

Symposium: Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency

Overview of the Proceedings from Experimental Biology 2004 Symposium: Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency¹

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This symposium was convened primarily to address the pressing need to define a new dietary requirement for vitamin D. Toward this goal, we also want to educate the nutrition community about the widespread prevalence of vitamin D insufficiency in North America (1–3) as well as other countries, e.g., Australia (4), Norway (5), Finland (6), Italy (7), and some very sunny countries (8). Also, we want to identify the data needs that have hindered the promulgation of an effective public health policy or dietary guidelines needed to prevent vitamin D deficiency and insufficiency. In addition, we explore the importance of vitamin D adequacy to disease prevention and inform the public about the growing body of evidence demonstrating vitamin D insufficiency and deficiency as significant risk factors in the development of specific chronic diseases (9). Last, based on the relationships between low circulating 25-hydroxy-vitamin D and the risk of chronic disease, we demonstrate how optimizing vitamin D intake may serve as a potentially effective prevention strategy against some of these chronic diseases. A new look at this nutrient takes into account the role of vitamin D insufficiency in the development of cancer and diabetes, as well as states of increased physiological needs. True to our primary objective, we identify appropriate biomarkers of vitamin D adequacy that would facilitate the development of new dietary recommen-

dations [estimated average requirement (EAR),³ recommended dietary allowance (RDA)] for optimal vitamin D intake relevant to prevention of specific chronic diseases, as well as bone health. With these objectives in mind, we organized the content of the symposium to address 6 critical questions.

The majority of circulating 25-hydroxyvitamin D [serum 25(OH)D] originates from exposure to sunlight; however, seasonal changes, living at high latitudes, dark skin pigmentation, aging, and other factors can impede this process, requiring periodic reliance on dietary sources to supply vitamin D, the immediate precursor to 25(OH)D (10). In the presence of adequate sunlight (specifically UV light in the wavelength range of 290 to 315 nm), a dietary intake of vitamin D is not required. However, when sun exposure is limited, as in winter months or a deliberate lack of sun exposure, food sources, such as oily fishes and fortified foods, maintain vitamin D status (Fig. 1). These dual sources of vitamin D, sunlight and food, have made it difficult to adequately address the dietary need for vitamin D, until recently.

I. Why reevaluate the current Dietary Reference Intakes (DRI) for vitamin D?

In the first paper in this symposium, we address the question of why there is a current need to re-evaluate the DRI for vitamin D (11). The RDA for adults for vitamin D remained at or below the 400 IU (10 μ g) level until 1997, when the recommended intake level of vitamin D was set as an adequate intake value rather than an RDA. Since setting the 1997 adequate intake, we now know much more about the metabolism of vitamin D that would allow us to set an EAR. The circulating metabolite 25(OH)D is the major static indicator of vitamin D status. Using 25(OH)D response to diet in the absences of sun exposure, a recent dose-response study suggests a mean requirement of at least 500 IU (12.5 μ g) from which an RDA could be set (12). The key factors needed to

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³ Abbreviations used: 1,25(OH)₂D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; DRI, Dietary Reference Intakes; EAR, estimated average requirement; RDA, recommended dietary allowance.

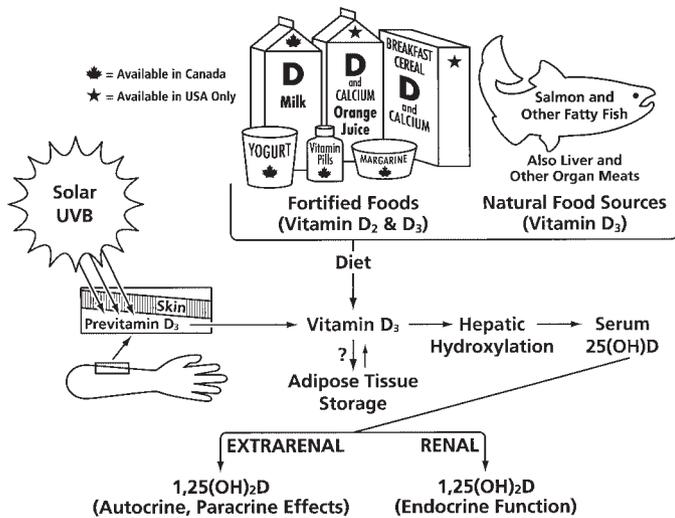


FIGURE 1 Synthesis of 25(OH)D from provitamin D-3 in skin or obtained as vitamin D in food, fortified foods and supplements. Note the difference in fortified foods between Canada and the United States. 25-Hydroxyvitamin D is converted to the active metabolite 1,25(OH)₂D by either a renal pathway or extrarenal pathways; the former is important for calciotropic functions, and the latter leads to paracrine or autocrine actions of 1,25(OH)₂D that are noncalciotropic.

