is important to note, given that according to Zemb et al. [10] a vitamin D deficiency is easily modifiable, and daily vitamin D supplementation with moderate doses is safe and cheap. Moreover, even a small decrease in Covid-19 infections would easily justify this intervention even though disputed by Hastie et al. [11].

Ali et al. [12] further propose that since vitamin D is known to mitigate the scope of acquired immunity and to help regenerate endothelial lining damage, its thoughtful usage may be especially beneficial in minimizing the damage that often accompanies damage to alveolar structures in cases of acute respiratory diseases. These protective effects appear as well to increase up to 19% in those individuals subject to daily or weekly regimens of vitamin D compared to those dosing on a monthly bolus of vitamin D. Furthermore, there is a possible 70% chance of an effective protective outcome when a vitamin D deficiency is corrected by supplementation according to this group.

Radujkovic et al. [13] who studied 185 patients diagnosed with Covid-19 as regards vitamin D status at

first presentation found 50% of these patients required hospitalization and a total of 22% were vitamin D deficient. When adjusted for age, gender, and comorbidities, this deficiency was associated with higher risk of severe illness and death, highlighting the need for interventional studies on vitamin D supplementation in this patient group.

According to Carpagnano et al. [14] who elected to examine the presence of vitamin D levels in 42 patients with acute respiratory failure due to Covid-19, 81% had hypovitaminosis D. As well their survival analysis showed that those patients with a severe vitamin D deficiency had a 50% chance of dying, while those with vitamin D levels ≥ 10 ng/mL had a 5% chance of dying at 10 days.

Similarly Brenner et al. [15] who assessed the extent of vitamin D insufficiency and deficiency, and their association with mortality from respiratory diseases during 15 years of follow-up among 9548 adults ages 50–75 found high rates of vitamin D insufficiency and deficiency among this cohort. Compared to those with sufficient vitamin D, these aforementioned participants had increased respiratory mortality rates, hence, implying that vitamin D supplementation may be helpful in efforts to limit the immense burden of the Covid-19 pandemic.

State of Research

As noted above, the reports documented in this review, which are largely current, stem predominantly from either hypothetical, analogous research in the realm of respiratory conditions, anecdotal or observational data, hence should be viewed with caution, despite their overall meaningful conclusions in the face of a pandemic that has produced few preventive pharmacologic based strategies or amelioration approaches that are readily accessible and cost-effective. Indeed, as per Grant et al. [16] several observational studies and clinical trials do imply that vitamin D supplementation may be able to reduce the risk of influenza, even if this is not a consistent finding, and must thus be of sufficient current import to examine further [17]. As well, even though support for this idea may not be universal, the design and basis for the few available contrary studies has been questioned

[17], thus these data too must be viewed cautiously to avoid discarding a potentially valuable adjunctive intervention, when in fact it may be helpful. Additionally, although several authors recommend that to reduce the risk of infection, very high vitamin D usage may be helpful to offset infection rates in vulnerable adults at risk for Covid-19, excess levels of vitamin D may prove more harmful than not, and should be studied carefully, before universally adopting its administration to the older severely affected adult with a Covid-19 infection.

On the other hand, as proposed by Caccialanza et al. [19] efforts towards ensuring safe efficacious vitamin D serum levels and methods of delivery should be examined carefully to establish if any of these can help to reduce the risk of respiratory failure requiring non-invasive ventilation or continuous positive airway pressure that limits food and beverage intake, and with this vitamin D analogs. According to Kakodkar et al. [20] there is also a need for assessing multiple parameters that influence and could influence the clinical course of Covid-19 infections and that may require optimization, as focusing on a single item may not prove efficacious in the long-term. However, as implied by D'Avolio et al. [21], moreover vitamin D concentrations in the plasma obtained from a cohort of patients in Switzerland did suggest vitamin D is one potentially important adjunct to bear in mind in the context of the Covid-19 'fight' [22].

As well a careful review of allied past, as well as several existing studies (sampled in Table1), shows vitamin D deficits may predispose to infection of the lungs, and that the multiple mechanisms involved can be explained by vitamin D presence and extent of availability [4, 23]. Other data show, older adults who are affected most by Covid-19 are more likely than not to be vitamin D deficient, as well as experience the observed generally worse Covid-19 infection outcomes than younger patients. To the contrary, Ohaegbulam [25] found Covid-19 patients who received a high dose of vitamin D supplementation achieved more observable levels of vitamin D normalization, as well as improved clinical recovery rates. How the presence of lung disease and/or chronic smoke or pollution exposure can impact lung tissue vitamin D status and functioning, is not clear though, and

Table 1. Summary key study findings as of December 2, 2020 regarding the possible importance of efforts to identify vitamin D deficient older adults in the context of primary, secondary, and tertiary Covid-19 prevention approaches

