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# AQ: 1 Vitamin D requirements: current and future<sup>1,2</sup>

Connie M Weaver and James C Fleet

## ABSTRACT

AQ: 2 The requirements for vitamin D were last set in 1997 by the Food and Nutrition Board of the Institute of Medicine. Intakes were assumed to come from diet, and values were based on achievement of adequate vitamin D status and on observed values to prevent seasonal variations in parathyroid hormone concentrations. Serum 25-hydroxyvitamin D concentrations were considered the best indicator of vitamin D adequacy, because the production of 25-hydroxyvitamin D is not regulated. Normal ranges were obtained from reference populations, but the values varied widely with age and geographic region. Revised recommendations should take into consideration appropriate functional measures for multiple tissues and disease risks. Vitamin D-calcium interdependencies must be taken into account. Higher intakes of both vitamin D and calcium can reduce bone resorption, and higher concentrations of one nutrient might compensate for insufficiency in the other. Better ways to assess vitamin D (and calcium) inputs are needed. Food composition databases are incomplete for both vitamin D and calcium, especially in this era of food fortification, and are complicated by the poor quality control for vitamin D fortification. Upper levels of vitamin D intake were set at 50  $\mu\text{g}/\text{d}$  (2000 IU/d) for all ages. Some individuals would require higher levels than these to achieve serum 25-hydroxyvitamin D concentrations for optimal calcium absorption. So much new information on vitamin D and health has been collected since the requirements were set in 1997 that this nutrient is likely the most in need of revised requirements. *Am J Clin Nutr* 2004; 80(suppl):000S–000S.

**KEY WORDS** Vitamin D requirements, food sources of vitamin D

## INTRODUCTION

TI The current dietary recommendations for vitamin D, as set in 1997 by the Food and Nutrition Board of the Institute of Medicine (1), are presented in **Table 1**. The dietary reference intake (DRI) panel for calcium, phosphorus, magnesium, vitamin D, and fluoride thought that there was insufficient evidence to set estimated average requirements (EARs) (eg, recommended dietary allowances) for vitamin D; therefore, adequate intakes (AIs) were set. EARs are frequently determined with the factorial method, which adjusts nutrient demands for accretion and obligatory losses through absorption, or as the intake required for maximal retention. Neither of these approaches is appropriate for a nutrient such as vitamin D, which is metabolized like a hormone. In the absence of the ability to use these approaches, nutrient requirements can be determined as intakes observed

among healthy populations or as those that maximize a functional indicator.

EARs are difficult to set for vitamin D because inputs from sunlight and food are difficult to determine. Furthermore, the quantitative relationship of vitamin D input to health is uncertain (especially before 1997). An AI for vitamin D was set on the basis of intakes necessary to achieve normal ranges of serum 25-hydroxyvitamin D concentrations. In establishing the AI, the committee assumed that there was no cutaneous synthesis of vitamin D through sun exposure.

Serum 25-hydroxyvitamin D concentrations are the best indicators of vitamin D adequacy, because the production of 25-hydroxyvitamin D is not regulated and the concentrations thus reflect both absorption from the diet and cutaneous synthesis. After absorption from the lymph or entry into the circulation from the skin, vitamin D is hydroxylated to 25-hydroxyvitamin D in the liver. This step is catalyzed by vitamin D 25-hydroxylase, and the 25-hydroxylase is regulated by vitamin D and its metabolites. Optimal vitamin D status has been suggested to suppress parathyroid hormone (PTH) concentrations, which are associated with increased bone remodeling and fracture risks (2–6). Therefore, elevated PTH concentrations can also indicate vitamin D deficiency. The optimal concentrations of 25-hydroxyvitamin D and PTH for bone health are unclear, however. Normal ranges of serum 25-hydroxyvitamin D concentrations are the mean  $\pm$  SD values for a group of healthy individuals. The normal range is broad at 25–137.5 nmol/L (10–55 ng/mL), however, and the lower limit of the normal range can vary among populations, from as low as 20 nmol/L (8 ng/mL) to 37.5 nmol/L (15 ng/mL) or even 50 nmol/L (20 ng/mL) (1). Among adults  $\geq$  65 yr of age, there is a 4-fold decrease in the capacity to produce vitamin D<sub>3</sub>, compared with young adults (7). Furthermore, elderly women have a resistance to 1,25-dihydroxyvitamin D concentrations, compared with young women, as demonstrated by a reduced response in calcium absorption efficiency with 1,25-dihydroxyvitamin D supplementation (8). Therefore, the AI was set higher for older populations. The DRI panel noted that, among elderly subjects, serum concentrations of 25-hydroxyvitamin D of  $>$  50 nmol/L may be required to maintain normal PTH concentrations, and the panel called for more research in this area.

