REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Questions About Vitamin D for Primary Care Practice: Input From an NIH Conference

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ABSTRACT

There is considerable consumer and physician interest in vitamin D as a possible therapeutic agent for a range of clinical conditions and, despite mixed evidence, the interest does not appear to lessen. Some clinicians believe that consumption of vitamin D is inadequate and, in turn, advocate vitamin D supplementation to increase serum levels of the nutrient. However, evidence concerning the role of vitamin D in health and disease is conflicting, and primary care physicians have little time to sort through the data and may find it difficult to advise their patients. To better understand the challenges that primary care physicians face regarding vitamin D, and to help inform those who provide guidance for clinical decision-making, the Office of Dietary Supplements at the National Institutes of Health, with co-sponsorship from other federal health agencies, held a conference titled *Vitamin D: Moving Toward Evidence-based Decision Making in Primary Care* in December 2014. More than 20 invited presenters and panelists considered laboratory methods for measuring vitamin D status, discussed how clinical studies of vitamin D should be evaluated and used in developing recommendations, noted the role of values and preferences in clinical decision-making, debated the current science related to at-risk groups, and described emerging data about health risks of excessive intakes of vitamin D. Eight questions about vitamin D stem from the Conference presentations as well as other expert sources.

Published by Elsevier Inc. • The American Journal of Medicine (2015) 128, 1167-1170

KEYWORDS: 25-hydroxyvitamin D; 25(OH)D; Laboratory testing; Screening; Supplementation; Vitamin D; Vitamin D status

The following eight questions were developed based on discussions that took place during the conference titled *Vitamin D: Moving Toward Evidence-based Decision Making in Primary Care*.[1]

WHAT IS THE EVIDENCE FOR VITAMIN D HEALTH BENEFITS?

- There is widespread agreement that vitamin D promotes bone health and, together with calcium, helps to protect older adults from bone loss. Also, there appears to be benefit from vitamin D supplementation to prevent falls in the frail elderly who are at risk for vitamin D deficiency. Whether vitamin D supplementation offers the same benefit in healthy, well-nourished older individuals is unclear.
- Beyond bone health and possibly fall prevention, research during the last 15 years has provided tantalizing and well-publicized suggestions that adequate vitamin D status might provide other benefits including reduced risk for cardiovascular disease, cancer, diabetes, autoimmune diseases, and infectious respiratory diseases.
  - Most of the research linking vitamin D to non-bone-health outcomes stems from observational studies, which identify associations, rather than randomized controlled trials. Observational studies are poor guides for therapeutic interventions because of uncontrolled confounding.
  - Several large trials are in progress to investigate the effects of vitamin D supplementation on outcomes such

Funding: See last page of article.
Conflict of Interest: See last page of article.
Authorship: See last page of article.

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0002-9343/$ -see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.amjmed.2015.05.025

as cancer and cardiovascular disease. Results from these studies will not be available for several years, but they will help to clarify whether or not vitamin D is beneficial in ways other than bone health.[2]

- Some contend that promoting vitamin D even in the absence of data from clinical trials is a public-health good consistent with clinical judgment, while others believe that clinicians acting ahead of the science risk losing the confidence of patients should future research dispute the conclusions about vitamin D from observational data. Prior enthusiasm for high-dose nutritional therapies based on observational studies of vitamin E, beta-carotene, and selenium waned when clinical trials demonstrated not only lack of benefit, but potential harms.

CLINICAL SIGNIFICANCE

- Despite physician and patient interest in vitamin D, its role in health and disease beyond bone is conflicting, and guidance for clinical decision-making is needed.
- Serum 25-hydroxyvitamin D [25(OH)D] is the best indicator of vitamin D status, but disagreement exists about concentrations associated with health and whether 25(OH)D is a surrogate for health outcomes of interest.
- This review provides information focused on 8 questions a physician may ask about vitamin D.

WHAT DO SERUM MEASURES TELL US ABOUT VITAMIN D STATUS?

