Does Inconclusive Evidence for Vitamin D Supplementation to Reduce Risk for Cardiovascular Disease Warrant Pessimism?

TO THE EDITOR: In clinical trials of pharmaceutical agents, all participants start with the same serum level of the intervention: zero. In contrast, participants in clinical trials of nutritional agents, such as vitamin D, start with wildly varying levels.

This distinction is crucial. Far too many clinical trials of nutritional interventions report neither baseline nor ending serum levels, which is a significant type II error in nutritional research. Nutritional interventions can be administered with too small of a dose or for an insufficient period. In addition, without measurement of serum levels, there is no clear means of assessing adherence or absorption. These criticisms are certainly true for the 2 cardiovascular studies (1, 2) discussed by Guallar and colleagues (3) in their editorial.

Assessment of validity and generalizability of randomized, controlled trials (RCTs) of nutrients should be based on the achievement of a prestated serum level rather than the results of a potentially insufficient period. In addition, without measurement of serum levels, there is no clear means of assessing adherence or absorption. These criticisms are certainly true for the 2 cardiovascular studies (1, 2) discussed by Guallar and colleagues (3) in their editorial.

Keyword, or sought it explicitly in their titles, highlights why authors of systematic reviews need to have up-to-date content knowledge of the subject that they are reviewing.

Potential Conflicts of Interest: None disclosed.

References

TO THE EDITOR: I was very disappointed to find, in the world’s leading journal of internal medicine, 2 poorly conceived systematic reviews of vitamin D’s effects on the cardiovascular system (1, 2), accompanied by a largely supportive editorial (3). All 3 exhibit a limited awareness of vitamin D physiology. For example, the review by Wang and colleagues (1) identified 6 prospective studies, only 1 of which used actual vitamin D (cholecalciferol). The others all used various 1-hydroxylated derivatives. Nor did the editorial, citing those 6 studies, pick up this critical distinction. Presumably, the authors of the 6 studies used 1,25-dihydroxy vitamin D [1,25(OH)2D] (calcitriol) because it is the ultimate, active form of the vitamin. That use, in hindsight, is understandable, even if now it is recognized to be inappropriate. However, the authors of the systematic reviews should have been aware of the current biology and excluded these studies. That the authors of the reviews used the term “vitamin D” as a keyword, or sought it explicitly in their titles, highlights why authors of systematic reviews need to have up-to-date content knowledge of the subject that they are reviewing.

A very large body of literature, published over the past 10 years, makes clear that the noncalcium effects of vitamin D are autocrine (4), not endocrine, and that the 1-hydroxylated form is synthesized intracellularly by target tissues and is not derived from circulating calcitriol (5). Available evidence indicates that the concentration of calcitriol required to produce these noncalcium effects is higher than can be safely achieved through mediation of serum calcitriol (5). Instead, serum 25-hydroxyvitamin D [25(OH)D] is present in 1000-fold greater concentration than calcitriol and provides the substrate for cells to manufacture such calcitriol as they need, confined to the target tissues. But that works only as long as serum 25(OH)D levels are themselves adequate. Therefore, sufficient cholecalciferol input is critically important. Pittas and colleagues (2) hedge their conclusion with the qualifier “the dosages used,” which it turns out were small. Both the editorial and the review by Wang and colleagues refer to doses of 700 to 1000 IU/d as “high.” True, 700 to 800 IU is above the 1997 adequate intake for vitamin D, but more than 95% of what is currently known about vitamin D has been published since those 1997 recommendations. It is now clear that outdoor summer workers commonly have serum 25(OH)D values between 120 and 200 nmol/L, and that this may well be the primitive human level, based on values found in agricultural workers in the tropics (6). Both controlled dosing studies (7) and extensive experience in recent years have established that serum 25(OH)D levels increase by about 0.6 to 1.0 nmol/L per µg of cholecalciferol daily (or 1.5 to 2.5 nmol/L per 100 IU of cholecalciferol daily).

Thus, serum levels of 80 nmol/L require continuous inputs from all sources on the order of 4000 IU/d, and levels of 100 nmol/L require continuous inputs of 5000 IU/d. Not only are such doses not high, they are physiologic, because they occur in healthy persons under conditions approximating those of our ancestors. Finally, the editorial raises a note of caution by comparing these reviews with trials of carotene. Although moving participants from normal to high levels of vitamin A may well produce harm, that is quite different from moving participants from low to physiologic levels of vitamin D. In brief, the systematic reviews were largely noninformative, and the cautionary note struck by the editorial has essentially no basis in the evidence.

Robert P. Heaney, MD
Creighton University
Omaha, NE 68178

Potential Conflicts of Interest: None disclosed.

