Vitamin D and health in the 21st century: bone and beyond.
Executive summary¹⁻³

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ABSTRACT
Vitamin D is unique, in terms of its metabolism and physiologic features and the human reliance on both endogenous production (activation through exposure to ultraviolet light) and exogenous sources (diet, primarily fortified foods) to meet biological requirements. Recent evidence has indicated a reemergence of vitamin D-deficient rickets and an alarming prevalence of vitamin D insufficiency (ie, low circulating concentrations of 25-hydroxyvitamin D) in particular segments of the US population. Furthermore, evidence has emerged implicating vitamin D status in a range of adverse health conditions, including cancer and certain autoimmune diseases. Therefore, a conference organized by the National Institute of Child Health and Human Development and the National Institutes of Health Office of Dietary Supplements was held to explore current knowledge and to develop a research agenda to address the range of issues associated with vitamin D and health during the life cycle. These proceedings contain presentations about 1) existing data on vitamin D status in the United States and internationally, 2) the current state of knowledge regarding the biological functions of vitamin D, 3) the strength of evidence supporting reconsideration of current policies regarding vitamin D intake, 4) gaps in understanding of the factors affecting and current options for improving vitamin D status in the United States and internationally, and 5) research needs to address gaps in knowledge regarding vitamin D assessment, biological features, and requirements. This executive summary provides an overview of the conference and its conclusions. Am J Clin Nutr 2004;80(suppl):1673S–7S.

KEY WORDS Vitamin D, National Institutes of Health conference

INTRODUCTION
Vitamin D is an essential nutrient that is unique, in terms of both its metabolism/physiologic processes and the human reliance on endogenous production and exogenous sources to meet biological requirements. It is the interaction between the 2 primary sources of biologically active vitamin D, ie, diet and exposure to ultraviolet (UV) light, that has historically been the focal point of public policy aimed at meeting the population requirements and ameliorating environmentally mediated epidemics of vitamin D deficiency (vitamin D-related rickets).

Evidence was published indicating a reemergence of vitamin D-deficient rickets and alarming rates of low circulating concentrations of vitamin D (25-hydroxyvitamin D) in the US population (1–4). Until the revelation of those data, it had been assumed that vitamin D deficiency had been eliminated as a significant problem, and the strategy used to achieve this success (ie, food fortification) served as a model of a successful public health intervention. Speculation regarding factors that may be contributing to the increases in vitamin D deficiency (ie, significantly reduced concentrations of circulating 25-hydroxyvitamin D) and vitamin D-related rickets in the United States and internationally has included the following: 1) a perception, unsubstantiated by population-based surveillance data, of a high prevalence of lactose intolerance, leading to undesirable effects with consumption of milk and dairy foods, particularly among African Americans; 2) lower intakes of vitamin D-fortified foods, particularly fluid milk and fortified cereals; 3) concerns about fat intake contributing to reduced intake of vitamin D-fortified foods, such as milk; 4) reduced intake of calcium-rich foods, including milk, among adolescents and young women of reproductive age contributing to decreased concentrations of vitamin D and calcium in those populations; 5) increased use of sun block and decreased exposure to sunlight to reduce the risk of skin cancer attributable to exposure to UV radiation; 6) increased prevalence and duration

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² From the National Institutes of Health Conference titled “Vitamin D and Health in the 21st Century: Bone and Beyond,” held on October 9-10, 2003, in Bethesda, MD. The conference was sponsored by the National Institute of Child Health and Human Development and the Office of Dietary Supplements, National Institutes of Health, and was cosponsored by the US Centers for Disease Control and Prevention, Agricultural Research Service/US Department of Agriculture, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Disorders/Division of Nutrition Research Coordination, National Institutes of Health Office of Research on Women’s Health and Office of Women’s Health, Coca-Cola North America, and the National Dairy Council. The publication of these proceedings was cosponsored by the National Institute of Child Health and Human Development, the National Institutes of Health Office of Dietary Supplements, and Coca-Cola North America. The views and opinions expressed in the articles included in these proceedings do not necessarily reflect those of the sponsoring agencies and organizations.
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of exclusive breast-feeding, with the combination of human milk being a poor source of vitamin D and the high prevalence of low circulating 25-hydroxyvitamin D concentrations among US women, particularly African American mothers, resulting in an increased risk of vitamin D deficiency; 7) decreased vitamin D status associated with decreased UV light exposure resulting from increased air pollution in newly emerging industrialized countries in the developing world; and 8) effects of food insecurity (ie, limited access to and availability of calcium-rich and/or vitamin D-fortified foods) in resource-poor settings in the developing world.

