REPORT 4 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-09)
Appropriate Supplementation of Vitamin D
(Resolution 425, A-08)
(Reference Committee D)

EXECUTIVE SUMMARY

Objective: To highlight key information and considerations for physicians regarding vitamin D, including current recommendations for vitamin D intake and its potential for toxicity in the body. The report reviews the biochemistry and metabolism of vitamin D, as well as its association with various disease outcomes, with a focus on adults. Key limitations in the current literature are highlighted, as are areas requiring further research.

Methods: Literature searches for review articles were conducted in the PubMed database and the Cochrane Database of Systematic Reviews using the search term "vitamin D" in the article title and/or abstract. Web sites managed by federal agencies and applicable professional organizations were also reviewed for relevant information. Additional articles were identified by reviewing the reference lists of pertinent publications.

Results: Vitamins D2 (ergocalciferol) and D3 (cholecalciferol) are seco-steroid prohormones that are essential nutrients if sufficient levels of vitamin D3 cannot be produced in the skin. It is unclear how much sun or ultraviolet B radiation exposure, if any, allows for maximal cutaneous synthesis while minimizing the risk of skin cancer. Thus, fatty fish, fortified foods, and dietary supplements are recommended. 1,25-dihydroxyvitamin D is the active metabolite of vitamins D2 and D3, and is an important hormone, transcriptional activator, and immunomodulator. Since circulating levels of 1,25-dihydroxyvitamin D are tightly regulated by the body, serum 25-hydroxyvitamin D (25[OH]D) is the best indicator available of vitamin D status. A rapidly expanding literature has reported inverse associations between 25(OH)D and/or intakes of vitamin D and numerous outcomes related to bone health, several cancers, cognitive function, cardiovascular disease, diabetes, some infections, and several autoimmune diseases. However, clinical trials have yet to prove that vitamin D is causally related to most of these outcomes. It appears, nevertheless, that many people may have subclinically deficient or insufficient levels of vitamin D, prompting many to recommend intakes of 800 to 1,000 international units (IU) per day of vitamin D or even more, in the form of dietary supplements. However, there are significant limitations in the literature due to inadequate control of confounding variables, variability in serum 25(OH)D assays, and a lack of dose-response data on many skeletal and nonskeletal outcomes, including the potential for adverse outcomes. Caution is warranted given the surprising lack of effects, or sometimes even harmful effects, found in large, long-term trials of other previously promising nutrients and hormones, such as antioxidants and hormone replacement therapy. It is likely that greater vitamin D exposure will benefit at least some in the population, but more research is needed.

Conclusions: While the associations between vitamin D and various disease outcomes appear promising, clinical trials have yet to prove that vitamin D is causally related to most of these outcomes. More long-term, well-designed studies, including large intervention trials, are needed across all life stage and racial and ethnic groups to better understand vitamin D's role in disease prevention, to determine the optimal doses and serum 25(OH)D levels, and to fully elucidate the potential for adverse outcomes at various intakes. Nevertheless, physicians should consider measuring the serum concentration of 25(OH)D in patients at risk of vitamin D deficiency and counsel those with deficient or insufficient levels on ways to improve their vitamin D status.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 4-A-09

Subject: Appropriate Supplementation of Vitamin D
(Resolution 425, A-08)

Presented by: Carolyn B. Robinowitz, MD, Chair

Referred to: Reference Committee D
(James L. Milam, MD, Chair)

Resolution 425 (A-08) "Appropriate Supplementation of Vitamin D," introduced by the Pennsylvania Delegation at the 2008 American Medical Association (AMA) Annual Meeting and referred to the Board of Trustees, asks:

> That our AMA urge the Food and Nutrition Board of the Institute of Medicine to re-examine the Daily Reference Intake values for vitamin D in light of new scientific findings; and
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> That our AMA study the advisability of recommending that physicians consider adding the measurement of serum 25-hydroxyvitamin D levels to their health maintenance activities, and where appropriate, recommending dietary supplementation of vitamin D at a dosage of 1,000-2,000 international units (IU) per day, with a report back at the 2009 Annual Meeting.

The first resolve was completed in the fall of 2008. This report addresses the second resolve by reviewing current recommendations for vitamin D and describing its biochemistry, metabolism, and potential toxicity in the body. Vitamin D's association with various disease outcomes is outlined, as well as the optimal source and dose, with a focus on adults. Key limitations in the current literature are highlighted, as are areas requiring further research. This report is not intended to provide an exhaustive review of the literature on vitamin D, but rather to emphasize information and considerations that may be of particular interest to physicians.

CURRENT AMA POLICY RELATED TO VITAMIN D

The AMA currently has limited policy related to vitamin D. AMA Policy D-330.979 (AMA Policy Database) on Medicare reimbursement for vitamin D therapy for dialysis patients directs our AMA to "petition the Centers for Medicare and Medicaid Services and/or lobby Congress to defeat the 'Vitamin D Analogs Draft Local Medical Review Policy' and to prevent its implementation in Florida or any other state."

METHODS

Literature searches for review articles published in the last five years through December 2008 were conducted in the PubMed database and the Cochrane Database of Systematic Reviews using the

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Action of the AMA House of Delegates 2009 Annual Meeting: Council on Science and Public Health Report 4 Recommendations Adopted as Amended, and Remainder of Report Filed.

search term "vitamin D" in the article title and/or abstract. More than 1,500 review articles were identified, with over 300 published in 2008 alone. The most comprehensive and unique reviews were selected and reviewed. Web sites managed by federal agencies and applicable professional organizations were also reviewed for relevant information. Additional articles were identified by reviewing the reference lists of pertinent publications.

BACKGROUND: WHY IS VITAMIN D GETTING SO MUCH ATTENTION?

