

# Overview of the conference “Vitamin D and Health in the 21st Century: an Update”<sup>1–4</sup>

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## ABSTRACT

We summarize the key findings, strength of the evidence, and research needs identified in the National Institutes of Health conference “Vitamin D and Health in the 21st Century: an Update,” which was held in September 2007; a systematic evidence-based review; and a National Institutes of Health roundtable discussion held after the conference by scientists with relevant expertise. The evidence-based review addressed 5 questions on 25-hydroxyvitamin D [25(OH)D] and functional outcomes across the life cycle and response to exposure, bone health outcomes of supplementation, risks and benefits of sun exposure, and adverse outcomes. These questions also framed the conference and roundtable discussions. Researchers have made considerable progress in understanding the relation of 25(OH)D to bone health outcomes in the elderly and in postmenopausal women, but we know less about its impact on other stages of the life cycle and in racial and ethnic groups. Limitations of the existing data include the failure of many studies to control for important confounders [baseline 25(OH)D concentration, skin pigmentation, body mass index, compliance, etc], sparse data on key vulnerable populations (dark-skinned persons, reproducing women, infants, children, and adolescents), problems of accuracy and excessive variability in measuring 25(OH)D, lack of established relation of 25(OH)D with functional outcomes except in the elderly, and limited information on the effects of vitamin D independent of calcium, magnesium, and phosphate. Future research should determine and validate across the life cycle relevant functional outcomes for bone and other health factors as well as adverse outcomes for the biomarker of exposure, 25(OH)D, to enable assessment of the role of vitamin D status in health maintenance and disease prevention. *Am J Clin Nutr* 2008;88(suppl):483S–90S.

## INTRODUCTION

The National Institutes of Health (NIH) Office of Dietary Supplements, with joint sponsorship of the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the American Society for Nutrition, convened a conference titled “Vitamin D and Health in the 21st Century: an Update” on September 5–6, 2007, in Bethesda, MD. The conference, one aspect of a multifaceted NIH vitamin D initiative implemented after a previous conference on vitamin D and health held by NIH in 2003 (1), described progress in addressing several key research needs identified in the previous conference and determined additional current research needs.

As part of the NIH vitamin D initiative, the Office of Dietary Supplements requested and funded a systematic evidence-based

review (EBR), Effectiveness and Safety of Vitamin D in Relation to Bone Health, through the Agency for Healthcare Research and Quality Evidence-based Practice Center program (2). The article by Cranney et al (3) in this volume summarizes the EBR’s findings. The review focused only on bone health because initial evaluation of the literature indicated that the data were insufficient to examine other health outcomes, such as cancer, autoimmune disorders, and immune function. The EBR assessed the aggregate level of the evidence on the basis of the quantity and quality of the studies by using the validated Jadad scale and on the basis of the consistency of the results. The EBR team characterized the evidence across the studies as good if the results were consistent and at least one of the relevant studies was of “good” quality on the basis of variables such as the study population’s representativeness and whether the investigators controlled for and reported on bias and confounding factors. Fair evidence indicated sufficient evidence of an association that was limited by consistency of results or the lack of one “good” quality study, and inconsistent evidence indicated that the studies had conflicting results that made it impossible to draw a conclusion. When doing so is relevant to this summary, we report the EBR’s assessment of the evidence in these terms.

The National Cancer Institute convened a conference (co-sponsored by the Office of Dietary Supplements) on Vitamin D and Cancer: Current Dilemmas/Future Needs, on May 7–8, 2007. Participants in this conference considered the role of vitamin D in cancer prevention. Because the presenters at that meeting published the information they reported and the research

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<sup>2</sup> From the National Institutes of Health conference “Vitamin D and Health in the 21st Century: an Update,” held in Bethesda, MD, September 5–6, 2007, and the National Institutes of Health roundtable discussion held in Rockville, MD, September 6–7, 2007.

<sup>3</sup> The Office of Dietary Supplements, the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the American Society for Nutrition sponsored the conference. The views and opinions expressed in the articles included in these proceedings are those of the authors of the individual articles and do not necessarily reflect those of the sponsoring agencies and organizations.

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needs they identified (4), the September 2007 conference did not address the relation between vitamin D and cancer.

The NIH vitamin D initiative also includes funding for the development of standard reference materials for 25-hydroxyvitamin D [25(OH)D] by the National Institute of Standards and Technology, national monitoring of vitamin D status in the National Health and Nutrition Examination Survey (NHANES) in collaboration with the National Center for Health Statistics, and development of analytic methods to measure vitamin D content in foods and dietary supplements by the US Department of Agriculture.

After the September 2007 conference, 16 scientists with expertise in areas relevant to conference topics and issues that the EBR addressed participated in a roundtable discussion on September 6–7, 2007. The Office of Dietary Supplements organized this meeting to gather additional input on research needs concerning vitamin D and health. A summary of the roundtable discussion is available elsewhere in this supplement (5). The questions addressed in the EBR framed both the conference and the roundtable discussion:

1) Are specific serum 25(OH)D values associated with bone health and functional outcomes across life and reproductive stages?