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**TABLE 1**  
1997 dietary reference intakes for vitamin D

Population age	AI		Tolerable UL	
	$\mu\text{g}/\text{d}$	IU/d	$\mu\text{g}/\text{d}$	IU/d
0–50	5	200	50	2000
51–70	10	400	50	2000
> 70	15	600	50	2000

Vitamin D deficiency among elderly subjects causes secondary hyperparathyroidism and osteomalacia and exacerbates osteoporosis, resulting in increased risk of skeletal fractures (1). The prevalence of vitamin D deficiency or insufficiency was recently estimated from National Health and Nutrition Examination Survey (NHANES) III data for noninstitutionalized individuals according to northern or southern latitude, as well as age and sex (9). Among women living in latitudes of 25–41° N, 5% of those > 60 y of age had serum 25-hydroxyvitamin D concentrations of < 25 nmol/L. Another 15% of women 60–79 y of age and 18% of women ≥ 80 y of age had serum 25-hydroxyvitamin D concentrations of < 37.5 nmol/L; 36% and 37% of similarly aged women had serum 25-hydroxyvitamin D concentrations of < 50 nmol/L and 52% and 56% had concentrations of < 62.5 nmol/L, respectively. Therefore, one-half of the elderly women sampled who resided in more northern latitudes had vitamin D insufficiency, although overt deficiency was rare. The incidence of insufficiency was lower among men, with 38% of those 60–79 y of age and 47% of those ≥ 80 y of age having serum 25-hydroxyvitamin D concentrations of < 62.5 nmol/L. The incidence among institutionalized and homebound elderly individuals, who spend less time in the sunshine, and among those living at latitudes above 42° N is potentially much greater.

In setting the AI for vitamin D, the DRI panel also considered observed values to prevent seasonal variations in PTH concentrations. Individuals living at latitudes above 40° N or below 40° S have no cutaneous production of vitamin D<sub>3</sub> during the winter months (10). This was associated with spinal bone loss in the winter and bone gain in the summer among postmenopausal women living in Boston (11). Decreased bone mineral density (BMD) in the winter was associated with lower serum 25-hydroxyvitamin D concentrations. Among women given a daily supplement of 400 IU of vitamin D<sub>3</sub>, wintertime bone loss and serum PTH concentrations were reduced. Plasma 25-hydroxyvitamin D concentrations varied from 81.3 nmol/L at the end of the summer to 60.6 nmol/L at the end of the winter, ie, a mean difference of 20.7%, in contrast to a change in PTH concentrations of 3.5% (both significant at  $P < 0.001$ ). Vitamin D supplementation reduced the change in serum 25-hydroxyvitamin D concentrations to 4.9% ( $P < 0.005$ ) and that in PTH concentrations to 1.1% (NS). Calcium supplementation (1 g/d) also prevented seasonal bone loss in the greater trochanter and changes in biochemical markers of bone turnover among elderly New England women (12). In contrast to these reports, serum 25-hydroxyvitamin D concentrations did not vary according to season among women > 60 y of age as they did among women 30–59 y of age in NHANES III, possibly because latitudes below 40° N were included or because measurements according to season were performed among different women (9).

Lack of sun exposure through any means can increase dietary vitamin D requirements. For example, 85% of veiled Arab Danish women had severe vitamin D deficiencies of < 10 nmol/L (13).

Tolerable upper levels (ULs) for vitamin D<sub>3</sub> are currently set at 2000 IU/d. This level was set by the Food and Nutrition Board (1) to avoid hypervitaminosis D associated with serum 25-hydroxyvitamin D concentrations in excess of 400 nmol/L, which were thought to lead to hypercalcemia and enhanced bone resorption (14).