In recent years, the literature on vitamin D has expanded greatly, particularly since the discovery that most tissues and cells in the body have a vitamin D receptor. No longer just associated with bone health, vitamin D has been implicated in various disease outcomes, including type 1 and type 2 diabetes, multiple sclerosis, cardiovascular disease, and several cancers. Improved surveillance of the serum vitamin D status of the population, as opposed to just the prevalence of rickets, osteomalacia, and osteoporosis, has revealed that 30% to 100% of American and European subpopulations have serum levels of vitamin D that are considered deficient or insufficient, including some individuals consuming levels of vitamin D that meet or exceed currently recommended intakes.[1]

Thus, many researchers and health professionals are concerned that the current dietary reference intakes (DRI) for vitamin D are too low for most of the population, including the current tolerable upper intake levels (ULs), which some research suggests may provide the optimal amount needed to prevent cancer and other diseases. However, the best means of obtaining vitamin D is less clear. Supplementation has been recommended because of concerns about skin cancer and the inability of some individuals to produce adequate amounts of vitamin D from limited sun exposure. Concerns also remain about the optimal dose of supplemental vitamin D. While most supplementation trials of vitamin D have found doses above the UL to be safe, the majority of these trials were not adequately designed to assess harm, particularly from long-term supplementation in the general population.

BIOCHEMISTRY AND METABOLISM

Vitamin D, also known as calciferol, refers to a class of essential fat-soluble seco-sterols.[2] The two most physiologically relevant forms of vitamin D are the prohormones vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol).[2] Sometimes the term "vitamin D" also is used to refer to the metabolites of these prohormones, including the major transport form, 25-hydroxyvitamin D (calcidiol), and the biologically active hormone 1,25-dihydroxyvitamin D (calcitriol).

Vitamin D3 is synthesized endogenously in the skin: ultraviolet B (UVB) radiation converts 7-dehydrocholesterol in keratinocytes to previtamin D3. At skin temperature, previtamin D3 is quickly converted to vitamin D3.[1,2] Vitamin D3 is carried to the liver by the vitamin D binding protein, which binds and transports most forms of vitamin D and its metabolites in plasma.[1,3] Extended sunlight exposure does not cause vitamin D toxicity because the continued solar radiation destroys any excess previtamin D3 and vitamin D3 produced in the skin.[1]

Vitamin D can also be obtained from foods, fortified foods, and supplements as either vitamin D2 or vitamin D3. Specific dietary sources are described in more detail below and in the Appendix. Both dietary vitamin D2 and D3 are fat soluble and are thus absorbed through the lymphatic system carried by chylomicrons, which are then metabolized to remnant particles that carry dietary vitamin D to the liver.[3]

Both vitamin D2 and D3 can be stored in fat cells, and both can be hydroxylated in the liver to form 25-hydroxyvitamin D (25[OH]D), the main circulating form of vitamin D and the best functional

indicator of vitamin D nutritional status.[1,3] However, 25(OH)D is not biologically active; it must be further hydroxylated in the kidneys to 1,25-dihydroxyvitamin D ($1,25[OH]_2D$).[1,4] Production of $1,25(OH)_2D$ in the kidneys is tightly regulated by parathyroid hormone levels generated in response to serum levels of calcium and phosphorous,[2] as well as by fibroblast growth factor 23 and other factors.[1] $1,25(OH)_2D$ increases the efficiency of renal calcium and intestinal calcium and phosphorus absorption.[1] $1,25(OH)_2D$ regulates itself through a negative feedback loop, in which it decreases the production of parathyroid hormone and increases the synthesis of 25-hydroxyvitamin-D-24-hydroxylase, which in turn metabolizes $1,25(OH)_2D$ into calcitroic acid, a water-soluble, biologically inactive metabolite that is excreted in the bile.[1]

While the liver and kidneys are responsible for the metabolism of most of the vitamin D in the body, vitamins D2 and D3 can also be metabolized to 25(OH)D in the skin.[5] The enzyme 25-hydroxyvitamin D-1α-hydroxylase, which metabolizes 25(OH)D to $1,25(OH)_2D$, is present in the kidneys as well as many other tissues, including skin, osteoclasts, macrophages, placenta, colon, brain, prostate, endothelium, and parathyroid glands.[3] However, most $1,25(OH)_2D$ circulating in the blood is produced by the kidneys.[5]

$1,25(OH)_2D$ is a transcriptional activator[6] that binds to vitamin D receptors (VDR) throughout the body, including those in bone, brain, breast, adipose, intestinal, immune, kidney, liver, nerve, ovarian, pancreas, parathyroid gland, pituitary gland, prostate, and skin cells.[3,5] The VDR can then form a complex with the retinoid-x receptor (RXR); this VDR-RXR complex then binds to the vitamin D response elements in DNA and activates transcription of nearby genes and, in turn, proteins.[5] Either directly or indirectly, $1,25(OH)_2D$ is estimated to control at least 200 different genes, including those that regulate cell proliferation, differentiation, apoptosis, and angiogenesis.[1]

IS VITAMIN D A VITAMIN OR IS IT A HORMONE?

Vitamin D can be considered both a vitamin and a hormone, depending on its form and whether or not an individual's sun exposure is sufficient to produce enough vitamin D3 endogenously. If an individual has regular access to sufficient UVB radiation for skin production of vitamin D3, then vitamin D does not need to be consumed in the diet; in this case, vitamin D is technically not an essential nutrient. However, as described below, many factors can reduce the skin's exposure to sufficient UVB. Thus for many people in the modern world, vitamin D is an essential nutrient that must be obtained via the diet or supplements. Regardless of the source, both vitamins D2 and D3 are seco-steroid prohormones that can be metabolized to the biologically active form, $1,25(OH)_2D$, which is a hormone, as it is made in one part of the body and circulates to other tissues where it influences the activities of other cells.[4]

SOURCES OF VITAMIN D

Sun

The human body is designed to manufacture vitamin D3 from sunlight. Throughout history, and to this day, sunlight remains the primary source of vitamin D for most people around the world. Maximum vitamin D3 synthesis is achieved relatively quickly upon UVB exposure, with less than one minimal erythemal dose required.[3] This translates to about five to 30 minutes of sun exposure to the arms and legs between 10 AM and 3 PM twice a week for most people.[1] However, time of day, season, latitude, surrounding surface (sand, snow, water, etc.), amount of cloud cover, thickness of the ozone layer, level of air pollution, time spent outdoors, skin pigmentation (darker skin reduces vitamin D3 synthesis), body composition, age, clothing, and sunscreen use can affect the amount of

vitamin D the skin can produce.[7,8] For example, it is estimated that above about 42 degrees north latitude (Chicago, Boston), vitamin D3 cannot be synthesized by the skin from November to February because no UVB radiation reaches the ground.[8] Cutaneous synthesis of vitamin D is generally possible year round at latitudes below 34 degrees north (a line between Los Angeles and Columbia, South Carolina).[9]