Authors	Sample	Study mode	Vitamin D Findings
Brenner et al. [15]	9458 ARD cases	Prospective 15 yrs	Potentially protective
Baktash et al. [56]	Older Covid-19 cases	Prospective	May predict outcomes
Carpagnano et al. [14]	42 ARD cases	Retrospective	May predict mortality
Castillo et al. [73]	76 hospitalized cases	Pilot randomized trial	Reduced Covid severity
D'Avolio et al. [21]	Swiss patients	Retrospective	Correlates with Covid-19
Daneshkhah et al. [61]	Covid-19 patients	Prospective	May predict severity
Merzon et al. [5]	Members health grp	Observational	Covid-19 risk factor
Hastie et al. [11]	Biobank cases	Retrospective	No Covid relationship
Ilie et al. [54]	Published literature	Analytic	Suggests Covid-19 link
Kaufmann et al. [27]	National lab data	Observational	Is Covid-19 related
Karahan et al. [65]	149 Covid-19 patients	Retrospective	Vitamin D/severity linked
Maghbooli et al. [28]	235 Covid cases	Observational	May impact Covid-19
Mardani et al. [29]	65 male, 58 females	Prospective	May impact Covid-19
Munshi et al. [30]	7 studies	Analytic	May be linked to Covid
Ohaegbulam et al. [25]	4 cases low vitamin D	Case series	Supplements help
Panagiotou et al. [31]	Cohort ill patients	Retrospective	Severe Covid linkage
Pizzini et al. [32]	109 cases at 8 wks	Prospective	Low vitamin D-no effect
Radujkovic et al.[13]	185 Covid-19 cases	Prospective	Impacts Covid outcome
Sabetta et al. [33]	Healthy subjects	Prospective cohort	Lowers ARD risk

Abbreviations: ARD: Acute respiratory disease; Covid: Covid-19; grp: group; wks; weeks

warrants examination [26].

Discussion

Although modern medicine has previously been quite successful in managing infection rates globally, despite periodic epidemics, it is less successful in arresting rates of Covid-19 infections globally. While the world awaits an effective vaccine, as per Ebadi and Montano-Loza [24] it appears plausible however, to make a case for the possible use of vitamin D supplements in influencing the incidence and severity of the infection at the early stages of the disease, due to its protective immune response potential for eliminating the virus [39]. As the disease progresses, lung inflammation and fibrosis due to the release of pro-inflammatory cytokines may also be found to decrease, and if used appropriately, in line with its past importance in reducing the impact of respiratory virus processes [3], vitamin D may also slow the disease progression or even improve patient survival [3].

Moreover, cumulative evidence points not only to the impact of vitamin D on many genes with a well-established salience to airway infections, as well as immune processes [45], but to the additional fact that a low vitamin D status could potentially be important in explaining the mechanistic link between age, comorbidities and increased susceptibility to complications and mortality due to Covid-19 at least in some countries [46]. In countries such as Italy where vitamin D is predominantly prescribed to post-menopausal women with osteoporosis, it is possible older men are, at least in part, more vulnerable to the most serious consequences of the infection on this basis [46]. At the same time, vitamin D deficiency or insufficiency has been shown to be both a risk factor for acquiring Covid-19, but also for its severity [3], while multiple benefits of vitamin D have been reported that would be useful for Covid-19 risk reduction and intervention as shown in Box 1. Thus, given the magnitude of the public health problems caused by Covid-19 in an aging population, and no sound solution, it appears more research to confirm the potential for vitamin D to minimize the risk of infection, and its severity will most certainly prove advantageous. In addition to those gaps identified here through the

literature search, needed in particular, as well as urgently, are well designed adequately powered comparative studies of vitamin D similar dosages, dosage strategies, disease stages, and cohorts with varying age ranges and health status, as well as population-based prophylactic trials [3, 42].

At the same time, as outlined by Grant et al. [16], it is clear that the world remains in the grip of the Covid-19 pandemic, and that it does not seem intuitive to await the outcomes of these trials in the event the adult at risk clearly has a prevailing vitamin D deficit. Provided under the care of physicians, there appears to be sufficient evidence to implement such a personal as well as possible public health measure that can in all likelihood reduce infection risk and magnitude in the older adult, over and above isolation, distancing and masking, in a safe manner. Those who are obese, those who are food insecure, and those of Black or Asian origin may need to be preferentially targeted. Indeed, Ali and colleagues [12] who examined the role of vitamin D in preventing of Covid-19 infection, progression and severity concluded that despite the weak evidence base, people at higher risk of vitamin D deficiency during this global pandemic should consider taking safe levels of vitamin D supplements or food based sources to maintain the desired levels of circulating vitamin D. The observation of a quadratic relationship between the prevalence of vitamin D deficiency in most commonly affected countries by Covid-19 and the latitudes [47], plus possible additional health benefits of vitamin D supplementation alone in deficient older cases appears to be an added reason for considering this idea. As well, such improvements, as well as less severe Covid-19 disease are likely to significantly outweigh the risks of failing to do this. [48-50].

