COMMENTS AND RESPONSES

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 suboptimum one-size-fits-all intervention.

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Potential Conflicts of Interest: None disclosed.

References

1. Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med. 2010;152:315-23. [PMID: 20194238]

2. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, et al. Systematic review: vitamin D and cardiometabolic outcomes. Ann Intern Med. 2010;152:307-14. [PMID: 20194237]

3. Guallar E, Miller ER 3rd, Ordovas JM, Stranges S. Vitamin D supplementation in the age of lost innocence [Editorial]. Ann Intern Med. 2010;152:327-9. [PMID: 20194240]

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 as much 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.

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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 Pittas 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 septicemia 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 disingenuous, 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.

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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.

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