

Vitamin D Deficiency in COVID-19 Quadrupled Death Rate

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December 11, 2020

<https://www.medscape.com/viewarticle/942497>

Vitamin D deficiency on admission to hospital was associated with a 3.7-fold increase in the odds of dying from COVID-19, according to an observational study looking back at data from the first wave of the pandemic.

Nearly 60% of patients with COVID-19 were vitamin D deficient upon hospitalization, with men in the advanced stages of COVID-19 pneumonia showing the greatest deficit.

Importantly, the results were independent of comorbidities known to be affected by vitamin D deficiency, say the authors, led by Dieter De Smet, MD, from AZ Delta General Hospital, Roeselare, Belgium.

"[The findings] highlight the need for randomized controlled trials specifically targeting vitamin D-deficient patients at intake, and make a call for general avoidance of vitamin D deficiency as a safe and inexpensive possible mitigation of the SARS-CoV-2 pandemic," say De Smet and colleagues in their article, [published](#) online November 25 in the *American Journal of Clinical Pathology*.

A search of ClinicalTrials.gov [reveals](#) there are currently close to 40 ongoing intervention trials with vitamin D in COVID-19 around the world for varying purposes, including prevention, and varying forms of treatment.

Consider Vitamin D to Prevent COVID-19 Infection

With regard to the potential role in prevention, "Numerous observational studies have shown that low vitamin D levels are a major predictor for poor COVID outcomes," notes Jacob Teitelbaum, MD, an internist who specializes in treating chronic fatigue syndrome and fibromyalgia who also has an interest in COVID-19.

"This study shows how severe a problem this is," Teitelbaum told *Medscape Medical News*. "A 3.7-fold increase in death rate if someone's vitamin D level was below 20 [ng/mL] is staggering. It is arguably one of the most important risk factors to consider."

"What is not clear is whether vitamin D levels are acting as an acute-phase reactant, dropping because of the infection, with larger drops indicating more severe disease, or whether vitamin D deficiency is

causing worse outcomes," added Teitelbaum, who is director of the Center for Effective CFIDS/Fibromyalgia Therapies, Kailua-Kona, Hawaii.

Also asked to comment, Andrea Giustina, MD, president of the European Society of Endocrinology, said: "The paper by De Smet et al confirms what we [already hypothesized](#) in *BMJ* last March: that patients with low vitamin D levels are at high risk of hospitalization for COVID-19 and developing severe and lethal disease."

"This is likely due to the loss in the protective action of vitamin D on the immune system and against the SARS-CoV-2-induced cytokine storm."

He said it is particularly interesting that the authors of the new study had reported more prevalent vitamin D deficiency among men than women, most likely because women are more often treated with vitamin D for osteoporosis.

The new study should prompt all clinicians and health authorities to seriously consider vitamin D supplementation as an additional tool in the fight against COVID-19, particularly for the prevention of infection in those at high risk of both COVID-19 and hypovitaminosis D, such the elderly, urged Giustina, of San Raffaele Vita-Salute University, Milan, Italy.

Results Adjusted for Multiple Confounders

De Smet and colleagues looked at serum 25-hydroxyvitamin D (25(OH)D) levels in 186 patients hospitalized for severe COVID-19 infection as a function of radiologic stage of COVID-19 pneumonia as well as the association between vitamin D status on admission and COVID-19 mortality.

Cognizant of the potential for confounding by multiple factors, they adjusted for age, sex, and known vitamin D-affected comorbidities such as diabetes, chronic lung disease, and coronary artery disease.

Patients were hospitalized from March 1 to April 7, 2020 (the peak of the first wave of the pandemic) at their institution, AZ Delta General Hospital, a tertiary network hospital.

The mean age of patients was 69 years, 41% were women, and 59% had coronary artery disease. Upon admission to hospital, median vitamin D level was 18 ng/mL (women, 20.7 ng/mL; men, 17.6 ng/mL).

A remarkably high percentage (59%, 109/186) of patients with COVID-19 were vitamin D deficient (25(OH)D < 20 ng/mL) when admitted (47% of women and 67% of men), write the authors.

"What surprises me," said Teitelbaum, is that almost 60% "of these patients had 25(OH)D under 20 ng/mL but most clinicians consider under 50 to be low."

All patients had a chest CT scan to determine the radiologic stage of COVID-19 pneumonia and serum vitamin D measurement on admission. Radiologic stage of pneumonia was used as a proxy for immunologic phase of COVID-19.

Vitamin D Deficiency Correlated With Worsening Pneumonia

Among men, rates of vitamin D deficiency increased with advancing disease, with rates of 55% in stage 1, 67% in stage 2, and up to 74% in stage 3 pneumonia.

There is therefore "a clear correlation between 25(OH)D level and temporal stages of viral pneumonia, particularly in male patients," write the authors.

"Vitamin D dampens excessive inflammation," said Teitelbaum. "In these patients with acute respiratory distress syndrome, the immune system has gone wild."

"The study was carried out in Belgium, so there's less sunlight there than some other places, but even here in Hawaii, with plenty of sunshine, we have vitamin D deficiency," he added.