On the other hand, knowing that high doses may pose a risk to an older adult, avoiding these excess doses pending further study seems wise as discussed by Lanham-New et al. [49] and Bliezgys et al. [46]. Indeed, why the dosages discussed among the key strategies being studied in currently registered vitamin D Covid-19 trials have been selected warrants more definitive clarification [34], as collectively, they do not appear to

follow what works in other acute respiratory infections [42], nor are the majority uniform in delivery approaches or in compliance with daily recommended dosages to achieve and maintain optimal serum vitamin D levels. In addition, some of these trials assess multiple treatment approaches simultaneously, use unspecified vitamin D doses [NCT04449718], differing samples, time periods of study, plus outcome measures. Despite the urgency of one or more of these efforts, many however, have not begun recruitment, and those that have may only have results in more than a year from present time. Thus, how these diverse data sets, will inform practice either presently or in the future is unclear, especially if therapeutic doses tested do not concur with daily recommended doses in any comparable way. The ethics of studying high versus standard dose supplements of vitamin D in Covid-19 patients [NCT04344041], as well as the use of placebo interventions, must also be questioned. Finally, is it ethical to withhold a reasonably well established supplement from high risk older populations, who have high Covid-19 susceptibility, high mortality rates, along with predictable vitamin D deficits, when the need is so acute? Even if older adults have adequate vitamin D levels when admitted to hospital, they may surely suffer vitamin D deficits attributable to inflammatory respiratory disease dysregulation factors [42] that may delay their recovery if not addressed. As of October 2020, although there are 54 possible related trials cited at the ClinicalTrials.gov website, only 2 are completed with no results; 2 have results, but are not directly related to the determination of vitamin D efficacy in a Covid-19 context. One is a clinical trial of Ivermectin plus Doxycycline for the treating confirmed Covid-19 infections, the other examined whether Hydroxychloroquine is effective in reducing Covid-19 progression.

One of 22 cited studies and listed as 'actively recruiting' patients, proposes to test the efficacy of either daily high dose vitamin D supplementation (6000 IU vitamin D3/day) versus standard care. Those individuals ≥ 50 years of age or older who test positive for COVID-19 at baseline will be randomized to bolus vitamin D (20,000 IU/day for 3 days) followed by high dose (6000 IU vitamin D/day) vs. standard of care

for 12 months. All participants will receive a multivitamin containing vitamin D-but the rationale for these doses and mode of application do not seem to parallel the daily recommended doses for an older population, such as that being studied, and may be detrimental and are not recommended [51]. Even if advocated [16], these high doses seem impractical for purposes of fostering population wide health protection. There are only 140 cases being recruiting and completion is set for the end of 2021. This study also administers a placebo across the study time period-even though this may lower the overall health benefits that would be attained by applying the actual compound. Since all subjects are given a multivitamin with vitamin D, the precise benefits of vitamin D supplementation per se may not be discernible. Some of the studies presently recruiting subjects also examine other dietary sources, unspecified vitamin D doses, various pharmaceutical products, vitamin C, vitamin D as a prognostic marker, or apply varying vitamin D doses and modes of delivery to small samples across varying time periods, and often across multiple test sites. Moreover, samples vary in health status, ages studied, sample sizes, and primary and secondary outcomes assessed vary widely, and most proposed measurement approaches do not directly speak to issues of validity, blinding, subjectivity, and sensitivity, among other factors. For more data, the papers by Shakoore et al. [34] and Chakhtoura et al. [52] are relevant, as is the website of registered trials located at: <https://clinicaltrials.gov/ct2/results?cond=COVID&term=vitamin+d&cntry=&state=&city=&dist=>

<https://clinicaltrials.gov/ct2/results?cond=COVID&term=vitamin+d&cntry=&state=&city=&dist=>

In short, it appears low vitamin D levels, may adversely impact innate and adaptive immunity that can lead to Covid-19 infections and their severity and mortality [65], in part, through the activation of its antimicrobial peptides that are secreted at mucosal surfaces, among other different and interactive mechanisms [See Figure 1 and Box 1].

However, to validate these ideas, as well as to solidify the data, and overcome conjecture, well-powered and carefully conceived clinical, as well as epidemiological and environmental research should be conducted [35, 47, 50-52, 55, 70-75].

Box I. Specific examples of how vitamin D supplementation may hypothetically promote immunity or more favourable Covid-19 outcomes among older adults who are vitamin D deficient or at risk for deficiency via its multiple gene regulating abilities [5].