2) Does dietary intake (from fortified food or supplements) or sun exposure affect circulating 25(OH)D concentrations?

3) What is the evidence for efficacy of supplementary doses of vitamin D on BMD, fractures, and falls for women of reproductive age, elderly men, and postmenopausal women?

4) Is there a level of sun exposure that is sufficient to maintain adequate vitamin D levels but does not increase the risk of skin cancer?

5) Does intake of vitamin D above recommendations lead to toxicities (eg, hypercalcemia, kidney stones)?

The conference had 4 objectives. The first objective was to evaluate available evidence on the efficacy and safety of vitamin D, including the evidence in the EBR and other recent and current research, particularly new research and related research tools, that investigators have made available since the original 2003 vitamin D conference. This evaluation focused on vitamin D metabolism and status, 25(OH)D concentrations, and functional outcomes across the life cycle; the impact of dietary intakes of vitamin D and de novo production on circulating 25(OH)D concentrations; and the toxicity and adverse outcomes of vitamin D. The remaining objectives were to identify knowledge gaps concerning the efficacy and safety of vitamin D in general and across the life cycle, to inform NIH and other federal agencies of research needs concerning vitamin D and health, and to disseminate the conference proceedings and executive summary to inform the broader nutrition community.

In this article, we provide a brief summary of the EBR findings, September 2007 conference presentations, and discussions at the roundtable meeting following the conference. Other articles in this supplement provide more details on the conference presentations and speakers' views.

## BACKGROUND ON VITAMIN D

Vitamin D is a unique nutrient in several ways, as Anthony Norman described during the conference. Vitamin D is actually a prohormone that humans obtain from foods and dietary supplements and by endogenous skin synthesis from

7-dehydrocholesterol with sunlight exposure. This endogenous synthesis produces the form vitamin D<sub>3</sub> (cholecalciferol), which the vitamin D binding protein (DBP) transports to the liver. In foods and dietary supplements, vitamin D can exist in the form of either cholecalciferol or ergocalciferol (vitamin D<sub>2</sub>). Both are absorbed via the lymphatic system as part of chylomicrons, which are metabolized to remnant particles that then transport vitamin D to the liver. Vitamin D occurs naturally in a limited number of foods in highest amounts in fatty fish and in low amounts in meats and other animal food products; it is also available in fortified foods (including milk and milk products, margarines, and breakfast cereals). Fortified foods constitute the major dietary food sources of vitamin D in the United States (6).

The enzyme 25-hydroxylase converts vitamin D to 25(OH)D in the liver. 1 $\alpha$ -Hydroxylase (1 $\alpha$ -OHase) then converts 25(OH)D to the active form of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] in renal tissues. 1,25(OH)<sub>2</sub>D can depress the activity of 1 $\alpha$ -OHase, and the parathyroid hormone (PTH) can stimulate this activity. Many extrarenal tissues also express the 1 $\alpha$ -OHase, including osteoclasts, skin, macrophages, placenta, colon, brain, prostate, endothelium, and parathyroid glands. Extrarenal production of 1,25(OH)<sub>2</sub>D might play an important role in cell differentiation, proliferation, and immune function. Vitamin D could, therefore, play a role in physiologic processes independently of its well-known role in calcium metabolism. In contrast to renal 1 $\alpha$ -OHase, extrarenal 1 $\alpha$ -OHase does not respond to stimulation by PTH (7). Furthermore, 1 $\alpha$ -OHase may vary in expression with the physiologic state of a tissue as well as with disease progression.

DBP binds and transports vitamin D and its metabolites in the plasma. DBP is synthesized in liver and circulates at a concentration that is in excess of normal circulating vitamin D metabolite concentrations. DBP has a higher affinity for 25(OH)D than 1,25(OH)<sub>2</sub>D. Indeed, 25(OH)D is present in circulating concentrations  $\approx$ 1000 times those of 1,25(OH)<sub>2</sub>D, and DBP binds 99% of it. Native vitamin D appears in the plasma for only a short time because of its rapid metabolism in the liver or storage in adipose tissue. Glenville Jones stated that, with excessive intake, 25(OH)D concentrations rise to pharmacologic levels and act as toxic analogues to 1,25(OH)<sub>2</sub>D. The half-life of plasma 1,25(OH)<sub>2</sub>D is <4 h; the 25(OH)D half-life is 2–3 wk.

1,25(OH)<sub>2</sub>D exerts its effects by binding to a specific nuclear receptor (vitamin D receptor, or VDR), a ligand-dependent transcription factor that belongs to the superfamily of steroid-thyroid hormone-retinoid nuclear receptors and that recognizes specific DNA sequences known as vitamin D response elements (7). 1,25(OH)<sub>2</sub>D mineralizes the skeleton and prevents hypocalcemia. In addition to causing skeleton mineralization, it regulates parathyroid growth and PTH production. Vitamin D also maintains serum calcium and phosphorous concentrations at supersaturating levels by increasing active intestinal absorption of calcium and phosphate and, in concert with PTH, stimulating bone resorption and renal tubular calcium reabsorption.