- Serum concentration of 25-hydroxyvitamin D [25(OH)D]—the major and most stable circulating form of the vitamin—is the best available indicator of vitamin D status.
  - Serum 25(OH)D reflects the total supply of vitamin D to the body from all sources: food, dietary supplements, and sun exposure.
- There is disagreement about 25(OH)D concentrations associated with health, or whether 25(OH)D can serve as a surrogate for health outcomes of interest.
  - Different vitamin D experts suggest concentrations that range from 16-20 ng/mL (40-50 nmol/L)[3] to 30 ng/mL (75 nmol/L),[4] and a search of Internet sites finds recommendations of 50 ng/mL (125 nmol/L) or more.
    - The Institute of Medicine concluded that 20 ng/mL serum 25(OH)D is the top end of the requirement for a serum vitamin D level in almost all (97.5%) of the general population, and that many individuals have requirements that are satisfied at levels <20 ng/mL.[3] The Endocrine Society agreed with the Institute of Medicine conclusions for the general population, but not for those "at risk" such as older adults, pregnant women, and dark-skinned individuals, for whom they recommended 30 ng/mL.[4]
    - The Institute of Medicine has suggested that most individuals do not need more than 600-800 IU vitamin D per day. The Endocrine Society indicated that in order to ensure its suggested serum concentrations of 30 ng/mL or higher, vitamin D intakes should be 1000-2000 IU per day.
  - The majority of Americans have serum 25(OH)D concentrations above 20 ng/mL but not above 30 ng/mL.[3]
- Furthermore, newer understandings about genetic differences in population groups may affect our assessment about the vitamin D status of these groups when 25(OH)D is the measure of status.
  - For example, total serum 25(OH)D levels are systematically lower in African Americans, yet they experience notably better bone health. Recent studies have found that African Americans, despite having lower total 25(OH)D levels, have levels of free 25(OH)D [ie, 25(OH)D is not bound to the circulating protein and is "bioavailable"] similar to Caucasians. Because the free form of the substance is likely the form used by cells, African Americans may not be at greater risk of deficiency, as had been assumed in the past. Others are concerned about the laboratory assay used to measure both free 25(OH)D and the vitamin D binding protein. These issues must be resolved before conclusions can be drawn about the relative vitamin D status of African Americans.
  - Obese individuals tend to have lower serum 25(OH)D levels compared with those of normal weight. The reason(s) for this difference (eg, increased clearance from circulation, volume dispersion, or greater sequestration into adipose tissue) have not been elucidated, nor are its health consequences, if any, understood.

WHY DO SO MANY LABORATORY REPORTS INDICATE A DEFICIENCY?

- With no agreed-upon serum 25(OH)D level linked to vitamin D benefits, medical laboratories often establish cut-points based on their interpretation of the current literature.
  - These cut-points can vary greatly or change over time.
  - Clearly, the higher the cut-points selected by the laboratory, the more people are classified as deficient.
  - An apparent increase in the prevalence of vitamin D deficiency is explained by the use of high cut-points.
  - Some laboratories use a reference range from "low" to "high," and bracket the low end of the range by using a reference value established by the Institute of Medicine as the highest need (97.5%), and using as the top end of the range the reference value that demarcates the point at which the risk for harm from excess levels begins to increase (Upper Level). Clinicians can be misled by this

reporting method because by definition, the low end of the range is adequate for virtually all individuals.
- Despite the debates and related measurement issues, serum 25(OH)D concentrations below 12 ng/mL are universally associated with deficiencies and should trigger treatment. Likely candidates for low serum 25(OH)D concentrations are the frail institutionalized elderly, because their diets may be poor and they often lack exposure to the sun.

ARE LABORATORY TESTS FOR VITAMIN D STATUS RELIABLE?

- Primary care physicians may not be aware of issues surrounding the measurement of serum 25(OH)D. Medical laboratories use any of several test methods, including competitive protein binding, immunoassay, high-performance liquid chromatography, and combined high-performance liquid chromatography and mass spectrometry.[5]
  - The sensitivity and specificity of these methods varies, both among the methods of measurement and between laboratories using the same testing method. Moreover, there is no internationally recognized reference standard. Discrepancies between methods and laboratories likely range from 10% to 20%.
  - Also, 25(OH)D levels may decrease in response to inflammation and acute illness (and possibly as a result of changes in the related binding protein and other carriers), potentially explaining why vitamin D status appears low when patients are sick.
  - It is unclear whether common laboratory reference ranges are appropriate for all ethnic groups.
- The bottom line is that laboratory testing of vitamin D status may misclassify individuals as vitamin D insufficient or adequate due to the variability of the assay and laboratory used, especially when the individual's value is close to the cut-point selected.
  - This suggests the need for caution and the consideration of other factors when individuals present with measurements very close to whatever cut-point is used.