- T regulatory lymphocytes can be increased or modulated by vitamin D [1, 34, 62]
- May help to reduce cytokine storm severity [1, 61, 62, 66]
- May reduce thrombocytic episodes and have a significant anticoagulation effect [1, 35]
- Has potential antiviral properties [36]
- May limit the expression of anti-oxidant genes [34]
- May potentially prevent or mitigate the complications associated with acute respiratory infections [37]
- Suppresses the actions of the renin-angiotensin system, which has a determining role in inducing inflammatory response related to Covid-19 [38]
- May help induce antimicrobial peptides, such as cathelicidine [24, 39, 40, 66]
- May help to induce innate immune responses or act as an immunosuppressant [39, 40, 62]
- May prevent exaggerated inflammatory responses and further damage to mucosal lung tissue in cases of virus-induced inflammation [26, 39]
- May protect against acute respiratory infections [42, 53] by helping to maintain the integrity of lung based epithelial tight junctions [34]
- May positively impact macrophage modulation and mucus secretion [34, 62]
- May help to prevent getting infected or ward off the infection without mortality [62]
- May reduce disease severity and need for intensive care [73]

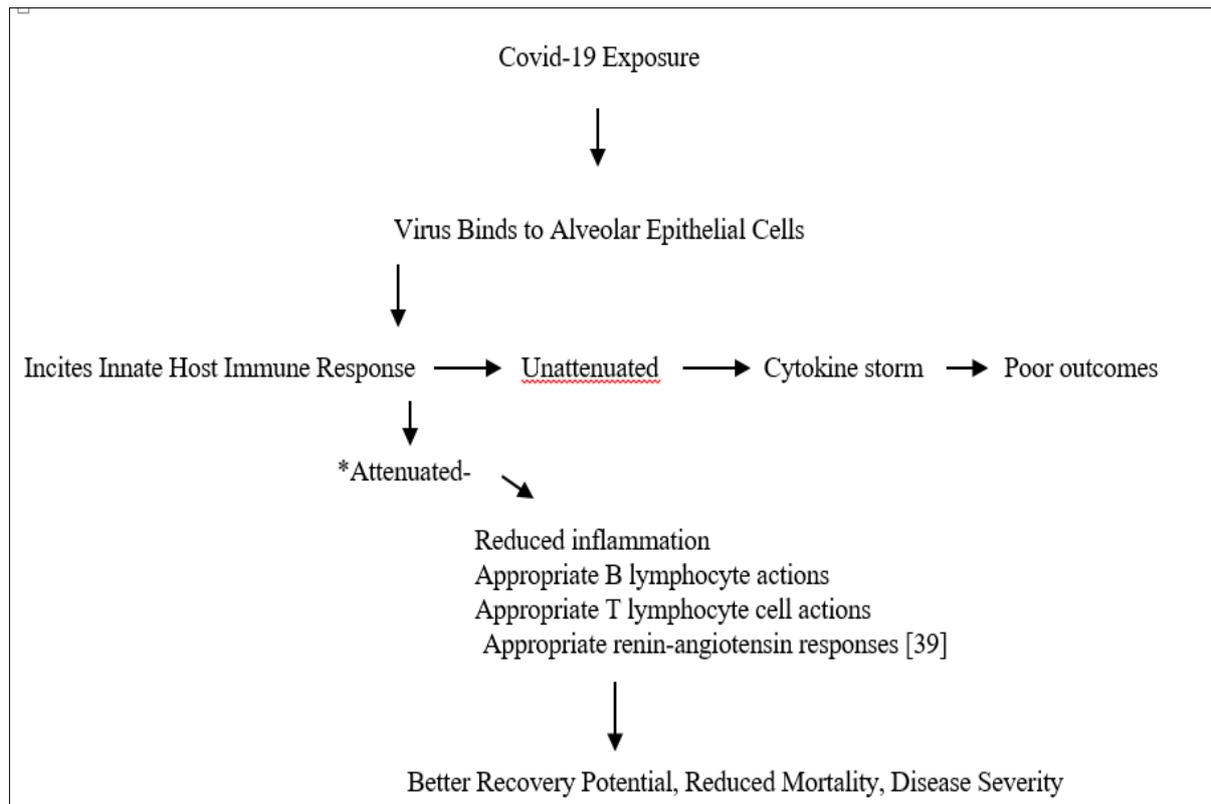


Figure 1. Possible Pathways of Covid-19 Infections: *-showing mechanisms where vitamin D may be helpful
[Adapted from; 1, 28, 34, 39, 62, 63, 65, 71-75]

Future Research Directions

Areas that could be fruitful to focus on in the future are:

- The correlates of prevailing health status, prescription medication usage, and/or cultural practices that may preclude adequate sunlight exposure.
- Air pollution and this possible Covid-19 correlate [31, 51, 53].

