

## Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline

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**Objective:** The objective was to provide guidelines to clinicians for the evaluation, treatment, and prevention of vitamin D deficiency with an emphasis on the care of patients who are at risk for deficiency.

**Participants:** The Task Force was composed of a Chair, six additional experts, and a methodologist. The Task Force received no corporate funding or remuneration.

**Consensus Process:** Consensus was guided by systematic reviews of evidence and discussions during several conference calls and e-mail communications. The draft prepared by the Task Force was reviewed successively by The Endocrine Society's Clinical Guidelines Subcommittee, Clinical Affairs Core Committee, and cosponsoring associations, and it was posted on The Endocrine Society web site for member review. At each stage of review, the Task Force received written comments and incorporated needed changes.

**Conclusions:** Considering that vitamin D deficiency is very common in all age groups and that few foods contain vitamin D, the Task Force recommended supplementation at suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances. The Task Force also suggested the measurement of serum 25-hydroxyvitamin D level by a reliable assay as the initial diagnostic test in patients at risk for deficiency. Treatment with either vitamin D<sub>2</sub> or vitamin D<sub>3</sub> was recommended for deficient patients. At the present time, there is not sufficient evidence to recommend screening individuals who are not at risk for deficiency or to prescribe vitamin D to attain the noncalcemic benefit for cardiovascular protection. (*J Clin Endocrinol Metab* 96: 1911–1930, 2011)

### Summary of Recommendations

#### 1.0 Diagnostic procedure

1.1 We recommend screening for vitamin D deficiency in individuals at risk for deficiency. We do not recommend population screening for vitamin D deficiency in individuals who are not at risk (1|⊕⊕⊕⊕).

1.2 We recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable

assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (525–725 nmol/liter). We recommend against using the serum 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] assay for this purpose and are in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism (1|⊕⊕⊕⊕).

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Abbreviations: BMD, Bone mineral density; BMI, body mass index; CI, confidence interval; I2, inconsistency; IOM, Institute of Medicine; MI, myocardial infarction; OHase, hydroxylase; 1,25(OH)<sub>2</sub>D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; OR, odds ratio; RCT, randomized controlled trials; RDA, recommended dietary allowance; RR, relative risk.

## 2.0 Recommended dietary intakes of vitamin D for patients at risk for vitamin D deficiency

2.1 We suggest that infants and children aged 0–1 yr require at least 400 IU/d (IU = 25 ng) of vitamin D and children 1 yr and older require at least 600 IU/d to maximize bone health. Whether 400 and 600 IU/d for children aged 0–1 yr and 1–18 yr, respectively, are enough to provide all the potential nonskeletal health benefits associated with vitamin D to maximize bone health and muscle function is not known at this time. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml (75 nmol/liter) may require at least 1000 IU/d of vitamin D (2|⊕⊕⊕⊕).

2.2 We suggest that adults aged 19–50 yr require at least 600 IU/d of vitamin D to maximize bone health and muscle function. It is unknown whether 600 IU/d is enough to provide all the potential nonskeletal health benefits associated with vitamin D. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1500–2000 IU/d of vitamin D (2|⊕⊕⊕⊕).

2.3 We suggest that all adults aged 50–70 and 70+ yr require at least 600 and 800 IU/d, respectively, of vitamin D. Whether 600 and 800 IU/d of vitamin D are enough to provide all of the potential nonskeletal health benefits associated with vitamin D is not known at this time. However, to raise the blood level of 25(OH)D above 30 ng/ml may require at least 1500–2000 IU/d of supplemental vitamin D (2|⊕⊕⊕⊕).

2.4 We suggest that pregnant and lactating women require at least 600 IU/d of vitamin D and recognize that at least 1500–2000 IU/d of vitamin D may be needed to maintain a blood level of 25(OH)D above 30 ng/ml (2|⊕⊕⊕⊕).

2.5 We suggest that obese children and adults and children and adults on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and medications for AIDS be given at least two to three times more vitamin D for their age group to satisfy their body's vitamin D requirement (2|⊕⊕⊕⊕).

2.6 We suggest that the maintenance tolerable upper limits (UL) of vitamin D, which is not to be exceeded without medical supervision, should be 1000 IU/d for infants up to 6 months, 1500 IU/d for infants from 6 months to 1 yr, at least 2500 IU/d for children aged 1–3 yr, 3000 IU/d for children aged 4–8 yr, and 4000 IU/d for everyone over 8 yr. However, higher levels of 2000 IU/d for children 0–1 yr, 4000 IU/d for children 1–18 yr, and 10,000 IU/d for children and adults 19 yr and older may be needed to correct vitamin D deficiency (2|⊕⊕⊕⊕).

## 3.0 Treatment and prevention strategies

3.1 We suggest using either vitamin D<sub>2</sub> or vitamin D<sub>3</sub> for the treatment and prevention of vitamin D deficiency (2|⊕⊕⊕⊕).

3.2 For infants and toddlers aged 0–1 yr who are vitamin D deficient, we suggest treatment with 2000 IU/d of

vitamin D<sub>2</sub> or vitamin D<sub>3</sub>, or with 50,000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> once weekly for 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 400–1000 IU/d (2|⊕⊕⊕⊕).

3.3 For children aged 1–18 yr who are vitamin D deficient, we suggest treatment with 2000 IU/d of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> for at least 6 wk or with 50,000 IU of vitamin D<sub>2</sub> once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 600–1000 IU/d (2|⊕⊕⊕⊕).

3.4 We suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> once a week for 8 wk or its equivalent of 6000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> daily to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/d (2|⊕⊕⊕⊕).

3.5 In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of 3000–6000 IU/d (2|⊕⊕⊕⊕).

3.6 In patients with extrarenal production of 1,25(OH)<sub>2</sub>D, we suggest serial monitoring of 25(OH)D levels and serum calcium levels during treatment with vitamin D to prevent hypercalcemia (2|⊕⊕⊕⊕).

3.7 For patients with primary hyperparathyroidism and vitamin D deficiency, we suggest treatment with vitamin D as needed. Serum calcium levels should be monitored (2|⊕⊕⊕⊕).

## 4.0 Noncalcemic benefits of vitamin D

4.1 We recommend prescribing vitamin D supplementation for fall prevention. We do not recommend prescribing vitamin D supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (2|⊕⊕⊕⊕).

## Method of Development of Evidence-Based Clinical Practice Guidelines

The Task Force commissioned the conduct of two systematic reviews of the literature to inform its key recommendations. The Task Force used consistent language and geographical descriptions of both the strength of recommendation and the quality of evidence using the recommendations of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.

The Clinical Guidelines Subcommittee of The Endocrine Society deemed vitamin D deficiency a priority area in need of practice guidelines and appointed a Task Force

to formulate evidence-based recommendations. The Task Force followed the approach recommended by the GRADE group, an international group with expertise in development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The Task Force used the best available research evidence to develop some of the recommendations. The Task Force commissioned the conduct of two systemic reviews of the literature to inform its key recommendations.

The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase “we recommend” and the number 1, and weak recommendations use the phrase “we suggest” and the number 2. *Cross-filled circles* indicate the quality of the evidence, such that ⊕○○○ denotes very low quality evidence; ⊕⊕○○, low quality; ⊕⊕⊕○, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person’s circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks should be considered suggestions.

## Vitamin D Photobiology, Metabolism, Physiology, and Biological Functions

Vitamin D is unique among hormones because it can be made in the skin from exposure to sunlight (3–7). Vitamin D comes in two forms. Vitamin D<sub>2</sub> is obtained from the UV irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms. Vitamin D<sub>3</sub> is synthesized in the skin and is present in oil-rich fish such as salmon, mackerel, and herring; commercially available vitamin D<sub>3</sub> is synthesized from the cholesterol precursor 7-dehydrocholesterol naturally present in the skin or obtained from lanolin (3). Both vitamin D<sub>2</sub> and vitamin D<sub>3</sub> are used for food fortification and in vitamin D supplements. Vitamin D (D represents D<sub>2</sub>, or D<sub>3</sub>, or both) that is

ingested is incorporated into chylomicrons, which are absorbed into the lymphatic system and enter the venous blood. Vitamin D that comes from the skin or diet is biologically inert and requires its first hydroxylation in the liver by the vitamin D-25-hydroxylase (25-OHase) to 25(OH)D (3, 8). However, 25(OH)D requires a further hydroxylation in the kidneys by the 25(OH)D-1 $\alpha$ -OHase (CYP27B1) to form the biologically active form of vitamin D 1,25(OH)<sub>2</sub>D (3, 8). 1,25(OH)<sub>2</sub>D interacts with its vitamin D nuclear receptor, which is present in the small intestine, kidneys, and other tissues (3, 8). 1,25(OH)<sub>2</sub>D stimulates intestinal calcium absorption (9). Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus are absorbed. Vitamin D sufficiency enhances calcium and phosphorus absorption by 30–40% and 80%, respectively (3, 10). 1,25(OH)<sub>2</sub>D interacts with its vitamin D receptor in the osteoblast to stimulate the expression of receptor activator of nuclear factor  $\kappa$ B ligand; this, in turn, interacts with receptor activator of nuclear factor  $\kappa$ B to induce immature monocytes to become mature osteoclasts, which dissolve the matrix and mobilize calcium and other minerals from the skeleton. In the kidney, 1,25(OH)<sub>2</sub>D stimulates calcium reabsorption from the glomerular filtrate (3, 11).

The vitamin D receptor is present in most tissues and cells in the body (3, 12). 1,25(OH)<sub>2</sub>D has a wide range of biological actions, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inhibiting renin production, and stimulating macrophage cathelicidin production (3, 12–14). In addition, 1,25(OH)<sub>2</sub>D stimulates its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-OHase (CYP24R) to metabolize 25(OH)D and 1,25(OH)<sub>2</sub>D into water-soluble inactive forms. There are several tissues and cells that possess 1-OHase activity (3, 7, 12, 13). The local production of 1,25(OH)<sub>2</sub>D may be responsible for regulating up to 200 genes (15) that may facilitate many of the pleiotropic health benefits that have been reported for vitamin D (3–7, 12).

## Prevalence of Vitamin D Deficiency

Vitamin D deficiency has been historically defined and recently recommended by the Institute of Medicine (IOM) as a 25(OH)D of less than 20 ng/ml. Vitamin D insufficiency has been defined as a 25(OH)D of 21–29 ng/ml (3, 10, 16–20). In accordance with these definitions, it has been estimated that 20–100% of U.S., Canadian, and European elderly men and women still living in the community are vitamin D deficient (3, 21–25). Children and young and middle-aged adults are at equally high risk for

vitamin D deficiency and insufficiency worldwide. Vitamin D deficiency is common in Australia, the Middle East, India, Africa, and South America (3, 26, 27). In the United States, more than 50% of Hispanic and African-American adolescents in Boston (28) and 48% of white preadolescent girls in Maine had 25(OH)D below 20 ng/ml (29). In addition, 42% of African-American girls and women aged 15–49 yr throughout the United States had a blood level of 25(OH)D below 15 ng/ml at the end of the winter (30), and 32% of healthy students and physicians at a Boston hospital had 25(OH)D below 20 ng/ml (31). Pregnant and lactating women who take a prenatal vitamin and a calcium supplement with vitamin D remain at high risk for vitamin D deficiency (32–34).