establish an EAR are functional indicators of status. Given the fact that the role of vitamin D in calcium metabolism is better understood, functional markers of bone turnover, parathyroid hormone concentration, and measurements of change in calcium absorption efficiency are all potential indicators that could be used in determining the EAR. However, use of these indicators is limited to defining skeletal requirements for vitamin D and do not necessarily reflect the needs of other tissues for adequate levels of 25(OH)D to serve as a substrate for the active metabolite of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)₂D]. In the last decade, there has been an important change in our thinking about the active metabolite of vitamin D; while 1,25(OH)₂D remains the active metabolite for calciotropic functions (endocrine), attention has now shifted to the need for 25-hydroxyvitamin D to be available in sufficient quantities for the 1- α hydroxylase enzyme in nonrenal tissues to synthesize the active metabolite in localized cells. This important shift in paradigm move us away from a single renal source of 1,25(OH)₂D for calciotropic functions to the concept of there being disease-preventing endocrine, paracrine, and autocrine uses of the active metabolite.

Vitamin D has noncalciotropic functions arising from extrarenal synthesis of the active metabolite 1,25(OH)₂D, involving cell proliferation and immunity, from which functional indicators of status may be derived. This change in paradigm and current reliance on sources other than sunlight are illustrated in Figure 1. Given the increasing evidence of vitamin D deficiency and insufficiency links to a risk of chronic diseases, including cancer and diabetes, we believe that, despite gaps in our knowledge and confounding factors in the use of some functional indicators, there is enough data to consider setting an estimated average requirement for vitamin D.

II. Can the food supply provide adequate vitamin D in the absence of sunlight?

High prevalence of vitamin D insufficiency and the reemergence of rickets observed worldwide, combined with a growing

body of evidence linking poor vitamin D status with a greater risk of chronic diseases, have stimulated recommendations to increase exposure to sun as a source of vitamin D (9). Concern over increased risk of melanoma with unprotected sun exposure, however, has led to the alternative recommendation that sufficient vitamin D should be supplied by the food supply. Because vitamin D deficiency is a global problem, in our second paper (13), we examined the issue of adequacy of vitamin D intake worldwide and evaluated the ability of current fortification policies and supplement use practices among various countries to meet current dietary guidelines. To illustrate the impact of food fortification on vitamin D intake, we compared vitamin D intake estimates from over 80 studies that reported quantified vitamin D intakes estimated from FFQs, 24 h recall, or multiple day food record, and plotted these values according to age and classification of the country of origin's fortification practices (mandatory, optional, or none). We observed that for many countries without mandatory staple food fortification, vitamin D intake is often too low to sustain healthy circulating levels of 25(OH)D. Even in some countries that require (mandatory) or allow fortification (optional), vitamin D intakes are low in some groups, due to their unique dietary patterns, such as low milk consumption, vegetarian diet, limited or no use of dietary supplements, or changes away from traditional food consumption, such as high fish intakes. It is clear from our review that reliance on the world food supply as an alternative to increased sun exposure for many nations will necessitate greater availability of fortified food staples, dietary supplement use, and/or change in dietary patterns to consume more fatty fish.

III. How prevalent is vitamin D insufficiency and deficiency and what confounding factors for the measurement of circulating levels of 25(OH)D influence these estimates of vitamin D nutritional status?

We asked Dr. David Hanley to address the use of measurements of circulating levels of 25(OH)D in determining prevalence of vitamin D insufficiency (2). He and others were instrumental in alerting us of the high prevalence of low 25(OH)D levels in apparently healthy young individuals in Canada and the United States (1). The studies that Dr. Hanley and others conducted used several different cutoff values and different assays to arrive at the prevalence estimates of vitamin D insufficiency. Hanley and Davison (2) describe the issues associated with these assays and the problems involved with determining vitamin D insufficiency, including the important issue of whether we should continue to refer to low 25(OH)D as insufficiency or not.