Other topics that might prove fruitful if examined more intently are Covid-19 associated inflammation, coagulopathy, reduced platelet count, and prolonged prothrombin time and other outcome correlates [24, 68].

Moreover, since the vitamin D dosages that would possibly prove impactful among various older adults at risk for Covid-19 are not well established at all, more attention to this issue appears necessary. At the same time, greater efforts towards controlling for

current medication and supplement usage, as well as sunlight in forthcoming studies is essential.

In addition, a sizeable number of scholars point to the value of specifically examining the potentially influential role of gender, geography, health status, living arrangements, nutrient intake and access on intrinsic vitamin D availability levels and need in efforts to heighten immune function and reduce Covid-19 risk and fatalities [31, 52, 59, 63, 64, 69, 70-75].

Conclusion

Covid-19 infections clearly remain immensely problematic to control and treat, especially among older adults, but could be impacted favourably by vitamin D supplements and intake, as indicated.

Ascertaining whether this may help seems imperative even if a vaccine is forthcoming.

Acknowledgements

None

Conflicts of Interest

None

References

1. Simonson W. (2020) Vitamin D and Coronavirus. *Geriatr Nurs* 41(4): 496-497. doi: 10.1016/j.gerinurse.2020.06.011.
2. Mok CK, Ng YL, Ahidjo BA et al. (2020) Calcitriol, the active form of vitamin D, is a promising candidate for COVID-19 prophylaxis. *bioRxiv* 2020.06.21.162396; doi: <https://doi.org/10.1101/2020.06.21.162396>
3. Annweiler C, Cao Z, Sabatier JM. (2020) Point of view: Should COVID-19 patients be supplemented with vitamin D? *Maturitas* 140: 24-26. doi: 10.1016/j.maturitas.2020.06.003.
4. Bergman P. (2020) The link between vitamin D and COVID-19: distinguishing facts from fiction. *J Intern Med* 11: 10.1111/joim.13158. doi: 10.1111/joim.13158.
5. Merzon E, Tworowski D, Gorohovski A, et al. (2020) Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: An Israeli population-based study. *FEBS J* 10.1111/febs.15495. doi:10.1111/febs.15495
6. Martineau AR, Jolliffe DA, Hooper RL, et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data. *BMJ* 15; 356:i6583. doi: 10.1136/bmj.i6583.
7. Mendy A, Apewokin S, Wells AA, et al. (2020) Factors associated with hospitalization and disease severity in a racially and ethnically diverse population of COVID-19 patients. *medRxiv* [Preprint]. 2020.06.25.20137323. doi: 10.1101/2020.06.25.20137323.
8. Laird E, Rhodes J, Kenny RA. (2020) Vitamin D and inflammation: Potential implications for severity of Covid-19. *Ir Med J* 113(5): 81.
9. Meltzer DO, Best TJ, Zhang H, et al. (2020) Association of vitamin D deficiency and treatment with COVID-19 incidence. *medRxiv* [Preprint]. 2020 May 13:2020.05.08.20095893. doi: 10.1101/2020.05.08.20095893.
10. Zemb P, Bergman P, Camargo CA Jr, et al. (2020) Vitamin D deficiency and the COVID-19 pandemic. *J Glob Antimicrob Resist* 22: 133-134. doi: 10.1016/j.jgar.2020.05.006.
11. Hastie CE, Mackay DF, Ho F, et al. (2020) Vitamin D concentrations and COVID-19 infection in UK Biobank. *Diabetes Metab Syndr* 14(4): 561-565. doi: 10.1016/j.dsx.2020.04.050
12. Ali N. (2020) Role of vitamin D in preventing of COVID-19 infection, progression and severity. *J Infect Public Health* 13(10): 1373-1380. doi: 10.1016/j.jiph.2020.06.021.
13. Radujkovic A, Hippchen T, Tiwari-Heckler S, et al. (2020) Vitamin D deficiency and outcome of COVID-19 patients. *Nutrients* 12(9): E2757. doi: 10.3390/nu12092757.
14. Carpagnano GE, Di Lecce V, Quaranta VN, et al. (2020) Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19. *J Endocrinol Invest* 2020;1-7. doi:10.1007/s40618-020-01370-x
15. Brenner H, Holleczeck B, Schöttker B. (2020) Vitamin D insufficiency and deficiency and mortality from respiratory diseases in a cohort of older adults: potential for limiting the death toll during and beyond the COVID-19 pandemic?. *Nutrients* 12(8): 2488.
16. Grant WB, Lahore H, McDonnell SL, et al. (2020) Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients* 12(4). pii: E988. doi:10.3390/nu12040988.
17. Benskin LL. (2020) A basic review of the preliminary evidence that COVID-19 Risk and severity is increased in Vitamin D deficiency. *Front Public Health*. 2020 Sep 10;8: 513. doi: 10.3389/fpubh.2020.00513.
18. Jakovac H. (2020) COVID-19 and vitamin D-Is there a link and an opportunity for intervention? *Am J Physiol Endocrinol Metab* 318(5): E589. doi: 10.1152/ajpendo.00138.2020.
19. Caccialanza R, Laviano A, Lobascio F, et al. (2020) Early nutritional supplementation in non-critically ill

- patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. *Nutrition* 2020 Apr 3:110835. doi: 10.1016/j.nut.2020.110835.
20. Kakodkar P, Kaka N, Baig MN. (2020) A comprehensive literature review on the clinical presentation, and management of the pandemic coronavirus disease 2019 (COVID-19). *Cureus* 12(4): e7560. doi: 10.7759/cureus.7560.
 21. D'Avolio A, Avataneo V, Manca A, et al. (2020) 25-Hydroxyvitamin D concentrations are lower in patients with positive PCR for SARS-CoV-2. *Nutrients* 12(5): 1359. doi: 10.3390/nu12051359.
 22. Kendrick M. (2020) Covid update – Focus on Vitamin D. Commentary. Available at: <https://drmalcolmkendrick.org/2020/04/28/covid-update-focus-on-vitamin-d/>
 23. Rhodes JM, Subramanian S, Laird E, et al. (2020) Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North-supports vitamin D as a factor determining severity. *Aliment Pharmacol Ther* 2020 Apr 20. doi: 10.1111/apt.15777.
 24. Ebadi M, Montano-Loza AJ. (2020) Perspective: improving vitamin D status in the management of COVID-19. *Eur J Clin Nutr* 74(6): 856-859. doi:10.1038/s41430-020-0661-0.
 25. Ohaegbulam KC, Swalih M, Patel P, et al. (2020) Vitamin D supplementation in COVID-19 patients: A clinical case series. *Am J Ther* 2020 Sep/Oct;27(5):e485-e490. doi: 10.1097/MJT.0000000000001222.
 26. Schrupf JA, van der Does AM, Hiemstra PS. (2020) Impact of the local inflammatory environment on mucosal vitamin D metabolism and signaling in chronic inflammatory lung diseases. *Front Immunol* 11: 1433. doi: 10.3389/fimmu.2020.01433.
 27. Kaufman HW, Niles JK, Kroll MH, et al. (2020) SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One* 15(9): e0239252. doi: 10.1371/journal.pone.0239252.
 28. Maghbooli Z, Sahraian MA, Ebrahimi M, et al. (2020) Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. *PLoS One* 15(9): e0239799. doi: 10.1371/journal.pone.0239799.
 29. Mardani R, Alamdary A, Mousavi Nasab SD, et al. (2020) Association of vitamin D with the modulation of the disease severity in COVID-19. *Virus Res* 289:198148. doi: 10.1016/j.virusres.2020.198148.
 30. Munshi R, Hussein MH, Toraih EA, et al. (2020) Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *J Med Virol* 2020 Jul 27. doi: 10.1002/jmv.26360.
 31. Panagiotou G, Tee SA, Ihsan Y, et al. (2020) Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalized with COVID-19 are associated with greater disease severity. *Clin Endocrinol* 2020 Jul 3:10.1111/cen.14276. doi: 10.1111/cen.14276.
 32. Pizzini A, Aichner M, Sahanic S, et al. (2020) Impact of vitamin D deficiency on COVID-19-A prospective analysis from the CovILD Registry. *Nutrients* 12(9): E2775. doi: 10.3390/nu12092775.
 33. Sabetta JR, DePetrillo P, Cipriani RJ, et al. (2020) Serum 25-hydroxyvitamin D and the incidence of acute viral respiratory tract infections in healthy adults. *PLoS One* 2010 5(6): e11088. doi: 10.1371/journal.pone.0011088.
 34. Shakoob H, Feehan J, Al Dhaheri AS, et al. (2021) Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19?. *Maturitas* 143: 1-9. doi:10.1016/j.maturitas.2020.08.003
 35. Liu G, Hong T, Yang J. (2020) A single large dose of vitamin D could be used as a means of coronavirus disease 2019 prevention and treatment. *Drug Des Devel Ther* 14: 3429-3434. doi: 10.2147/DDDT.S271754.
 36. Hribar CA, Cobbold PH, Church FC. (2020) Potential role of vitamin D in the elderly to resist COVID-19 and to slow progression of Parkinson's disease. *Brain Sci* 10(5): 284. doi: 10.3390/brainsci10050284.
 37. Chandran M, Chan Maung A, Mithal A, et al. (2020) Vitamin D in COVID - 19: Dousing the fire or averting the storm? - A perspective from the Asia-Pacific. *Osteoporos Sarcopenia* 2020 Jul 23.

