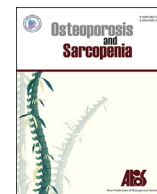




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## Editorial

# Vitamin D and COVID-19: Is something better than nothing?



## A B S T R A C T

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There is no abstract.

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The report on vitamin D and COVID-19 by Chandran and colleagues in this journal [1] provides an overview on the pathophysiology of COVID-19, a rationale for possible beneficial effects of vitamin D in this setting, and offers some cautious and reasonable recommendations for the use of vitamin D in the midst of the pandemic. The focus is on the Asia-Pacific region, but the recommendations are likely to be applicable worldwide. In the course of the review, the authors quoted a Latin aphorism of obscure origin, *Melius Anceps Remedium Quam Nullum*, which was translated into English and transposed into the question, “Is it better to do something than do nothing?” The answer, with respect to vitamin D and COVID-19, was a qualified yes. In consideration of circumstantial evidence supporting the use of vitamin D in COVID-19 patients and the favorable safety profile of vitamin D supplementation, the authors developed several recommendations, paraphrased as follows:

1. Current public health guidelines for optimizing vitamin D status should be followed.
2. Patients hospitalized with COVID-19 should have baseline serum 25(OH)D measured and be supplemented to a level  $\geq 10$  ng/mL, especially when the baseline level is  $< 10$  ng/mL.
3. When it is not possible to measure baseline 25(OH)D in COVID-19 patients, consider supplementing with 1000–2000 IU per day.

It is noteworthy that *Melius Anceps Remedium Quam Nullum* has alternative meanings, depending on which English version of the adjective *anceps* is used. Some of these may be relevant to an array of potential treatments for COVID-19. Translations of *anceps* include “uncertain” and “dangerous” (<https://worldofdictionary.com/dict/latin-english/meaning/anceps>). Using the latter version, a direct translation from Latin to English is “Better a dangerous remedy than none.” This was purportedly the view of Gottlieb Burckhardt, the “father” of psychosurgery, in reference to brain surgery for

patients with schizophrenia [2]. When Burckhardt reported surgical outcomes for 6 of his patients, the results were unimpressive, but that was in 1891, when there was no known treatment for schizophrenia. Now that psychopharmaceuticals are widely available, approaches to the treatment of schizophrenia are vastly different. There are certainly instances when dangerous remedies are not better than none. They may simply be dangerous. Some proposed but unproven treatments for COVID-19 have been followed by harmful outcomes (eg, adverse effects of hydroxychloroquine) and even death (eg, ingestion of disinfectants). When recommendations from governments and public health experts are inconsistent or late in coming, rumors and misinformation are likely to influence behavior of many individuals, resulting in panic buying and treatments that may be ineffective or dangerous [3]. For non-COVID disorders, sometimes doing nothing is better than doing something, such as not prescribing an antibiotic for viral pharyngitis, the use of which could ultimately result in emergence of antibiotic-resistant microorganisms, or not doing a prostate biopsy in an elderly man with borderline high prostate specific antigen, which would expose the patient to potential adverse effects of surgery with minimal benefit [4]. In some situations, doing “nothing” is actually an active beneficial process, as when a patient with osteoporosis who does not want drug therapy is monitored periodically to reassess fracture risk and treatment strategies.

What about vitamin D and COVID-19? Does vitamin D fall into the category of “something,” “uncertain,” or “dangerous?” The classical endocrine function of vitamin D is regulation of calcium and phosphate homeostasis. This involves bone, gut, and kidneys in coordination with the actions of parathyroid hormone and fibroblast growth factor 23. Low vitamin D levels are associated with secondary hyperparathyroidism with an increase of bone turnover, bone loss, and increase of fracture risk. Extremely low vitamin D levels cause rickets in children and osteomalacia in adults. Vitamin D toxicity, usually defined as hypercalcemia in the setting of high blood levels of vitamin D, is typically caused by excessive intake of over-the-counter vitamin D supplements or inadvertent ingestion of vitamin D included in nutritional supplements or food products. Maintaining adequate blood levels of vitamin D can effectively