As discussed at the conference by Frank Greer and Ann Prentice, the classic vitamin D deficiency diseases are rickets in infants and children and osteomalacia in adults. Investigations of vitamin D's non-bone-related functions are expanding because of the recognition that the VDR appears not only in the target cells of enterocytes, osteoblasts, and distal renal tubule cells, but also in parathyroid gland cells, skin keratinocytes, promyelocytes, lymphocytes, colon cells, pituitary gland cells, and ovarian

cells (8). Areas of promising research include osteoporosis, type 1 diabetes, some cancers, autoimmune diseases (such as multiple sclerosis), and infectious diseases (such as tuberculosis).

## SUMMARY OF FINDINGS FROM THE EVIDENCE-BASED REVIEW, CONFERENCE, AND ROUNDTABLE MEETING

### Question 1: Are specific serum 25(OH)D values associated with bone health and functional outcomes across life and reproductive stages?

According to the conference speakers and roundtable participants, the best available biomarker of vitamin D status is circulating 25(OH)D, but this biomarker has limitations. The interpretability and usefulness of an ideal biomarker of nutritional status is best achieved if it relates to a functional endpoint (or its indicator) in a sensitive, specific, and reliable manner, as Lars Ovesen and Ann Prentice described. However, the status of other nutrients, such as calcium and **magnesium**, also affect many endpoints, such as hip fracture, that are affected by 25(OH)D concentrations. 25(OH)D is a biomarker of relatively recent "exposure," but many bone health outcomes, such as fractures and bone mineral density (BMD), are long-term effects, making interpretation of a single point measurement of 25(OH)D problematic. Ovesen noted that, as with all biomarkers, 25(OH)D is subject to variations stemming from genetics, environment, health status, and seasonal variability and to analytic variations in specimen collection, storage, and analysis procedures. Bruce Hollis described the importance of the technical skills required to perform the available assays to achieve optimal precision and reduce measurement variability (9). Compounding these problems is the absence of a standard reference material for 25(OH)D; as a result, laboratories cannot ensure analytic quality and comparability. However, a much-needed standard reference material will soon be available, as described by Karen Phinney (10)

#### Infants

The EBR found only fair evidence that infants and young children with vitamin D deficiency rickets have low circulating 25(OH)D concentrations (2). Both the EBR and Greer agreed that the evidence is too inconsistent to establish a threshold value for circulating 25(OH)D concentrations above which rickets does not occur, for which scientists could establish normal bone health by using bone mineral content and PTH measures, or for which they could define vitamin D sufficiency or insufficiency.

#### Older children

Fair evidence supports a relation of 25(OH)D to baseline or changes in BMD and to vitamin D exposure in children and adolescents (2). However, these relations do not hold in African American adolescents, who have higher calcium absorption and retention than do their white peers with lower 25(OH)D concentrations, as John Aloia explained (11). Confounding influences include the different effects of chronological and biological age, growth rates, and hormonal changes in adolescents that researchers might not adequately consider in designing their studies, as Christel Lamberg-Allardt explained. Furthermore, PTH elevations in puberty are the result of physiologic changes to support normal bone growth and are not necessarily related to vitamin D status, as Prentice pointed out.

#### Pregnancy and lactation

The EBR indicated that the existing evidence is insufficient to support a relation between 25(OH)D and changes in BMD, but fair evidence exists for an inverse relation between 25(OH)D and PTH in pregnancy (2). However, maternal calcium regulation appears to depend less on vitamin D status during pregnancy because 25(OH)D concentrations either do not change or decline slightly, as Christopher Kovacs described. In addition, vitamin D status has less influence on PTH concentrations in this life stage, as Prentice pointed out, possibly because fetal calcium needs are high. Kovacs explained that maternal vitamin D deficiency can lead to fetal skeletal rickets or early-onset rickets at birth or in the first 2 mo of life, but maternal supplementation with vitamin D increases cord blood 25(OH)D concentrations only and has no effect on skeletal variables or cord calcium concentrations.

Good evidence exists to support an association between 25(OH)D and BMD in lactation (2). However, calcium and vitamin D supplementation during lactation does not reduce maternal skeletal losses, according to Kovacs.

#### Postmenopausal women and elderly men

Presentations at the conference offered evidence supporting a relation of 25(OH)D concentrations to functional bone health outcomes in adults, especially the elderly. However, the EBR found inconsistent results on the relation between 25(OH)D concentrations and fracture risk in elderly and postmenopausal women because of confounding factors and variable results that limited the data's interpretability (2). For example, although 9 of 12 case-control studies found that lower 25(OH)D concentrations were associated with fracture risk, no randomized controlled trials (RCTs) have addressed this issue, and only 1 of 3 cohort studies found an association between lower 25(OH)D concentrations and fracture risk. Moreover, Aloia presented data documenting that African Americans have one-half the osteoporosis prevalence and one-half the fracture risk of whites, even though they have lower 25(OH)D concentrations.

