

VIEWPOINT

Vitamin D Research and Clinical Practice At a Crossroads

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Long recognized as important for bone health, vitamin D has attracted recent interest for its possible non-skeletal benefits. Many primary care clinicians now include blood tests to measure vitamin D concentrations as part of routine laboratory work¹ and recommend vitamin D supplements, often at high doses, to their patients for the possible prevention of cancer, cardiovascular disease (CVD), diabetes, autoimmune disorders, cognitive decline, and other conditions. Thus, screening rates and sales of vitamin D supplements have increased substantially in recent years.^{1,2}

However, clinical enthusiasm for supplemental vitamin D has outpaced available evidence on its effectiveness and threatens to jeopardize the ability of researchers to conduct randomized trials in "usual-risk" populations. Based on its recent systematic reviews of the literature, the US Preventive Services Task Force (USPSTF) concluded that data are insufficient to recommend vitamin D screening in routine clinical practice¹ or to assess the effectiveness and overall balance of benefits and risks of supplemental vitamin D taken for the primary prevention of cancer and CVD.³ In an earlier review, the Institute of Medicine (IOM) reached the same conclusion—namely, whether supplemental vitamin D lowers risk of nonskeletal health outcomes, and what dose might be required to do so, is uncertain.⁴

Given the lack of convincing evidence for nonbone benefits of vitamin D, the IOM set the recommended dietary allowance (RDA) for vitamin D based on the amount required for skeletal health: 600 IU per day for persons aged 1 to 70 years and 800 IU per day for those 71 years and older. This is equivalent to 3 to 4 daily servings of fortified foods such as milk, yogurt, soy beverages, orange juice, or cereal, plus fatty fish twice per week. These amounts are adequate for at least 97.5% of US and Canadian residents, including those living in the north during the winter, and correspond to a total 25-hydroxyvitamin D (25[OH]D) serum concentration of approximately 20 ng/mL (to convert to nmol/L, multiply by 2.496). Many laboratories consider a level of 30 or 40 ng/mL to be "optimal," but the IOM found little research to support this claim. The IOM's report challenges the notion that a majority of US adults are vitamin D deficient and does not endorse universal 25(OH)D testing. Even though there is dissent from some individual experts,⁵ no major medical organization endorses population-wide screening for low vitamin D. Moreover, in addition to the lack of consensus on the definition of optimal 25(OH)D concentrations, emerging evidence suggests that "bioavailable" and "free" 25(OH)D may be more physiologically relevant indicators of vitamin D status than total 25(OH)D.¹ Although these findings cast further doubt on the utility of wide-

spread 25(OH)D testing, they do not negate the importance of targeted vitamin D assessment and therapeutic intervention for patients with risk factors for, or clinical conditions associated with, vitamin D insufficiency, such as malabsorption or osteoporosis.

That vitamin D might confer benefits beyond bone health was first suggested by ecologic studies showing lower cancer and cardiovascular mortality in regions with greater exposure to solar UV-B radiation (associated with greater cutaneous synthesis of vitamin D). Laboratory investigations subsequently confirmed the existence of plausible mechanisms of vitamin D action in pathways relevant to CVD, cancer, and other chronic diseases, as well as the expression of the vitamin D receptor and 1 α -hydroxylase in many tissues.^{4,6} Observational studies also provide some support for nonskeletal benefits, with associations between low intakes or serum levels of vitamin D and increased risk for CVD, cancer, diabetes, and other nonskeletal diseases in some cohorts. However, the observational data are inconsistent and are susceptible to confounding and other biases that preclude their use for establishing causality.^{4,6} Major confounders include outdoor physical activity (which correlates with sun exposure), adiposity (which decreases 25[OH]D bioavailability), and overall nutritional status. These factors may act singly or in combination to yield spurious protective effects for vitamin D, whereas null findings may result from vitamin D intakes that are too low to yield significant benefits. Of note, a U-shaped relation has been found in several cohorts, with elevated risk for adverse outcomes—including CVD and all-cause mortality—observed at not only low but also at high levels (≥ 50 -60 ng/mL of 25[OH]D).⁴ These findings suggest that, although moderate doses of vitamin D may be beneficial, more is not necessarily better—and may be worse.