Nevertheless, even in older adults, in whom production of vitamin D by the skin can be greatly diminished due to thinner skin and lower concentrations of 7-dehydrocholesterol,[3,8] regular exposure to sunlight or other sources of UVB radiation can correct deficiencies and reduce fracture risks.[1] Additionally, although sunscreens with a sun protection factor (SPF) of 15 reduce vitamin D3 synthesis by 99%,[1] in practice, vitamin D3 synthesis is not completely blocked, since most people do not apply or reapply sunscreen as directed. However, there is no established threshold for a level of UVB exposure that does not increase skin cancer risk.[3]

Diet and Supplements

Fatty fish is the richest natural food source of vitamin D (Appendix), although milk and ready-to-eat breakfast cereals are the primary food sources of vitamin D in the United States.[2,10] Nearly all milk in the United States is fortified with 100 IU of vitamin D (usually D3) per cup (8 oz),[9,10] as are most ready-to-eat breakfast cereals.[10] Contrary to public perception, milk products such as yogurt, butter, ice cream, sour cream, cream, cottage cheese, and most varieties of hard and soft cheeses are not regularly fortified with vitamin D.[10] In fact, unlike Canada and Finland, no foods are required to be fortified with vitamin D in this country, although many categories of food are eligible for controlled levels of vitamin D fortification, including milk, milk products, and cereal flours and related products.[10] Even milk is not required to be fortified unless it is labeled as such.[10] The Food and Drug Administration regulates the amount of vitamin D that can be added to foods to prevent over-fortification.[10]

Vitamin D2 used in foods and supplements is manufactured via the ultraviolet irradiation of ergosterol in yeast and plants.[1] Vitamin D3 added to foods and supplements is made via the ultraviolet irradiation of 7-dehydrocholesterol from lanolin.[1] Lanolin is an animal product, generally obtained from sheep, and thus, this source of vitamin D may not suitable for some vegetarians.

Dietary supplements containing vitamin D2 or D3 are widely available over-the-counter as single supplements and as part of standard multivitamins and other multiple vitamin supplements (Table). High doses of vitamin D2 are available by prescription. Also available by prescription are vitamin D2 and D3 analogs and their metabolites, including $1,25(OH)_2D$ and its synthetic analogs (Table). Calcitriol ($1,25[OH]_2D$) and its active analogs are used to treat psoriasis (generally topically), secondary hyperparathyroidism, hypocalcemia, and metabolic bone disease in patients with severe chronic renal or liver disease and hypoparathyroidism.[11-13]

What Source(s) Are Best?

If skin cancer risk were not an issue, the sun would likely be considered the best source of vitamin D, as the human body is designed to synthesize vitamin D3 from sunlight. In addition, other factors described above, such as seasonality, time spent outdoors, clothing, etc., can limit the skin's ability to make vitamin D. Therefore, dietary sources are widely recommended to supplement minimal sun exposure. Since relatively few Americans frequently consume fatty fish, and the natural vitamin D content of other foods is generally low or nonexistent per serving, fortified foods and/or supplements are the best source of vitamin D for many people.[10]

As to the best form of dietary vitamin D, vitamin D2 has been reported to be only one third as effective as vitamin D3 at increasing and sustaining serum 25(OH)D levels,[4,14,15] although recent research suggests that both forms may be equally effective in raising and maintaining serum 25(OH)D levels.[16] Other factors, such as availability and affordability of supplements, and food preferences, such as fish intake and vegetarianism, may ultimately determine the "best" source for many people.

Can Individuals Get Enough Vitamin D from Food or Should They Take Supplements?

It is possible to get sufficient amounts of vitamin D from food alone, although most people would need to include foods fortified with vitamin D, like milk, orange juice, and breakfast cereal. Whether or not people need to take a supplement depends on the foods they regularly consume and the recommended intake for their life stage group and health status (assuming no endogenous synthesis from UVB radiation). As described below, research continues on the optimal intakes needed to achieve optimal serum levels of 25(OH)D, the current biomarker of vitamin D status.

INTERACTIONS BETWEEN VITAMIN D AND OTHER SUPPLEMENTS OR MEDICATIONS

A few supplements and dietary components may interfere with the absorption or action of vitamin D in the body. High doses of vitamin A may inhibit absorption of vitamin D in the intestine, and vitamin A and retinols may interfere with vitamin D's action on bone.[8] The non-absorbable, non-caloric fat substitute olestra may also prevent the absorption of vitamin D if consumed at the same time.[8]

Several medications may affect vitamin D absorption or metabolism. Medications that reduce fat absorption, such as bile acid sequestrants (e.g., cholestyramine, colestipol), orlistat, and mineral oil, may also limit the absorption of vitamin D if consumed at the same time.[1,8] Anti-convulsants (e.g., phenytoin, phenobarbital), glucocorticoids, highly active antiretroviral therapy (HAART), anti-rejection medications, or other drugs that activate the steroid and xenobiotic receptors may increase catabolism of vitamin D.[1] In hypoparathyroid patients, vitamin D may also interact with thiazide diuretics to cause hypercalcemia.[12] In contrast, use of oral contraceptive pills is associated with higher serum 25(OH)D levels.[17] Other medications also may affect vitamin D metabolism; as with any drug or dietary supplement, physicians should evaluate the full list of possible interactions and side effects in the context of each individual patient.

CURRENT RECOMMENDATIONS

The Food and Nutrition Board of the Institute of Medicine (IOM) established the current dietary reference intakes (DRIs) for adults in 1997.[2] The recommendations are based on the amount of vitamin D needed to maintain adequate calcium metabolism and bone health. The Food and Nutrition Board felt that the state of knowledge at the time was insufficient to establish an Estimated Average Requirement (EAR) and in turn a Recommended Dietary Allowance (RDA); both cover the nutrient needs of a specific percentage of individuals. Therefore, it established Adequate Intake (AI) levels for vitamin D, which nevertheless are estimated to cover the nutrient needs of all individuals in the life stage group.[2] The AIs for vitamin D assume that no vitamin D is available from exposure to sunlight or other sources of UVB radiation.[2] The AIs for adults are listed below.