The EBR reported fair evidence from 1 RCT and 2 of 3 cohort studies to support an inverse relation between 25(OH)D and risk of falling in the elderly (2). The highest risk of falling was associated with circulating 25(OH)D concentrations <39 nmol/L. Bess Dawson-Hughes presented data showing a positive association between 25(OH)D concentrations in the elderly and walk time and time to stand, but the EBR found inconsistent results on physical performance (2). Dawson-Hughes noted that research has not established a 25(OH)D concentration for optimal muscle performance in the elderly.

The EBR found a major discordance between RCTs (5 of 6 reported no effect) and observational studies on the relation of 25(OH)D and BMD (2). Nonetheless, fair evidence supports an association between 25(OH)D concentrations and bone loss when 25(OH)D concentrations are <30–80 nmol/L (2). Dawson-Hughes and Heaney presented data supporting a positive relation between 25(OH)D and BMD in elderly persons with 25(OH)D concentrations >74 nmol/L; a combination of 25(OH)D at these concentrations with adequate calcium intake is probably optimal for bone health. Aloia reported that compared with whites, African Americans with lower 25(OH)D concentrations have higher BMC, lower bone turnover rates, and different histomorphology.



### Limitations of existing research

Many of the studies in the literature failed to control for all relevant confounders, such as seasonality, baseline vitamin D and calcium status, body mass index, age, underlying disease, and compliance. Researchers do not report 25(OH)D units in a consistent way; some investigators use ng/L and others use nmol/L. Various 25(OH)D assays are available, but results differ by analytic method, within the same analytic method, and among analytic laboratories using the same method; these discrepancies lead to inadequate quality control of assays. The availability of a standard reference material for 25(OH)D should soon improve this situation.

The Vitamin D External Quality Assessment Scheme (DEQAS) certifies laboratories that meet performance targets for 25(OH)D assays (information on DEQAS is available at <http://www.deqas.org/>). Hollis encouraged research and clinical laboratories conducting 25(OH)D assays to enroll in DEQAS.

### Summary

Researchers have most strongly documented the relation of 25(OH)D with functional bone health outcomes (falls, hip fractures, and BMD) in elderly and postmenopausal white women, but have not documented this relation well in infants or young children. The evidence supports an association in pregnant and lactating women and older children, but physiologic changes can affect biomarkers (such as PTH and bone health) more than vitamin D status in these life stages.

### Question 2: Does dietary intake (from fortified food or supplements) or sun exposure affect circulating 25(OH)D concentrations?

#### Response to fortified foods

Evidence from 10 of 11 RCTs showed that 25(OH)D concentrations increase with consumption of fortified foods (2); however, this response might depend on baseline 25(OH)D concentrations, because responses are greater in persons with baseline concentrations <50 nmol/L. Still, associations between dietary intakes and serum concentrations are inconsistent because endogenous 25(OH)D production varies and the ability to assess dietary intake is limited. Heaney et al (12) showed a 0.7 nmol/L increase in 25(OH)D in healthy young men for each additional 1  $\mu$ g (40 IU) of vitamin D.

#### Response to ultraviolet radiation exposure

Fair evidence suggests that artificial and solar exposure increases 25(OH)D concentrations in vitamin D–deficient and replete persons (2), including the elderly, even though the ability to produce vitamin D decreases with age. The EBR and Barbara Gilchrist discussed evidence showing that sunscreen might not fully block the production of vitamin D. Aloia described recent results showing that vitamin D production varies with skin color (11). However, ultraviolet (UV) exposure increases skin cancer (melanoma and other skin cancers) risk, according to Gilchrist. She suggested that people should, therefore, obtain needed vitamin D from their diet or supplements.

#### Response to supplementation

Supplemental vitamin D increases 25(OH)D concentrations in infants, pregnant and lactating women, children and adolescents,

premenopausal women and younger men, and postmenopausal women and elderly men, as the EBR, conference presenters, and roundtable participants noted. The authors of the EBR completed a meta-analysis of 16 studies that demonstrated an increased 25(OH)D concentration of  $\approx$ 1–2 nmol/L for each 2.5  $\mu$ g (100 IU) per day of supplemental vitamin D (2). However, postmenopausal African American women do not have this response. Aloia reported on his study in which supplementation with 20–25  $\mu$ g (800–1000 IU) vitamin D per day for 3 y did not change 25(OH)D or PTH concentrations in this population group (11).

### Limitations of the evidence

The difficulty of assessing vitamin D exposure and the variability in responses to vitamin D among individuals limits our understanding of the quantitative response of 25(OH)D concentrations to dietary vitamin D intake or sun exposure. Assessment of dietary intake is difficult because of variability in food sources, limitations of current food-composition tables, and bioavailability, as Ovesen described. James Harnly added that measuring vitamin D in foods and supplements is also challenging because it involves time-consuming extraction procedures, because standard reference materials do not exist, because researchers have only validated existing assay methods primarily for dairy products, and because vitamin D content is unstable in foods. Joanne Holden also described the limited analytic data on vitamin D in existing food-composition databases and described the US Department of Agriculture plan to evaluate systematically the vitamin D content of foods and supplements.