### Causes of Vitamin D Deficiency

The major source of vitamin D for children and adults is exposure to natural sunlight (3, 7, 35–37). Very few foods naturally contain or are fortified with vitamin D. Thus, the major cause of vitamin D deficiency is inadequate exposure to sunlight (5–7, 38). Wearing a sunscreen with a sun protection factor of 30 reduces vitamin D synthesis in the skin by more than 95% (39). People with a naturally dark skin tone have natural sun protection and require at least three to five times longer exposure to make the same amount of vitamin D as a person with a white skin tone (40, 41). There is an inverse association of serum 25(OH)D and body mass index (BMI) greater than 30 kg/m<sup>2</sup>, and thus, obesity is associated with vitamin D deficiency (42). There are several other causes for vitamin D deficiency (3, 38). Patients with one of the fat malabsorption syndromes and bariatric patients are often unable to absorb the fat-soluble vitamin D, and patients with nephrotic syndrome lose 25(OH)D bound to the vitamin D-binding protein in the urine (3). Patients on a wide variety of medications, including anticonvulsants and medications to treat AIDS/HIV, are at risk because these drugs enhance the catabolism of 25(OH)D and 1,25(OH)<sub>2</sub>D (43). Patients with chronic granuloma-forming disorders, some lymphomas, and primary hyperparathyroidism who have increased metabolism of 25(OH)D to 1,25(OH)<sub>2</sub>D are also at high risk for vitamin D deficiency (44, 45).

### Consequences of Vitamin D Deficiency

Vitamin D deficiency results in abnormalities in calcium, phosphorus, and bone metabolism. Specifically, vitamin D deficiency causes a decrease in the efficiency of intestinal calcium and phosphorus absorption of dietary calcium and phosphorus, resulting in an increase in PTH levels (3,

10, 22, 23). Secondary hyperparathyroidism maintains serum calcium in the normal range at the expense of mobilizing calcium from the skeleton and increasing phosphorus wasting in the kidneys. The PTH-mediated increase in osteoclastic activity creates local foci of bone weakness and causes a generalized decrease in bone mineral density (BMD), resulting in osteopenia and osteoporosis. Phosphaturia caused by secondary hyperparathyroidism results in a low normal or low serum phosphorus level. This results in an inadequate calcium-phosphorus product, causing a mineralization defect in the skeleton (3, 46). In young children who have little mineral in their skeleton, this defect results in a variety of skeletal deformities classically known as rickets (24, 47). In adults, the epiphyseal plates are closed, and there is enough mineral in the skeleton to prevent skeletal deformities so that this mineralization defect, known as an osteomalacia, often goes undetected. However, osteomalacia causes a decrease in BMD and is associated with isolated or generalized aches and pains in bones and muscles (48, 49). Vitamin D deficiency also causes muscle weakness; affected children have difficulty standing and walking (47, 50), whereas the elderly have increasing sway and more frequent falls (51, 52), thereby increasing their risk of fracture.

### Sources of Vitamin D

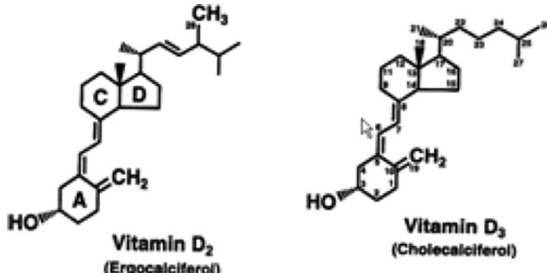
A major source of vitamin D for most humans comes from exposure of the skin to sunlight typically between 1000 h and 1500 h in the spring, summer, and fall (3–5, 7). Vitamin D produced in the skin may last at least twice as long in the blood compared with ingested vitamin D (53). When an adult wearing a bathing suit is exposed to one minimal erythemal dose of UV radiation (a slight pinkness to the skin 24 h after exposure), the amount of vitamin D produced is equivalent to ingesting between 10,000 and 25,000 IU (5). A variety of factors reduce the skin's production of vitamin D<sub>3</sub>, including increased skin pigmentation, aging, and the topical application of a sunscreen (3, 39, 40). An alteration in the zenith angle of the sun caused by a change in latitude, season of the year, or time of day dramatically influences the skin's production of vitamin D<sub>3</sub> (3, 5). Above and below latitudes of approximately 33°, vitamin D<sub>3</sub> synthesis in the skin is very low or absent during most of the winter.

Few foods naturally contain vitamin D<sub>2</sub> or vitamin D<sub>3</sub> (Table 1).

In the United States and Canada, milk is fortified with vitamin D, as are some bread products, orange juices, cereals, yogurts, and cheeses (3). In Europe, most countries do not fortify milk with vitamin D because in the 1950s,



**TABLE 1.** Sources of vitamin D<sub>2</sub> and vitamin D<sub>3</sub>

| Source                                      | Vitamin D content  |
|---|--|
| Natural sources                             |  |
|   |    |
| Cod liver oil                               | ~400–1,000 IU/teaspoon vitamin D <sub>3</sub>  |
| Salmon, fresh wild caught                   | ~600–1,000 IU/3.5 oz vitamin D <sub>3</sub>  |
| Salmon, fresh farmed                        | ~100–250 IU/3.5 oz vitamin D <sub>3</sub> , vitamin D <sub>2</sub>   |
| Salmon, canned                              | ~300–600 IU/3.5 oz vitamin D <sub>3</sub>  |
| Sardines, canned                            | ~300 IU/3.5 oz vitamin D <sub>3</sub>  |
| Mackerel, canned                            | ~250 IU/3.5 oz vitamin D <sub>3</sub>  |
| Tuna, canned                                | 236 IU/3.5 oz vitamin D <sub>3</sub>   |
| Shiitake mushrooms, fresh                   | ~100 IU/3.5 oz vitamin D <sub>2</sub>  |
| Shiitake mushrooms, sun-dried               | ~1,600 IU/3.5 oz vitamin D <sub>2</sub>  |
| Egg yolk                                    | ~20 IU/yolk vitamin D <sub>3</sub> or D <sub>2</sub>   |
| Sunlight/UVB radiation                      | ~20,000 IU equivalent to exposure to 1 minimal erythral dose (MED) in a bathing suit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting ~3,000 IU vitamin D <sub>3</sub> . |
| Fortified foods                             |  |
| Fortified milk                              | 100 IU/8 oz, usually vitamin D <sub>3</sub>  |
| Fortified orange juice                      | 100 IU/8 oz vitamin D <sub>3</sub>   |
| Infant formulas                             | 100 IU/8 oz vitamin D <sub>3</sub>   |
| Fortified yogurts                           | 100 IU/8 oz, usually vitamin D <sub>3</sub>  |
| Fortified butter                            | 56 IU/3.5 oz, usually vitamin D <sub>3</sub>   |
| Fortified margarine                         | 429 IU/3.5 oz, usually vitamin D <sub>3</sub>  |
| Fortified cheeses                           | 100 IU/3 oz, usually vitamin D <sub>3</sub>  |
| Fortified breakfast cereals                 | ~100 IU/serving, usually vitamin D <sub>3</sub>  |
| Pharmaceutical sources in the United States |  |
| Vitamin D <sub>2</sub> (ergocalciferol)     | 50,000 IU/capsule  |
| Drisdol (vitamin D <sub>2</sub> ) liquid    | 8,000 IU/cc  |
| Supplemental sources                        |  |
| Multivitamin                                | 400, 500, 1,000 IU vitamin D <sub>3</sub> or vitamin D <sub>2</sub>  |
| Vitamin D <sub>3</sub>                      | 400, 800, 1,000, 2,000, 5,000, 10,000, and 50,000 IU   |

IU = 25 ng. [Reproduced with permission from M. F. Holick: *N Engl J Med* 357:266–281, 2007 (3). © Massachusetts Medical Society.]

there was an outbreak of vitamin D intoxication in young children, resulting in laws that forbade the fortification of foods with vitamin D. However, Sweden and Finland now fortify milk, and many European countries add vitamin D to cereals, breads, and margarine (3).

Multivitamin preparations contain 400-1000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub>, whereas pharmaceutical preparations in the United States contain only vitamin D<sub>2</sub> (Table 1) (3).

## 1.0 Diagnostic Procedure

### Recommendation

1.1 We recommend screening for vitamin D deficiency in individuals at risk for deficiency. We do not recommend

population screening for vitamin D deficiency in individuals who are not at risk (1|⊕⊕⊕⊕).

### 1.1 Evidence

There is no evidence demonstrating benefits of screening for vitamin D deficiency at a population level. Such evidence would require demonstration of the feasibility and cost-effectiveness of such a screening strategy, as well as benefits in terms of important health outcomes. In the absence of this evidence, it is premature to recommend screening at large at this time.

Currently, 25(OH)D measurement is reasonable in groups of people at high risk for vitamin D deficiency and in whom a prompt response to optimization of vitamin D status could be expected (Table 2) (3, 25, 52, 54–56).

**TABLE 2.** Indications for 25(OH)D measurement (candidates for screening)

|   |
|---|
| Rickets   |
| Osteomalacia  |
| Osteoporosis  |
| Chronic kidney disease                                  |
| Hepatic failure   |
| Malabsorption syndromes                                 |
| Cystic fibrosis   |
| Inflammatory bowel disease                              |
| Crohn's disease   |
| Bariatric surgery                                       |
| Radiation enteritis                                     |
| Hyperparathyroidism                                     |
| Medications   |
| Antiseizure medications                                 |
| Glucocorticoids   |
| AIDS medications  |
| Antifungals, e.g. ketoconazole                          |
| Cholestyramine  |
| African-American and Hispanic children and adults       |
| Pregnant and lactating women                            |
| Older adults with history of falls                      |
| Older adults with history of nontraumatic fractures     |
| Obese children and adults (BMI > 30 kg/m <sup>2</sup> ) |
| Granuloma-forming disorders                             |
| Sarcoidosis   |
| Tuberculosis  |
| Histoplasmosis  |
| Coccidiomycosis   |
| Berylliosis   |
| Some lymphomas  |

## Recommendation

1.2 We recommend using the serum circulating 25(OH)D level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D below 20 ng/ml (50 nmol/liter), and vitamin D insufficiency as a 25(OH)D of 21–29 ng/ml (525–725 nmol/liter). We recommend against using the serum 1,25(OH)<sub>2</sub>D assay for this purpose and are in favor of using it only in monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism (1|⊕⊕⊕⊕).

## 1.2 Evidence

25(OH)D is the major circulating form of vitamin D, with a circulating half-life of 2–3 wk, and it is the best indicator to monitor for vitamin D status (3, 8, 25, 54, 56). The circulating half-life of 1,25(OH)<sub>2</sub>D is approximately 4 h. It circulates at 1000 times lower concentration than 25(OH)D, and the blood level is tightly regulated by serum levels of PTH, calcium, and phosphate. Serum 1,25(OH)<sub>2</sub>D does not reflect vitamin D reserves, and measurement of 1,25(OH)<sub>2</sub>D is not useful for monitoring the vitamin D status of patients. Serum 1,25(OH)<sub>2</sub>D is frequently either normal or even elevated in those with vitamin D deficiency, due to secondary hyperparathyroidism. Thus, 1,25(OH)<sub>2</sub>D measurement does not reflect vitamin

D status. Measurement of 1,25(OH)<sub>2</sub>D is useful in acquired and inherited disorders in the metabolism of 25(OH)D and phosphate, including chronic kidney disease, hereditary phosphate-losing disorders, oncogenic osteomalacia, pseudovitamin D-deficiency rickets, vitamin D-resistant rickets, as well as chronic granuloma-forming disorders such as sarcoidosis and some lymphomas (3, 11, 50, 57, 58).

## 1.2 Remarks

All clinical assays, including 25(OH)D measurements, are subject to variability. Such variability confounds attempts to define a single “cut point” value as indicating low vitamin D status. Multiple methodologies for 25(OH)D measurement exist, including RIA, HPLC, and liquid chromatography tandem mass spectroscopy (3, 54, 59). For clinical care, it appears that all current methodologies are adequate if one targets a 25(OH)D value higher than current cut points; for example, a value of 40 ng/ml is without toxicity and virtually ensures that the individual's “true” value is greater than 30 ng/ml. A clinical approach of targeting a higher 25(OH)D value seems prudent in that improving vitamin D status should reduce multiple adverse consequences of vitamin D deficiency at extremely low cost with minimal toxicity risk. Finally, the comparability of 25(OH)D results seems likely to improve as uniform standards available through the National Institute of Standards and Technology become widely implemented.

