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_2 or vitamin D_3 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 [$1,25(OH)_2D$] 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; $1,25(OH)_2D$, 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_2 or vitamin D_3 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_2 or vitamin D_3, or with 50,000 IU of vitamin D_2 or vitamin D_3 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_2 or vitamin D_3 for at least 6 wk or with 50,000 IU of vitamin D_2 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_2 or vitamin D_3 once a week for 8 wk or its equivalent of 6000 IU of vitamin D_2 or vitamin D_3 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 $1,25(OH)_2D$, 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_2 is obtained from the UV irradiation of the yeast sterol ergosterol and is found naturally in sun-exposed mushrooms. Vitamin D_3 is synthesized in the skin and is present in oil-rich fish such as salmon, mackerel, and herring; commercially available vitamin D_3 is synthesized from the cholesterol precursor 7-dehydrocholesterol naturally present in the skin or obtained from lanolin (3). Both vitamin D_2 and vitamin D_3 are used for food fortification and in vitamin D supplements. Vitamin D (D represents D_2, or D_3, 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-1α-OHase (CYP27B1) to form the biologically active form of vitamin D $1,25(OH)_2D$ (3, 8). $1,25(OH)_2D$ interacts with its vitamin D nuclear receptor, which is present in the small intestine, kidneys, and other tissues (3, 8). $1,25(OH)_2D$ 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). $1,25(OH)_2D$ interacts with its vitamin D receptor in the osteoblast to stimulate the expression of receptor activator of nuclear factor κB ligand; this, in turn, interacts with receptor activator of nuclear factor κB to induce immature monocytes to become mature osteoclasts, which dissolve the matrix and mobilize calcium and other minerals from the skeleton. In the kidney, $1,25(OH)_2D$ 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). $1,25(OH)_2D$ 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, $1,25(OH)_2D$ stimulates its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-OHase (CYP24R) to metabolize 25(OH)D and $1,25(OH)_2D$ into water-soluble inactive forms. There are several tissues and cells that possess 1-OHase activity (3, 7, 12, 13). The local production of $1,25(OH)_2D$ 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^2, 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 $1,25(OH)_2D$ (43). Patients with chronic granuloma-forming disorders, some lymphomas, and primary hyperparathyroidism who have increased metabolism of 25(OH)D to $1,25(OH)_2D$ 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.

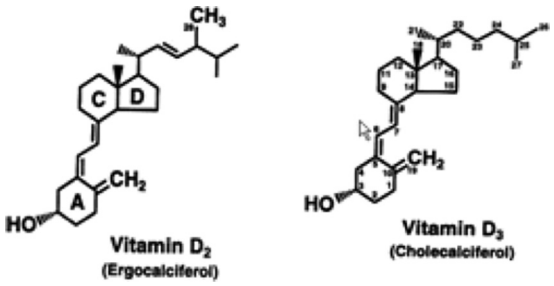
Sources of Vitamin D

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_3, 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_3 (3, 5). Above and below latitudes of approximately 33°, vitamin D_3 synthesis in the skin is very low or absent during most of the winter.

Few foods naturally contain vitamin D_2 or vitamin D_3 (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_2 and vitamin D_3

Source	Vitamin D content
Natural sources	
Cod liver oil	~400–1,000 IU/teaspoon vitamin D_3
Salmon, fresh wild caught	~600–1,000 IU/3.5 oz vitamin D_3
Salmon, fresh farmed	~100–250 IU/3.5 oz vitamin D_3, vitamin D_2
Salmon, canned	~300–600 IU/3.5 oz vitamin D_3
Sardines, canned	~300 IU/3.5 oz vitamin D_3
Mackerel, canned	~250 IU/3.5 oz vitamin D_3
Tuna, canned	236 IU/3.5 oz vitamin D_3
Shiitake mushrooms, fresh	~100 IU/3.5 oz vitamin D_2
Shiitake mushrooms, sun-dried	~1,600 IU/3.5 oz vitamin D_2
Egg yolk	~20 IU/yolk vitamin D_3 or D_2
Sunlight/UVB radiation	~20,000 IU equivalent to exposure to 1 minimal erythemal 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_3.
Fortified foods	
Fortified milk	100 IU/8 oz, usually vitamin D_3
Fortified orange juice	100 IU/8 oz vitamin D_3
Infant formulas	100 IU/8 oz vitamin D_3
Fortified yogurts	100 IU/8 oz, usually vitamin D_3
Fortified butter	56 IU/3.5 oz, usually vitamin D_3
Fortified margarine	429 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	~100 IU/serving, usually vitamin D_3
Pharmaceutical sources in the United States	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid	8,000 IU/cc
Supplemental sources	
Multivitamin	400, 500, 1,000 IU vitamin D_3 or vitamin D_2
Vitamin D_3	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_2 or vitamin D_3, whereas pharmaceutical preparations in the United States contain only vitamin D_2 (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^2)
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 $1,25(OH)_2D$ 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 $1,25(OH)_2D$ 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 $1,25(OH)_2D$ does not reflect vitamin D reserves, and measurement of $1,25(OH)_2D$ is not useful for monitoring the vitamin D status of patients. Serum $1,25(OH)_2D$ is frequently either normal or even elevated in those with vitamin D deficiency, due to secondary hyperparathyroidism. Thus, $1,25(OH)_2D$ measurement does not reflect vitamin D status. Measurement of $1,25(OH)_2D$ 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_2 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[a]						
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.