Life Stage	**Adequate Intake (AI) for vitamin D per day**
Aged 19 – 50 years	200 IU (5.0 μg)

Aged 51 – 70 years	400 IU (10 μg)
Aged > 70 years	600 IU (15 μg)
Pregnant, Aged 14 – 50 years	200 IU (5.0 μg)
Lactating, Aged 14 – 50 years	200 IU (5.0 μg)

The UL for all adults is currently 2,000 IU (50 μg) per day. This level is based on one study, which observed hypercalcemia (serum calcium level above 2.75 mmol/L) in adults consuming 3,800 IU (95 μg) of vitamin D per day for three months. In the same study, no observed adverse effects were reported at intakes of 2,400 IU (60 μg) per day. After factoring in the lack of certainty about the effect of these doses in a larger population of individuals, some of whom might be more sensitive to supplemental vitamin D, as well as the short duration and small sample size of the study, the UL was set at 2,000 IU per day. While not explicitly considered in its analysis, the Food and Nutrition Board noted case reports of severe adverse effects (described under Toxicity, below) from intakes of 10,000 to 50,000 IU (250 to 1,250 μg) per day over many years.[2]

An ad hoc expert committee for the Food and Nutrition Board is currently reviewing the DRIs for vitamin D and calcium.[18] Its thorough examination of the literature will include studies on vitamin D's relation to risk of cancer and other chronic diseases and conditions. This new DRI report is expected to be released in 2010.

In the meantime, the American Academy of Pediatrics (AAP), which previously endorsed the AI of 200 IU vitamin D for healthy infants, children, and adolescents, recently revised its recommendation to a minimum 400 IU per day beginning soon after birth.[7] The AAP cited evidence that 200 IU of vitamin D per day fails to maintain serum 25(OH)D concentrations above 20 ng/mL (50 nmol/L) in infants, which is the level some researchers have associated with deficiency in adults. The AAP agrees with the Centers for Disease Control and Prevention, American Cancer Society, and many other organizations that sunlight exposure should be minimized to reduce the risk of skin cancers, and therefore recommends that adequate vitamin D levels be achieved through supplementation.[7]

The AAP further recommends that health care professionals providing obstetric care consider measuring the serum 25(OH)D concentrations of pregnant women and recommends supplements for those women with 25(OH)D concentrations below 32 ng/mL (80 nmol/L), the level at which the AAP defined vitamin D sufficiency in adults. It noted that prenatal vitamins containing 400 IU of vitamin D3 appear to have minimal impact on maternal serum 25(OH)D levels.[7] For lactating women, vitamin D doses of 1000 to 2000 IU per day do not significantly increase the 25(OH)D levels in their breastfeeding infants, although studies on the effect of higher doses are limited. Therefore, the AAP advised against universal high-dose supplementation of lactating women and recommended giving vitamin D supplements directly to breast-fed infants.[7]

Like the AAP, other organizations have recently recommended intakes of vitamin D that exceed the current AIs. The North American Menopause Society recommends that women at risk of vitamin D deficiency due to inadequate sunlight exposure take 700 to 800 IU of vitamin D per day.[19] The National Osteoporosis Foundation recommends that adults under age 50 years consume 400 to 800 IU of vitamin D (either D2 or D3) daily and that adults aged 50 years and older consume 800 to 1,000 IU vitamin D per day for optimal bone health.[20] The Canadian Cancer Society advises adults to talk to their physician about taking 1,000 IU of vitamin D per day during the fall and winter, and all year if they are elderly, have dark skin, spend limited time outdoors, or wear clothing that covers most of their skin.[21] In 2006, the Canadian Cancer Society, along with several other organizations, including the American Cancer Society, American College of Rheumatology, Canadian Dermatology

Association, and the World Health Organization Collaborative Centre for the Promotion of Sun Protection endorsed the message that supplementation and small amounts of sun exposure are the preferred methods of achieving optimal vitamin D status.[22] However, the American Academy of Dermatology recommends that vitamin D be obtained from foods and/or supplements and not from unprotected ultraviolet radiation exposure.[23]

ASSOCIATIONS OF VITAMIN D WITH HEALTH OUTCOMES

Bone Health

Vitamin D is most well known for its impact on bone health. Vitamin D is necessary for proper growth and skeletal development in utero and during childhood and adolescence,[1,7] which also may help prevent osteoporosis and fracture in adulthood.[24] In adults, insufficient vitamin D can lead to osteopenia, osteoporosis, osteomalacia, muscle weakness, and fracture.[1]

In general, serum 25(OH)D concentrations are directly associated with bone mineral density (BMD). Some research has found that maximal BMD, and lowest risk of hip and other nonvertebral fracture, is achieved at serum concentrations of approximately 36 to 40 ng/mL (90 to 100 nmol/L), although the slope of this association may vary between ethnic and racial groups.[25] For example, African Americans tend to have higher BMD than whites, and lower risk of osteoporotic fractures, despite lower levels of 25(OH)D.[26] Still, low serum 25(OH)D levels result in higher parathyroid hormone concentrations and lower BMD even among blacks.[25,27] A recent systematic evidence-based review found fair evidence that serum 25(OH)D levels were inversely associated with both BMD and falls in older adults.[28] However, this same review found inconsistent evidence that serum 25(OH)D concentrations are associated with reduced fracture risk in elderly and postmenopausal women.[3,28]

Inconsistent results have also been observed for the effect of vitamin D supplementation on fracture risk and falls, even though vitamin D-fortified foods and supplements are associated with increases in serum 25(OH)D concentrations in most,[28] but not all populations.[26] Uncontrolled confounding variables (e.g., seasonality, baseline vitamin D and calcium status, body mass index, age, underlying disease, and compliance) likely contributed, at least in part, to the inconsistency across studies. In addition, the doses studied may have been insufficient to increase serum levels of 25(OH)D to a high enough degree. It appears that to reduce fracture risk, mean serum concentrations of 25(OH)D need to be approximately 40 ng/mL (100 nmol/L). Doses of 400 IU/d of vitamin D3 appear generally ineffective at achieving this serum concentration and, in turn, reducing fracture risk. Most effective have been doses of 700 to 800 IU vitamin D3/d, particularly in those with baseline concentrations of 25(OH)D between 17 and 31 ng/mL (44 and 77 nmol/L).[25] On the whole, however, the evidence appears insufficient that supplemental doses of vitamin D alone decrease risk of bone fracture or increase BMD in pre- and postmenopausal women and elderly men, although supplementation with calcium and vitamin D combined does.[3] Risk of falls, though, remains inconsistent in postmenopausal women for supplemental vitamin D and calcium combined.[3]