#### FUTURE REVISIONS OF REQUIREMENTS

The goal of future requirements for vitamin D should be to establish an EAR (or an optimal 25-hydroxyvitamin D concentration) on the basis of functional outcome measures. Use of serum 25-hydroxyvitamin D concentrations alone has been inadequate, because we do not know optimal levels for health and serum concentrations do not necessarily reflect optimal status in target tissues. We need to determine optimal concentrations of vitamin D metabolites in various tissues that are associated with health or minimization of disease risk. Since the 1997 AIs were released, progress has been made toward determining the vitamin D intake needed to produce changes in serum 25-hydroxyvitamin D concentrations (13, 15–17).

Some argue that the optimal serum 25-hydroxyvitamin D concentrations are those at which serum PTH concentrations reach a minimum. Maximal suppression of serum PTH concentrations occurs at ~80 nmol/L 25-hydroxyvitamin D, although the range among studies is wide (75–110 nmol/L) (2, 6). Use of serum PTH concentrations as an indicator of vitamin D status is only a surrogate measure of bone resorption. Furthermore, it was hypothesized that, if serum 25-hydroxyvitamin D concentrations exceed sufficiency, then vitamin D receptors might be activated directly by 25-hydroxyvitamin D, leading to increased bone resorption (18). This possibility has not been critically evaluated and is important for establishing ULs.

More-direct functional outcome measures for vitamin D adequacy would be calcium absorption or bone resorption. Calcium absorption, assessed with a pharmacokinetic approach of measuring the area under the curve of serum calcium profiles after an oral load, was recently determined as a function of serum 25-hydroxyvitamin D concentrations (19). Calcium absorption efficiency increased with serum 25-hydroxyvitamin D concentrations until levels of 80–90 nmol/L were achieved. This relationship should be verified with more-sensitive isotopic tracer techniques for measuring calcium absorption. Nevertheless, this evidence could be used by the next DRI panel to set an EAR for vitamin D. It is interesting to note that vitamin D-deficient individuals may require vitamin D intakes that exceed the current ULs to achieve serum 25-hydroxyvitamin D concentrations of ≥ 80 nmol/L. Additional vitamin D intakes required to achieve serum 25-hydroxyvitamin D concentrations of 80 nmol/L can be estimated for various subgroups with the slope (0.7 nmol/L per 1  $\mu\text{g}$  vitamin D) from the regression equation developed in a dose-response study among men, in which changes in serum 25-hydroxyvitamin D concentrations in response to extended oral dosing with cholecalciferol were determined (15). The mean serum 25-hydroxyvitamin D concentrations determined in NHANES III and the calculated additional intakes needed to increase serum concentrations to 80 nmol/L are

**TABLE 2**

Mean vitamin D status of the US population (winter, low latitude) and vitamin D intakes required to achieve 80 nmol/L 25-hydroxyvitamin D

Subgroup	No.	Serum 25-	Additional vitamin D	
		hydroxyvitamin D	intake to achieve	80 nmol/L
		nmol/L	μg/d	IU/d
<b>Male</b>				
12–19 y	625	78.6	2	80
20–39 y	1289	69.1	16	623
40–59 y	864	70.6	13	537
60–79 y	827	72.5	11	429
≥ 80	204	68.7	16	646
<b>Female</b>				
12–19 y	699	64.9	22	863
20–39 y	1459	62.7	25	989
40–59 y	959	61.6	26	1051
60–79 y	757	63.5	24	943
≥ 80 y	208	59.6	29	1166
<b>Male</b>				
12–29 y			No change	No change
White	162	83.4		
Black	340	50.0	43	1714
Mexican American	524	69.0	16	629
30–59 y				
White	314	75.0	7	286
Black	354	48.8	45	1783
Mexican American	521	63.5	24	943
≥ 60 y				
White	329	75.6	6	251
Black	149	53.3	38	1526
Mexican American	370	65.8	20	811
<b>Female</b>				
12–29 y				
White	181	74.8	7	297
Black	447	42.3	54	2154
Mexican American	530	57.8	32	1269
30–59 y				
White	322	66.0	34	1371
Black	447	41.8	55	2183
Mexican American	580	53.5	38	1514
≥ 60 y				
White	336	64.5	22	886
Black	143	47.0	5	189
Mexican American	318	58.8	30	1211