The response of 25(OH)D concentrations to vitamin D intake also depends on baseline 25(OH)D concentrations. In addition, season can affect 25(OH)D response, as both NHANES 1988–1994 (13) and the British National Diet and Nutrition Survey of the elderly have shown. In NHANES, concentrations were higher in the fall than in the spring. Oral contraceptive pill use can also affect 25(OH)D concentrations in women aged 15–49 y; according to NHANES 1988–1994, concentrations were higher in women who used the pill than those who did not (13).

### Summary

Good evidence shows that fortified foods and supplemental vitamin D increase 25(OH)D concentrations; the evidence for increases in 25(OH)D concentration by UV radiation exposure is fair (2). However, 25(OH)D responses vary depending on the baseline 25(OH)D concentration; responses are greatest in people whose baseline 25(OH)D concentration is lower than 50 nmol/L. Future research needs to consider baseline 25(OH)D concentrations because of these response variations. In addition, responses vary by ethnicity; for example, postmenopausal African Americans have no response or only limited response to vitamin D from fortified foods and supplements.

### Question 3: What is the evidence for efficacy of supplementary doses of vitamin D on bone mineral density, fractures, and falls for women of reproductive age, elderly men, and postmenopausal women?

#### Bone mineral density

The EBR found that most evidence on the effects of vitamin D supplements on BMD, fractures, and falls comes from studies of

combined vitamin D and calcium supplementation in postmenopausal women and a few studies in elderly men and premenopausal women. As a result, vitamin D's independent effects are difficult to determine (2). Combined supplementation with vitamin D and calcium consistently yielded small increases in total body, femoral, neck, lumbar spine, and hip BMD (2). However, a 3-y study found that combined supplementation in African American women did not change bone mineral content, as Aloia discussed, which suggests that one cannot generalize beneficial effects to all subpopulations. In one study that provided 10  $\mu$ g (400 IU) per day for 2 y of vitamin D supplementation, only femoral and neck BMD increased (2).

#### Fracture risk

Pooled analysis of 13 RCTs in the EBR found no significant effect of vitamin D supplementation on fracture risk; however, when the analysis included only trials in institutionalized persons, it found a significant reduction in total and hip fracture risk (2). Oral vitamin D supplementation of 700–800 IU per day in one study reduced the risk of hip and nonvertebral fractures in ambulatory or institutionalized elderly, as Dawson-Hughes discussed (14). Consistent with these findings, a meta-analysis suggested that vitamin D in combination with calcium decreases fracture risk (15); the Women's Health Initiative found similar results in women aged 60 y and older (16).

#### Falls

The EBR found inconsistent evidence that supplemental vitamin D reduces falls in postmenopausal women or elderly men (2). A pooled analysis of 12 of 14 RCTs showed a small reduction in falls only with combined vitamin D and calcium supplementation (odds ratio: 0.8) but not with vitamin D alone (2). One of 2 cluster-design studies found an effect but the other did not (2). Of the studies that Dawson-Hughes discussed, one found a 49% decrease in falls with 20  $\mu$ g (800 IU) vitamin D and 1200 mg Ca/d compared with calcium supplementation of 1200 mg/d (17); a 3-y RCT of vitamin D plus calcium supplementation found similar results for elderly women but not men (18). In addition to reducing falls per se, vitamin D and calcium supplementation increases muscle strength in institutionalized elderly women, as Dawson-Hughes noted.

#### Summary

Combined calcium and vitamin D supplementation decreases the risk of bone fracture and increases BMD but vitamin D alone does not. Supplemental vitamin D and calcium might reduce the risk of falls in postmenopausal women, but results across all studies on this topic are inconsistent.

#### **Question 4: Is there a level of sun exposure that is sufficient to maintain adequate vitamin D levels but does not increase the risk of skin cancer?**

Solar radiation contains both UVA and UVB radiation, and both types of radiation increase the risk of skin cancer. Vitamin D photosynthesis depends only on UVB radiation. Solar UVA intensity is the predominant source of radiation from the sun and is relatively constant, but UVB intensity varies with latitude, altitude, time of day, time of year, and many other variables.

Relying on UVB radiation to meet vitamin D needs through endogenous synthesis is a subject of current controversy for 2

major reasons: 1) solar radiation increases the risk of skin cancer, and limiting sun exposure can reduce the risk of this disease, and 2) differences of unknown importance exist in the initial metabolic partitioning and safety profiles of endogenously produced versus dietary sources of vitamin D. A key question is whether a threshold exists for meeting people's vitamin D needs through UVB exposure while minimizing the risk of several types of skin cancer (ie, basal cell carcinoma, squamous cell carcinoma, and melanoma).

#### *Increased risk of skin cancers*

Skin cancers constitute a significant public health concern because, as a group, they are the most frequent cancer in the world and account for about one-half of the human cancers in the United States. Because the UVB action spectra for vitamin D photosynthesis and increased risk of skin cancer are identical, persons who photosynthesize vitamin D<sub>3</sub> most effectively (eg, fair-skinned persons) have the highest risk of skin cancer; the converse is true for darker skinned persons, who have lower cutaneous vitamin D<sub>3</sub> synthesis and lower skin cancer risk.