Other Musculoskeletal Outcomes

VDRs are present in skeletal muscle and deficiency of vitamin D is associated with muscle weakness.[1] Performance speed and muscle strength have been found to improve as 25(OH)D levels increase to at least 40 ng/mL (100 nmol/L).[1] However, in the elderly, results for physical performance have been inconsistent[3] and a recent randomized trial of vitamin D plus calcium found no effect on physical functioning or performance in older women.[29]

There is some evidence that chronic nonspecific musculoskeletal pain, a symptom of hypovitaminosis D, is being misdiagnosed and mistreated. One study observed that 93% of patients aged 10 to 65 years admitted to a hospital emergency department complaining of persistent, nonspecific muscle aches and bone pain were deficient in vitamin D.[30] Over 90% had been previously evaluated by a health care provider regarding their chronic pain and all had used over-the-counter or prescription analgesics without improvement; none had been tested for vitamin D deficiency. Patients with nondetectable levels of serum 25(OH)D had previously had their symptoms attributed to stress, depression, gestational diabetes, nondegenerative joint disease, and other causes.

Cancer Prevention

Some, but not all, studies have found that individuals living at higher latitudes (i.e., with presumably less sun exposure) have a higher risk of contracting and dying from several cancers, including Hodgkin's lymphoma, colon, pancreatic, prostate, ovarian, breast, and others,[1] although latitude is not necessary directly associated with serum 25(OH)D levels, particularly in Europe.[8] Epidemiological evidence has found a 30% to 50% increased risk of cancers of the colon, prostate, and breast in individuals with serum 25(OH)D levels less than 20 ng/mL (50 nmol/L), as well as increased mortality from these cancers.[1]

A recent extensive review of the literature concurred that there is consistent evidence supporting an inverse association between serum 25(OH)D levels and colorectal cancer and sporadic colorectal adenoma; however, only limited evidence supported an actual causal link, as two large randomized trials did not support an effect of vitamin D on colorectal cancer risk.[8,31,32] This same extensive review found only limited evidence that vitamin D reduced risk of breast cancer; only one randomized trial examined this association and observed no effect of vitamin D plus calcium on breast cancer incidence.[33] The review found no evidence for reduced risk of prostate cancer and insufficient evidence to evaluate other cancers.[8] Evidence was suggestive that vitamin D supplements (range 300 to 2000 IU/d; mean dose 528 IU) may lower all-cause mortality,[8] based primarily on a meta-analysis of randomized trials.[34]

Many possible explanations account for the lack of efficacy in trials: supplemental doses of vitamin D may have been too low (400 to 830 IU/d), vitamin D may have interacted with hormone replacement therapy, poor compliance, short study durations, lack of baseline serum 25(OH)D data, etc., but the fact remains that good evidence showing a causal effect of vitamin D on any cancer risk is lacking.[8] It is possible that vitamin D exerts more influence on cancer progression and mortality rather than on cancer incidence, and/or that serum 25(OH)D is a risk marker of cancer occurrence rather than a causal risk factor.[8]

Cognitive Function

Some cross-sectional studies suggest that vitamin D may be associated with cognitive function and Alzheimer's disease.[35-38] Vitamin D receptors are found in neurons, as well as regions often affected in Alzheimer's disease, such as the hypothalamus, substantia nigra, cortex, and hippocampus.[36] In vitro and animal studies also suggest vitamin D may have neuroprotective effects.[36] However, no prospective studies or randomized trials have confirmed this association in the general population.

Depression and Mood

Deficient levels of vitamin D have been associated with higher rates of depression and low mood.[1,38-40] Few randomized trials have attempted to confirm this association.[40]

Cardiovascular Disease

Hypertension and cardiovascular disease risk have been directly associated with latitude.[1] Deficiencies in vitamin D have been associated with hypertension,[41] cardiovascular disease,[42,43] and congestive heart failure, as well as with inflammatory factors such as C-reactive protein and interleukin-10.[1] However, two randomized trials involving vitamin D supplementation failed to find an effect on cardiovascular disease risk.[31,44] In hypertensive patients (as opposed to the general population), a small trial of UVB radiation three times per week for three months resulted in a reduction of both systolic and diastolic blood pressure by 6 mm Hg to normal levels.[45] While recognizing the need for more research, a recent review of vitamin D and cardiovascular disease risk recommended monitoring serum 25(OH)D status and outlined specific therapies for correcting vitamin D deficiency.[46]

Diabetes

Research suggests that supplemental vitamin D in pregnant women, infants, and children reduces the risk of type 1 diabetes.[1] In adults, a recent cross-sectional study found that low levels of 25(OH)D were associated with increased insulin resistance in nondiabetic persons.[47] A large prospective study observed that supplementation of 800 IU of vitamin D plus 1200 mg of calcium per day decreased the risk of type 2 diabetes.[48] However, a large randomized controlled trial of 400 IU of vitamin D3 plus 1000 mg of calcium per day did not reduce diabetes incidence over seven years of follow-up.[49]

Immunity and Autoimmune Disease

$1,25(OH)_2D$ is considered a powerful immunomodulator,[1] particularly for its effects in suppressing the immune response.[50] Vitamin D in various forms has been inversely associated with several autoimmune diseases, including multiple sclerosis,[51] rheumatoid arthritis, osteoarthritis,[1] systemic lupus erythematosus,[52,53] and inflammatory bowel diseases such as Crohn's disease and ulcerative colitis.[50] While some of these associations may be in part a consequence of the disease and/or treatment (e.g., malabsorption and corticosteroid treatments), research suggests that vitamin D plays a role in the development, progression, and/or severity of the disease.[50,52] For example, increasing latitude of residence has been associated with increased risk of multiple sclerosis and Crohn's disease.[1] Likewise, higher intakes of vitamin D have been associated with reduced incidence of multiple sclerosis[54] and rheumatoid arthritis[55] and with the slower progression of osteoarthritis.[56]