"More studies are needed, but I think there are enough data to suggest a multivitamin should be used to aid prophylaxis, and this is reflected in [some] infectious disease recommendations," he noted.

Low Vitamin D in COVID-19 Predicts ICU Admission, Poor Survival

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September 17, 2020

<https://www.medscape.com/viewarticle/937567>

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Having low serum vitamin D levels was an independent risk factor for having symptomatic COVID-19 with respiratory distress requiring admission to intensive care — as opposed to having mild COVID-19 — and for not surviving, in a new study from Italy.

"Our data give strong observational support to previous suggestions that reduced vitamin D levels may favor the appearance of severe respiratory dysfunction and increase the mortality risk in patients affected with COVID-19," the researchers report.

Luigi Gennari, MD, PhD, Department of Medicine, Surgery, and Neurosciences, University of Siena, Italy, presented these findings during the virtual [American Society of Bone and Mineral Research \(ASBMR\) 2020 annual meeting](#).

Gennari told *Medscape Medical News* that this analysis suggests determining vitamin D levels (25 hydroxyvitamin D) in people testing positive for SARS-Cov-2 infection might help predict their risk of severe disease.

However, further research is needed to explore whether vitamin D supplements could prevent the risk of respiratory failure in patients with SARS-Cov-2 infection, he stressed.

In the meantime, Gennari said: "I believe that, particularly in the winter season (when the solar ultraviolet-B (UVB) radiation exposure does not allow the skin to synthesize vitamin D in most countries), the use of vitamin D supplementation and correction of vitamin D deficiency might be of major relevance for the reduction of the clinical burden of the ongoing and future outbreaks of SARS-CoV-2 infection."

Invited to comment, David Meltzer, MD, PhD, chief of hospital medicine at University of Chicago Medicine, Illinois, who was not involved with the study, agrees.

"I think this body of work suggests that people should be taking supplements if they cannot increase sun exposure on a sustained basis," Meltzer said. "The abstract supports multiple prior findings that suggest that higher vitamin D levels are associated with improved outcomes."

And JoAnn E. Manson, MD, DrPH, of Harvard Medical School and Brigham and Women's Hospital, who was not involved with the research but has spoken about the topic in a [video report](#) for *Medscape*, said: "We know from several studies that a low vitamin D level is associated with a higher risk of having COVID-19 and severe illness, but correlation does not prove causation."

"I think that improving vitamin D status is a promising way to reduce the risk of severe illness, but we need randomized controlled trials to prove cause and effect," she told *Medscape Medical News*.

103 Patients With Severe COVID-19, 52 With Mild COVID-19, 206 Controls

Gennari said several lines of evidence suggest that vitamin D deficiency might be a risk factor for COVID-19 severity.

Countries with lower average levels of vitamin D or lower UVB radiation exposure have higher COVID-19 mortality, and "demographic groups known to be at higher risk of vitamin D deficiency (such as black individuals, the elderly, nursing home residents, and those with obesity and diabetes) are at high risk of COVID-19 hospitalization/mortality," he noted.

There is a high prevalence of vitamin D deficiency in Italy, where mortality rates from COVID-19 have been particularly high.

To examine the relationship between vitamin D levels and COVID-19 severity/mortality, the researchers studied three groups:

- 103 symptomatic patients with COVID-19 with respiratory insufficiency who were admitted to a Milan hospital from March 9 to April 30.
- 52 patients with mild COVID-19, recruited from patients and staff from a nearby nursing home who had a positive test for COVID-19.
- 206 healthy controls, matched 2:1 with symptomatic patients of the same age, weight, and gender, from 3174 patients who had vitamin D measured during a routine check-up from January to March 2020.

Patients in the hospitalized group had lower mean vitamin D levels (18.2 ng/mL) than those with mild COVID-19 (30.3 ng/mL) or those in the control group (25.4 ng/mL).

Patients with symptomatic versus mild COVID-19 were slightly older and more likely to have at least one comorbidity and less likely to be taking a vitamin D supplement at baseline (30% vs 79%).

Among symptomatic patients, mean vitamin D levels were inversely associated with interleukin (IL)-6 and C-reactive protein, "both of which are a direct expression of the inflammatory status," Gennari noted.

About half of the hospitalized patients (49) were admitted to a ward and discharged after a mean stay of 16 days (none died).

The other 54 hospitalized patients were admitted to the intensive care unit (ICU) with severe acute respiratory distress; 38 patients received continuous positive airway pressure (CPAP) and 16 patients received endotracheal intubation.

Of the 54 patients admitted to ICU, 19 patients died from respiratory distress after a mean of 19 days, "consistent with the literature," and the other 35 patients were discharged after a mean of 21 days.

Patients with severe COVID-19 who were admitted to ICU, as opposed to a ward, were more likely to be male, have at least one comorbidity, have higher baseline IL-6 levels and neutrophil counts, and lower lymphocyte and platelet counts.

They also had lower mean vitamin D levels (14.4 vs 22.4 ng/mL) and were more likely to have vitamin D deficiency (vitamin D < 20 ng/mL; 80% vs 45%).

Patients admitted to ICU who died had lower baseline vitamin D levels than those who survived (13.2 vs 19.3 ng/mL).