presented in **Table 2**. Current mean vitamin D intakes from NHANES III range from 5.3 to 9.8 μg/d for various sex and age categories (20). Therefore, for some subgroups, especially for blacks, vitamin D intakes required to achieve serum concentrations of 80 nmol/L might exceed 46–62 μg (1860–2480 IU) of vitamin D<sub>3</sub> (current intake plus calculated extra amount) per day. Two assumptions of this approach that may not be applicable to all subgroups are that 1) 80 nmol/L is the optimal target goal and 2) the slope of the regression equation for intakes of vitamin D that produce changes in serum 25-hydroxyvitamin D concentrations is 0.7 nmol/L per 1 μg vitamin D. Intakes of up to 10 000 IU have been shown to achieve adequate vitamin D status without increasing serum 25-hydroxyvitamin D concentrations to toxic levels (15). Therefore, both the requirements and ULs need to be revisited.

The ULs should also be revised in light of recent data demonstrating the safety of concentrations higher than the current UL of

2000 IU/d. Vieth et al (21) gave healthy men and women, 23–56 y of age, 4000 IU/d vitamin D<sub>3</sub> for 2–5 mo. Serum 25-hydroxyvitamin D concentrations plateaued at an average of 96 nmol/L, with no signs of hypercalcemia or hypercalciuria. Heaney et al (16) then administered even higher doses of 10 000 IU/d vitamin D<sub>3</sub> to adult men for 20 wk, with no significant changes in serum calcium concentrations. A discussion of biomarkers for vitamin D adequacy is presented in the article by Heaney (22) in this supplement.

For health outcomes related to bone, it would be better to determine the relationship between vitamin D status and bone resorption or bone gain or loss. For elderly subjects, the incidence of fractures is the optimal outcome measure. The relationship between vitamin D and bone resorption has not been studied. Calcium tracer kinetic studies could be used to study this relationship. Alternatively, use of a novel approach to measure bone resorption, <sup>41</sup>Ca technology, is described elsewhere in this supplement (23). Most studies of vitamin D and bone used a combination of vitamin D and calcium supplementation (2, 3, 18). Two studies of vitamin D without calcium supplementation found that 15 000 IU/wk vitamin D<sub>2</sub> reduced the loss of metacarpal cortical thickening among elderly women (24) and 400 IU/d vitamin D<sub>3</sub> prevented bone loss at the femoral neck among women for 2 y (25), but another showed no effect on hip fractures (26). A 5-y study of oral vitamin D supplements (10 000 IU, 4 times/y) indicated decreased fracture incidence among > 2000 men and women (27).

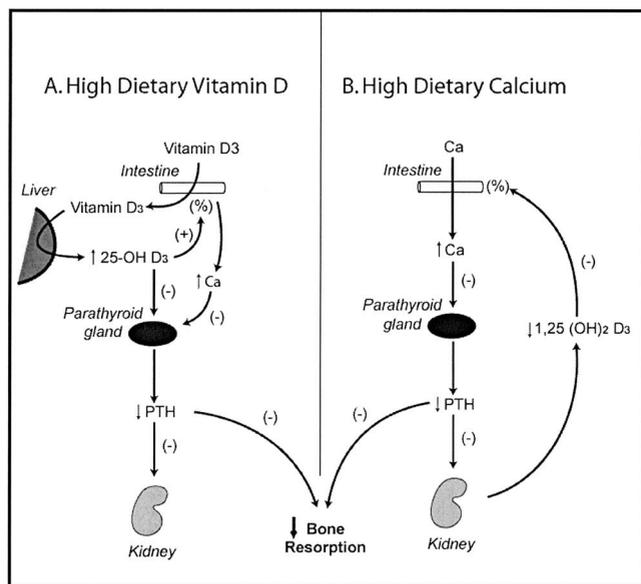
It is likely that multiple outcome measures are appropriate for determining vitamin D requirements in the future. Many relationships between vitamin D and health beyond bone are emerging, including reduced risks of diabetes mellitus, obesity, and certain cancers (28).