The current situation regarding vitamin D status and the development of effective policies to address problems associated with vitamin D insufficiency in the United States and internationally reflects data needs regarding several key issues, including the following: 1) lack of biological data for development of meaningful, racially relevant, dietary requirements to achieve vitamin D nutritional/dietary adequacy, in the context of bone health and the potential relationship of vitamin D status to other health conditions; 2) inadequate knowledge about the functional effects of low circulating concentrations of vitamin D (25-hydroxyvitamin or other forms of vitamin) on bone health and other bodily systems throughout the life cycle; 3) effects of the environment (eg, diet and level of UV light exposure) on vitamin D status; and 4) an understanding of the effects of the unique confluence of influences from several public health policies that have resulted in unintended adverse health outcomes (eg, efforts to decrease the risk of skin cancer resulting from overexposure to UV radiation and attempts to increase the prevalence and duration of exclusive breast-feeding).

The number of outstanding issues hinders the promulgation of meaningful public health policies in this regard. Many of these issues were identified by an expert panel convened by the Centers for Disease Control and Prevention (CDC) (5). The findings of this expert panel may be categorized into the following areas of interest: epidemiology/demographics, biological issues, and public health implications.

Epidemiologic/demographic issues reported by the CDC expert panel include concerns about the adequacy of data regarding the prevalence of vitamin D deficiency in the United States and internationally, methods for assessing vitamin D status, and biomarkers of vitamin D status. The biological concerns identified included the need for a sound knowledge base for determination of vitamin D needs for various segments of the population and factors capable of affecting those requirements and the lack of data on the functional consequences of vitamin D insufficiency or deficiency (as reflected by low circulating concentrations of various forms of vitamin D) throughout the life cycle but particularly for women, infants, and children. A critical area of concern is the identification of essential data needs for establishment of realistic, meaningful, dietary requirements for vitamin D, with particular reference to different ethnic/racial groups. Such data needs might include consideration of potential genetic polymorphisms in vitamin D metabolism and racial differences in vitamin D requirements. Particular attention should be paid to specific ethnic groups and practitioners of specific cultural practices, to determine whether and how ethnicity and specific practices may affect vitamin D status and perhaps contribute to documented health disparities between these groups and the general population. The adequacy of the evidence base supporting a decision regarding food sources of vitamin D was highlighted, along with the potential evidence base supporting the need for supplementation for selected target groups, both domestically and internationally. A related issue involves data needs to allow decisions regarding whether high-dose supplementation for mothers, infants, or both can prevent vitamin D deficiency among infants and for which groups it is feasible. Among the considerations in this regard is determination of the best dose and method, if supplementation is found to be warranted. Related to this issue would be discussions of efficacy and safety, domestically and internationally.

In terms of public health implications, the CDC expert panel discussed how best to meet the goals of existing public health messages (eg, reduction of exposure to UV radiation) and still achieve adequate vitamin D status. Another issue discussed was how to ensure vitamin D adequacy of lactating mothers and their infants in the context of current public health policies regarding breast-feeding in the United States and internationally. The expert panel encouraged an examination of the effects of changes in public policy in the United States on international food and nutrition policies related to infant feeding practices.