[a] 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 ± 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 ± 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 ± 14 *vs.* 24 ± 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 μg/d (100–400 IU/d) (94). When in-

takes were less than 2.5 μg/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_3 for 1 yr. Those who received 1400 IU/wk increased their blood level of 25(OH)D from 14 ± 8 to 17 ± 6 ng/ml, whereas the children who received 14,000 IU/wk for 1 yr increased their blood levels from 14 ± 8 to 38 ± 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 $1,25(OH)_2D$ increases. In turn, the increased blood levels of $1,25(OH)_2D$ 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 $1,25(OH)_2D$ 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 $1,25(OH)_2D$ 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 ± 84 and 145 ± 73 IU/d, respectively, revealed that serum 25(OH)D levels were in the insufficient or deficient range (circulating concentrations of 21.4 ± 4 and 18.3 ± 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_3 for 3 months during the winter increased their 25(OH)D from 19.6 ± 11.1 to 28.9 ± 7.7 ng/ml (101).

A dose-ranging study reported that men who received 10,000 IU/d of vitamin D_3 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_2 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_3 (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_3 (high-quality trials with oral vitamin D_2 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_3 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.

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-

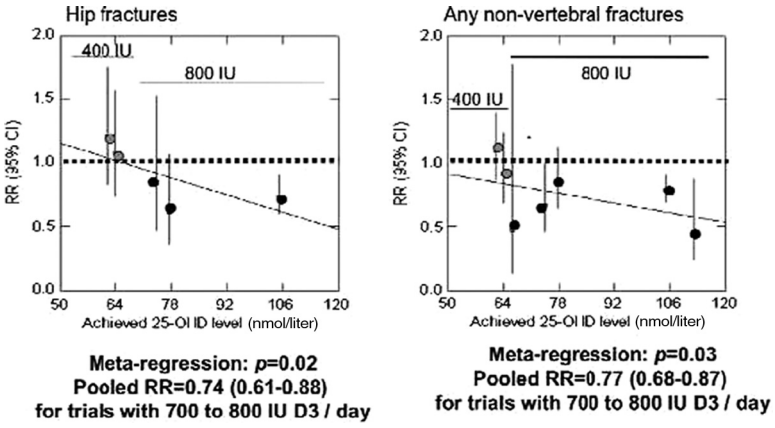


FIG. 1. Fracture efficacy by achieved 25(OH)D levels. To convert nmol/liter to ng/ml, divide by 2.496. [Reproduced with permission from H. A. Bischoff-Ferrari *et al.*: *JAMA* 293:2257–2264, 2005 (51). © American Medical Association.]

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_3 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 $1,25(OH)_2D$ by the mother's kidneys and placenta. Circulating concentrations of $1,25(OH)_2D$ 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 $1,25(OH)_2D$, 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 $1,25(OH)_2D$ is enhanced in response to this new demand. However, because circulating concentrations of $1,25(OH)_2D$ 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^2) 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_2, 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/d IU 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_3 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_2 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 $1,25(OH)_2D$ 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_2 or vitamin D_3 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_2 and vitamin D_3 are effective in maintaining serum 25(OH)D levels. Two meta-analyses of double-blind RCT suggested reduction in falls and nonvertebral fractures with vitamin D_2 compared with vitamin D_3 (52, 56).

Several studies using vitamin D_2 and vitamin D_3 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_2 or vitamin D_3 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_2 or vitamin D_3, or with 50,000 IU of vitamin D_2 or vitamin D_3 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_2 or vitamin D_3 daily or 50,000 IU of vitamin D_2 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_2 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_2 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_2 or vitamin D_3 for at least 6 wk or with 50,000 IU of vitamin D_2 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_2 or vitamin D_3 daily or 50,000 IU of vitamin D_2 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_2 or vitamin D_3 once a week for 8 wk or its equivalent of 6000 IU/d of vitamin D_2 or vitamin D_3 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_2 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_2 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_2 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 $1,25(OH)_2D$ 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 $1,25(OH)_2D$, 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 $1,25(OH)_2D$ 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 $1,25(OH)_2D$ 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_3 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; $P = 0.08$; I2 = 0%). There was no significant effect on MI (RR = 1.02; 95% CI, 0.93–1.13; $P = 0.64$; I2 = 0%), stroke (RR = 1.05; 95% CI, 0.88–1.25; $P = 0.59$; I2 = 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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