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More Evidence on Vitamin D and COVID-19 Risk? CME / ABIM MOC / CE

News Author: Megan Brooks; CME Author: Laurie Barclay, MD

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Note: This is the sixty-sixth of a series of clinical briefs on the coronavirus outbreak. The information on this subject is continually evolving. The content within this activity serves as a historical reference to the information that was available at the time of this publication. We continue to add to the collection of activities on this subject as new information becomes available.

Clinical Context

Vitamin D deficiency affects nearly half the US population, with higher rates among persons with darker skin or less sun exposure, including nursing home residents and healthcare workers. Especially in patients with vitamin D deficiency, treatment with vitamin D has been shown to reduce viral respiratory tract infection incidence.

It is still undetermined whether vitamin D status is linked to incidence of COVID-19. The goal of this retrospective cohort study by Meltzer and colleagues at an urban academic medical center was to assess whether the last vitamin D status before COVID-19 testing was associated with COVID-19 test results.

Study Synopsis and Perspective

Persons who are deficient in vitamin D may be at higher risk of contracting COVID-19 than persons with sufficient levels, according to the results of a new retrospective study from Illinois. Individuals with untreated vitamin D deficiency were nearly twice as likely to test positive for COVID-19 relative to their peers with adequate vitamin D levels.

"These findings appear to support a role of vitamin D status in COVID-19 risk," the authors said in the study, published September 3 in *JAMA Network Open*.

"Vitamin D is important to the function of the immune system and vitamin D supplements have previously been shown to lower the risk of viral respiratory tract infections. Our statistical analysis suggests this may be true for the COVID-19 infection," lead author David Meltzer, MD, PhD, chief of hospital medicine at University of Chicago Medicine (UCM), Chicago, Illinois, said in a news release from his institution.

Important for Immune Function

Meltzer and colleagues studied 489 UCM patients (mean age, 49 ±18 years; 75% women) whose vitamin D level was determined in the 2 months before being tested for COVID-19.

They defined vitamin D deficiency as < 20 ng/mL 25-hydroxycholecalciferol (calcifediol) or < 18 pg/mL 1,25-dihydroxycholecalciferol (calcitriol).

Vitamin D status was categorized as likely deficient for 124 participants (25%), likely sufficient for 287 (59%), and uncertain for 78 (16%).

A total of 71 participants (15%) tested positive for COVID-19.

In multivariate analysis, a positive COVID-19 test was significantly more common in persons with likely vitamin D deficiency than in persons with likely sufficient vitamin D levels at the time of COVID testing (relative risk [RR] = 1.77 [95% CI: 1.12, 2.81]; *P* = .02).

The estimated mean rate of COVID-19 in the deficient group was 21.6% compared with 12.2% in the sufficient group.

Testing positive for COVID-19 was also associated with increasing age up to age 50 years (RR = 1.05 [95% CI: 1.01, 1.09] ; *P* = .02) and race other than White (RR = 2.54 [95% CI: 1.26, 5.12]; *P* = .009).

Protective Effect of Treatment?

The findings also raised the possibility that treatment for vitamin D deficiency may lower the risk for COVID-19, the researchers said.

Patients with deficient vitamin D levels who had their vitamin D treatment increased did not appear to have increased risk for COVID-19.

This suggests a "protective effect of treatment, but the confidence intervals on estimated rates for these groups are too wide to exclude the possibility of no treatment effect," Meltzer and colleagues noted.

"If vitamin D does reduce COVID-19 incidence, it is tempting to consider whether it might reduce COVID-19 transmission," they hypothesized.

Because vitamin D strengthens innate immunity, it could be expected to decrease COVID-19 infection and transmission. Vitamin D also affects zinc metabolism, which decreases replication of coronaviruses.

As previously reported by Medscape Medical News, a recent study from Israel suggested low plasma vitamin D levels are an independent risk factor for COVID-19 and hospitalization.

In that study, participants positive for COVID-19 were 50% more likely to have low vs normal vitamin D levels in a multivariate analysis that controlled for other confounders.

Half of Americans are deficient in vitamin D, with much higher rates seen in Blacks, Hispanics, and individuals living in areas such as Chicago, where it is difficult to get enough sun exposure in winter.

"Understanding whether treating vitamin D deficiency changes COVID-19 risk could be of great importance locally, nationally, and globally," Meltzer said. "Vitamin D is inexpensive, generally very safe to take, and can be widely scaled."

Meltzer and colleagues said randomized clinical trials are now needed to see whether broad population interventions and interventions among groups at increased risk for vitamin D deficiency and COVID-19 could reduce COVID-19 cases.