While vitamin D is linked to the suppression of autoimmune disease, it also can stimulate the immune response to at least some microorganisms.[50] Before the development of antibiotics, sunshine was recognized as a cure for many tuberculosis patients.[5] Recently, researchers discovered that exposure to *Mycobacterium tuberculosis* causes monocytes and macrophages to up-regulate gene expression of the VDR and the enzyme that converts 25(OH)D to $1,25(OH)_2D$ (25(OH)D-1-α-hydroxylase), which in turn increases production of the antimicrobial peptide cathelicidin and the destruction of intracellular *M. tuberculosis*.[57] A recent trial confirmed that supplemental vitamin D augments a marker of antimycobacterial immunity in healthy adults exposed to tuberculosis, possibly through other mechanisms as well.[58] Low serum 25(OH)D levels have also been associated with increased risk for upper respiratory tract infections such as the common cold.[59]

CLINICAL MEASUREMENT OF VITAMIN D STATUS

Which Form of Vitamin D Should be Measured?

As described above, 25(OH)D is the main circulating form of vitamin D and best functional indicator of vitamin D nutritional status.[1,2] Levels of the biologically active vitamin D metabolite (i.e., the hormone), $1,25(OH)_2D$, are tightly regulated and will often be normal or even elevated in those with vitamin D deficiency because of secondary hyperparathyroidism.[1] Serum levels of vitamin D2 and D3 are likewise not good indicators of vitamin D status due to their relative short half-lifes, as they are quickly stored in fat or metabolized in the liver.[2] The half-life of 25(OH)D is estimated at 10 days to three weeks.[2] Clinicians should note that some laboratories report 25(OH)D2 and 25(OH)D3 separately; however, these may be simply added together to obtain the total of both types of 25(OH)D.[1,11]

Identifying Deficiency

Traditionally, vitamin D deficiency has been defined by its overt clinical symptoms related to the inadequate mineralization or demineralization of the skeleton, such as rickets and osteomalacia.[2] However, subclinical deficiency or insufficiency of vitamin D is believed to be much more common, and is typically identified by measuring serum levels of 25(OH)D;[11] values below 20 ng/mL (50 nmol/L) are generally considered deficient[1,11] (although some argue this level may be unnecessarily high[8]). Serum 25(OH)D levels of 21 to 29 ng/mL (52 to 72 nmol/L) are considered insufficient, based on research that parathyroid hormone levels do not level off until serum 25(OH)D levels are in the range of 30 to 40 ng/mL (75 to 100 nmol/L) and that intestinal calcium transport is diminished at 25(OH)D levels below 32 ng/mL (80 nmol/L).[1] Using these definitions, an estimated one billion people are vitamin D deficient or insufficient, including an estimated 30% to 100% of American and European subpopulations.[1]

Deficient levels of vitamin D may be caused by a number of factors, including:

- Inadequate skin synthesis due to dark skin pigmentation, age, clothing, season, etc.
- Inadequate intakes of vitamin D from foods or supplements.
- Decreased bioavailability of vitamin D due to fat malabsorption, which may be caused by various disorders (e.g., cystic fibrosis, celiac disease, Crohn's disease), gastric bypass surgery, medications that reduce cholesterol absorption, or obesity, which is believed to sequester vitamin D in body fat.
- Increased catabolism of 25(OH)D and/or $1,25(OH)_2D$ by certain medications, including anticonvulsants, glucocorticoids, HAART, and anti-rejection medications.
- Reduced production of 25(OH)D due to liver dysfunction.
- Increased loss of 25(OH)D in the urine due to nephrotic syndrome.
- Reduced production of $1,25(OH)_2D$ due to chronic kidney disease.
- Heritable rickets disorders, including vitamin D-resistant rickets.
- Acquired disorders, such as tumor-induced osteomalacia, primary hyperparathyroidism, granulomatous disorders, sarcoidosis, tuberculosis, certain lymphomas, and hyperthyroidism.[1]

Optimal Serum Levels of Vitamin D

While optimal levels have yet to be established, serum 25(OH)D levels of 30 ng/mL (75nmol/L) or greater are generally recognized as sufficient.[1,60] Some researchers believe that values of 40 to 60

ng/mL (100 to 150 nmol/L) are more appropriate,[61] while others suggest levels as high as 55 to 90 ng/mL (137.5 to 225 nmol/L)[62] are necessary to sufficiently prevent adverse health outcomes. Others are less comfortable using even serum 25(OH)D values as high as 20 or 30 ng/mL (50 to 75 nmol/L) to define sufficiency in the absence of more rigorous randomized trial data.[8] Notably, in some people, such as those with chronic granulomatous disorders, serum 25(OH)D levels should not exceed 30 ng/mL (75 nmol/L) because at higher levels macrophage synthesis of $1,25(OH)_2D$ leads to hypercalciuria and hypercalcemia.[1]

Limitations in Measuring Serum 25(OH)D

Circulating levels of the prehormone 25(OH)D is the best biomarker available of dietary and endogenous vitamin D exposure, although it also reflects other processes like absorption and metabolism.[63] It is not an ideal biomarker because it has not been specifically and reliably related to any functional outcomes or indicators, in part because it is related to outcomes impacted by many other factors, such as BMD, which also reflect long-term exposures.[3] In addition, results of 25(OH)D assays vary by analytic method and even sometimes within the same analytic method and by laboratory, due primarily to the lack of a standard reference material. However, a new standard reference material for 25(OH)D is expected to be available soon.[64] Because of these limitations, serum 25(OH)D is most clinically useful at identifying toxicity and deficiency, compared with status in the middle range, where it is less predictive of adverse health outcomes in the general population.[63]

Optimal Dose of Vitamin D

It is unknown exactly how much supplemental vitamin D needs to be consumed to increase serum 25(OH)D levels, even to minimally sufficient levels, because individual responses vary widely and depend on the nature and extent of the deficiency,[5,11] as well as other factors related to endogenous synthesis, absorption, storage, metabolism, and some that may be yet unknown.[3,63] The greatest responses to vitamin D from foods and sun exposure are typically seen when serum 25(OH)D levels are below 20 ng/mL (50 nmol/L).[3]