IV. Vitamin D sufficiency: how should it be defined, and what are its functional indicators?

Dr. Bruce Hollis, an early pioneer in the development of assays to measure vitamin D status, was asked by us to define what is a "normal" or "sufficient" concentration of the main status indicator of vitamin D, circulating 25(OH)D (14). It has been more than 3 decades since the first assay assessing circulating 25(OH)D in human subjects was performed, laying the foundation for the definition of "normal" nutritional vitamin D status in human populations. The early definition of "normal" circulating 25(OH)D was based on Gaussian distributions of concentrations from human subjects apparently free of disease, but did not take into account lifestyle habits, poor dietary vitamin D intake, race, age, use of sunscreen, latitude, or manner of usual dress, all of which can have enormous

influence on circulating levels of 25(OH)D. In defining “normal” circulating concentrations of 25(OH)D, Dr. Hollis emphasizes that consideration should be given to the significance of the amount synthesized with modest sunlight exposure as experienced with a 10–15 min whole body exposure to peak summer sun, which will generate and release up to 20,000 IU vitamin D-3 into the circulation. Recent studies, which orally administered up to 10,000 IU/d vitamin D-3 to human subjects for several months, successfully elevated circulating 25(OH)D levels to those observed in individuals from sun-rich environments. Dr. Hollis further points out that we are now able to accurately assess sufficient circulating 25(OH)D levels using specific biomarkers instead of merely guessing what an adequate level is. Those biomarkers for which we have the greatest amount of data include intact parathyroid hormone, calcium absorption, bone turnover markers, and bone mineral density. Using the data from these biomarkers, Dr. Hollis states that vitamin D sufficiency or “normal” concentrations should be defined as circulating levels of 25(OH)D > 30 µg/L (75 nmol/L). Data from the NHANES III surveys averaging serum concentrations in samples from Caucasian adults, over all seasons and latitudes in the United States (13), support this definition, as do findings from a recent supplementation trial conducted over several seasons in Europe (15).

V. Can vitamin D supplementation in infancy prevent type 1 diabetes?

Dr. Susan Harris was asked to revisit an important question that she had addressed earlier, “can vitamin D supplementation in infancy prevent type 1 diabetes” (16,17)? In so doing, we hoped to ferret out possible candidates for use as functional end points to assess vitamin D requirements of disease-specific, extrarenal tissue, such as the pancreas. Limited data from human observational studies suggest that early supplementation with 10 µg/d (400 IU/d) or less of vitamin D may not reduce the risk for type 1 diabetes but that doses of 50 µg/d (2000 IU/d) and higher may have a strong protective effect. Current U.S. recommendations (5–25 µg/d, 200–1000 IU/d) fall in the largely unstudied dose range in between. All infants and children should receive between 5 µg/d and 25 µg/d (200 and 1000 IU/d) of supplemental vitamin D, particularly if they have limited sun exposure, live in northern areas, are exclusively breastfed, or are dark skinned. Dr. Harris advises that additional studies are needed that investigate the association between 25(OH)D and autoantibodies predictive of type 1 diabetes in infancy and beyond, and that would test the ability of vitamin D supplement doses between 5 and 50 µg/d (200 and 2000 IU/d) to prevent autoantibodies and/or type 1 diabetes in infancy and beyond. Finally, she emphasizes the clear need to examine the safety of vitamin D intakes of 25 µg/d (1000 IU/d) and higher in infants and young children. A study published since this symposium presents data showing a positive correlation of low circulating 25(OH)D concentrations with functional end measures of type 2 diabetes, specifically insulin resistance and pancreatic β cell dysfunction (18). These findings further underscore the importance of determining the vitamin D requirements of tissues other than bone.

VI. Is there a significant role for vitamin D and calcium in the prevention of prostate and colon cancer? What new approaches or biomarkers could we use to identify nutrient needs?

Evidence has emerged in recent years that low (suboptimal) intakes of micronutrients, e.g., vitamin D, are associated with

an elevated risk of chronic diseases. Nonetheless, it is an oversimplification to describe the association of low intake of micronutrients with chronic disease as a deficiency disease, because this description does not capture the complexity of these relationships. We asked Dr. Myron Gross, an expert in the use of biomarkers in epidemiologic studies, to reflect on how epidemiologic study designs are able to assist our understanding of the complex micronutrient–chronic disease relationships, using the specific examples of vitamin D and cancer. Dr. Gross (19) describes potential biomarker candidates for use in epidemiologic studies focusing on vitamin D and prostate cancer, and for biomarkers used in vitamin D and colon cancer. The biomarkers of exposure for vitamin D not only include serum 25(OH)D measurements but also intermediary markers of noncalcitropic effects of vitamin D in specific tissues.

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