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manage these conditions. Lower than desirable vitamin D levels are common, while vitamin D toxicity is very rare. Despite tremendous advances in our understanding of vitamin D, many controversies and uncertainties persist. Among these are variability in defining adequacy of vitamin D, lack of standardization in vitamin D assays, understanding the numerous potential skeletal and non-skeletal effects of vitamin D, and appropriate use of vitamin D as a therapeutic agent. These issues were addressed at the “International Conference on Controversies in Vitamin D,” reported in 2019 [5], and a follow-up conference that resulted in publication of a consensus statement in 2020 [6]. The consensus statement identified areas of agreement and proposed a research agenda to investigate ongoing uncertainties, including the role of vitamin D in the pathogenesis of autoimmune diseases, such as celiac disease and multiple sclerosis. Since the release of that statement, the COVID-19 pandemic, caused by the SARS-CoV-2 virus, has emerged as a global public health concern of immense proportions. Numerous interventions that might prevent the disease or mitigate its protean consequences are being considered and investigated, while others have already been evaluated and dismissed due to being ineffective or dangerous. It is now timely to consider what we know and what we don't know about interactions of vitamin D, immunity, and COVID-19, and what should be done to close knowledge gaps. It is biologically plausible that vitamin D might have some sort of effect in patients infected with COVID-19, since it is known to play a role in the regulation of innate and adaptive immunity [7].

Innate immunity is the first line of defense against bacteria, viruses, and cancer cells, activated within hours of exposure to the pathogen. The innate immune system is comprised of a vast array of defensive weapons that includes physical barriers (eg, skin, respiratory and intestinal mucosa), enzymes expressed by epithelial and phagocytic cells, antimicrobial peptides and proteins (eg, defensins, cathelicidins), inflammatory humoral components, toll-like receptors that rapidly recognize pathogens, and cellular components such as dendritic cells, macrophages, mast cells, and neutrophils [8]. Vitamin D receptors are expressed by most immune cells, which can convert 25(OH)D to 1,25(OH)<sub>2</sub>D through the actions of 1- $\alpha$ -hydroxylase. Local, intracellularly produced 1,25(OH)<sub>2</sub>D (distinct from 1,25(OH)<sub>2</sub>D produced in kidneys and released into the systemic circulation) is thought to have autocrine and paracrine functions that enhance host immunity by upregulating antimicrobial peptides. Vitamin D also has beneficial immune effects on the gastrointestinal tract, where it acts to maintain the integrity of the intestinal mucosal barrier and prevent the passing of pathogenic microbes [9].

Adaptive immunity is the process by which immunological memory to a specific antigen is established with a timeline that is slower than innate immunity. It is mediated through 2 types of lymphocytes, B cells that are responsible for humoral immunity and T cells for cell-mediated immunity. Activated B cells produce antibodies to the offending pathogen and neutralize or destroy it through a variety of mechanisms. Autoimmune diseases, such as rheumatoid arthritis, are examples of maladaptive immunity, with immune reactions against healthy cells and tissues. Vitamin D suppresses adaptive immunity, at least in animal models, and low vitamin D levels are associated with autoimmune and chronic inflammatory diseases [8]. There is no evidence that vitamin D is effective at treating these diseases.

“Cytokine storm” is a term used to describe a hyperactive immune response to COVID-19. Although there is much yet to be

learned about the pathophysiology of cytokine storm, it appears to be mediated by chronic activation of the innate immune system with an overly exuberant release of pro-inflammatory cytokines and chemokines, leading to excessive activation of adaptive immunity [7,10]. The clinical manifestations include acute lung injury, wide-spread tissue damage, multi-organ failure, and death. It has been postulated by some that vitamin D might help to mitigate the severity of cytokine storm by downregulating toll-like receptors and diminishing activation of mediators of inflammation.

In the spectrum of translations of *anceps*, where should we place vitamin D and COVID-19? Considering the best available evidence at this time, maintaining an adequate level of vitamin D is “something” that should be recommended for all of us, especially those at risk for vitamin D deficiency. It is an “uncertain” remedy for the treatment of COVID-19, but with further investigation we may soon know more. It is important to learn whether adequacy of vitamin D is simply a marker of good health that is associated with lower risk and better outcomes with COVID-19, or a useful medication for prevention and treatment of the disease. Vitamin D is clearly not a “dangerous” remedy for COVID-19 and is unlikely to cause harm.

### Conflicts of interest

The author has no conflict of interest relevant to the content of this editorial.

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