The current guidelines of the IOM's Food and Nutrition Board and other organizations were outlined above. Recommended intake values range from 200 to 1,000 IU per day. The upper range of these recommendations is consistent with the daily doses of 800 to 1,000 IU of vitamin D3 currently recommended by many researchers to achieve minimally sufficient serum 25(OH)D values of 30 ng/mL or greater[1,5,11]; some recommend daily doses as high as 2000 IU.[61] Sensible sun exposure or use of tanning beds or other UVB radiation lamps is also recommended by some,[1] although others adamantly recommend avoiding all exposure to sunlight and other sources of UVB radiation.[23] Higher doses of supplemental vitamin D2 or D3 may be warranted in those whose deficiencies are secondary to comorbid conditions or medication use, as previously reviewed by Holick.[1]

Others remain cautious about increasing current recommendations for vitamin D intakes due to the lack of solid randomized trial evidence.[8] Concerns also exist about potentially increasing serum 25(OH)D levels above what some people might naturally produce from sun exposure alone.[3,65] Such caution is warranted given the surprising lack of effects, or sometimes even harmful effects, noted in trials of other previously promising nutrients and hormones (e.g., antioxidants, hormone replacement therapy).[8]

Toxicity

Serum 25(OH)D levels above 150 ng/mL (375 nmol/L) are indicative of vitamin D intoxication,[1] which leads to hypercalcemia and hyperphosphatemia.[1,2] Prolonged intakes of vitamin D have been associated with reduced renal function, and calcification of soft tissues in the kidney, blood vessels, heart, and lungs, as well as with severe depression, anorexia, nausea, and vomiting.[2] Toxic serum levels of 25(OH)D are observed after ingestion of 40,000 to 50,000 IU per day or more for several week or years.[1,5] Researchers believe that 25(OH)D is the form of vitamin D that is most likely responsible for toxic effects in the body, rather than vitamin D2 or D3 itself, but this has not been established.[63]

While some argue that it is highly unlikely that doses up to 10,000 IU per day (250 ug) are harmful,[66] others believe much remains unknown about the mechanisms of vitamin D action and potentially toxic forms of vitamin D.[3] For example, the α-tocopherol, β-carotene Cancer Prevention Trial (ATBC) in Finnish smokers reported a three times greater risk of pancreatic cancer in men with the highest 25(OH)D concentrations (>65.5 nmol/L vs. < 32.0 nmol/L; or >26.2 ng/mL vs. <12.8 ng/mL).[67] Furthermore, although several trials reported no kidney stones in those taking vitamin D supplements,[3] at least one found an absolute increase in the number of women reporting kidney stones who consumed 400 IU of vitamin D3 and 1000 mg of calcium per day.[68]

Several other concerns remain about the potential adverse effects of vitamin D supplementation, including the lack of long-term studies; studies in all life stage and racial and ethnic groups; and studies on the potential nonskeletal effects, such as aortic and other soft-tissue calcification.[3] There are no established toxic endpoints for vitamin D and few studies were designed to assess its potential toxicity. Most studies were inadequately powered to detect adverse effects, nor did they test relatively high doses or include individuals with potentially greater susceptibility to adverse outcomes, such as those with liver or kidney disease. This may have biased the literature against the finding of adverse effects.[3]

AREAS REQUIRING FURTHER RESEARCH OR ATTENTION

Despite significant gains in knowledge about vitamin D in the last decade, recent reviews and expert discussions[3] have identified substantial limitations in the literature:

- Many studies failed to control for important potential confounders, such as baseline 25(OH)D concentrations, skin pigmentation, seasonality, body mass index, compliance, disease status, and physical activity.
- Variability in serum 25(OH)D assays, including the lack of a standard reference material.
- Limited data on vitamin D's effects independent of calcium, magnesium, and phosphate.
- Lack of dose-response studies for both skeletal and nonskeletal outcomes.
- Lack of studies on the relation of extrarenal hydroxylation to functional outcomes.
- Inadequate data on the vitamin D content of foods.

In addition, concerns remain about the potential significance of differences in the metabolic partitioning of endogenously produced vitamin D and that from dietary sources – in other words, does the initial transport and metabolism of dietary vitamin D on chylomicrons have significant consequences compared to cutaneously produced vitamin D3 that enters circulation on vitamin D binding proteins?[3,63] Likewise, little is understood about the extent of vitamin D storage in the body and the potential hazards of high stores in adipose tissue, including any effects of saturating the storage pools.[63] This is particularly important because serum 25(OH)D concentrations do not specify

whether vitamin D is entering and leaving the tissues, which could be relevant to the potential for excess exposure in some people.[63]

Furthermore, daily intakes of 800 IU vitamin D or greater are difficult to obtain from food alone, even including fortified food sources. Not everyone wants to consume, or has access to, fortified foods or supplements. For these people, is there a minimal sunlight exposure that could raise serum 25(OH)D levels to sufficient levels, without increasing risk of skin cancer? What is the risk of skin cancer in such individuals relative to increased risk of other cancers due to a lack of vitamin D? How does this vary across populations?

Clearly, much more research is needed to answer these and other questions, particularly in the form of:

- Long-term, well-designed dose-response trials on bone health and other functional outcomes (e.g., immune function and chronic disease prevention) that also address adverse outcomes and potential confounders across all life stage groups.
- Studies to determine serum 25(OH)D threshold values to relevant functional outcomes across life stage and racial and ethnic groups.
- Studies on the bioavailability, storage, mobilization, and turn-over of vitamin D metabolites across a range of intakes to assess how these might be affected by age, changes in body weight and composition, or other factors.[63]
- Long-term studies to establish the doses at which vitamin D toxicity begins to occur, and if this dose varies by population subgroups.[3]

SUMMARY AND CONCLUSION

The vitamins D2 and D3 are seco-sterol prohormones whose active metabolite, $1,25(OH)_2D$, is an important hormone, transcriptional activator, and immunomodulator. Serum 25(OH)D is the best functional indicator available of vitamin D status, and a rapidly expanding literature has reported inverse associations between serum 25(OH)D and/or intakes of vitamin D and numerous outcomes related to bone health, several cancers, cognitive function, cardiovascular disease, diabetes, and several autoimmune diseases. However, clinical trials have yet to prove that vitamin D is causally related to most of these outcomes. Nevertheless, improved surveillance of the 25(OH)D status of the population indicates many people may have subclinically deficient or insufficient levels of vitamin D, prompting many researchers and health organizations to recommend intakes of 800 to 1,000 IU per day of vitamin D; some researchers recommend even 2,000 IU per day, which is currently the UL set by the Food and Nutrition Board. It is difficult for most Americans to consume that much vitamin D from food alone, even including fortified food. Since it is unclear how much sun or UVB exposure, if any, allows for maximal cutaneous synthesis of vitamin D while minimizing risk of skin cancer, this means most Americans would have to take a dietary supplement to achieve these levels of vitamin D in their diet.