## Suggested 25(OH)D levels

Vitamin D deficiency in children and adults is a clinical syndrome caused by a low circulating level of 25(OH)D (3, 10, 25, 47, 50). The blood level of 25(OH)D that is defined as vitamin D deficiency remains somewhat controversial. A provocative study in adults who received 50,000 IU of vitamin D<sub>2</sub> once a week for 8 wk along with calcium supplementation demonstrated a significant reduction in their PTH levels when their initial 25(OH)D was below 20 ng/ml (16). Several, but not all, studies have reported that PTH levels are inversely associated with 25(OH)D and begin to plateau in adults who have blood levels of 25(OH)D between 30 and 40 ng/ml (20–22, 60); these findings are consistent with the threshold for hip and nonvertebral fracture prevention from a recent meta-analysis of double-blind randomized controlled trials (RCT) with oral vitamin D (56). When postmenopausal women who had an average blood level of 25(OH)D of 20 ng/ml increased their level to 32 ng/ml, they increased the efficiency of intestinal calcium absorption by 45–65% (17). Thus, based on these and other studies, it has been suggested that vitamin D deficiency be defined as a 25(OH)D

below 20 ng/ml, insufficiency as a 25(OH)D of 21–29 ng/ml, and sufficiency as a 25(OH)D of 30–100 ng/ml (3). The IOM report (20) also concluded, based in part on the PTH data, that vitamin D deficiency was defined as 25(OH)D below 20 ng/ml. They dismissed the calcium absorption study by Heaney *et al.* (17) as being a single study that did not directly measure calcium absorption and noted studies such as Hansen *et al.* (18), which showed no increase in intestinal calcium absorption across a broad range of serum 25(OH)D levels. However, the Heaney *et al.* (17) study was strengthened by the fact that they investigated a change in intestinal calcium absorption in the same women who had a blood level of 25(OH)D of approximately 20 ng/ml that was raised to an average of 32 ng/ml. The normalization of PTH at certain levels of 25(OH)D indirectly implies that these values can be suggested to define deficiency and insufficiency and indirectly informs treatment decisions. Studies of vitamin D replacement and treatment showing changes in patient-important outcomes (61) at certain levels of 25(OH)D are needed and would provide higher quality evidence that would lead to stronger recommendations.

## 2.0 Recommended Dietary Intakes of Vitamin D for Patients at Risk for Vitamin D Deficiency

Several recent studies have suggested that the recommended dietary allowances (RDA) of the IOM (20) may be inadequate, especially for patients who have underlying conditions or are receiving medications that put them at risk for vitamin D deficiency. The studies were reviewed, and Table 3 summarizes what the present RDA recommendations are and what we believe should be the recommended dietary intakes, especially for patients who are at risk based on the most current literature. These recommendations are often based on lower quality evidence (expert opinion, consensus, inference from basic science experiments, noncomparative or comparative observational studies); therefore, they should be considered as suggestions for patient care.

### Recommendation

2.1 We suggest that infants and children aged 0–1 yr require at least 400 IU/d (IU = 25 ng) of vitamin D, and

**TABLE 3.** Vitamin D intakes recommended by the IOM and the Endocrine Practice Guidelines Committee

| Life stage group       | IOM recommendations |                |                |                   | Committee recommendations for patients at risk for vitamin D deficiency |           |
|------------------------|---------------------|----------------|----------------|-------------------|---|-----------|
|                        | AI                  | EAR            | RDA            | UL                | Daily requirement   | UL        |
| Infants                |                     |                |                |                   |   |           |
| 0 to 6 months          | 400 IU (10 µg)      |                |                | 1,000 IU (25 µg)  | 400–1,000 IU  | 2,000 IU  |
| 6 to 12 months         | 400 IU (10 µg)      |                |                | 1,500 IU (38 µg)  | 400–1,000 IU  | 2,000 IU  |
| Children               |                     |                |                |                   |   |           |
| 1–3 yr                 |                     | 400 IU (10 µg) | 600 IU (15 µg) | 2,500 IU (63 µg)  | 600–1,000 IU  | 4,000 IU  |
| 4–8 yr                 |                     | 400 IU (10 µg) | 600 IU (15 µg) | 3,000 IU (75 µg)  | 600–1,000 IU  | 4,000 IU  |
| Males                  |                     |                |                |                   |   |           |
| 9–13 yr                |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 600–1,000 IU  | 4,000 IU  |
| 14–18 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 600–1,000 IU  | 4,000 IU  |
| 19–30 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| 31–50 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| 51–70 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| >70 yr                 |                     | 400 IU (10 µg) | 800 IU (20 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| Females                |                     |                |                |                   |   |           |
| 9–13 yr                |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 600–1,000 IU  | 4,000 IU  |
| 14–18 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 600–1,000 IU  | 4,000 IU  |
| 19–30 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| 31–50 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| 51–70 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| >70 yr                 |                     | 400 IU (10 µg) | 800 IU (20 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| Pregnancy              |                     |                |                |                   |   |           |
| 14–18 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 600–1,000 IU  | 4,000 IU  |
| 19–30 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| 31–50 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| Lactation <sup>a</sup> |                     |                |                |                   |   |           |
| 14–18 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 600–1,000 IU  | 4,000 IU  |
| 19–30 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |
| 31–50 yr               |                     | 400 IU (10 µg) | 600 IU (15 µg) | 4,000 IU (100 µg) | 1,500–2,000 IU  | 10,000 IU |

AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

<sup>a</sup> Mother’s requirement, 4,000–6,000 IU/d (mother’s intake for infant’s requirement if infant is not receiving 400 IU/d).

children 1 yr and older require at least 600 IU/d to maximize bone health. Whether 400 and 600 IU/d for children 0–1 yr and 1–18 yr, respectively, are enough to provide all the potential nonskeletal health benefits associated with vitamin D is not known at this time. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1000 IU/d of vitamin D (2|⊕⊕⊕⊕).

## 2.1 Evidence

### Birth to 18 yr

Risk factors for vitamin D deficiency and rickets in an infant include breast-feeding without vitamin D supplementation, dark skin pigmentation, and maternal vitamin D deficiency (38, 50, 62–68). *In utero*, the fetus is wholly dependent on the mother for vitamin D. The 25(OH)D passes from the placenta into the blood stream of the fetus. Because the half-life for 25(OH)D is approximately 2–3 wk, the infant can remain vitamin D sufficient for several weeks after birth, as long as the mother was vitamin D sufficient. However, most pregnant women are vitamin D deficient or insufficient (33–35). In a study of 40 mother-infant pairs, Lee *et al.* (33) reported that 76% of mothers and 81% of newborns had a 25(OH)D below 20 ng/ml at the time of birth, despite the fact that during pregnancy, the mothers ingested about 600 IU/d of vitamin D from a prenatal supplement and consumption of two glasses of milk.

Infants depend on either sunlight exposure or dietary vitamin D to meet their requirement from birth. Human breast milk and unfortified cow's milk have very little vitamin D (32). Thus, infants who are fed only human breast milk are prone to developing vitamin D deficiency, especially during the winter when neither they nor their mothers can obtain vitamin D from sunlight. Conservative estimates suggest that to maintain serum 25(OH)D concentrations above 20 ng/ml, an infant in the Midwest fed human milk must be exposed to sunlight in the summer about 30 min/wk while wearing just a diaper (69, 70).

Human milk and colostrum contain low amounts of vitamin D, on average  $15.9 \pm 8.6$  IU/liter (32). There is a direct relationship between vitamin D intake and vitamin D content in human milk. However, even when women were consuming between 600 and 700 IU/d of vitamin D, the vitamin D content in their milk was only between 5 and 136 IU/liter (71). Preliminary data suggest that only after lactating women were given 4000–6000 IU/d of vitamin D was enough vitamin D transferred in breast milk to satisfy her infant's requirement (32).

Vitamin D intakes between 340 and 600 IU/d have been reported to have the maximum effect on linear growth of infants (72, 73). When Chinese infants were given 100, 200, or 400 IU/d of vitamin D, none demonstrated any

evidence of rickets (74). This observation is consistent with what Jeans (75) observed in 1950, and it was the basis for recommending that children only need 200 IU/d of vitamin D. However, Markestad and Elzouki (76) reported that Norwegian infants fed formula containing 300 IU/d obtained blood levels of 25(OH)D above 11 ng/ml, which at the time was considered the lower limit of normal. However, the IOM report says that the blood level should be at least 20 ng/ml, which implies that consuming even 300 IU/d is not adequate for infants (20, 47, 77).

Pediatric health care providers need to be aware of the deleterious effects of rickets on growth and bone development, including potential effects on bone density and development of peak bone mass (78). Musculoskeletal signs of rickets are well-described (47, 50, 66, 79, 80).

The American Academy of Pediatrics and the Canadian Pediatric Association (77) both recommended 400 IU/d. The IOM (20) recommended that the adequate intake and RDA for children 0–1 and 1–18 yr should be 400 and 600 IU/d, respectively. Whether 400 and 600 IU/d for these children is enough to provide all the health benefits associated with vitamin D is not known at this time.

Infants who received at least 2000 IU/d of vitamin D during the first year of life in Finland reduced their risk of developing type 1 diabetes in the ensuing 31 yr by 88%, without any reports of toxicity (81). Japanese children who received 1200 IU/d of vitamin D from December through March compared with placebo reduced their risk of influenza A by 42% (82). African-American normotensive children ( $16.3 \pm 1.4$  yr) who received 2000 IU/d compared with 400 IU/d for 16 wk in a randomized controlled trial had significantly higher serum 25(OH)D levels ( $36 \pm 14$  vs.  $24 \pm 7$  ng/ml) and significantly lower arterial wall stiffness (83).

In the past, children of all races obtained most of their vitamin D from exposure to sunlight and drinking vitamin D-fortified milk, and therefore, they did not need to take a vitamin D supplement (3, 84). However, children are spending more time indoors now, and when they go outside, they often wear sun protection that limits their ability to make vitamin D in their skin. Children and adolescents are also drinking less vitamin D-fortified milk (28, 29, 85–90). There are reports that children of all ages are at high risk for vitamin D deficiency and insufficiency and its insidious health consequences (91–93), but with the cutoff of 20 ng/ml set by the IOM (20), the prevalence of vitamin D deficiency should be reevaluated. There are no data on how much vitamin D is required to prevent vitamin D deficiency in children aged 1–9 yr. A few studies have shown that during the pubertal years, children maintained a serum 25(OH)D above 11 ng/ml with dietary vitamin D intakes of 2.5–10  $\mu$ g/d (100–400 IU/d) (94). When in-



takes were less than 2.5  $\mu\text{g}/\text{d}$ , Turkish children aged 12–17 yr had 25(OH)D levels consistent with vitamin D deficiency, *i.e.* below 11 ng/ml (95). A 2008 study by Maalouf *et al.* (91) suggests that this age group needs 2000 IU/d vitamin D to maintain a blood level above 30 ng/ml. Another study, by El-Hajj Fuleihan (96), provides an insight into the vitamin D requirement for children aged 10–17 yr (who were presumably exposed to an adequate amount of sun-mediated vitamin D because they lived in Lebanon) who ingested weekly doses of either 1,400 or 14,000 IU vitamin D<sub>3</sub> for 1 yr. Those who received 1400 IU/wk increased their blood level of 25(OH)D from  $14 \pm 8$  to  $17 \pm 6$  ng/ml, whereas the children who received 14,000 IU/wk for 1 yr increased their blood levels from  $14 \pm 8$  to  $38 \pm 31$  ng/ml. No signs of intoxication (hypercalcemia) were noted in the group receiving 14,000 IU/wk, although three subjects had a high 25(OH)D at the end of the study (103, 161, and 195 ng/ml) (96).