Several factors might influence the risk-benefit ratio of sun exposure. Because UVA exposure is constant, unprotected late-summer-afternoon or midday-winter exposures might involve almost no UVB exposure (and therefore no vitamin D photosynthesis) but might still contribute to photoaging and photocarcinogenesis. Other factors, such as clothing that prevents sunlight from reaching the skin, living in an environment (such as an inner city) in which air pollution and other factors block sunlight, and living in an institution, can also result in inadequate UVB exposures for vitamin D synthesis. In addition, some individuals might benefit less and synthesize less vitamin D endogenously in response to UVB exposures than others. For example, the epidermal melanin in dark-skinned persons protects them from DNA damage but also limits their ability to photosynthesize vitamin D, and elderly persons have less capacity to synthesize vitamin D because they have thinner epidermis and lower concentrations of 7-dehydrocholesterol, the cell membrane constituent that UVB converts to pre-vitamin D.

Although skin cancer risk increases continuously with UV radiation exposure, maximum vitamin D<sub>3</sub> synthesis occurs within a relatively short period of UVB exposure (less than one minimal erythemal dose); beyond this period, further synthesis of vitamin D<sub>3</sub> ceases (19). Gilchrist suggested that a fair-skinned person could achieve maximum pre-vitamin D production in 5 min of sun exposure. Because sunscreens allow continuous transmission of a small fraction of the erythemogenically weighted incident UV photons (about 7% for an SPF 15 product), Gilchrist also suggested that individuals who require 2–8 min of unprotected summer sun exposure to optimize cutaneous vitamin D synthesis could accomplish this with somewhat longer exposures (eg, 10–30 min) when they use sunscreen.

The roundtable participants and the EBR noted that no established threshold exists for UV exposure below which people do not increase their risk of skin cancer. They therefore suggested caution in using the minimal erythemal dose as an endpoint to evaluate increased risk of skin cancer and DNA damage (2, 5).

#### *Differences in metabolic partitioning and safety profiles*

The roundtable participants discussed several potentially important differences between endogenously produced vitamin D

and vitamin D from dietary sources. Questions remain about the potential importance of differences in the initial metabolic partitioning of endogenously synthesized vitamin D (binding to DBP) and orally ingested vitamin D (transported in chylomicrons via the lymph). In addition, researchers believe that cutaneously synthesized vitamin D<sub>3</sub> probably does not produce toxic effects, unlike excessive oral intakes, because metabolic spillover pathways convert excess vitamin D to inactive metabolites in the skin during prolonged UV radiation exposure and therefore prevent overproduction of the precursor molecule (5).

#### *Limitations of the evidence on risk-benefit ratio of sun exposure and vitamin D*

The EBR suggested that recommending a uniform amount of sunlight exposure might be impractical, given the numerous factors that play a role in forming vitamin D from UV radiation (2). The EBR also stated that reporting bias and inadequate assessment of UV exposure dose in published reviews make it difficult to define a dose that constitutes minimal risk of skin cancer. The roundtable participants noted that although healthcare providers often recommend obtaining vitamin D from foods and supplements as substitutes for UVB exposure, not everyone has access to suitable food and supplement sources. Moreover, some persons lack access to sufficient UVB radiation exposure for vitamin D<sub>3</sub> synthesis. Gilchrest suggested that sun exposure is unlikely to produce the serum 25(OH)D concentrations that some researchers currently suggest as indicative of optimal vitamin D status. She cited a study in which only one-half of healthy and racially diverse young adult Hawaiian participants with a mean sun exposure of 29 h/wk for 3 mo achieved serum 25(OH)D concentrations of  $\geq 75$  nmol/L (20). In addition, the roundtable participants expressed concern about the potential importance of differences in the metabolic partitioning and safety profiles of endogenously synthesized versus dietary sources of vitamin D, as described above.

#### **Question 5: Does intake of vitamin D above recommendations lead to toxicities (eg, hypercalcemia, kidney stones)?**

Researchers assume that intake of vitamin D, like that of other micronutrients, has a curvilinear risk curve. Both low and excessively high intakes are associated with increased risk of adverse effects, and optimum intakes occur between these 2 extremes, as discussed by Daniel Hayes (21, 22). We need to understand the full range of potential adverse effects and their mechanisms of action to establish a threshold below which adverse effects are unlikely to occur. However, Jones stated that we know surprisingly little about the mechanisms of vitamin D toxicity (23), and whether sufficient evidence is available to define a threshold vitamin D intake at or above which adverse effects occur is controversial. Reinhold Vieth suggested that the available evidence is so strong that further research is unlikely to implicate vitamin D<sub>3</sub> intakes up to at least 250  $\mu\text{g}$  (10 000 IU) per day in any harm. He also suggested that intakes of 10 000 IU/d raise blood 25(OH)D concentrations to levels comparable with those that occur in the upper range of UV exposure. Gilchrest discussed a Hawaiian study in which none of the participants achieved a 25(OH)D concentration  $> 155$  nmol/L after 3 mo of  $\geq 15$  h of sun exposure per week (20).