Despite significant gains in knowledge in this rapidly evolving area of research, substantial limitations remain due to inadequate control for confounding variables, variability in serum 25(OH)D assays, the inability to discern vitamin D's effects independent of other factors such as calcium intake, the lack of dose-response data on both skeletal and nonskeletal outcomes, inadequate data on the vitamin D content of foods, and a lack of understanding of the metabolic partitioning of different sources of vitamin D as well as the extent of vitamin D storage capacity in the body. These are significant issues to consider when recommending supplementation for the population at large, particularly given the surprising lack of effects, or sometimes even harmful effects, found in large,

long-term randomized trials of other previously promising nutrients and hormones, such as antioxidants and hormone replacement therapy. More long-term, well-designed studies are needed across all life stage and racial and ethnic groups, to address these and other issues, including the potential for adverse outcomes at various doses, to determine serum 25(OH)D threshold values relevant to functional outcomes, and to better understand the bioavailability and turnover of vitamin D metabolites.

The Food and Nutrition Board is currently reviewing the literature on vitamin D and is expected to release new guidelines in 2010. In the meantime, clinicians may wish to assess the serum 25(OH)D levels of their patients who may be at risk of vitamin D deficiency, and counsel those with deficient or insufficient levels on how they might improve their vitamin D status.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted in lieu of Resolution 425 (A-08) and the remainder of this report be filed:

1. That our American Medical Association (AMA) support continued research on vitamin D and its metabolites, particularly long-term studies that address the benefits, adverse outcomes and potential confounders across all life stage groups. (Directive to Take Action)

2. That our AMA educate physicians about the evolving science of vitamin D and its impact on health and develop resources about vitamin D for patients. (Directive to Take Action)

3. That our AMA encourage physicians to consider measuring the serum concentration of 25-hydroxyvitamin D in patients at risk of vitamin D deficiency and counsel those with deficient or insufficient levels on ways to improve their vitamin D status. (New HOD Policy)

4. That our AMA monitor the development of new dietary references intakes for vitamin D in 2010 and respond as appropriate. (Directive to Take Action)

Fiscal Note: $ 3,500

TABLE. SOURCES OF VITAMIN D AND SELECTED METABOLITES[1, 9, 12, 13, 69]

Source	**Estimated dose (IU)**[a]	**Form of vitamin D**
Natural		
Sunlight or UVB radiation, minimum 0.5 erythemal dose[b]	3000	D3
Salmon		
Fresh, wild salmon, 3.5 oz	600 – 1000	D3
Fresh, farmed salmon, 3.5 oz	100 – 250	D3 or D2
Canned salmon, 3.5 oz	300 – 600	D3
Sardines, canned in oil, drained, 1.75 oz	250	D3
Mackerel, jack, canned, drained, 3.5 oz	250	D3
Tuna, light, canned in oil, drained, 3.5 oz	230	D3
Cod liver oil (1 tsp)	400-450	D3
Shiitake mushrooms Fresh, 3.5 oz Sun-dried, 3.5 oz	 100 1600	 D2 D2
Egg yolk	20	D3 or D2
Liver, beef, cooked, 3.5 oz	15	D3
Fortified Foods[c]		
Milk, 8 oz	100	Usually D3
Vitamin D-fortified soy milk, 8 oz	100	Usually D2
Vitamin D-fortified orange juice, 8 oz	100	D3
Fortified breakfast cereals, 1 serving	40 - 100	Usually D3
Supplements[d]		
Over the counter		
Multivitamin	400	D3 or D2
Vitamin D3	400, 800, 1000, or 2000	D3
Prescription		
Alendronate sodium plus cholecalciferol (Brand name: *Fosamax plus D™*) Tablet	 2800 or 5600	D3
Ergocalciferol[e] (Brand name: *Drisdol®*) Gelatin capsule Drisdol liquid supplements (per mL)	 50,000 8000	D2
Prescription Vitamin D Metabolites		
Doxercalciferol (Brand name: *Hectorol®*) Gelatin capsule Intravenous solution (per 1 mL)	 0.5 μg or 2.5 μg 2 μg	1α-hydroxyvitamin D2
Calcitriol (Brand name: *Rocaltrol®, Calcijex®*) Gelatin capsule[e] Oral solution (per mL) [e] Intravenous solution (per 1 mL ampul) [e]	 0.25 μg or 0.5 μg 1 μg 1 μg	1,25-dihydroxyvitamin D3
Paricalcitol (calcitriol analog) (Brand name: *Zemplar®*) Gelatin capsule Intravenous solution (per 1 mL)	 1 μg, 2 μg, or 4 μg 2 μg or 5 μg	19-*nor*-1-α-dihydroxyvitamin D2

Calcipotriene (vitamin D3 analog) (Brand name: *Dovonex®, Taclonex®*) Ointment, cream, or solution [e]	0.005%	Vitamin D3 derivative

[a]All doses given in international units (IU), where 1 IU = 25 ng, unless otherwise noted.
[b]An estimated 0.5 minimal erythemal dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure of the arms and legs to direct sunlight (the exact amount depends on the time of day, season, latitude, and skin sensitivity).
[c]Note that vitamin D3 is manufactured from lanolin, an animal product, and thus may not be suitable for some vegetarians.
[d]Products labeled "vitamin D," "calciferol," or "ergocalciferol" usually contain vitamin D2, while products labeled "vitamin D3" or "cholecalciferol" contain vitamin D3.
[e]Generic equivalent available.

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