Children aged 9–18 yr have a rapid growth spurt characterized by a marked increase in their requirement of calcium and phosphorus to maximize skeletal mineralization. During puberty, the metabolism of 25(OH)D to 1,25(OH)<sub>2</sub>D increases. In turn, the increased blood levels of 1,25(OH)<sub>2</sub>D enhance the efficiency of the intestine to absorb dietary calcium and phosphorus to satisfy the growing skeleton's requirement for these minerals during its rapid growth phase. However, although production of 1,25(OH)<sub>2</sub>D is increased, there is no scientific evidence to date demonstrating an increased requirement for vitamin D in this age group, possibly because circulating concentrations of 1,25(OH)<sub>2</sub>D are approximately 500–1000 times lower than those of 25(OH)D (*i.e.* 15–60 pg/ml *vs.* 20–100 ng/ml, respectively) (97).

## Recommendation

2.2 We suggest that adults aged 19–50 yr require at least 600 IU/d of vitamin D to maximize bone health and muscle function. It is unknown whether 600 IU/d is enough to provide all the potential nonskeletal health benefits associated with vitamin D. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least 1500–2000 IU/d of vitamin D (2|⊕⊕⊕⊕).

## 2.2 Evidence

### Ages 19–50 yr

This age group is at risk for vitamin D deficiency because of decreased outdoor activities and aggressive sun protection. Available data have not sufficiently explored the relationship between total vitamin D intake *per se* and health outcomes, nor have data shown that a dose-response relationship between vitamin D intake and bone health is lacking (20).

Very few studies have evaluated this age group's vitamin D requirement. However, in the large Third National Health and Nutrition Examination Survey (NHANES III) population-based study, a threshold for optimal 25(OH)D and hip bone density has been addressed among 13,432 younger (20–49 yr) and older (50+ yr) individuals with different ethnic and racial background (98). Compared with the lowest quintile of 25(OH)D, the highest quintile had higher mean bone density by 4.1% in younger whites (test for trend;  $P < 0.0001$ ), by 1.8% in younger Mexican-Americans ( $P = 0.004$ ), and by 1.2% in younger blacks ( $P = 0.08$ ). In the regression plots, higher serum 25(OH)D levels were associated with higher BMD throughout the reference range of 10 to 38 ng/ml in all subgroups. In younger whites and younger Mexican-Americans, higher 25(OH)D was associated with higher BMD, even beyond 40 ng/ml. An evaluation of 67 white and 70 black premenopausal women ingesting  $138 \pm 84$  and  $145 \pm 73$  IU/d, respectively, revealed that serum 25(OH)D levels were in the insufficient or deficient range (circulating concentrations of  $21.4 \pm 4$  and  $18.3 \pm 5$  ng/ml, respectively) (99).

During the winter months (November through May) in Omaha, Nebraska, 6% of young women aged 25–35 yr ( $n = 52$ ) maintained serum concentrations of 25(OH)D above 20 ng/ml but below 30 ng/ml when estimated daily vitamin D intake was between 131 and 135 IU/d (100). Healthy adults aged 18–84 yr who received 1000 IU/d vitamin D<sub>3</sub> for 3 months during the winter increased their 25(OH)D from  $19.6 \pm 11.1$  to  $28.9 \pm 7.7$  ng/ml (101).

A dose-ranging study reported that men who received 10,000 IU/d of vitamin D<sub>3</sub> for 5 months did not experience any alteration in either serum calcium or urinary calcium excretion (127). Adults older than 18 yr who received 50,000 IU vitamin D<sub>2</sub> every 2 wk (which is equivalent to 3000 IU/d) for up to 6 yr had a normal serum calcium and no evidence of toxicity (102).

## Recommendation

2.3 We suggest that all adults aged 50–70 and 70+ yr require at least 600 and 800 IU/d, respectively, of vitamin D to maximize bone health and muscle function. Whether 600 and 800 IU/d of vitamin D are enough to provide all of the potential nonskeletal health benefits associated with vitamin D is not known at this time. (Among those age 65 and older we recommend 800 IU/d for the prevention of falls and fractures.) However, to raise the blood level of 25(OH)D above 30 ng/ml may require at least 1500–2000 IU/d of supplemental vitamin D (2|⊕⊕⊕⊕).

## 2.3 Evidence

Men and women older than 51 yr depend on sunlight for most of their vitamin D requirement. Increased use of

clothing and sunscreen over sun-exposed areas and decreased consumption of vitamin D-fortified milk increases the risk for vitamin D deficiency (3, 31, 39, 103). In addition, age decreases the capacity of the skin to produce vitamin D<sub>3</sub> (3). Although it has been suggested that aging may decrease the ability of the intestine to absorb dietary vitamin D, studies have revealed that aging does not alter the absorption of physiological or pharmacological doses of vitamin D (101, 104–106).

The IOM report (20) suggests that 25(OH)D levels need to be at least 20 ng/ml to maintain skeletal health. Prior estimates have ranged from as little as 12 to as high as 40 ng/ml (107). Recently, Priemel *et al.* (108) examined 675 iliac crest biopsies from male and female German adults (401 males, mean age, 58.2 yr; and 270 females, mean age, 68.2 yr) for structural histomorphometric parameters including osteoid indices. They reported that although they could not establish a minimum 25(OH)D level that was inevitably associated with mineralization defects, they did not find pathological accumulation of osteoid in any patients with circulating 25(OH)D above 30 ng/ml. They concluded that in conjunction with sufficient calcium intake, the dose of vitamin D supplementation should ensure that circulating levels of 25(OH)D reach a minimum threshold of 30 ng/ml to maintain skeletal health. In contrast, the IOM (20) concluded from the same study that a level of 25(OH)D of 20 ng/ml was adequate to prevent osteomalacia in at least 97.5% of the population and therefore recommended a threshold of 20 ng/ml to maintain skeletal health in 97.5% of the adult population.

Many studies have evaluated the influence of dietary vitamin D supplementation on serum 25(OH)D, PTH, and bone health as measured by BMD and fracture risks in older men and women. Several randomized, double-blind clinical trials of senior men and women who had an intake of 400 IU/d showed insufficient 25(OH)D levels (25, 55, 80, 109–112). When men and women received

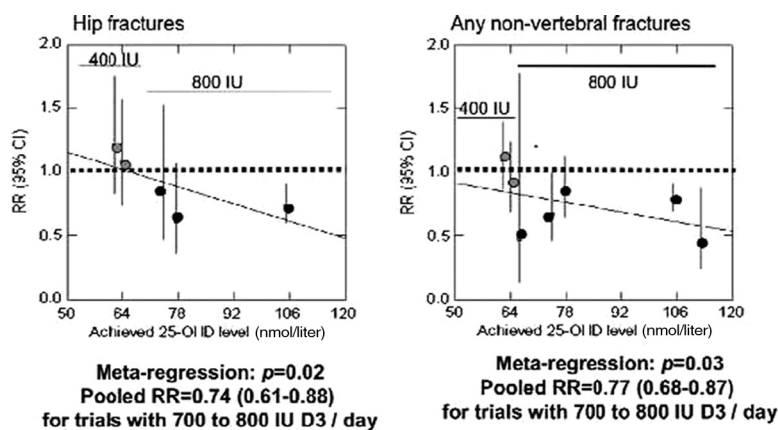
supplements of 400–1000 IU/d, they had a significant reduction in bone resorption. In a randomized, placebo-controlled trial of elderly French women, those given calcium and 800 IU/d of vitamin D had significantly fewer vertebral and nonvertebral fractures (113). A similar observation was made in free-living men and women aged 65 yr and older who received 500 mg of calcium and 700 IU/d of vitamin D (114).

A threshold for optimal 25(OH)D and hip BMD has been addressed among 13,432 individuals studied in the NHANES III, including both younger (20–49 yr) and older (>50 yr) individuals with different ethnic and racial backgrounds (98). In the regression plots, higher hip BMD was associated with higher serum 25(OH)D levels throughout the reference range of 9–37 ng/ml in all subgroups.

A 2005 meta-analysis of high-quality primary prevention RCT of vitamin D and fracture risk consistently found that antifracture efficacy of vitamin D increases with a higher achieved level of 25(OH)D (Fig. 1) (51). Antifracture efficacy started at 25(OH)D levels of at least 30 ng/ml. This level was reached only in trials that gave 700–800 IU/d vitamin D<sub>3</sub> (high-quality trials with oral vitamin D<sub>2</sub> were not available at the time).

The most up-to-date meta-analysis focused on antifracture efficacy from high-quality double-blind RCT (55). The higher received dose (treatment dose\*adherence) of 482–770 IU/d vitamin D reduced nonvertebral fractures in community-dwelling (–29%) and institutionalized (–15%) older individuals, and its effect was independent of additional calcium supplementation (–21% with additional calcium supplementation; –21% for the main effect of vitamin D). As with the 2005 meta-analysis, antifracture efficacy started at 25(OH)D levels of at least 30 ng/ml (75 nmol/liter).

Muscle weakness is a prominent feature of the clinical syndrome of severe vitamin D deficiency. Clinical findings in vitamin D-deficiency myopathy include proximal muscle weakness, diffuse muscle pain, and gait impairments such as a waddling way of walking (115, 116). Double-blind RCT demonstrated that 800 IU/d vitamin D<sub>3</sub> resulted in a 4–11% gain in lower extremity strength or function (80, 117), an up to 28% improvement in body sway (117, 118), and an up to 72% reduction in the rate of falling (119) in adults older than 65 yr after 5 months of treatment.



**FIG. 1.** Fracture efficacy by achieved 25(OH)D levels. To convert nmol/liter to ng/ml, divide by 2.496. [Reproduced with permission from H. A. Bischoff-Ferrari *et al.*: *JAMA* 293:2257–2264, 2005 (51). © American Medical Association.]

Several systematic reviews and meta-analyses have demonstrated a reduction in falls associated with interventions to raise 25(OH)D levels. Murad *et al.* (120) demonstrated that such interventions were associated with statis-

tically significant reduction in the risk of falls [odds ratio (OR) = 0.84; 95% confidence interval (CI), 0.76–0.93; inconsistency ( $I^2$ ) = 61%; 23 studies). This effect was more prominent in patients who were vitamin D deficient at baseline. Results of other reviews were consistent. A meta-analysis of only five high-quality double-blind RCT (n = 1237) found that vitamin D reduced the falling risk by 22% (pooled corrected OR = 0.78; 95% CI, 0.64–0.92) compared with calcium or placebo (116). For two trials with a total of 259 subjects using 800 IU/d of vitamin D<sub>3</sub> over 2 to 3 months (117, 121), the corrected pooled OR was 0.65 (95% CI, 0.40–1.00) (116), whereas 400 IU/d was insufficient to reduce falls (122). The importance of dose of supplemental vitamin D in minimizing risk of falls was confirmed by a multidose double-blind RCT among 124 nursing home residents receiving 200, 400, 600, or 800 IU/d vitamin D or placebo over 5 months (119) and by a 2009 meta-analysis (52). Participants receiving 800 IU/d had a 72% lower rate of falls than those taking placebo or a lower dose of vitamin D (rate ratio = 0.28; 95% CI, 0.11–0.75).