**INTERDEPENDENCY OF CALCIUM AND VITAMIN D REQUIREMENTS**

The relative importance of calcium and vitamin D at one level each was evaluated in a 4-y trial in which men and women ≥ 50 y of age were randomized to receive either 750 mg calcium, 600 IU 25-hydroxyvitamin D<sub>3</sub>, or a placebo (29). Basal calcium intakes for the postmenopausal women in this trial were within the range of average intakes for American women ≥ 50 y of age (530–600 mg/d) and at the mean or below for men (629–740 mg/d). The supplement brought the levels to ~1350 mg/d calcium. Basal 25-hydroxyvitamin D concentrations averaged 60 nmol/L for women and 65 nmol/L for men, which are above the nominal reference limits but are likely not optimal. The placebo group lost ~0.5% total hip BMD per year, whereas the calcium-supplemented group demonstrated an effectively stable bone mass for the 4 y of the trial. The vitamin D-treated group lost ~0.4% total hip BMD per year, which was not significantly different from either the placebo or calcium-supplemented groups. Therefore, supplementation with vitamin D for individuals with severe calcium deficiency was not as effective in bone sparing as was repletion of calcium alone among individuals with marginally adequate vitamin D status. The combined effects of calcium and vitamin D were not investigated. The relationship between serum 25-hydroxyvitamin D concentrations and changes in total hip BMD was stronger among subjects consuming less than the median calcium intakes, and the slope of calcium concentrations versus hip BMD was more positive for subjects

AQ: 5

T2  
AQ: 4



**FIGURE 1.** Dietary vitamin D (A) and calcium (B) leading to reduced bone resorption.

**TABLE 3**

Food sources of vitamin D

	Vitamin D content	
	$\mu\text{g}$	IU
Fish	5–15 per 100 g	200–600 per 100 g
Fortified milk	2.5 per cup	100 per cup
Fortified juice	2.5 per cup	100 per cup
Fortified cereals	1–1.5 per cup	40–60 per cup
Fortified breakfast bars	2.5 per bar	100 per bar

production of 1,25-dihydroxyvitamin D (ie, extrarenal production). 3) High vitamin D status is valuable only when dietary calcium intake is moderate or low; high 25-hydroxyvitamin D concentrations become a reservoir for optimal renal production of 1,25-dihydroxyvitamin D (not shown). The protective advantage conferred by high vitamin D status in mechanisms 1 and 2 would likely be independent of dietary calcium intake. In mechanism 3, however, the advantage of high vitamin D status would disappear with high calcium intake (which would suppress renal 1,25-dihydroxyvitamin D production). With mechanism 1 or 2, vitamin D toxicity might be observed when combined with high dietary calcium intake, leading to hypercalcemia. With mechanism 3, toxicity would likely not be a concern.

**FOOD SOURCES OF VITAMIN D**

The AIs in Table 1 assume no vitamin D input from sun-mediated cutaneous production. For various subpopulations, this assumption is relevant (26). Those who remain indoors or who live at northern latitudes have no cutaneous production in winter (10). Those who protect their skin from ultraviolet-B radiation with clothing or sunscreen, elderly subjects, and dark-skinned individuals have limited capacity to produce vitamin D. Even elderly populations in countries in which cutaneous production might be possible throughout the year have low serum 25-hydroxyvitamin D concentrations (31).

Food composition databases for vitamin D are woefully inadequate. Therefore, it is difficult to estimate vitamin D intakes. With a modified database and a provisional table of vitamin D concentrations in ~50 foods, vitamin intakes were estimated from NHANES II data and were found to range from 0 to 1960 IU/d, with a median intake of 114 IU/d (32). With NHANES III data, mean intakes ranged from 212 to 392 IU/d for various populations (20). Among an older group of women in Boston, median intakes were estimated to be 90 IU/d (33).