NATIONAL INSTITUTES OF HEALTH WORKSHOP GOALS

To begin the process of expanding the evidence base needed to address the issues raised by the CDC expert panel and concerns raised by recent evidence regarding the importance of vitamin D not only for bone health but also for other health areas, the National Institute of Child Health and Human Development, in partnership with the National Institutes of Health Office of Dietary Supplements and with support from the National Cancer Institute, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health Office on Women’s Health Research, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Office of Women’s Health, Office of the Secretary, US Department of Health and Human Services, CDC, US Department of Agriculture, National Dairy Council, and Coca-Cola North America, conducted a conference titled “Vitamin D and Health in the 21st Century: Bone and Beyond,” on October 9–11, 2003, at the National Institutes of Health campus in Bethesda, MD. The conference, which was attended by >200 members of the scientific, policy, academic, corporate, and consumer communities, addressed the following issues: 1) the quality and quantity of existing data on vitamin D status in the United States and internationally; 2) the current state of knowledge with respect to the biological functions of vitamin D, including potential roles in immune function and chronic diseases, including cancer; 3) the strength of the evidence to support reconsideration of current policies regarding vitamin D intake; 4) gaps in understanding of factors affecting and current options for improving vitamin D status in the United States and internationally, with particular reference to women, infants, and children; and 5) gaps in knowledge regarding vitamin D assessment, biological processes, and requirements.

SUMMARY OF THE CONFERENCE

To address these core issues, the conference was organized into 5 sessions. Session I consisted of an overview of the field and our current understanding of the biological processes of vitamin...
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The session included a presentation on the physiologic features and functions of vitamin D by Dr Hector DeLuca (6). Dr Michael Holick provided an historical overview of vitamin D from a public health perspective (7). Coverage of the importance of vitamin D as a global public health issue was provided by Dr Gerald Combs.

Session II focused on the epidemiologic and demographic features of vitamin D status in the United States and internationally. An additional emphasis was on methodologic considerations in the assessment of vitamin D status and the evaluation of data in terms of relevant biological outcomes. Reports were presented that reflected the current status in the United States and current issues globally. Dr Kelley Scanlon presented the domestic state of affairs (8), followed by Dr Christel Lamberg-Allardt, who provided the global perspective, with particular emphasis on European and Scandinavian countries. Dr Robert Heaney followed with a review of current thinking with respect to biomarkers for assessment of vitamin D status (9). This session concluded with a presentation by Dr Mona Calvo on the history of vitamin D fortification of food, up to and including the recent addition to beverages, including orange juice, and the process through which that decision was made (10). At the end of this session and the subsequent plenary session, an interactive panel discussion ensued, which included active participation by conference attendees and culminated in the formulation of responses to a series of questions relevant to the session topic themes. In this case, the questions were as follows.

What are 5 research priorities? There was a consensus of opinion that a need exists for better definitions and measures of vitamin D toxicity/safety, in terms of dietary exposure and in combination with UV light exposure. A related issue is how best to determine the optimal level of vitamin D intake, through the diet, UV light exposure, or some combination thereof. A need exists for validation studies comparing current techniques used in national nutrition-monitoring efforts with biologically relevant outcome measures. The lack of biomarkers for bone health and other conditions in which vitamin D may play an important role is a major obstacle.

What are the major needs with respect to methods? Again emphasizing the importance of biomarkers, the panel members and attendees agreed that the development of relevant biomarkers and related methods are key components in the vitamin D research endeavor, for surveillance and clinical research. A major concern with respect to the interpretation of current surveillance data is the lack of clear understanding of the biological significance of given concentrations of circulating vitamin D (25-hydroxyvitamin D or any other biologically relevant form). In this context, concern was expressed about the current reference ranges for vitamin D and what constitutes a normal concentration, compared with optimal concentrations.

The theme of session III was the current understanding of the role of vitamin D in health, including conditions beyond bone health, and potential mechanisms for vitamin D roles in disease. The session was opened with an overview by Dr William Grant of the range of conditions in which vitamin D insufficiency has been implicated, through inadequate dietary intake or a combination of dietary inadequacy and reduced UV light exposure. This presentation was followed by talks focusing on the role of vitamin D in immune function by Dr Margherita Cantorna (11) and breast cancer as a possible model for other types of cancer by Dr JoEllen Welsh (12). Dr John Pettit discussed the current thinking with respect to the causes of nutritional rickets in resource-limited settings, from a global perspective (13). The session concluded with a presentation by Dr James Fleet on the current and emerging methods that might be effectively used to study the role of vitamin D in health (14). The panel discussion for session III included the following questions.