- doi: 10.1016/j.afos.2020.07.003.
38. Ferder L, Martín Giménez VM, Inserra F. (2020) Vitamin D supplementation as a rational pharmacological approach in the Covid-19 pandemic. *Am J Physiol Lung Cell Mol Physiol* 2020 Sep 30. doi: 10.1152/ajplung.00186.2020.
39. Xu Y, Baylink DJ, Chen CS, et al. (2020) The importance of vitamin d metabolism as a potential prophylactic, immunoregulatory and neuroprotective treatment for COVID-19. *J Transl Med* 26; 18 (1):322. doi: 10.1186/s12967-020-02488-5.
40. Charoenngam N, Holick MF. (2020) Immunologic effects of vitamin D on human health and disease. *Nutrients* 12(7): 2097. 2020 Jul 15. doi:10.3390/nu12072097
41. Vyas N, Kurian SJ, Bagchi D, et al. (2020) Vitamin D in prevention and treatment of COVID-19: current perspective and future prospects. *J Am Coll Nutr* 2020 Sep 1: 1-14. doi: 10.1080/07315724.2020.1806758.
42. Martineau AR, Forouhi NG. (2020) Vitamin D for COVID-19: A case to answer? *Lancet Diabetes Endocrinol* 8(9): 735-736. doi:10.1016/S2213-8587(20)30268-0
43. Maretzke F, Bechthold A, Egert S, et al. (2020) Role of Vitamin D in preventing and treating selected extraskkeletal diseases-an umbrella review. *Nutrients* 12(4): 969. 2020 Mar 31. doi:10.3390/nu12040969
44. Musavi H, Abazari O, Barartabar Z, et al. (2020) The benefits of vitamin D in the COVID-19 pandemic: Biochemical and immunological mechanisms. *Arch Physiol Biochem* 2020 Oct 8: 1-9.
45. Crane-Godreau MA, Clem KJ, Payne P, et al. (2020) Vitamin D deficiency and air pollution exacerbate COVID-19 through suppression of antiviral peptide LL37. *Front Public Health* 8: 232. doi: 10.3389/fpubh.2020.00232.
46. Bleizgys A. (2020) Vitamin D and COVID-19: It is time to act. *Int J Clin Pract* 2020 Oct 4: e13748. doi: 10.1111/ijcp.13748.
47. Kara M, Ekiz T, Ricci V, et al. (2020) (2020)'Scientific Strabismus' or two related pandemics: coronavirus disease and vitamin D deficiency. *Br J Nutr* 124 (7):736-741. doi: 10.1017/S0007114520001749.
48. Bilezikian JP, Bikle D, Hewison M, et al. (2020) Mechanisms in endocrinology: Vitamin D and COVID-19. *Eur J Endocrinol* 183(5): R133-R147. doi: 10.1530/EJE-20-0665.
49. Lanham-New SA, Webb AR, Cashman KD, et al. (2020) Vitamin D and SARS-CoV-2 virus/COVID-19 disease. *BMJ Nutrition, Prevention & Health* 2020;bmjnph-2020-000089. doi:10.1136/bmjnph-2020-000089
50. Mitchell F. (2020) (2020) Vitamin-D and COVID-19: Do deficient risk a poorer outcome? *Lancet Diabetes Endocrinol* 8(7): 570. doi:10.1016/S2213-8587(20)30183-2
51. Ribeiro H, Santana KVS, Oliver SL, et al. (2020) Does vitamin D play a role in the management of Covid-19 in Brazil? *Rev Saude Publica* 2020;54: 53. doi:10.11606/s1518-8787.2020054002545
52. Chakhtoura M, Napoli N, El Hajj Fuleihan G. (2020) Commentary: Myths and facts on vitamin D amidst the COVID-19 pandemic. *Metabolism* 2020;109: 154276. doi:10.1016/j.metabol.2020.154276
53. Panarese A, Shahini E. (2020) Letter: Covid-19, and vitamin D. *Aliment Pharmacol Ther* 51(10): 993-995. doi:10.1111/apt.15752
54. Ilie PC, Stefanescu S, Smith L. (2020) The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin Exp Res* 32 (7): 1195-1198. doi: 10.1007/s40520-020-01570-8.
55. Carter SJ, Baranauskas MN, Fly AD. (2020) Considerations for obesity, vitamin D, and physical activity amidst the COVID-19 pandemic. *Obesity* 2020 Apr 16. doi: 10.1002/oby.22838.
56. Baktash V, Hosack T, Patel N, et al. (2020) Vitamin D status and outcomes for hospitalised older patients with COVID-19. *Postgrad Med J* 2020 Aug 27;postgradmedj-2020-138712. doi: 10.1136/postgradmedj-2020-138712.
57. Quesada-Gomez JM, Entrenas-Castillo M, Bouillon R. (2020) Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: *J Steroid Biochem Mol Biol*. 2020;202: 105719.