In the 2009 meta-analysis for supplemental vitamin D, eight high-quality RCT (n = 2426) were identified, and heterogeneity was observed for dose of vitamin D (low dose, <700 IU/d, *vs.* higher dose, 700 to 1000 IU/d;  $P$  = 0.02) and achieved 25(OH)D level (<24 ng/ml *vs.* 24 ng/ml;  $P$  = 0.005). Higher dose supplemental vitamin D reduced fall risk by 19% [pooled relative risk (RR) = 0.81; 95% CI, 0.71–0.92; n = 1921 from seven trials]. Falls were not reduced by low-dose supplemental vitamin D (pooled RR = 1.10; 95% CI, 0.89–1.35 from two trials) or by achieved serum 25(OH)D concentrations below 24 ng/ml (pooled RR = 1.35; 95% CI, 0.98–1.84). At the higher dose of vitamin D, the meta-analysis documented a 38% reduction in the risk of falling with treatment duration of 2 to 5 months and a sustained effect of 17% fall reduction with treatment duration of 12 to 36 months (52). Most recently, the IOM did a very thorough review on the effect of vitamin D on fall prevention (20). Their synopsis is that the evidence of vitamin D on fall prevention is inconsistent, which is in contrast to the 2010 assessment by the International Osteoporosis Foundation and the 2011 assessment of the Agency for Healthcare Research and Quality for the U.S. Preventive Services Task Force (123), both of which identified vitamin D as an effective intervention to prevent falling in older adults.

## Recommendation

2.4 We suggest that pregnant and lactating women require at least 600 IU/d of vitamin D and recognize that at least 1500–2000 IU/d of vitamin D may be needed to

maintain a blood level of 25(OH)D above 30 ng/ml (2|⊕⊕⊕⊕).

## 2.4 Evidence

### *Pregnancy and lactation*

During the first and second trimesters, the fetus is developing most of its organ systems and laying down the collagen matrix for its skeleton. During the last trimester, the fetus begins to calcify the skeleton, thereby increasing maternal demand for calcium. This demand is met by increased production of 1,25(OH)<sub>2</sub>D by the mother's kidneys and placenta. Circulating concentrations of 1,25(OH)<sub>2</sub>D gradually increase during the first and second trimesters, owing to an increase in vitamin D-binding protein concentrations in the maternal circulation. However, the free levels of 1,25(OH)<sub>2</sub>D, which are responsible for enhancing intestinal calcium absorption, are only increased during the third trimester. Pregnant women are at high risk for vitamin D deficiency, which increases the risk of preeclampsia (34) and cesarean section (124). Daily doses of 600 IU do not prevent vitamin D deficiency in pregnant women (34, 124). Their daily regimen should at least include a prenatal vitamin containing 400 IU vitamin D with a supplement that contains at least 1000 IU vitamin D.

During lactation, the mother needs to increase the efficiency of dietary absorption of calcium to ensure adequate calcium content in her milk. The metabolism of 25(OH)D to 1,25(OH)<sub>2</sub>D is enhanced in response to this new demand. However, because circulating concentrations of 1,25(OH)<sub>2</sub>D are 500–1000 times less than 25(OH)D, the increased metabolism probably does not significantly alter the daily requirement for vitamin D. To satisfy their requirement to maintain a 25(OH)D above 30 ng/ml, lactating women should take at least a multivitamin containing 400 IU vitamin D along with at least 1000 IU vitamin D supplement every day. To satisfy the requirements of an infant who is fed only breast milk, the mother requires 4000 to 6000 IU/d to transfer enough vitamin D into her milk (32). Thus, at a minimum, lactating women may need to take 1400–1500 IU/d, and to satisfy their infant's requirement, they may need 4000–6000 IU/d if they choose not to give the infant a vitamin D supplement.

## Recommendation

2.5 We suggest that obese children and adults and children and adults on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and medications for AIDS be given at least two to three times more vitamin D for their age group to satisfy their body's vitamin D requirement (2|⊕⊕⊕⊕).



## 2.5 Evidence

### **Obesity and medications**

Obese adults (BMI > 30 kg/m<sup>2</sup>) are at high risk for vitamin D deficiency because the body fat sequesters the fat-soluble vitamin. When obese and nonobese adults were exposed to simulated sunlight or received an oral dose of 50,000 IU of vitamin D<sub>2</sub>, they were able to raise their blood levels of vitamin D by no more than 50% compared with nonobese adults. Patients on multiple anticonvulsant medications, glucocorticoids, or AIDS treatment are at increased risk for vitamin D deficiency because these medications increase the catabolism of 25(OH)D (3, 42, 43).

### **Recommendation**

2.6 We suggest that the maintenance tolerable UL of vitamin D, which is not to be exceeded without medical supervision, should be 1000 IU/d for infants up to 6 months, 1500 IU/d for infants from 6 months to 1 yr, at least 2500 IU/d for children aged 1–3 yr, 3000 IU/d for children aged 4–8 yr, and 4000 IU/d for everyone over 8 yr. However, higher levels of 2000 IU/d for children 0–1 yr, 4000 IU/d for children 1–18 yr, and 10,000 IU/d for children and adults 19 yr and older may be needed to correct vitamin D deficiency (2|⊕⊕⊕⊕).

## 2.6 Evidence

Vitamin D is a fat-soluble vitamin and is stored in the body's fat. Thus, there is concern about the potential toxicity of vitamin D. Bariatric patients who were found to have vitamin D in their fat (4–320 ng/g) showed no significant change in their serum 25(OH)D levels 3, 6, and 12 months after surgery (125). Limited human data (125, 126) show relatively low levels of vitamin D storage in fat at prevailing inputs. Neonates who were given at least 2000 IU/d of vitamin D for 1 yr in Finland not only did not experience any untoward side effect but also had the benefit of reducing their risk of developing type 1 diabetes by 88% in later life (81).

Preteen and teen girls who received an equivalent of 2000 IU/d of vitamin D for 1 yr showed improvement in muscle mass without any untoward side effects (96). A dose-ranging study reported that 10,000 IU/d of vitamin D<sub>3</sub> for 5 months in men did not alter either urinary calcium excretion or their serum calcium (127). A 6-yr study of men and women aged 18–84 yr who received an equivalent of 3000 IU/d of vitamin D<sub>2</sub> reported no change in serum calcium levels or increased risk of kidney stones (102). However, long-term dose-ranging studies in children are lacking.

Based on all of the available literature, the panel concluded that vitamin D toxicity is a rare event caused by

inadvertent or intentional ingestion of excessively high amounts of vitamin D. Although it is not known what the safe upper value for 25(OH)D is for avoiding hypercalcemia, most studies in children and adults have suggested that the blood levels need to be above 150 ng/ml before there is any concern. Therefore, an UL of 100 ng/ml provides a safety margin in reducing risk of hypercalcemia (3, 96). The IOM report (20) recommended that the tolerable UL for vitamin D should be 1000 IU/d for children 0–6 months, 1500 IU/d for children 6 months to 1 yr, 2500 IU/d for children 1–3 yr, and 3000 IU/d for children 4–8 yr. For children 9 yr and older and all adults, they recommend that the UL be 4000 IU/d. These recommendations were based on a variety of observations dating back to the 1940s. They also recognized that high intakes of calcium along with high intakes of vitamin D exacerbate the risk for hypercalcemia. Hyppönen *et al.* (81) observed that children during their first year of life received 2000 IU/d of vitamin D without any untoward toxicity. To prevent rickets, children during their first year of life received as much as 250,000 IU of vitamin D as a single im injection without any reported toxicity. Therefore, it is reasonable for the UL to be 2000 IU/d for children 0–1 yr of age. Toddlers who received 2000 IU/d of vitamin D for 6 wk raised their blood level from 17 to 36 ng/ml without any reported toxicity (47). Although no long-term studies have examined these higher doses of vitamin D on serum calcium levels, there are no reported cases of vitamin D intoxication in the literature to suggest that intakes of up to 4000 IU/d of vitamin D cause hypercalcemia. In healthy adults, 5 months of ingesting 10,000 IU/d of vitamin D neither caused hypercalcemia nor increased urinary calcium excretion, which is the most sensitive indicator for potential vitamin D intoxication (127). Therefore, a UL of 10,000 IU/d of vitamin D for adults is reasonable.

Hence, vitamin D supplementation should not be a major concern except in certain populations who may be more sensitive to it. Patients who have chronic granuloma-forming disorders including sarcoidosis or tuberculosis, or chronic fungal infections, and some patients with lymphoma have activated macrophages that produce 1,25(OH)<sub>2</sub>D in an unregulated fashion (3, 44). These patients exhibit an increase in the efficiency of intestinal calcium absorption and mobilization of calcium from the skeleton that can cause hypercalciuria and hypercalcemia. Thus, their 25(OH)D and calcium levels should be monitored carefully. Hypercalciuria and hypercalcemia are usually observed only in patients with granuloma-forming disorders when the 25(OH)D is above 30 ng/ml (44).



### 3.0 Treatment and Prevention Strategies

#### Recommendation

3.1 We suggest using either vitamin D<sub>2</sub> or vitamin D<sub>3</sub> for the treatment and prevention of vitamin D deficiency (2|⊕⊕⊕⊕).

#### 3.1 Evidence

Some (47, 101, 128) but not all (129–131) studies have shown that both vitamin D<sub>2</sub> and vitamin D<sub>3</sub> are effective in maintaining serum 25(OH)D levels. Two meta-analyses of double-blind RCT suggested reduction in falls and non-vertebral fractures with vitamin D<sub>2</sub> compared with vitamin D<sub>3</sub> (52, 56).

Several studies using vitamin D<sub>2</sub> and vitamin D<sub>3</sub> as an intervention have recorded changes in serum 25(OH)D after up to 6 yr of treatment (47, 96, 102), and dose-ranging studies extending out to 5 months of continuous therapy produced data with respect to the steady-state inputs needed to produce and sustain a specified level of 25(OH)D (127). Results of these studies converge on a rate of rise in serum 25(OH)D at approximately 0.4 ng/ml/μg/d, which means that ingesting 100 IU/d of vitamin D increases serum 25(OH)D by less than 1 ng/ml approximately (101, 127). For example, a typical patient with a serum 25(OH)D level of 15 ng/ml would require an additional daily input of about 1500 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> to reach and sustain a level of 30 ng/ml. Most of these studies have been conducted in adults. Similar changes in 25(OH)D have been observed in children (47, 96); two to three times as much vitamin D, however, is required to achieve this same increase in serum 25(OH)D levels in patients who are obese (3, 38, 42).

Vitamin D can be taken on an empty stomach or with a meal. It does not require dietary fat for absorption. Vitamin D given three times a year, once a week, or once a day can be effective in maintaining serum 25(OH)D levels in both children and adults (23, 47, 61, 96, 102).

#### Recommendation

3.2 For infants and toddlers aged 0–1 yr who are vitamin D deficient, we suggest treatment with 2000 IU/d of vitamin D<sub>2</sub> or vitamin D<sub>3</sub>, or with 50,000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> once weekly for 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml followed by maintenance therapy of 400–1000 IU/d (2|⊕⊕⊕⊕).

#### 3.2 Evidence

Vitamin D-deficient infants and toddlers who received either 2000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> daily or 50,000 IU of vitamin D<sub>2</sub> weekly for 6 wk demonstrated equivalent increases in their serum 25(OH)D levels (47). No signs of

vitamin D intoxication were seen with any of the three regimens studied.

Children with rickets have been successfully treated with 600,000 IU of vitamin D either orally or im once a year (47, 50). In the United States, there are two pharmaceutical formulations of vitamin D. For the pediatric population, vitamin D<sub>2</sub> is available in a liquid form at a concentration of 8000 IU/ml, and for older children and adults, a gelatin capsule containing 50,000 IU of vitamin D<sub>2</sub> is available.

#### Recommendation

3.3 For children aged 1–18 yr who are vitamin D deficient, we suggest treatment with 2000 IU/d of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> for at least 6 wk or with 50,000 IU of vitamin D<sub>2</sub> once a week for at least 6 wk to achieve a blood level of 25(OH)D above 30 ng/ml followed by maintenance therapy of 600–1000 IU/d (2|⊕⊕⊕⊕).