References

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TO THE EDITOR: The editorial by Guallar and colleagues (1) on vitamin D supplementation is unduly pessimistic regarding the benefits. The review by Pitas and colleagues (2), which formed the basis of the editorial, investigated cardiometabolic outcomes as a function of serum 25(OH)D. It reported a significant inverse correlation between serum 25(OH)D level and cardiovascular disease (CVD), in agreement with another article (3), which also found significant inverse correlations for the metabolic syndrome and diabetes mellitus.

The review by Wang and colleagues (4) reported a statistically nonsignificant reduction in risk for CVD (pooled relative risk, 0.90 [95% CI, 0.77 to 1.05]) with vitamin D supplementation at moderate to high doses (approximately 1000 IU/d). The main problems with RCTs of vitamin D are that solar ultraviolet-B irradiance contributes to serum 25(OH)D levels (5); many participants in RCTs have additional oral intake (6); and the response of serum 25(OH)D levels to oral dosing varies with genetics, body mass index, and dietary factors. In addition, many earlier RCTs used too little vitamin D to have a significant effect.

Some important RCTs were not included by Guallar and colleagues. One RCT showing significant benefits for influenza A and asthma (6) was published after the editorial but seems representative of well-conducted trials. The only RCT that studied the effect of vitamin D dosages greater than 1000 IU/d on cancer (7) found a 40% reduced risk for cancer between the ends of the first and fourth years.

It is undeniable that oral vitamin D raises serum 25(OH)D levels. Meta-analyses of observational studies are considered just slightly lower evidence than RCTs. On the basis of the relationship between serum 25(OH)D level and disease outcomes for cancer, CVD, influenza, falls, and sepsis from meta-analyses of observational studies and RCTs, an estimated 400,000 premature deaths per year could be avoided if all Americans raised their serum 25(OH)D levels to 45 ng/mL. This would reduce the mortality rate by 15% and extend life expectancy by about 2 years. The adverse effects of higher oral vitamin D are minimal, mainly affecting persons with specific preexisting conditions.

Comparing vitamin D with β-carotene and vitamin E is dubious, because only vitamin D is based on robust observational studies and is associated with manifest genetic differences with respect to natural availability and skin pigmentation.

William B. Grant, PhD
Sunlight, Nutrition, and Health Research Center
San Francisco, CA 94164-1603


References

IN RESPONSE: We appreciate the opinions and comments on our editorial. All 3 letters question whether the inconclusive evidence for vitamin D supplementation to reduce risk for CVD, which was reported in the 2 accompanying meta-analyses (1, 2), justifies our cautionary note against supplementation.

We agree with Dr. Plotnikoff that clinical trials of nutritional agents need to assess baseline (preintervention) levels of study nutrients to interpret trial results, evaluate their generalizability, and design targeted nutritional interventions. However, for interventions aimed at wide segments of the population that may be administered without screening of nutrient levels (for instance, through food fortification), it is also important to include participants with a wide range of nutrient levels in randomized trials to understand the full range of effects in the general population.

Dr. Heaney and Dr. Grant believe that mechanistic data, evolutionary arguments, and observational studies are sufficient to infer the safety and efficacy of vitamin D supplementation when applied to large segments of the population. On the basis of experience, we believe that this approach tends to overestimate the efficacy and underestimate the potential harm of nutritional interventions. Interventions that may affect tens of millions of persons need to be properly tested in large, high-quality RCTs. These trials should provide precise information on the effects of vitamin D supplementation on total mortality and on CVD incidence, 2 end points of unquestionable clinical and public health relevance. Large-scale supplementation programs should be considered only after this information is available. In the meantime, the cost-effectiveness of vitamin D supplementation in the general population is uncertain.

Eliseo Guallar, MD, DrPH
Edgar R. Miller III, MD, PhD
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD 21205

Jose M. Ordovas, PhD
Tufts University
Boston, MA 02111

Letters
Saverio Stranges, MD, PhD
University of Warwick Medical School
Coventry CV4 7AL, United Kingdom

Potential Conflicts of Interest: None disclosed.

References

Misleading Statement in Trial on False-Positive Results in Lung Cancer Screening

TO THE EDITOR: The introduction to the article by Croswell and colleagues (1) on false-positive results in lung cancer screening acknowledges the increasing public attention and political advocacy for lung cancer screening in recent years. It then says that “surveys of U.S. community physicians . . . found that two thirds of family practitioners, internists, and gynecologists and 82% of general surgeons recommended chest radiography for lung cancer screening every 1 to 2 years” (1). I believe this statement is misleading.