What are the 5 priority areas in the vitamin D-disease relationship? In the context of immune function, clarifying the role of vitamin D in relation to infections, such as acute respiratory tract infections, is a high priority, particularly internationally.

With respect to the range of diseases in which vitamin D might play a role, a need exists for prevalence data. Clearly, obtaining those data would require meeting the needs identified in session II, regarding assessment methods and biomarkers. The panel and the audience strongly urged additional efforts to elucidate the biological processes of vitamin D beyond its role in calcium/bone metabolism. Emphasis was placed on the important role of maternal vitamin D status in the context of infant growth and development, as well as functions such as immunocompetence. It was noted that, particularly in international settings, the complexity of multiple nutritional deficits makes it difficult to attribute specific outcomes to individual nutrients.

What are the current obstacles (eg, methods) to exploration of the vitamin D-health relationship? With respect to bone disease, which remains a global concern, a need exists for better diagnostic tools (both radiologic and biochemical) that are field-appropriate, particularly for resource-limited settings. With respect to other potential vitamin D-health relationships, the need for biomarkers was again emphasized.

What is the best approach to addressing vitamin D and health in international settings? Because of the lack of consensus regarding what constitutes normal and/or optimal ranges of vitamin D intake, it is difficult to make specific recommendations with respect to the protective effects of vitamin D for given conditions. It is not known whether there are distinctions between the blood concentrations of vitamin D (presumably 25-hydroxyvitamin D) needed to address dietary insufficiency/deficiency and concentrations that might provide prophylactic effects for a given condition (eg, cancer or infections).

Session IV focused on developmental, ethnic, and racial considerations with respect to generating recommendations for vitamin D intake and exposure. The session was opened with a presentation by Dr Connie Weaver of current recommendations for vitamin D intake, with a primary focus on the dietary reference intake recommendations promulgated through the Institute of Medicine of the National Academy of Sciences (15). This was followed by talks on the importance of vitamin D as a predictor of subsequent bone health, from the prenatal/fetal and infant perspective, by Dr Nick Bishop (16), the state of knowledge regarding vitamin D status in pregnancy by Dr Bonnie Specker (17), and current knowledge regarding vitamin D and lactation by Dr Bruce Hollis (18). Dr Frank Greer presented an overview of the recent efforts by the American Academy of Pediatrics to develop new guidance with respect to vitamin D status among breast-fed infants (19). Dr Bess Dawson-Hughes concluded the session with a report on ethnic/racial considerations in generating recommendations for vitamin D for adult and elderly subjects (20). The panel discussion for session IV focused on the following questions.

Are the current dietary recommendations for vitamin D adequate? Because the daily reference intakes for vitamin D were...
published in 1997 and were based on data obtained up to 1995 and because a significant amount has been learned about vitamin D biological and epidemiologic features in the intervening years, the panel members and the attendees suggested a need for systematic review of the extant literature, to determine the necessity of revising the current recommendations.

What are the research priorities (data needs for meaningful recommendations for different developmental and/or racial/ethnic groups)? A universal finding for all developmental and racial groups is the lack of sensitive specific biomarkers for assessment of the functional consequences of dietary insufficiency, toxicity, or under- or overexposure to UV radiation.

For adults, comparative absorption studies for racial groups and other high-risk groups are needed. Another important area is assessment of the relative effects of supplementation for different racial groups, to identify when and whether differing doses might be warranted to achieve desired goals (eg, amelioration of insufficiency or prophylaxis against certain adverse health outcomes).

Issues during pregnancy and lactation include biomarkers to determine the functional significance of vitamin D insufficiency for both mothers and infants. The questions of whether, when, and how much vitamin D might need to be supplied, through supplementation or other means, remain unresolved, in terms of maternal needs and the needs of the developing infant during gestation.

