Screening for Vitamin D Deficiency: Is the Goal Disease Prevention or Full Nutrient Repletion?

Since its founding, the U.S. Preventive Services Task Force (USPSTF) has sought to provide a firm evidential base for early detection strategies, evaluating such screening methods as mammography and prostate-specific antigen testing. Although it has also evaluated a few interventions, its predominant focus has been testing for markers that identify persons at risk who are likely to benefit from preventive action. Only recently has the USPSTF ventured into the field—or perhaps the minefield—of nutrition, a territory distant from screening tests and risk assessment, with different and unfamiliar landmarks.

In this issue, the USPSTF presents its conclusions on testing for vitamin D deficiency (1), reporting that it was unable to find evidence for or against such testing. It noted that one of the likely reasons was the absence of a scientific consensus on both the level of vitamin D status that should be judged “deficient” and what the measurable manifestations of deficiency might be. These are also issues for many other nutrients, such as folate, ascorbate, calcium, and protein. Vitamin D may have seemed to offer a way out of this confusion because serum 25-hydroxyvitamin D [25-(OH)D] concentration is generally recognized as one of the best indicators of status for any of a broad array of nutrients. Also, it is now readily measurable and widely utilized.

One of the reasons its promise has not been realized is that most studies of vitamin D efficacy have used a disease-avoidance model, which is the standard approach used by the Institute of Medicine (IOM) for most nutrients (2). Furthermore, disease prevention is the explicit focus of the USPSTF. Nevertheless, the IOM and USPSTF approaches effectively equate health with the absence of disease, an equivalence that nutritionists have long rejected. Instead, nutritionists focus on full nutrient repletion when possible. The inevitable gap between disease prevention and nutrient repletion is still largely unexplored territory. For many nutrients, it can be surprisingly wide, as suggested in this case by studies of the intake required to provide vitamin D in human breast milk in quantities sufficient to meet the needs of infants (3). The IOM’s adult requirement for vitamin D is 600 IU/d (4), which is judged to be sufficient to protect against osteoporotic fracture. In contrast, quantitative and empirical evidence indicates that vitamin D intake from breastfeeding needs to be approximately 6000 IU/d (3, 5). Although high compared with the adult recommendation, such an intake almost exactly reproduces the measured vitamin D status of contemporary Africans leading ancestral lifestyles (6). Such populations provide perhaps our best window on vitamin D levels prevailing during the millennia over which human physiology was adapted to its environment by natural selection.

Whatever the actual requirement or 25-(OH)D cutoff may be, there is another likely reason that the evidence is unclear. The USPSTF drew from systematic reviews and meta-analyses of studies of vitamin D effects, such as the one accompanying the current report (7). In general, the criteria for including studies in such reviews are methodological rather than biological. Of the 6 published biological criteria (8) for including published reports in meta-analyses, the review published in this issue met only 2 (comparable basal status and same chemical form), and several of its component studies met none. Including studies that could never have been informative in the first place (especially when they are large) inevitably biases any review toward the null.

What seems not to have been widely appreciated is that vitamin D exhibits flat response regions at both low and high values of vitamin D status, with a sharp rise in the approximate center of the physiologic range of 25-(OH)D values (8). Studies like the WHI (Women’s Health Initiative), which enrolled women with low vitamin D status values and used a vitamin D dose insufficient to move them into the response range, provide little useful information about vitamin D efficacy. Yet, precisely such studies were included in the review by LeBlanc and colleagues (7). This is not to criticize the WHI, which was designed more than 20 years ago (before vitamin D pharmacology was well-understood), but it is to criticize contemporary reviews and meta-analyses that fail to take advantage of newer information or to use critical biological criteria (8) for selection of studies for analysis of biological effects.

In addition, a disease-avoidance approach becomes problematic for micronutrients in general (and vitamin D in particular) when one understands that micronutrients do not actually cause any of the effects simplicistically attributed to them. Although necessary for cell response, such micronutrients by themselves do not initiate or cause the response concerned. For example, vitamin D is a component of the biochemical apparatus that opens the genome to allow access to DNA information needed for a particular cell or tissue response. In terms of cell function, this dependence means that when supplies of the micronutrient are inadequate, cellular response is blunted. This is dysfunction, but not clinically manifest disease. Such dysfunction may indeed lead ultimately to various diseases, but disease prevention remains a dull tool for discerning the defect, and a disease-prevention approach clearly does not measure whether the organism has enough of the nutrient to enable appropriate physiologic responses, such as lactation.

Finally, and aside from the USPSTF’s findings, one must ask whether treating without first testing is sound
practice. Certainly, it would be rational to do so if the condition being treated is prevalent and the treatment is safe and inexpensive. That is the case with another micronutrient, iodine, and the iodination of salt. However, the current situation is different because consuming sufficient iodine generally does not require conscious adherence to a particular regimen, whereas taking vitamin D does. Usually, testing improves patient adherence because it provides patient-specific, personally applicable information. General assurances that one probably needs extra vitamin D are not as compelling a motivator as knowing one’s number. Thus, whether the practitioner adheres to the widely divergent guidelines of the IOM (4), the Endocrine Society (9), or the American Geriatrics Society (10), measuring vitamin D status seems to be warranted, not so much to diagnose deficiency but to determine patient status relative to the selected guideline.

Robert P. Heaney, MD
Laura A.G. Armas, MD
Creighton University
Omaha, Nebraska

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Requests for Single Reprints: Robert P. Heaney, MD, Creighton University, Suite 4841, 601 North 30th Street, Omaha, NE 68131.

Current author addresses are available at www.annals.org.


References
Current Author Addresses: Dr. Heaney: Creighton University, Suite 4840, 601 North 30th Street, Omaha, NE 68131. Dr. Armas: Creighton University, Suite 4820, 601 North 30th Street, Omaha, NE 68131.