The sources of vitamin D in the diet are limited. A few examples are presented in Table 3. Natural food sources are mostly fatty fish and liver and fat from fish-eating mammals. The major dietary sources in the United States are fortified foods. Milk is fortified at 2.5  $\mu\text{g}$  (100 IU) per cup, but quality control is highly variable. Chen et al (34) analyzed 79 milk samples and found a wide range of vitamin D contents (Figure 2). Quality control is expected to be better for commercial manufacturers, compared with individual local dairies. However, infant formulas also exhibit wide variability in vitamin D contents (35). Fortified cereals and orange juice are also important sources, as described elsewhere in this supplement (36). The available fortified foods change frequently, which contributes to the difficulty of meeting vitamin D recommendations through the diet and assessing intakes accurately.

below the median for serum 25-hydroxyvitamin D concentrations ( $P < 0.06$ ). Both calcium and 25-hydroxyvitamin D reversed the hyperparathyroidism observed at baseline. However, calcium had a much greater effect on bone turnover (measured as serum osteocalcin concentrations and urinary N-telopeptide/creatinine ratios) than did vitamin D, which suggests that calcium supplementation increased the supply of calcium to the bone as well as suppressing PTH. Our understanding of interrelationships is limited, however, with data on only one level of supplementation with calcium and vitamin D. Studies of the effects of a range of calcium intakes, at a range of vitamin D intakes, on bone and other outcome measures are needed to determine optimal requirements.

The optimal intake of vitamin D is likely to be influenced by calcium intake and vice versa. For criteria related to bone health, it is important to note that both high dietary calcium intake and high vitamin D intake are thought to lead to reduced levels of bone resorption, as outlined in Figure 1. It is reasonable to assume that there are optimal levels of both vitamin D and calcium for minimizing bone resorption and that higher concentrations of one nutrient could compensate for insufficiency of the other nutrient. Figure 1A is consistent with the observation that serum PTH concentrations are inversely related to serum 25-hydroxyvitamin D concentrations but not serum 1,25-dihydroxyvitamin D concentrations (29, 30). This paradoxical observation is inconsistent with the concept of homeostatic control of serum calcium concentrations, as depicted in Figure 1B, which has no independent role for 25-hydroxyvitamin D as a regulator of calcium homeostasis. Several mechanisms may explain this paradox, as follows. 1) High concentrations of 25-hydroxyvitamin D overcome the low affinity of this metabolite for the vitamin D receptor, leading to changes in the expression of vitamin D-regulated genes (eg, suppressing PTH production and stimulating intestinal calcium absorption through production of CaT1 and calbindin  $D_{9k}$ ). 2) High serum 25-hydroxyvitamin D concentrations lead to enhanced vitamin D action through local

AQ: 8  
T3

F2

AQ: 6

F1

AQ: 7

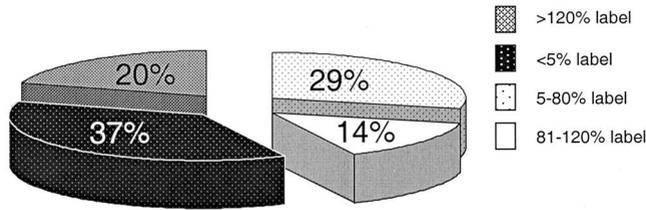


FIGURE 2. Vitamin D contents of 79 milk samples in the United States, as a percentage of the amount stated on the label. Adapted from reference 33.

RESEARCH GAPS

Vitamin D requirements need to be based on good functional outcome measures. Many data have become available since the 1997 AIs and the UL for vitamin D were released. The relationship between vitamin D supplementation and vitamin D status was studied by several groups, and intakes exceeding the current UL of 2000 IU/d had no apparent adverse effects. Furthermore, the report of the relationship between serum 25-hydroxyvitamin D concentrations and fractional calcium absorption should allow determination of a recommended dietary allowance in future versions of the DRI. Direct measurements of bone resorption as a function of vitamin D status should be a goal for future studies. We need sensitive, short-term assessment tools for the study of nutrient requirement interdependencies, such as those for calcium and vitamin D. We need to know the relationship of vitamin D status to health for tissues other than bone.

To translate vitamin D requirements into dietary recommendations, we need better information on vitamin D intakes. To achieve this, we need better food composition databases for vitamin D. The accuracy of these databases would depend on improved quality control for fortified foods. Ultimately, vitamin D intakes and requirements need to be established for diverse populations.

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AQ: 9

## AUTHOR QUERIES

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1

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