JAMA Netw Open. 2020;3:e2019722.[1]

Study Highlights

- The retrospective cohort for this study at an urban academic medical center included 489 patients with a calcifediol or calcitriol level measured ≤ 1 year before being tested for COVID-19 from March 3 to April 10.
- Mean age was 49.2 ± 18.4 years; 75% were women; and 68% were race other than White.
- Researchers defined vitamin D deficiency by the last calcifediol measurement < 20 ng/mL or calcitriol < 18 pg/mL before COVID-19 testing.
- Changes in vitamin D type and dose between the date of the last vitamin D level measurement and the date of COVID-19 testing defined treatment changes, which were combined with vitamin D deficiency to categorize the most recent vitamin D status before COVID-19 testing.
- Investigators categorized vitamin D status as likely deficient (last level deficient and treatment not increased), likely sufficient (last level not deficient and treatment not decreased), or uncertain deficiency (last level deficient and treatment increased, or last level not deficient and treatment decreased).
- The main study endpoint was a positive COVID-19 polymerase chain reaction test result.
- Researchers examined associations between vitamin D status before COVID-19 testing and positive COVID-19 test with multivariable analysis, with adjustment for demographic and comorbidity factors.
- Overall COVID-19 positivity was 15%.
- Vitamin D status before COVID-19 testing was likely deficient for 124 (25%) participants, likely sufficient for 287 (59%), and uncertain for 78 (16%).
- Positive tests for COVID-19 were associated with increasing age < 50 years (RR = 1.05 [95% CI: 1.01, 1.09]; *P* = .02); non-White race (RR = 2.54 [95% CI: 1.26, 5.12]; *P* = .009), and likely deficient vitamin D status (RR = 1.77 [95% CI: 1.12, 2.81]; *P* = .02) compared with likely sufficient vitamin D status, according to multivariate analysis.
- In the deficient group, predicted rates of COVID-19 were 21.6% (95% CI: 14%, 29.2%) vs 12.2% (95% CI: 8.9%, 15.4%) in the sufficient group.
- According to their findings, the investigators concluded that likely deficient vitamin D status was associated with increased COVID-19 risk, meriting randomized trials to examine whether vitamin D affects COVID-19 risk and whether interventions in the general broad population and in groups at increased risk for vitamin D deficiency could lower COVID-19 incidence.

- Patients with deficient last vitamin D levels who then had increased treatment were not at increased risk for COVID-19 compared with patients with likely sufficient vitamin D status, which may suggest a protective effect of treatment.
- The CIs on estimated rates were too wide, however, to rule out the possibility of no treatment effect.
- Factors supporting population-level supplementation of vitamin D include low costs and general safety, at least at doses < 4000 IU/d.
- In the United States, Black and Hispanic populations have high rates of vitamin D deficiency as well as a disproportionate burden of morbidity and mortality from COVID-19, suggesting that they may be particularly important populations to target in trials of whether vitamin D can lower COVID-19 incidence and burden.
- Vitamin D testing levels may be useful to guide treatments, and the availability of low-cost home testing for vitamin D may improve feasibility of testing, given the need for social distancing during the COVID-19 pandemic.
- Vitamin D might theoretically reduce COVID-19 transmission as well as incidence, as it strengthens innate immunity and affects metabolism of zinc, which reduces coronavirus replication.
- Still, the investigators stressed the need for caution in light of the potential role of asymptomatic persons in COVID-19 spread.
- Vitamin D modulates immune function through effects on dendritic cells and T cells, which may facilitate viral clearance and decrease inflammatory responses that produce symptoms.
- Higher vitamin D levels are associated with lower levels of interleukin 6, which is implicated in COVID-19--related cytokine storm.
- Vitamin D treatment might reduce transmission by preventing infection, decreasing viral replication, and/or accelerating viral clearance.
- Conversely, by reducing inflammation, vitamin D may increase asymptomatic carriage and reduce cough and other symptomatic presentations, hindering prediction of its effect on viral transmission.
- Study limitations include possible confounding by chronic health conditions or behavioral factors that could increase risk for COVID-19 and for vitamin D deficiency and data limited to those available in the UCM electronic health record.
- In addition, only a few study participants received higher doses of vitamin D_3 or had relative high vitamin D levels, limiting the power to determine whether vitamin D dose or levels were associated with the likelihood of COVID-19, and the sample had a high proportion of persons with vitamin D deficiency because of the large number of Blacks, adults with chronic illness, and healthcare workers, all living in a northern city and exposed to COVID-19 during winter.

Clinical Implications

- In a retrospective cohort study by Meltzer and colleagues, likely deficient vitamin D status was associated with increased COVID-19 risk.
- The findings merit randomized trials to examine whether vitamin D affects COVID-19 risk and whether interventions in the general broad population and in groups at increased risk for vitamin D deficiency could lower COVID-19 incidence.
- Implications for the Healthcare Team: Clinicians should continue to encourage vitamin D supplementation for immune health. Factors supporting population-level supplementation of vitamin D include low costs and general safety, at least at doses < 4000 IU/d.

Earn Credit

References

1. Meltzer DO, Best TJ, Zhang H, et al. Association of vitamin D status and other clinical characteristics with COVID-19 test results. *JAMA Netw Open*. 2020;3:e2019722. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770157. Accessed September 4, 2020. Article full text.

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