Aloia reported that 50  $\mu\text{g}$  (2000 IU) vitamin D/d for 1 y had no observable adverse effects in African American postmenopausal

women (11). Cindy Davis (24) noted that the study by Lappe et al (25), in which white women older than 55 y received 21.5  $\mu\text{g}$  (1100 IU) of vitamin D per day for 4 y, did not report any adverse events. However in the nested case-control study of the  $\alpha$ -Tocopherol,  $\beta$ -Carotene Cancer Prevention Trial (ATBC) in Finnish smokers, higher 25(OH)D concentrations were associated with a 3-fold higher risk of pancreatic cancer (highest versus lowest quintile,  $>65.5$  versus  $<32.0$  nmol/L) (26). Jones suggested that current animal and human data indicate that the plasma 25(OH)D biomarker must rise above 750 nmol/L to produce vitamin D toxicity (23).

The EBR noted that fair evidence exists that vitamin D intakes above current recommended levels produce few adverse outcomes, such as hypercalcemia or kidney stones (nephrolithiasis). However, one must interpret these results cautiously because of the limitations, discussed below, of the available evidence.

#### *Hypercalcemia and hypercalciuria*

The EBR reported that biochemical abnormalities, such as hypercalcemia and hypercalciuria, were the most frequent adverse effects of vitamin D in published reports; however, the differences in the number of these events between the vitamin D groups and the control groups were neither statistically significant nor associated with clinical symptoms (2).

#### *Kidney stones*

The EBR stated that 5 of 7 trials reported no cases of kidney stones in persons taking vitamin D supplements (2). One of these trials found no difference in the number of kidney stone cases between the vitamin D and control groups. However, the Women's Health Initiative reported an absolute increase in the number of kidney stone cases with 10  $\mu\text{g}$  (400 IU) vitamin D<sub>3</sub> and 1000 mg Ca daily (16).

#### *Limitations of the evidence*

The roundtable participants and the EBR (2) identified the following limitations in the evidence on adverse effects: 1) a predominance of short-term studies, which limits our knowledge of long-term (including lifetime) effects; 2) the lack of information on potential nonskeletal effects (eg, aortic and other soft-tissue calcification); and 3) limited data relevant to the full range of life stage and racial and ethnic groups. The EBR also noted the difficulty of establishing a safety intake threshold because of the lack of established toxic endpoints, the lack of systematic examinations or reports of adverse outcomes in published studies, the assessment of safety as secondary outcomes in intervention studies, the inadequate statistical power in most studies to detect adverse effects, the limited number of studies with relatively high vitamin D intakes, and the exclusion in studies of individuals with higher risk of or susceptibility to adverse outcomes than that of the general population (eg, persons with preexisting conditions, such as liver or kidney disease). The roundtable participants noted that the exclusion of persons who might be more susceptible to adverse outcomes and the insufficient statistical power to identify adverse effects in published studies could bias these studies against finding adverse effects. The previously discussed limitations in measuring 25(OH)D concentrations and the lack of a standard reference material for this biomarker, of course, compound all of the above limitations.





### Summary

Despite some evidence that persons tolerate up to 250  $\mu\text{g}$  (10 000 IU) per day of vitamin D, controversy exists regarding the strength and adequacy of the evidence supporting this conclusion. Although one speaker suggested that the evidence was sufficiently robust to preclude the need for more research in this area, the EBR, roundtable participants, and several conference participants expressed concern about the lack of knowledge about mechanisms of action and toxic forms of vitamin D, the many limitations in the available evidence, and the limited generalizability of the results to lifetime exposures in the general population and across life-stage and racial and ethnic groups. In particular, the Women's Health Initiative's finding of increased numbers of kidney stones with modest vitamin D and 1000 mg of calcium supplementation and the ATBC trial's finding that smokers with 25(OH)D concentrations  $>65$  nmol/L have a 3-fold higher risk of pancreatic cancer than do smokers with 25(OH)D concentrations  $<32$  nmol/L demonstrate the need for additional research at what levels of vitamin D toxic effects begin to be seen.

### KEY RESEARCH NEEDS IDENTIFIED

The EBR (2), the roundtable participants (5), the conference presenters, and the conference participants identified many research needs relative to vitamin D. Here, we summarize the key research needed to address the most pressing gaps in our knowledge of vitamin D. We have organized these research needs according to the 5 questions that framed the EBR, the conference, and the roundtable discussion.

#### Question 1: Are specific serum 25(OH)D values associated with bone health and functional outcomes across life and reproductive stages?