- doi:10.1016/j.jsbmb.2020.105719
58. Tramontana F, Napoli N, El-Hajj Fuleihan G, et al. (2020) The D-side of COVID-19: musculoskeletal benefits of vitamin D and beyond. *Endocrine* 69(2): 237-240. doi: 10.1007/s12020-020-02407-0.
59. Mandal AKJ, Baktash V, Hosack T, et al. (2020) Vitamin D status and COVID-19 in older adults. *Aging Clin Exp Res* 2020 Sep 21:1–2. doi: 10.1007/s40520-020-01716-8.
60. Weir EK, Thenappan T, Bhargava M, et al. (2020) Does vitamin D deficiency increase the severity of COVID-19? *Clin Med* 20(4): e107-e108. doi: 10.7861/clinmed.2020-0301.
61. Daneshkhah A, Agrawal V, Eshein A, et al. (2020) Evidence for possible association of vitamin D status with cytokine storm and unregulated inflammation in COVID-19 patients. *Aging Clin Exp Res* 32(10): 2141-2158. doi: 10.1007/s40520-020-01677-y.
62. Razdan K, Singh K, Singh D. (2020) Vitamin D Levels and COVID-19 susceptibility: is there any correlation? *Med Drug Discov* 100051. doi: 10.1016/j.medidd.2020.100051.
63. Jovic TH, Ali SR, Ibrahim N, et al. (2020) Could vitamins help in the fight against COVID-19? *Nutrients* 12(9): E2550. doi: 10.3390/nu12092550.
64. Lau FH, Majumder R, Torabi R, et al. (2020) Vitamin D insufficiency is prevalent in severe COVID-19. medRxiv. 2020 doi: 10.1101/2020.04.24.20075838.
65. Karahan S, Katkat F. (2020) Impact of serum 25 (OH) Vitamin D level on mortality in patients with COVID-19 in Turkey *J Nutr Health Aging* 2020; 1-8. doi:10.1007/s12603-020-1479-0
66. Aslan MT, Aslan İÖ, Özdemir Ö. (2020) Is vitamin D one of the key elements in COVID-19 Days? *J Nutr Health Aging* 2020; 1-2. doi:10.1007/s12603-020-1413-5
67. Ouedraogo LSP, Apeti S, Ouedraogo DA (2020) New perspective on Covid-19 treatment: When a paradigm changes in infectiology become necessary against an emerging virus as the SARS-Cov2. Preprints 2020, 2020090561 doi: 10.20944/preprints202009.0561.v1.
68. Tomasa-Irriguible T, Bielsa-Berrocal L. (2020) Up to 40% of COVID-19 critically ill patients have vitamin D deficiency. Preprints 2020, 2020090555 (doi: 10.20944/preprints202009.0555.v1).
69. Faniyi AA, Lugg ST, Faustini SE, et al. (2020) Vitamin D status and seroconversion for COVID-19 in UK healthcare workers who isolated for COVID-19 like symptoms during the 2020 pandemic medRxiv 2020.10.05.20206706; doi: https://doi.org/10.1101/2020.10.05.20206706
70. Ghasemian R, Shamshirian A, Heydari K et al. (2020) The role of vitamin d in the age of COVID-19: A systematic review and meta-analysis along with an ecological approach. medRxiv 2020.06.05.20123554; doi: https://doi.org/10.1101/2020.06.05.20123554
71. Pereira M, Dantas Damascena A, Galvão Azevedo LM, et al. (2020) . Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. *Crit Rev Food Sci Nutr* 2020 Nov 4:1-9. doi: 10.1080/10408398.2020.1841090.
72. Mercola J, Grant WB, Wagner CL. (2020) Evidence regarding vitamin D and risk of COVID-19 and its severity. *Nutrients* 2020 Oct 31;12(11):E3361. doi: 10.3390/nu12113361.
73. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, et al. (2020) Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID -19: A pilot randomized clinical study. *J Steroid Biochem Mol Biol* 2020;203:105751. doi: 10.1016/j.jsbmb.2020.105751.
74. Hoong CWS, Huilin K, Cho S, et al. (2020) Are adequate Vitamin D levels helpful in fighting COVID-19? A look at the evidence. *Horm Metab Res* 52(11):775-783. doi: 10.1055/a-1243-5462.
75. Martín Giménez VM, Inserra F, Tajer CD, et al. (2020) Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. *Life Sci* 2020;254:117808. doi: 10.1016/j.lfs.2020.117808.