Well-designed randomized clinical trials overcome biases inherent to observational studies and are necessary to establish the long-term consequences of taking high-dose supplemental vitamin D. However, most vitamin D trials completed to date have been of modest size and have focused on bone-related outcomes; when cancer, CVD, or other nonskeletal end points have been examined, analyses have often been underpowered, post hoc, and without rigorous end point adjudication. It is perhaps not surprising that such trials have yielded mostly null results. To fill the knowledge gap, several large-scale, general-population vitamin D supplementation trials with cancer, CVD, or total mortality as primary prespecified end points have been launched in the past 5 years and are under way (Table). In aggregate, these trials are expected to enroll close to 100 000 par-

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Table. Ongoing Large-Scale Randomized Trials (N ≥ 10 000 Participants) of Vitamin D Supplementation Worldwide^a

Trial, Location	Sample Size ^b	Age Range, y	Treatment Duration, y	Vitamin D Intervention	Primary End Points	Trial Registry No.
Vitamin D and Omega-3 Trial (VITAL), United States	25 874	≥50 for men; ≥55 for women	5	2000 IU/d (oral)	Cancer, CVD	NCT01169259
D-Health, Australia	20 000	60-84	5	60 000 IU/mo (oral)	Total mortality, cancer	ACTRN12613000743763
Finnish Vitamin D trial (FIND), Finland	18 000	≥60 for men; ≥65 for women	5	1600 IU/d or 3200 IU/d (oral)	Cancer, CVD	NCT01463813
Vitamin D and Longevity (VIDAL), United Kingdom ^c	20 000	65-84	5	100 000 IU/mo (oral)	Total mortality, cancer	ISRCTN46328341

Abbreviations: CVD, cardiovascular disease.

^bVITAL has completed recruitment; enrollment for other trials is in progress.

^a Several moderate-sized randomized trials (2000-10 000 participants) also are in progress in the United States and worldwide.

^c In pilot phase.

participants in the United States, Europe, and Australia. Their eventual results, the first of which are expected to be available in late 2017, should allow a definitive determination of whether high-dose vitamin D offers a more favorable balance of benefits and risks than vitamin D taken at the current RDA. However, these trials will be informative only if the results are not diluted by widespread out-of-study prescription and use of high-dose vitamin D supplementation in the enrolled populations. Primary care physicians who routinely screen for 25(OH)D and prescribe high-dose supplements in the absence of a clear clinical indication may reduce differences in intakes between study groups, jeopardizing the opportunity for the trials to yield informative results.

The medical community's past experience with several other nutritional interventions should raise a note of caution regarding high-dose supplementation. Many times in recent decades, promising preliminary findings were not confirmed when rigorously tested in randomized trials. Large trials of other widely used supplements have sometimes found benefits, but in other cases—such as with high doses of beta carotene, vitamin E, and selenium—have disproven some health claims for these supplements and identified health risks that may not have otherwise been detected.^{3,4,6}

Skepticism regarding the value of high-dose vitamin D supplementation is increasing in the research literature. One group of investigators has asserted the "futility" of conducting additional randomized trials, arguing that recent meta-analyses of completed randomized trials have proven that supplemental vitamin D is largely ineffective for disease prevention and that future trials are "unlikely to...substantially alter" these conclusions.⁷ Although this assertion could be challenged (because of the aforementioned limitations of available randomized trial data), this viewpoint—considered in juxtaposition with that of the IOM and other influential authorities that more trials "are desperately needed"⁸—highlights the lack of scientific consensus on vitamin D.

When there is uncertainty about whether supplementation is warranted, the usual medical principle is to err on the side of caution and to avoid excess. Thus, while awaiting the results of the large trials now in progress, physicians would be well advised to follow current USPSTF and IOM recommendations and avoid overscreening and overprescribing supplemental vitamin D. Doing so is not only in the best interest of current patients but will also help advance knowledge to benefit future patients and inform future public health recommendations.

ARTICLE INFORMATION

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