ARE THERE RECOMMENDATIONS ABOUT SCREENING FOR VITAMIN D STATUS?

- Most organizations do not recommend universal screening for vitamin D.
  - The US Preventive Services Task Force concluded that the benefits as well as any potential harms from vitamin D screening and early interventions cannot be determined.[5]
  - Further more, groups such as the Endocrine Society,[4] the American Geriatrics Society,[6] the American Academy of Pediatrics,[7] and the American College of Obstetricians and Gynecologists[8] have concluded that routine screening is not necessary.
  - Nevertheless, routine laboratory blood work on patients may include screening for 25(OH)D levels. Some clinicians may be concerned about potential legal liability if they fail to screen their patients for vitamin D status, particularly if it is part of a clinical pathways or standard order sheet, but vitamin D screening is not considered a mandatory health care practice.
- Widespread screening in the face of these recommendations can incur unnecessary health care costs.
  - The marked increase in routine vitamin D screening in the last several years has undoubtedly incurred substantial costs for the health care system.
  - Sales of vitamin D dietary supplements have increased dramatically, from approximately $108 million in 2007 to $713 million in 2013.[9]

DOES VITAMIN D TREAT DEPRESSION OR IMPROVE MOOD?

- Patients who present with fatigue and depression are sometimes tested for vitamin D deficiency or treated empirically.
  - Virtually no evidence links vitamin D status to depression or these related conditions.
  - While vitamin D therapy may be used at the discretion of the clinician, it is important to note that vitamin D supplementation is not necessarily benign and should be used cautiously and judiciously.

ARE THERE CONCERNS ABOUT OVER-SUPPLEMENTING WITH VITAMIN D?

- There is a common misconception that vitamin D supplementation is safe at any reasonable level, or that if some is good, more may be better.
  - It is clear that vitamin D intakes and serum 25(OH)D must be very high—perhaps 200-400 ng/mL—to cause the classic toxicity of marked hypercalcemia and kidney and liver damage.
  - However, emerging observational data suggest that adverse outcomes may occur at much lower levels, such as in the 50-75 ng/mL range. These suspected adverse outcomes appear to include increases in all-cause mortality and increases in the rate of heart disease and some cancers. Limited evidence suggests that African Americans may be more susceptible to these adverse effects.

Nevertheless, there is little concern about vitamin D excess at doses between 400 and 1000 IU per day. Concerns have been raised about supplementation in the range of 10,000-50,000 IU per day, which may be excessive.

IS VITAMIN D A TOPIC FOR SHARED DECISION-MAKING?

- Testing for vitamin D status and potentially deciding on the use of supplements might be the subject of a conversation between the clinician and patient that includes taking into account values and preferences of the patient.

- While the many uncertainties surrounding vitamin D may make it a good candidate for shared decision-making in the minds of some, others argue that there are too many uncertainties to allow a meaningful conversation. As suggested by those in the latter group, clinicians have limited time to spend with their patients and there are likely other health matters more pressing than vitamin D, so the best course of action would be not to bring up the issue of vitamin D unless the patient asks or there is a clinical reason to do so.

ACKNOWLEDGMENT

The authors thank Drs Patsy Brannon, Andrew Hoofnagle, Susan Mayne, and J. Sanford Schwartz for their help in the initial development of this article and its contents. They also thank Joyce Merkel for her help in preparing this manuscript for publication.

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Funding: This review was prepared from a conference held at the National Institutes of Health (NIH) on December 2-3, 2014 titled "Vitamin D: Moving Toward Evidence-based Decision Making in Primary Care." At the NIH, the primary sponsor was the Office of Dietary Supplements, with co-sponsorship by the National Center for Complementary and Alternative Medicine (now the National Center for Complementary and Integrative Health; NCCIH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute on Aging (NIA). Additional co-sponsorship was provided by the Agency for Healthcare Research and Quality (AHRQ), Division for Heart Health and Stroke Prevention of the Centers for Disease Control and Prevention (CDC), National Institute of Standards and Technology (NIST), Office of Disease Prevention and Health Promotion (ODPHP) at the Department of Health and Human Services, and the US Food and Drug Administration.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.