- Critically, we need a standard reference material for accurately measuring 25(OH)D concentrations.
- We need to determine the threshold 25(OH)D concentration (from the inflection point) associated with optimal functional outcomes in different life or reproductive stages and ethnic groups.
- We need longitudinal dose-response studies to delineate the functional outcomes of vitamin D and their relevant biomarkers for skeletal and nonskeletal outcomes, paying particular attention to outcomes other than bone health. Research in this area must consider understudied populations such as dark-skinned persons, reproducing women, children and adolescents, and those with health disparities. In the fetus, neonate, child, and adolescent, we need to understand the dose-response relation in childhood and chronic illness as well as with respect to bone health outcomes. In particular, we need better surveillance and biomarkers of rickets. In reproducing women, we need to understand the impact of physiologic changes in DBP and 25(OH)D concentrations on maternal vitamin D metabolism and the effect of these changes on the fetus during development and throughout life. Finally, we need to understand the relation of functional outcomes to extrarenal hydroxylation.

#### Question 2: Does dietary intake (from fortified food or supplements) or sun exposure affect circulating 25(OH)D concentrations?

- How much vitamin D is in foods? To answer this question, researchers need to develop new analytic methods, including methods for measuring 25(OH)D content in foods, for foods and supplements using relevant standard reference materials.
- We need to develop better methods to assess vitamin D intakes from foods and supplements.
- Finally, we need to understand vitamin D storage and mobilization in terms of its compartments, metabolites, turnover, and bioavailability as well as the effect and variability of vitamin D storage and mobilization with changes in body weight and composition as well as age. To help to understand vitamin D storage and mobilization, we need to assess whether the difference between the initial transport and metabolism of dietary vitamin D (chylomicrons) and cutaneously produced vitamin D (DBP) alters its metabolic fate and, thus, affects vitamin D status.

#### Question 3: What is the evidence for efficacy of supplementary doses of vitamin D on bone mineral density, fractures, and falls for women of reproductive age, elderly men, and postmenopausal women?

- We need to assess the independent and interactive effects of vitamin D and calcium on BMD, fractures, and falls in rigorously designed studies that address critical confounders such as baseline vitamin D (which the study must both report and the statistical modeling must include, given its effects on response to supplementation), compliance, and mode of supplemental vitamin D administration. In addition, we need to determine risk factors for fracture in elderly males, postmenopausal women, and reproductive-age females.
- We need to determine the mechanism through which vitamin D decreases the risk of falls in elderly persons. This effort should include defining the 25(OH)D concentration required for optimal muscle function and strength and the relation of this concentration to PTH.

#### Question 4: Is there a level of sun exposure that is sufficient to maintain adequate vitamin D levels but does not increase the risk of skin cancer?

- We need to determine the risks and benefits of UVB exposure to achieve vitamin D sufficiency and, specifically, the threshold of sun exposure sufficient to maintain a healthy vitamin D status without measurable cancer risk.

#### Question 5: Does intake of vitamin D above recommendations lead to toxicities (eg, hypercalcemia, kidney stones)?

- We need to determine vitamin D's mechanism of action relative to toxicity.
- We need an extensive and systematic approach to assess the adverse outcomes associated with high vitamin D intake. Long-term studies need to assess the nonskeletal effects,

such as soft-tissue calcification, associated with high doses and include developmental toxicity studies. In addition, clinical trials need to document adverse events systematically. Developing relevant animal models will be helpful to both the delineation of vitamin D's mechanism of toxicity and assessing the adverse outcomes of toxicity.

We note that, subsequent to our conference, the British Standing Advisory Committee on Nutrition published an independent assessment of vitamin D (27). The committee also identified many of the same research needs as those listed above.

## SUMMARY AND CONCLUSIONS

Researchers have made considerable progress in furthering our understanding of the relation of 25(OH)D to bone health outcomes in the elderly and postmenopausal women, but we know less about other stages of the life cycle and vulnerable groups. The EBR, conference presentations and discussions, and roundtable discussions identified several key issues concerning our present knowledge of vitamin D dietary intakes and endogenous production, as well as the relation between 25(OH)D as a biomarker of vitamin D exposure and functional health outcomes across the life cycle and in key vulnerable populations. The first issue is how the following factors limit the existing data:

- Many studies failed to control for confounders (including diet, baseline vitamin D status, body mass index, age, pubertal stage, disease, season, compliance, and physical activity).
- Few studies have examined the effects of vitamin D independently of calcium or other nutrients.
- Existing 25(OH)D assays are excessively variable, and the lack of a standard reference material exacerbates this problem.
- Research has not validated 25(OH) concentrations with functional outcomes in key populations at various life and reproductive stages and ethnicities.
- We do not understand the relation between 25(OH)D, extrarenal hydroxylation, and paracrine functional outcomes.
- We lack evidence on the nonskeletal functional outcomes of vitamin D, such as soft-tissue calcification, and the role of vitamin D in preventing chronic diseases such as diabetes, immune function, and cancer.

In light of these limitations, significant uncertainties exist about establishing a "threshold" of 25(OH)D for vitamin D status relative to bone and other health outcomes, except in elderly and postmenopausal women

Because of the gaps in our knowledge and limitations in the evidence concerning vitamin D, researchers need to determine and validate relevant functional outcomes for bone and other health aspects relative to the biomarker of vitamin D exposure, 25(OH)D, to enable assessment of vitamin D status across the life cycle.

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