For infants, data are lacking to indicate the long-term consequences of given levels of UV light exposure. Another need emphasized by the panel was the lack of biomarkers of non-bone functions that might be affected by vitamin D. A related concern was the lack of data on the functional consequences, again beyond bone health, of vitamin D insufficiency. Areas of concern were immunocompetence and neurologic growth and development. With respect to children, the current evidence is insufficient for definition of normal concentrations of circulating vitamin D (25-hydroxyvitamin D) that would be reflected in maintenance of normal or healthy activity, as indicated by relevant biomarkers of health outcomes.

Given the current state of knowledge, what are the public health approaches to achieving vitamin D adequacy? What factors need to be considered with respect to amount, duration, and target groups for dietary or other (eg, UV light exposure) interventions or recommendations? In addition to previously expressed concerns about data needs to support meaningful dietary requirements, the panel cited the relative safety of differing levels of UV light exposure and the timing of sunscreen use as 2 key factors to be considered with respect to messages about UV light exposure. Data are needed to support specific recommendations for each of these factors, particularly as they may pertain to different age and/or racial groups.

How can we account for the potential confluence of health messages creating adverse outcomes (UV protection versus vitamin D adequacy)? This issue was discussed extensively by the CDC expert panel on vitamin D (5). Of particular interest was the combination of the desire to meet goals with respect to rates of exclusive breast-feeding and concerns regarding exposure of infants < 6 mo of age to UV radiation. In addition to the need for additional data on vitamin D requirements and methods of achieving those levels is the need for better public education about the potential benefits and risks associated with particular health messages.

Is there a need for special considerations regarding health disparities? The panel stressed the need for additional data on the genetic and biological features of vitamin D across ethnic/racial groups, to support racially appropriate recommendations for vitamin D adequacy and health. Additional emphasis was placed on education regarding the importance of vitamin D in health and the available sources of vitamin D, and clear public health messages were highlighted as important needs.

**CONCLUSIONS**

Session V was intended to be an extended discussion with the audience and the chairs of the 4 sessions plus the meeting organizers, to summarize what had transpired during the 2 d of the meeting. The organizers, with the materials presented by the plenary speakers and in the interactive panel discussions at the end of each topical session, have begun the process of developing a focused research program to begin to provide data essential for the promulgation of evidence-based public policy regarding achieving vitamin D adequacy in the United States and elsewhere. The following is a summary of the needs identified during the conference and drawn together during the final discussions of session V.

1. Better definitions of adequate and insufficient, with meaningful cutoff values and biomarkers that have functional relevance; assessment methods are also a priority. We need sufficient evidence to make practical evidence-based recommendations. We need a quantitative measure for the evaluation of UV light exposure.
2. Establishment of a dose-response relationship for benefit and harm for UV light exposure, particularly with reference to specific health outcomes. What is the relative incidence of certain adverse health outcomes (eg, cancers) among racial/genetic groups?
3. Determination of biomarkers and functional outcomes for bone and non-bone tissues that might reflect vitamin D status.
4. A systematic evidence review to determine the need for reevaluation of the daily reference intake.
5. Better information for the public regarding vitamin D requirements for health. A public information shortfall was identified that might create problems because of the confluence of different messages (eg, increasing breast-feeding, avoiding dietary supplements, and avoiding UV light exposure).
6. Investigation of genomic polymorphisms. Polymorphisms should be a focal point, with tissue-specific roles of vitamin D.
7. Better prevalence estimates, domestically and globally. What is suboptimal, compared with frank deficiency?
8. Better surveillance of at-risk groups (eg, African American women) and determination of whether current surveillance approaches are sufficient.
10. Exploration of the relationships between obesity, adiposity, and weight loss and vitamin D.
11. More complete data for food composition tables, particularly with the advent of new fortification programs and increased use of dietary supplements.

The National Institute of Child Health and Human Development and the Office of Dietary Supplements thank the participants and the sponsors for their input, support, and contributions in helping achieve the goals of this conference. The National Institute of Child Health and Human Development, the Office of Dietary Supplements, and their partners within the National Institutes of Health and the federal research community will work together to determine the most appropriate follow-up activities to address the needs identified in this meeting and to move proactively to advance our understanding of the importance of vitamin D for public health, in the United States and globally.
REFERENCES