#### 3.3 Evidence

Children of all ages are at risk for vitamin D deficiency and insufficiency (3, 29, 47, 77, 84–90), with the caveat that at present we do not know optimal serum 25(OH)D levels for any functional outcome. Vitamin D-deficient infants and toddlers who received either 2000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> daily or 50,000 IU of vitamin D<sub>2</sub> weekly for 6 wk demonstrated equivalent increases in their serum 25(OH)D levels (47). There are sparse data to guide pediatric clinicians in the treatment of young children with vitamin D deficiency. One study showed that infants with vitamin D deficiency who receive doses of ergocalciferol exceeding 300,000 IU as a one-time dose were at high risk for hypercalcemia (132). Therefore, most pediatric providers use lower dose daily or weekly regimens. Caution also needs to be shown in children with Williams syndrome or other conditions predisposing to hypercalcemia (133).

Some studies indicate that children who receive adult doses of vitamin D experience changes in 25(OH)D similar to those seen in adults (47, 96). In accordance with the findings of Maalouf *et al.* (91), this age group needs 2000 IU/d vitamin D to maintain a blood level above 30 ng/ml. Children who received 1400 IU/wk increased their blood level of 25(OH)D from 14 ± 9 to 17 ± 6 ng/ml, whereas children who received 14,000 IU/wk for 1 yr increased their blood levels from 14 ± 8 to 38 ± 31 ng/ml.

#### Recommendation

3.4 We suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> once a week for 8 wk or its equivalent of 6000 IU/d of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> to achieve a blood level of

25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/d (2|⊕⊕⊕⊕).

### 3.4 Evidence

A dose of 50,000 IU of vitamin D<sub>2</sub> once a week for 8 wk is often effective in correcting vitamin D deficiency in adults (3, 16). Patients who do not show an increase in their blood level of 25(OH)D should be worked up for celiac disease or occult cystic fibrosis, assuming that they were compliant with treatment. To prevent recurrence of vitamin D deficiency, 50,000 IU of vitamin D<sub>2</sub> once every other week was effective in maintaining blood levels of 25(OH)D between 35 and 50 ng/ml without any untoward toxicity (102). Obese adults need at least two to three times more vitamin D to treat and prevent vitamin D deficiency (38, 42).

Alternative strategies for nursing home residents include 50,000 IU of vitamin D<sub>2</sub> three times per week for 1 month (134) or 100,000 IU of vitamin D every 4 months (61).

### Recommendation

3.5 In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of at least 3000–6000 IU/d (2|⊕⊕⊕⊕).

### 3.5 Evidence

Obese adults need at least two to three times more vitamin D (at least 6000–10,000 IU/d) to treat and prevent vitamin D deficiency (42, 135). Patients receiving anticonvulsant medications, glucocorticoids, and a wide variety of other medications that enhance the activation of the steroid xenobiotic receptor that results in the destruction of 25(OH)D and 1,25(OH)<sub>2</sub>D often require at least two to three times more vitamin D (at least 6000–10,000 IU/d) to treat and prevent vitamin D deficiency (3, 43). In both groups, the serum 25(OH)D level should be monitored and vitamin D dosage adjusted to achieve a 25(OH)D level above 30 ng/ml.

### Recommendation

3.6 In patients with extrarenal production of 1,25(OH)<sub>2</sub>D, we suggest serial monitoring of 25(OH)D levels and serum calcium levels during treatment with vitamin D to prevent hypercalcemia (2|⊕⊕⊕⊕).

### 3.6 Evidence

Patients who suffer from chronic granuloma-forming disorders including sarcoidosis, tuberculosis, and chronic fungal infections and some patients with lymphoma have activated macrophages that produce 1,25(OH)<sub>2</sub>D in an

unregulated fashion (3, 44). This results in an increase in the efficiency of intestinal calcium absorption and mobilization of calcium from the skeleton that can cause hypercalciuria and hypercalcemia. These patients may require vitamin D treatment to raise their blood level of 25(OH)D to approximately 20–30 ng/ml to prevent vitamin D-deficiency metabolic bone disease while mitigating hypercalciuria and hypercalcemia.

The 25(OH)D levels need to be carefully monitored for these patients. Hypercalciuria and hypercalcemia are usually observed when the 25(OH)D is above 30 ng/ml (44).

### Recommendation

3.7 For patients with primary hyperparathyroidism and vitamin D deficiency, we suggest treatment with vitamin D as needed. Serum calcium levels should be monitored (2|⊕⊕⊕⊕).

### 3.7 Evidence

Patients with primary hyperparathyroidism and hypercalcemia are often vitamin D deficient. It is important to correct their vitamin D deficiency and maintain sufficiency. Most patients will not increase their serum calcium level, and serum PTH may even decrease (45). Their serum calcium should be monitored.

## 4.0 Noncalcemic Benefits of Vitamin D

### Recommendation

4.1 We recommend prescribing vitamin D supplementation for fall prevention. We do not recommend prescribing vitamin D supplementation beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (2|⊕⊕⊕⊕).

### 4.1 Evidence

Because most tissues and cells in the body have a vitamin D receptor and 1,25(OH)<sub>2</sub>D influences the expression levels along with other factors of up to one third of the human genome, it is not at all unexpected that a numerous of studies has demonstrated an association of vitamin D deficiency with increased risk of more than a dozen cancers, including colon, prostate, breast, and pancreas; autoimmune diseases, including both type 1 and type 2 diabetes, rheumatoid arthritis, Crohn's disease, and multiple sclerosis; infectious diseases; and cardiovascular disease. There are, however, very few RCT with a dosing range adequate to provide level I evidence for the benefit of vitamin D in reducing the risk of these chronic diseases (20). In the cancer prevention study by Lappe *et al.* (136), postmenopausal women who received 1100 IU of vitamin D<sub>3</sub> daily along with calcium supplementation reduced their

overall risk of all cancers by more than 60%. This was associated with an increase in mean serum 25(OH)D levels from 29–39 ng/ml. Several observational studies have reported that colon cancer risk became progressively lower as serum 25(OH)D increased up to 30–32 ng/ml. However, because population values above 30–32 ng/ml are uncommon, most observational studies do not extend much beyond this level of repletion, and thus, observational data are largely silent about the optimal 25(OH)D levels.

Several studies found associations between 25(OH)D levels and hypertension, coronary artery calcification, as well as prevalent and incident heart disease (137–140). Prevalent myocardial infarction (MI) was found to be inversely associated with plasma 25(OH)D levels. The RR of MI for subjects with levels at the median or above was 0.43 (95% CI, 0.27–0.69), compared with subjects below the median. Similarly, individuals with levels below 15 ng/ml had a multivariable-adjusted hazard ratio of 1.62 (95% CI, 1.11–2.36) for incident cardiovascular events compared with those with levels above 15 ng/ml (137). Furthermore, although vitamin D deficiency is documented in long-term stroke survivors and is associated with post-stroke hip fractures, recent reports demonstrated low levels of 25(OH)D in patients presenting with acute strokes, suggesting that this deficiency had likely preceded the stroke and may be a potential risk factor for it (141).

Therefore, two systematic reviews were conducted as well as meta-analyses to summarize the best available research evidence regarding the effect of vitamin D-raising interventions on functional outcomes (falls, pain, quality of life) and cardiovascular outcomes (death, stroke, MI, cardiometabolic risk factors) (120, 142).

Vitamin D-raising interventions were associated with a not significant and potentially trivial reduction in mortality that was consistent across studies (RR = 0.96; 95% CI, 0.93–1.00;  $P = 0.08$ ;  $I^2 = 0\%$ ). There was no significant effect on MI (RR = 1.02; 95% CI, 0.93–1.13;  $P = 0.64$ ;  $I^2 = 0\%$ ), stroke (RR = 1.05; 95% CI, 0.88–1.25;  $P = 0.59$ ;  $I^2 = 15\%$ ), lipid fractions, glucose, or blood pressure; blood pressure results were inconsistent across studies, and the pooled estimates were trivial in absolute terms (142). In terms of functional outcomes, there was a clear reduction in the risk of falls as mentioned earlier, but no effect on pain or quality of life. The evidence supporting the latter outcomes was sparse, inconsistent, and of lower quality.

#### 4.1 Values

The Task Force acknowledges the overall low-quality evidence in this area (20) and the fact that many of their recommendations are based on understanding of the biology of vitamin D pharmacokinetics, bone and minerals, basic science experiments, and epidemiological studies.

Nevertheless, in making recommendations, the panel placed the highest value on preserving musculoskeletal health and preventing childhood rickets and adult bone disease, and less value on vitamin D cost and potential for toxicity. Vitamin D supplementation/treatment is likely inexpensive and would be cost-effective, particularly in treating entities such as osteoporosis, rickets, and osteomalacia. Cost and resource utilization in other preventive indications are less known. Ample evidence provided the panel with a high level of confidence that toxicity of vitamin D at the recommended dosages is quite unlikely. The Task Force also acknowledges that science is changing rapidly in this field and that recommendations will likely need to be revised as future evidence accumulates.

#### Future Directions

There needs to be an appreciation that unprotected sun exposure is the major source of vitamin D for both children and adults and that in the absence of sun exposure it is difficult, if not impossible, to obtain an adequate amount of vitamin D from dietary sources without supplementation to satisfy the body's requirement. Concerns about melanoma and other types of skin cancer necessitate avoidance of excessive exposure to midday sun. These observations strengthen the arguments for supplementation, especially for people living above 33° latitude (143). All available evidence suggests that children and adults should maintain a blood level of 25(OH)D above 20 ng/ml to prevent rickets and osteomalacia, respectively. However, to maximize vitamin D's effect on calcium, bone, and muscle metabolism, the 25(OH)D blood level should be above 30 ng/ml. Numerous epidemiological studies have suggested that a 25(OH)D blood level above 30 ng/ml may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease, and infectious diseases.

Few RCT have used an amount of vitamin D that raises the blood level above 30 ng/ml, and thus there remains appropriate skepticism about the potential noncalcemic benefits of vitamin D for health. Concern was also raised by the IOM report (20) that some studies have suggested that all-cause mortality increased when blood levels of 25(OH)D were greater than approximately 50 ng/ml. RCT that evaluate the effects of vitamin D doses in the range of 2000–5000 IU/d on noncalcemic health outcomes are desperately needed. There is no evidence that there is a downside to increasing vitamin D intake in children and adults, except for those who have a chronic granuloma-forming disorder or lymphoma.