The reference cited is a 1994 study (2) in which physicians were surveyed by telephone or mail between October 1989 and March 1990. The survey asked participants how often they would recommend specific screening tests for breast, colon, cervical, and lung cancer, offering options of “every 6 months or less,” “every 7 to 11 months,” “every 12 months,” and so on. Thus, the survey did not ascertain actual practice, but what the clinicians believed the guidelines at that time would recommend; it did not offer an option of “no screening recommended;” and, even if responses were consistent with practice, it would reflect opinion and practice from 20 years ago.

Citing these data in the article might suggest to readers that they are outliers by not routinely ordering lung cancer screening. Croswell and colleagues make a cogent argument for why such screening might lead to psychological and physical harm from false-positive computed tomography findings.

H. Nancy Sokol, MD
Harvard Medical School
Boston, MA 02115

Potential Conflicts of Interest: None disclosed.

References

IN RESPONSE: Dr. Sokol expresses concern over our citation of a 1994 study (1) that attempted to gain a better understanding of the cancer screening preferences of community physicians. Although the title of the article is “Preferences of Community Physicians for Cancer Screening Guidelines,” the survey directly asked about individual practice patterns and not simply “what the clinicians thought the guidelines at that time would recommend.” The specific question posed for each screening modality was not, “What do guidelines say you should do regarding screening for this cancer?” but rather, “How often would you recommend screening by a physician for an individual who has no known risk factor for that cancer type?” Of note, for lung cancer, no professional society at that time recommended the use of chest radiography as a screening test in asymptomatic persons. Despite this, 70% of physicians polled across multiple specialties agreed that it should be performed annually or every 1 to 2 years. This is a striking departure from guidelines and points to a clear discrepancy between national recommendations and community practices. Furthermore, although the survey did not explicitly offer a “no screening recommended” option, it did have an option for “other interval/specify,” in which an individual could respond with “never.” Because the authors of the study point out that internists and gynecologists were less likely to “ever recommend chest radiography for patients at normal risk” compared with other specialties, this clearly did occur.

Dr. Sokol also points out that the data published in 1994 may not accurately reflect current opinions or practice. This highlights the challenge we faced in finding reliable estimates of the frequency of lung cancer screening in the United States. As noted in the article, to our knowledge it is not possible to accurately assess true patterns of use, a deficiency that we hope will be rectified with future research. It was most certainly not our intention to suggest that physicians who do not routinely utilize chest radiography or computed tomography for lung cancer screening are “outliers” in any way, given that, as in 1994, no professional society guidelines recommend such testing. Because of the known harms and currently theoretical benefits of lung cancer screening, it is essential to await the results of ongoing randomized, controlled trials to better assess ultimate utility before continuing to promote such programs to the general public.

Jennifer M. Croswell, MD, MPH
Barnett S. Kramer, MD, MPH
National Institutes of Health
Bethesda, MD 20892

Potential Conflicts of Interest: None disclosed.

Reference

Herpes Zoster Vaccine in Nursing Facility Residents: Safety Questions Remain

TO THE EDITOR: In the SPS (Shingles Prevention Study) safety analysis, Simberkoff and colleagues (1) concluded that “herpes zoster vaccine was well tolerated and safe in older immunocompetent adults,” which supports recommendations for routine use. We are concerned that these published recommendations and product labeling specifically include nursing facility residents (2, 3). The SPS did
not include participants who were immunocompromised, had significant cognitive impairment, were nonambulatory, or had limited life expectancy. In fact, overall mortality in SPS participants was less than half of what would be expected in the general population.

Simberkoff and colleagues do not clarify the many safety concerns for nursing facility residents (1). Zostavax (Merck & Co., Whitehouse Station, New Jersey) includes live attenuated virus. In such facilities, contact is likely between vaccinated and unvaccinated residents, some of whom might have nonintact skin, immunosuppression, or other contraindications to vaccination. Although transmission of the herpes zoster vaccine was not detected in the SPS, product labeling states that “transmission of vaccine virus may occur rarely between vaccinees and susceptible contacts” (3), raising concerns about cross-transmission. Given their prognosis, some nursing facility residents without known contraindications will probably be vaccinated only to develop a contraindication immediately afterward, possibly increasing adverse events. Also, immunocompromised elderly persons may be more likely to develop localized reactions, leading to systemic inflammatory responses and resultant vascular inflammation. This was a concern in the SPS: Transient varicella-like rash occurred at the inoculation site in 0.11% of recipients versus 0.04% of control participants, and acute vascular pathology (myocardial infarction, stroke) occurred in 17 recipients (0.52%) versus 9 control participants (0.27%) (P = 0.104) (1).

