25-hydroxyvitamin D concentration is key to analyzing vitamin D's effects

The recent Practice Alert by Dr. Campos-Outcalt, "How to proceed when it comes to vitamin D" (*J Fam Pract.* 2021;70:289-292) claimed that the value of vitamin D supplements for prevention is nil or still unknown.[1] Most of the references cited in support of this statement were centered on randomized controlled trials (RCTs) based on vitamin D dose rather than achieved 25-hydroxyvitamin D [25(OH)D] concentration. Since the health effects of vitamin D supplementation are correlated with 25(OH)D concentration, the latter should be used to evaluate the results of vitamin D RCTs—a point I made in my 2018 article on the topic.[2]

There are significant benefits of vitamin D supplementation to achieve a 25(OH)D concentration of 30 to 60 ng/mL for important health outcomes.

For example, in the Vitamin D and Type 2 Diabetes (D2d) Study, in which participants in the treatment arm received 4000 IU/d vitamin D_3, there was no reduced rate of progression from prediabetes to diabetes. However, when 25(OH)D concentrations were analyzed for those in the vitamin D arm during the trial, the risk was found to be reduced by 25% (hazard ratio [HR] = 0.75; 95% CI, 0.68-0.82) per 10 ng/mL increase in 25(OH)D.[3]

Another trial, the Harvard-led VITamin D and OmegA-3 TriaL (VITAL), enrolled more than 25,000 participants, with the treatment arm receiving 2000 IU/d vitamin D_3.[4] There were no significant reductions in incidence of either cancer or cardiovascular disease for the entire group. The mean baseline 25(OH)D concentration for those for whom values were provided was 31 ng/mL (32.2 ng/mL for White participants, 24.9 ng/mL for Black participants). However, there were ~25% reductions in cancer risk among Black participants (who had lower 25(OH)D concentrations than White participants) and those with a body mass index < 25. A posthoc analysis suggested a possible benefit related to the rate of total cancer deaths.

A recent article reported the results of long-term vitamin D supplementation among Veterans Health Administration patients who had an initial 25(OH)D concentration of < 20 ng/mL.[5] For those who were treated with vitamin D and achieved a 25(OH)D concentration of > 30 ng/mL (compared to those who were untreated and had an average concentration of < 20 ng/mL), the risk of myocardial infarction was 27% lower (HR = 0.73; 95% CI, 0.55-0.96) and the risk of all-cause mortality was reduced by 39% (HR = 0.61; 95% CI, 0.56-0.67).

An analysis of SARS-CoV-2 positivity examined data for more than 190,000 patients in the United States who had serum 25(OH)D concentration measurements taken up to 1 year prior to their SARS-CoV-2 test. Positivity rates were 12.5% (95% CI, 12.2%-12.8%) for those with a 25(OH)D concentration < 20 ng/mL vs 5.9% (95% CI, 5.5%-6.4%) for those with a 25(OH)D concentration ≥ 55 ng/mL.[6]

Thus, there are significant benefits of vitamin D supplementation to achieve a 25(OH)D concentration of 30 to 60 ng/mL for important health outcomes.

William B. Grant, PhD
San Francisco, CA

Dr. Grant is the director of the Sunlight, Nutrition, and Health Research Center, which seeks to "do research on and provide information on the prevention of chronic disease through lifestyle and dietary choices." The Center receives funding from Bio-Tech Pharmacal, Inc, a dietary supplements manufacturer.

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Author's response

I appreciate the letter from Dr. Grant in response to my previous Practice Alert, as it provides an opportunity to make some important points about assessment of scientific evidence and drawing conclusions based on sound methodology. There is an overabundance of scientific literature published, much of which is of questionable quality, meaning a "study" or 2 can be found to support any preconceived point of view.

In 2011, the Institute of Medicine (now the National Academy of Medicine) published a series of recommendations on how trustworthy recommendations and guidelines should be produced.[1,2] Key among the steps recommended is a full assessment of the totality of the literature on the subject by an independent, nonconflicted panel. This should be based on a systematic review that includes standard search methods to find all pertinent articles, an assessment of the quality of each study using standardized tools, and an overall assessment of the quality of the evidence. A high-quality systematic review meeting these standards was the basis for my review article on vitamin D.[3]

To challenge the findings of the unproven benefits of vitamin D, Dr. Grant cited 4 studies to support the purported benefit of achieving a specific serum 25(OH)D level to prevent cardiovascular disease, diabetes, cancer, and COVID-19. After reading these studies, I would not consider any of them a "game changer."

The first study was restricted to those with prediabetes, had limited follow-up (mean of 2.5 years), and found different results for those with the same 25(OH)D concentrations in the placebo and treatment groups.[4] The second study was a large, well-conducted clinical trial that found no benefit of vitamin D supplementation in preventing cancer and cardiovascular disease.[5] While Dr. Grant claims that benefits were found for some subgroups, I could locate only the statistics on cancer incidence in Black participants, and the confidence intervals showed no statistically significant benefit. It is always questionable to look at multiple outcomes in multiple subgroups without a prior hypothesis because of the likely occurrence of chance findings in so many comparisons. The third was a retrospective observational study with all the potential biases and challenges to validity that such studies present.[6] A single study, especially 1 with observational methods, almost never conclusively settles a point.

The role of vitamin D in the prevention or treatment of COVID-19 is an aspect that was not covered in the systematic review by the US Preventive Services Task Force. The study on this issue cited by Dr. Grant was a large retrospective observational study that found an inverse relationship between serum 25(OH)D levels and SARS-CoV-2 positivity rates.[7] This is 1 observational study with interesting results. However, I believe the conclusion of the National Institutes of Health is currently still the correct one: "There is insufficient evidence to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19."[8]

With time and further research, Dr. Grant may eventually prove to be correct on specific points. However, when challenging a high-quality systematic review, one must assess the quality of the studies used while also placing them in context of the totality of the literature.

Doug Campos-Outcalt, MD, MPA
Phoenix, AZ

A "study" or 2 can be found to support any preconceived point of view.

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