Vitamin D levels were inversely associated with respiratory distress requiring ICU admission [odds ratio, 1.06; $P = .038$] and with mortality (odds ratio, 1.18, $P = .029$), independent of IL-6 levels and other comorbidities.

"That vitamin D levels are associated with improved outcomes independent of IL-6 could reflect that IL-6 is an imperfect measure of the inflammatory process or that vitamin D is related to outcomes for other reasons, such as enhancement of innate or adaptive immunity," said Meltzer.

He added that "this is not to exclude the possibility that vitamin D has important immunomodulatory effects."

Gennari, Meltzer, and Manson have reported no relevant financial relationships.

ASBMR 2020 annual meeting. Presented September 11, 2020.

Link Between Vitamin D and ICU Outcomes Unclear

Ingrid Hein

October 19, 2020

<https://www.medscape.com/viewarticle/939354>

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We can "stop putting money on vitamin D" to help patients who require critical care, said Todd Rice, MD.

Todd Rice

"Results from vitamin D trials have not been uniformly one way, but they have been pretty uniformly disappointing," Rice, from Vanderbilt University Medical Center in Nashville, Tennessee, reported at CHEST 2020.

Low levels of vitamin D in critically ill COVID-19 patients have been reported in numerous recent studies, and researchers are looking for ways to boost those levels and improve outcomes.

We are seeing "the exact same story" in the critically ill COVID-19 population as we see in the general ICU population, said Rice. "The whole scenario is repeating itself. I'm pessimistic."

Still, vitamin D levels can be elevated so, in theory, "the concept makes sense," he said. There is evidence that, "when given enterally, the levels rise nicely" and vitamin D is absorbed reasonably well." But is that enough?

When patients are admitted to the ICU, some biomarkers in the body are too high and others are too low. Vitamin D is often too low.

So far, though, "supplementing vitamin D in the ICU has not significantly improved outcomes," said Rice.

In the Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial, Rice and his colleagues found no statistical benefit when a 540,000 IU boost of vitamin D was administered to 2624 critically ill patients, as [reported](#) by *Medscape Medical News*.

"Early administration of high-dose enteral vitamin D₃ did not provide an advantage over placebo with respect to 90-day mortality or other nonfatal outcomes among critically ill, vitamin D-deficient patients," the researchers write in their [recent report](#).

In fact, VIOLET ended before enrollment had reached the planned 3000-patient cohort because the statistical analysis clearly did not show benefit. Those enrolled were in the ICU because of, among other things, pneumonia, sepsis, the need for mechanical ventilation or vasopressors, and risk for acute respiratory distress syndrome.

"It doesn't look like vitamin D is going to be the answer to our critical care problems," Rice told *Medscape Medical News*.

Maintenance Dose Needed?

One theory suggests that VIOLET might have failed because a maintenance dose is needed after the initial boost of vitamin D.

In the ongoing [VITDALIZE trial](#), critically ill patients with severe vitamin D deficiency (12 ng/mL or less at admission) receive an initial 540,000 IU dose followed by 4000 IU per day.

The highly anticipated VITDALIZE results are expected in the middle of next year, Rice reported, so "let's wait to see."

"Vitamin D may not have an acute effect," he theorized. "We can raise your levels, but that doesn't give you all the benefits of having a sufficient level for a long period of time."

Another theory suggests that a low level of vitamin D is simply a signal of the severity of disease, not a direct influence on disease pathology.

Some observational data have shown an association between low levels of vitamin D and outcomes in COVID-19 patients ([D'Avolio et al](#), [Lau et al](#), [Meltzer et al](#), [Merzon et al](#), [Panagiotou et al](#)), but some have shown no association ([Hastie et al](#), [Raisi-Estabragh et al](#)).

RICE conducted a search of Clinicaltrials.gov immediately before his presentation on Sunday, and found 41 ongoing interventional studies — "not observational studies" — looking at COVID-19 and vitamin D.

"They're recruiting, they're enrolling; hopefully we'll have data soon," he said.

Researchers have checked a lot of boxes with a resounding yes on the vitamin D question, so there's reason to think an association does exist for ICU patients, whether or not they have COVID-19.

"Is there a theoretical benefit of vitamin D in the ICU?" Rice asked. "Yes. Is vitamin D deficient in patients in the ICU? Yes. Is that deficiency associated with poor outcomes? Yes. Can it be replaced safely? Yes."

However, "we're not really sure that it improves outcomes," he said.

A Chronic Issue?

"Do you think it's really an issue of the patients being critically ill with vitamin D," or is it "a chronic issue of having low vitamin D?" asked session moderator Antine Stenbit, MD, PhD, from the UC San Diego School of Medicine.

"We don't know for sure," Rice said. Vitamin D might not have a lot of acute effects; it might have effects that are chronic, that work with levels over a period of time, he explained.

"It's not clear we can correct that with a single dose or with a few days of giving a level that is adequate," he acknowledged.

Rice is an investigator in the PETAL network. Stenbit has disclosed no relevant financial relationships.

CHEST 2020: American College of Chest Physicians Annual Meeting. Presented October 18, 2020.