This concern may seem far-fetched, but it is worthy of consideration in older residents of nursing facilities, who are already at increased risk for infection and vascular events. More than half of nursing facility residents is aged 85 years or older. Vaccine efficacy against herpes zoster decreases with increasing age, decreasing from 64% in persons aged 60 to 69 years to 18% in those aged 80 to 84 years and to only 12% in those aged 85 years or older, although efficacy against postherpetic neuralgia may be better maintained (4).

We are enthusiastic about herpes zoster vaccine, but we recognize that nursing facility residents are heterogeneous. We do not formally recommend routine use of the herpes zoster vaccine as part of the American Medical Directors Association’s immunization program guidelines (5) because of questions on safety and efficacy. Potential vaccine benefit in an individual resident requires careful assessment of immune competency based on comorbid conditions, age, nutrition, and prognosis. We would appreciate further insights from the authors and the Advisory Committee on Immunization Practices to help optimize patient selection and monitoring. We hope that public health officials will actively monitor vaccine safety and efficacy in nursing facilities.

David A. Nace, MD, MPH
University of Pittsburgh Institute on Aging
Pittsburgh, PA 15213

Paul J. Drinka, MD
University of Wisconsin—Madison
Madison, WI 53703

Christopher J. Crnich, MD, MS
University of Wisconsin School of Medicine and Public Health
Madison, WI 53705

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References

IN RESPONSE: Dr. Nace and colleagues raise questions that were not specifically addressed in the SPS (1). We agree that most nursing facility populations are heterogeneous and may include persons with recognized or unrecognized immunosuppression. Although the herpes zoster vaccine is safe for most nursing facility residents, decisions to administer it should be individualized, in accordance with the recommendations of the Advisory Committee on Immunization Practices (2). However, we believe that herpes zoster vaccine can be safely administered to most nursing facility residents for several reasons.

First, the vaccine is remarkably safe. As we reported, local side effects after administration to a large population of older adults were mild and transient; serious adverse events, including hospitalizations and death, occurred with equal frequency in persons receiving vaccine and placebo. A few volunteers received herpes zoster vaccine before their protocol-disqualifying conditions were recognized. These included 3 participants who had recently received immunosuppressive therapy and 2 participants with active neoplastic disease. None reported any serious adverse events related to vaccination. Furthermore, Weinberg and colleagues (3) reported that the less potent Oka/Merck varicella vaccine (Merck & Co., Whitehouse Station, New Jersey) was well tolerated and immunogenic in adults with HIV-1 who had low or undetectable HIV viral loads and CD4 cell counts.

Second, the risk for transmitting the attenuated vaccine virus from recipients of herpes zoster vaccine to unvaccinated contacts is very small. Despite a theoretical risk for transmission from the transient rash that can occur at the injection site, such spread occurs rarely, if ever. No transmissions of the attenuated vaccine virus to household or other contacts were reported by recipients of herpes zoster vaccine in the SPS, and no cases of vaccine virus transmission after administration have been documented in the literature. Finally, use of the attenuated herpes zoster vaccine in most nursing facility residents should reduce the occurrence of herpes zoster and thus exposure to wild-type varicella zoster virus in this closed community. Some nursing facility residents (and staff) may not have had varicella and thus may lack acquired immunity to varicella zoster virus, particularly persons born and raised in tropical climates outside of the United States, where acquisition of varicella is delayed. Exposure of such persons to wild-type varicella zoster virus, especially if they are immunosuppressed, could result in a life-threatening, disseminated
infection. Administration of herpes zoster vaccine to most nursing facility residents will reduce their risk for herpes zoster (1) and thus provide a measure of herd immunity to those who have an absolute contraindication to vaccination.

Michael S. Simberkoff, MD
Veterans Affairs New York Harbor Healthcare System
New York, NY 10010

Robert D. Arbeit, MD
Tufts Medical Center
Boston, MA 02111

Gary Johnson, MS
Veterans Affairs Connecticut Healthcare System
West Haven, CT 06516

Michael N. Oxman, MD
Veterans Affairs Medical Center
San Diego, CA 92161

For the Shingles Prevention Study Group

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References


CORRECTION

Correction: The Social Mission of Medical Education

In the recent article by Mullan and colleagues (1), several institutions were named incorrectly. Morehouse College should be listed as Morehouse School of Medicine. Baylor University should be listed as Baylor College of Medicine. Michigan State University should be listed as Michigan State University College of Human Medicine. University of Medicine and Dentistry of New Jersey should be listed as University of Medicine and Dentistry of New Jersey—NJ. Association of American Colleges of Osteopathic Medicine should be listed as American Association of Colleges of Osteopathic Medicine. University at Albany, State University of New York should be listed as Albany Medical College.

Reference