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## References

1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer TT, Varonen H, Vist GE, Williams Jr JW, Zaza S 2004 Grading quality of evidence and strength of recommendations. *BMJ* 328:1490
2. Swiglo BA, Murad MH, Schünemann HJ, Kunz R, Vigersky RA, Guyatt GH, Montori VM 2008 A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J Clin Endocrinol Metab* 93:666–673
3. Holick MF 2007 Vitamin D deficiency. *N Engl J Med* 357:266–281
4. Holick MF 2008 Vitamin D: a D-lightful health perspective. *Nutr Rev* 66(10 Suppl 2):S182–S194
5. Holick MF, Chen TC 2008 Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr* 87:1080S–1086S
6. Holick MF, Chen TC, Sauter ER 2007 Vitamin D and skin physiology: a D-lightful story. *J Bone Miner Res* 22(Suppl 2):V28–V33
7. Moan J, Porojnicu AC, Dahlback A, Setlow RB 2008 Addressing the health benefits and risks, involving vitamin D or skin cancer, of increased sun exposure. *Proc Natl Acad Sci USA* 105:668–673
8. DeLuca H 2004 Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 80(6 Suppl):1689S–1696S
9. Christakos S, Dhawan P, Liu Y, Peng X, Porta A 2003 New insights into the mechanisms of vitamin D action. *J Cell Biochem* 88:695–705
10. Heaney RP 2004 Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr* 80(6 Suppl):1706S–1709S
11. Dusso AS, Brown AJ, Slatopolsky E 2005 Vitamin D. *Am J Physiol Renal Physiol* 289:F8–F28
12. Adams JS, Hewison M 2010 Update in vitamin D. *J Clin Endocrinol Metab* 95:471–478
13. Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schaubert J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL 2006 Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 311:1770–1773
14. Bouillon R, Bischoff-Ferrari H, Willett W 2008 Vitamin D and health: perspectives from mice and man. *J Bone Miner Res* 23:974–979
15. Nagpal S, Na S, Rathnachalam R 2005 Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* 26:662–687



16. Malabanan A, Veronikis IE, Holick MF 1998 Redefining vitamin D insufficiency. *Lancet* 351:805–806
17. Heaney RP, Dowell MS, Hale CA, Bendich A 2003 Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. *J Am Coll Nutr* 22:142–146
18. Hansen KE, Jones AN, Lindstrom MJ, Davis LA, Engelke JA, Shafer MM 2008 Vitamin D insufficiency: disease or no disease? *J Bone Miner Res* 23:1052–1060
19. Bischoff-Ferrari HA, Can U, Staehelin HB, Platz A, Henschkowski J, Michel BA, Dawson-Hughes B, Theiler R 2008 Severe vitamin D deficiency in Swiss hip fracture patients. *Bone* 42:597–602
20. IOM (Institute of Medicine) 2011 Dietary reference intakes for calcium and vitamin D. Washington DC: The National Academies Press
21. Chapuy MC, Schott AM, Garnero P, Hans D, Delmas PD, Meunier PJ 1996 Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter: EPIDOS Study Group. *J Clin Endocrinol Metab* 81:1129–1133
22. Holick MF, Siris ES, Binkley N, Beard MK, Khan A, Katzer JT, Petruschke RA, Chen E, de Papp AE 2005 Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab* 90:3215–3224
23. Lips P, Hosking D, Lippuner K, Norquist JM, Wehren L, Maalouf G, Ragi-Eis S, Chandler J 2006 The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *J Intern Med* 260:245–254
24. Holick MF 2006 High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 81:353–373
25. Greene-Finestone LS, Berger C, de Groh M, Hanley DA, Hidioglou N, Sarafin K, Poliquin S, Krieger J, Richards JB, Goltzman D 2011 25-Hydroxyvitamin D in Canadian adults: biological, environmental, and behavioral correlates. *Osteoporos Int* 22:1389–1399
26. Marwaha RK, Tandon N, Reddy DR, Aggarwal R, Singh R, Sawhney RC, Saluja B, Ganie MA, Singh S 2005 Vitamin D and bone mineral density status of healthy schoolchildren in northern India. *Am J Clin Nutr* 82:477–482
27. Thacher TD, Fischer PR, Strand MA, Pettifor JM 2006 Nutritional rickets around the world: causes and future directions. *Ann Trop Paediatr* 26:1–16
28. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ 2004 Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc Med* 158:531–537
29. Sullivan SS, Rosen CJ, Halteman WA, Chen TC, Holick MF 2005 Adolescent girls in Maine at risk for vitamin D insufficiency. *J Am Diet Assoc* 105:971–974
30. Nesby-O'Dell S, Scanlon KS, Cogswell ME, Gillespie C, Hollis BW, Looker AC, Allen C, Dougherty C, Gunter EW, Bowman BA 2002 Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 76:187–192
31. Tangpricha V, Pearce EN, Chen TC, Holick MF 2002 Vitamin D insufficiency among free-living healthy young adults. *Am J Med* 112:659–662
32. Hollis BW, Wagner CL 2004 Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr* 80:1752S–1758S
33. Lee JM, Smith JR, Philipp BL, Chen TC, Mathieu J, Holick MF 2007 Vitamin D deficiency in a healthy group of mothers and newborn infants. *Clin Pediatr (Phila)* 46:42–44
34. Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM 2007 High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. *J Nutr* 137:447–452
35. Hollis BW 2005 Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. *J Nutr* 135:317–322
36. Maeda SS, Kunii IS, Hayashi L, Lazaretti-Castro M 2007 The effect of sun exposure on 25-hydroxyvitamin D concentrations in young healthy subjects living in the city of Sao Paulo, Brazil. *Braz J Med Biol Res* 40:1653–1659
37. Brot C, Vestergaard P, Kolthoff N, Gram J, Hermann AP, Sorensen OH 2001 Vitamin D status and its adequacy in healthy Danish perimenopausal women: relationships to dietary intake, sun exposure and serum parathyroid hormone. *Br J Nutr* 86(Suppl 1):S97–S103
38. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA 2008 Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared to 2000–2004. *Am J Clin Nutr* 88:1519–1527
39. Matsuoka LY, Ide L, Wortsman J, MacLaughlin JA, Holick MF 1987 Sunscreens suppress cutaneous vitamin D<sub>3</sub> synthesis. *J Clin Endocrinol Metab* 64:1165–1168
40. Clemens TL, Henderson SL, Adams JS, Holick MF 1982 Increased skin pigment reduces the capacity of skin to synthesise vitamin D<sub>3</sub>. *Lancet* 1:74–76
41. Hintzpete B, Scheidt-Nave C, Müller MJ, Schenk L, Mensink GB 2008 Higher prevalence of vitamin D deficiency is associated with immigrant background among children and adolescents in Germany. *J Nutr* 138:1482–1490
42. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF 2000 Decreased bioavailability of vitamin D in obesity. *Am J Clin Nutr* 72:690–693
43. Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, Thummel KE 2006 Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. *J Clin Invest* 116:1703–1712
44. Adams JS, Hewison M 2006 Hypercalcemia caused by granuloma-forming disorders. In: Favus MJ, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 6th ed. Washington, DC: American Society for Bone and Mineral Research; 200–202
45. Grey A, Lucas J, Horne A, Gamble G, Davidson JS, Reid IR 2005 Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. *J Clin Endocrinol Metab* 90:2122–2126
46. Aaron JE, Gallagher JC, Anderson J, Stasiak L, Longton EB, Nordin BE, Nicholson M 1974 Frequency of osteomalacia and osteoporosis in fractures of the proximal femur. *Lancet* 1:229–233
47. Gordon CM, Williams AL, Feldman HA, May J, Sinclair L, Vasquez A, Cox JE 2008 Treatment of hypovitaminosis D in infants and toddlers. *J Clin Endocrinol Metab* 93:2716–2721
48. Malabanan AO, Turner AK, Holick MF 1998 Severe generalized bone pain and osteoporosis in a premenopausal black female: effect of vitamin D replacement. *J Clin Densitometr* 1:201–204
49. Plotnikoff GA, Quigley JM 2003 Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. *Mayo Clin Proc* 78:1463–1470
50. Holick MF 2006 Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 116:2062–2072
51. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B 2005 Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA* 293:2257–2264
52. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, Wong JB, Egli A, Kiel DP, Henschkowski J 2009 Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ* 339:b3692
53. Haddad JG, Matsuoka LY, Hollis BW, Hu YZ, Wortsman J 1993 Human plasma transport of vitamin D after its endogenous synthesis. *J Clin Invest* 91:2552–2555

54. Holick MF 2009 Vitamin D status: measurement, interpretation and clinical application. *Ann Epidemiol* 19:73–78
55. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Stachelin HB, Orav EJ, Thoma A, Kiel DP, Henschkowski J 2009 Prevention of nonvertebral fractures with oral vitamin D and dose dependency. *Arch Intern Med* 169:551–561
56. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, Hathcock J, Giovannucci E, Willett WC 2010 Benefit-risk assessment of vitamin D supplementation. *Osteoporos Int* 21:1121–1132
57. Demay MB 1995 Hereditary defects in vitamin D metabolism and vitamin D receptor defects. In: DeGroot L, ed. *Endocrinology*. Philadelphia: WB Saunders; 1173–1178
58. Drezner MK 2005 Clinical disorders of phosphate homeostasis. *Vitamin D*. 2nd ed. Boston: Elsevier Academic Press; 1159–1187
59. Singh RJ, Taylor RL, Reddy GS, Grebe SK 2006 C-3 epimers can account for a significant proportion of total circulating 25-hydroxyvitamin D in infants, complicating accurate measurement and interpretation of vitamin D status. *J Clin Endocrinol Metab* 91:3055–3061
60. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS 1998 Hypovitaminosis D in medical inpatients. *N Engl J Med* 338:777–783
61. Trivedi DP, Doll R, Khaw KT 2003 Effect of four monthly oral vitamin D<sub>3</sub> (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. *BMJ* 326:469
62. Gessner BD, deSchweinitz E, Petersen KM, Lewandowski C 1997 Nutritional rickets among breast-fed black and Alaska Native children. *Alaska Med* 39:72–74:87
63. Ziegler EE, Hollis BW, Nelson SE, Jeter JM 2006 Vitamin D deficiency in breastfed infants in Iowa. *Pediatrics* 118:603–610
64. Shaikh U, Alpert PT 2006 Nutritional rickets in Las Vegas, Nevada. *J Pediatr Endocrinol Metab* 19:209–212
65. Hayward I, Stein MT, Gibson MI 1987 Nutritional rickets in San Diego. *Am J Dis Child* 141:1060–1062
66. Kreiter SR, Schwartz RP, Kirkman Jr HN, Charlton PA, Calikoglu AS, Davenport ML 2000 Nutritional rickets in African American breast-fed infants. *J Pediatr* 137:153–157
67. Shah M, Salhab N, Patterson D, Seikaly MG 2000 Nutritional rickets still afflict children in north Texas. *Tex Med* 96:64–68
68. Rajakumar K, Greenspan SL, Thomas SB, Holick MF 2007 SOLAR ultraviolet radiation and vitamin D: a historical perspective. *Am J Public Health* 97:1746–1754
69. Specker BL, Tsang RC 1987 Cyclical serum 25-hydroxyvitamin D concentrations paralleling sunshine exposure in exclusively breast-fed infants. *J Pediatr* 110:744–747
70. Specker BL, Valanis B, Hertzberg V, Edwards N, Tsang RC 1985 Sunshine exposure and serum 25-hydroxyvitamin D. *J Pediatr* 107:372–376
71. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board Institute of Medicine 1999 Vitamin D. In: *Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press; 250–287
72. Feliciano ES, Ho ML, Specker BL, Falciglia G, Shui QM, Yin TA, Chen XC 1994 Seasonal and geographical variations in the growth rate of infants in China receiving increasing dosages of vitamin D supplements. *J Trop Pediatr* 40:162–165
73. Fomon SJ, Younoszai MK, Thomas LN 1966 Influence of vitamin D on linear growth of normal full-term infants. *J Nutr* 88:345–350
74. Specker BL, Ho ML, Oestreich A, Yin TA, Shui QM, Chen XC, Tsang RC 1992 Prospective study of vitamin D supplementation and rickets in China. *J Pediatr* 120:733–739
75. Jeans PC 1950 Vitamin D. *JAMA* 143:177–181
76. Markestad T, Elzouki AY 1991 Vitamin D deficiency rickets in northern Europe and Libya. In: Glorieux FH, ed. *Rickets: Nestle Nutrition Workshop Series*. Vol 21. New York: Raven Press
77. Wagner CL, Greer FR; Section on Breast Feeding and Committee on Nutrition 2008 Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 122:1142–1152
78. Zamora SA, Rizzoli R, Belli DC, Slosman DO, Bonjour JP 1999 Vitamin D supplementation during infancy is associated with higher bone mineral mass in prepubertal girls. *J Clin Endocrinol Metab* 84:4541–4544
79. Binet A, Kooh SW 1996 Persistence of vitamin D-deficiency rickets in Toronto in the 1990s. *Can J Public Health* 87:227–230
80. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B 2006 Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 84:18–28
81. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM 2001 Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 358:1500–1503
82. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H 2010 Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr* 91:1255–1260
83. Dong Y, Stallmann-Jorgensen IS, Pollock NK, Harris RA, Keeton D, Huang Y, Li K, Bassali R, Guo DH, Thomas J, Pierce GL, White J, Holick MF, Zhu H 2010 A 16-week randomized clinical trial of 2,000 IU daily vitamin D<sub>3</sub> supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab* 95:4584–4591
84. Pettifor JM, Ross FP, Moodley G, Wang J, Margo G, Skjolde C 1978 Serum calcium, magnesium, phosphorus, alkaline phosphatase and 25-hydroxyvitamin D concentrations in children. *S Afr Med J* 53:751–754
85. Lehtonen-Veromaa MK, Möttönen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS 2002 Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. *Am J Clin Nutr* 76:1446–1453
86. Weng FL, Shults J, Leonard MB, Stallings VA, Zemel BS 2007 Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. *Am J Clin Nutr* 86:150–158
87. Das G, Crocombe S, McGrath M, Berry JL, Mughal MZ 2006 Hypovitaminosis D among healthy adolescent girls attending an inner city school. *Arch Dis Child* 91:569–572
88. Harkness LS, Cromer BA 2005 Vitamin D deficiency in adolescent females. *J Adolesc Health* 37:75
89. El-Hajj Fuleihan G, Nabulsi M, Choucair M, Salamoun M, Hajj Shahine C, Kizirian A, Tannous R 2001 Hypovitaminosis D in healthy schoolchildren. *Pediatrics* 107:E53
90. Huh SY, Gordon CM 2008 Vitamin D deficiency in children and adolescents: epidemiology, impact and treatment. *Rev Endocr Metab Disord* 9:161–170
91. Maalouf J, Nabulsi M, Vieth R, Kimball S, El-Rassi R, Mahfoud Z, El-Hajj Fuleihan G 2008 Short- and long-term safety of weekly high-dose vitamin D<sub>3</sub> supplementation in school children. *J Clin Endocrinol Metab* 93:2693–2701
92. Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML 2009 Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001–2004. *Pediatrics* 124:e362–e370
93. Reis JP, von Mühlen D, Miller 3rd ER, Michos ED, Appel LJ 2009 Vitamin D status and cardiometabolic risk factors in the United States adolescent population. *Pediatrics* 124:e371–e379
94. Aksnes L, Aarskog D 1982 Plasma concentrations of vitamin D metabolites in puberty: effect of sexual maturation and implications for growth. *J Clin Endocrinol Metab* 55:94–101
95. Gültekin A, Ozalp I, Hasanoğlu A, Unal A 1987 Serum-25-hydroxycholecalciferol levels in children and adolescents. *Turk J Pediatr* 29:155–162
96. El-Hajj Fuleihan G, Nabulsi M, Tamim H, Maalouf J, Salamoun M, Khalife H, Choucair M, Arabi A, Vieth R 2006 Effect of vitamin D replacement on musculoskeletal parameters in school children:

- a randomized controlled trial. *J Clin Endocrinol Metab* 91:405–412
97. Abrams SA, Hicks PD, Hawthorne KM 2009 Higher serum 25-hydroxyvitamin D levels in school-age children are inconsistently associated with increased calcium absorption. *J Clin Endocrinol Metab* 94:2421–2427
  98. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Dawson-Hughes B 2004 Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger and older adults. *Am J Med* 116:634–639
  99. Meier DE, Luckey MM, Wallenstein S, Clemens TL, Orwoll ES, Waslien CI 1991 Calcium, vitamin D, and parathyroid hormone status in young white and black women: association with racial differences in bone mass. *J Clin Endocrinol Metab* 72:703–710
  100. Barger-Lux MJ, Heaney RP 2002 Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. *J Clin Endocrinol Metab* 87:4952–4956
  101. Holick MF, Biancuzzo RM, Chen TC, Klein EK, Young A, Bibuld D, Reitz R, Salameh W, Ameri A, Tannenbaum AD 2008 Vitamin D<sub>2</sub> is as effective as vitamin D<sub>3</sub> in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab* 93:677–681
  102. Pietras SM, Obayan BK, Cai MH, Holick MF 2009 Vitamin D<sub>2</sub> treatment for vitamin D deficiency and insufficiency for up to 6 years. *Arch Intern Med* 169:1806–1808
  103. Holick MF 2004 Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Robert H. Herman Memorial Award in Clinical Nutrition Lecture, 2003. *Am J Clin Nutr* 79:362–371
  104. Holick MF 1986 Vitamin D requirements for the elderly. *Clin Nutr* 5:121–129
  105. Clemens TL, Zhou XY, Myles M, Endres D, Lindsay R 1986 Serum vitamin D<sub>2</sub> and vitamin D<sub>3</sub> metabolite concentrations and absorption of vitamin D<sub>2</sub> in elderly subjects. *J Clin Endocrinol Metab* 63:656–660
  106. Harris SS, Dawson-Hughes B 2002 Plasma vitamin D and 25OHD responses of young and old men to supplementation with vitamin D<sub>3</sub>. *J Am Coll Nutr* 21:357–362
  107. Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R 2005 Estimates of optimal vitamin D status. *Osteoporos Int* 16:713–716
  108. Priemel M, von Domarus C, Klatter TO, Kessler S, Schlie J, Meier S, Proksch N, Pastor F, Netter C, Streichert T, Püschel K, Amling M 2010 Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *J Bone Miner Res* 25:305–312
  109. Krall EA, Dawson-Hughes B 1991 Relation of fractional <sup>47</sup>Ca retention to season and rates of bone loss in healthy postmenopausal women. *J Bone Miner Res* 6:1323–1329
  110. Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G 1991 Effect of vitamin D supplementation on wintertime and overall bone loss in healthy postmenopausal women. *Ann Intern Med* 115:505–512
  111. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL 1995 Rates of bone loss in postmenopausal women randomly assigned to one of two dosages for vitamin D. *Am J Clin Nutr* 61:1140–1145
  112. Lips P, Wiersinga A, van Ginkel FC, Jongen MJ, Netelenbos JC, Hackeng WH, Delmas PD, van der Vijgh WJ 1988 The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. *J Clin Endocrinol Metab* 67:644–650
  113. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ 1992 Vitamin D<sub>3</sub> and calcium to prevent hip fractures in elderly women. *N Engl J Med* 327:1637–1642
  114. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE 1997 Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 337:670–676
  115. Schott GD, Wills MR 1976 Muscle weakness in osteomalacia. *Lancet* 1:626–629
  116. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlsson EW, Dawson-Hughes B 2004 Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or = 60 y. *Am J Clin Nutr* 80:752–758
  117. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C 2000 Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res* 15:1113–1118
  118. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H 2009 Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporos Int* 20:315–322
  119. Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP 2007 A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *J Am Geriatr Soc* 55:234–239
  120. Murad MH, Elamin KB, Abu Elnour NO, Elamin MB, Alkatib AA, Fataourechi MM, Almandoz JP, Mullan RJ, Lane MA, Liu H, Erwin PJ, Hensrud DD, Montori VM 2011 Interventions to raise vitamin D level and functional outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab*
  121. Bischoff HA, Stähelin HB, Dick W, Akos R, Knecht M, Salis C, Nebiker M, Theiler R, Pfeifer M, Begerow B, Lew RA, Conzelmann M 2003 Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *J Bone Miner Res* 18:343–351
  122. Graafmans WC, Ooms ME, Hofstee HM, Bezemer PD, Bouter LM, Lips P 1996 Falls in the elderly: a prospective study of risk factors and risk profiles. *Am J Epidemiol* 143:1129–1136
  123. Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R 2010 Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 153:815–825
  124. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF 2009 Association between severe vitamin D deficiency and primary caesarean section. *J Clin Endocrinol Metab* 94:940–945
  125. Holick MF 2006 Vitamin D deficiency in obesity and health consequences. *Curr Opin Endocrinol Diabetes Obes* 13:412–418
  126. Blum M, Dolnikowski G, Seyoum E, Harris SS, Booth SL, Peterson J, Saltzman E, Dawson-Hughes B 2008 Vitamin D(3) in fat tissue. *Endocrine* 33:90–94
  127. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ 2003 Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 77:204–210
  128. Biancuzzo RM, Young A, Bibuld D, Cai MH, Winter MR, Klein EK, Ameri A, Reitz R, Salameh W, Chen TC, Holick MF 2010 Fortification of orange juice with vitamin D<sub>2</sub> or vitamin D<sub>3</sub> is as effective as an oral supplement in maintaining vitamin D status in adults. *Am J Clin Nutr* 91:1621–1626
  129. Armas LA, Hollis BW, Heaney RP 2004 Vitamin D<sub>2</sub> is much less effective than vitamin D<sub>3</sub> in humans. *J Clin Endocrinol Metab* 89:5387–5391
  130. Trang HM, Cole DE, Rubin LA, Pierratos A, Siu S, Vieth R 1998 Evidence that vitamin D<sub>3</sub> increases serum 25-hydroxyvitamin D more efficiently than does vitamin D<sub>2</sub>. *Am J Clin Nutr* 68:854–858
  131. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA 2011 Vitamin D<sub>3</sub> is more potent than vitamin D<sub>2</sub> in humans. *J Clin Endocrinol Metab* 96:E447–E452
  132. Cesur Y, Caksen H, Gündem A, Kirimi E, Odabağ D 2003 Comparison of low and high dose vitamin D treatment for nutritional vitamin D deficiency rickets. *J Pediatr Endocrinol Metab* 16:1105–1109
  133. Cagle AP, Waguespack SG, Buckingham BA, Shankar RR, Dimeglio LA 2004 Severe infantile hypercalcemia associated with Williams syndrome successfully treated with intravenously administered pamidronate. *Pediatrics* 114:1091–1095
  134. Przybelski R, Agrawal S, Krueger D, Engelke JA, Walbrun F, Bin-

- kley N 2008 Rapid correction of low vitamin D status in nursing home residents. *Osteoporos Int* 19:1621–1628
135. Arunabh S, Pollack S, Yeh J, Aloia JF 2003 Body fat content and 25-hydroxyvitamin D levels in healthy women. *J Clin Endocrinol Metab* 88:157–161
136. Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP 2007 Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 85:1586–1591
137. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, Benjamin EJ, D'Agostino RB, Wolf M, Vasan RS 2008 Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 117:503–511
138. Kristal-Bonch E, Froom P, Harari G, Ribak J 1997 Association of calcitriol and blood pressure in normotensive men. *Hypertension* 30:1289–1294
139. Scragg R, Jackson R, Holdaway IM, Lim T, Beaglehole R 1990 Myocardial infarction is inversely associated with plasma 25-hydroxyvitamin D3 levels: a community-based study. *Int J Epidemiol* 19:559–563
140. Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Detrano R, Demer LL 1997 Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation* 96:1755–1760
141. Poole KE, Loveridge N, Barker PJ, Halsall DJ, Rose C, Reeve J, Warburton EA 2006 Reduced vitamin D in acute stroke. *Stroke* 37:243–245
142. Elamin MB, Abu Elnour NO, Elamin KB, Murad MH, Fatourehchi MM, Alkatib AA, Almandoz JP, Liu H, Lane MA, Mullan RJ, Erwin PJ, Hensrud DD, Montori VM 2011 Vitamin D supplementation and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 10.1210/jc.2011-0398
143. Grant WB, Cross HS, Garland CF, Gorham ED, Moan J, Peterlik M, Porojnicu AC, Reichrath J, Zittermann A 2009 Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe. *Prog Biophys Mol Biol* 99:104–113



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