Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety[1,2]

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See corresponding editorial on page 825.

ABSTRACT For adults, the 5-μg (200 IU) vitamin D recommended dietary allowance may prevent osteomalacia in the absence of sunlight, but more is needed to help prevent osteoporosis and secondary hyperparathyroidism. Other benefits of vitamin D supplementation are implicated epidemiologically: prevention of some cancers, osteoarthritis progression, multiple sclerosis, and hypertension. Total-body sun exposure easily provides the equivalent of 250 μg (10 000 IU) vitamin D/d, suggesting that this is a physiologic limit. Sailors in US submarines are deprived of environmentally acquired vitamin D equivalent to 20–50 μg (800–2000 IU)/d. The assembled data from many vitamin D supplementation studies reveal a curve for vitamin D dose versus serum 25-hydroxyvitamin D [25(OH)D] response that is surprisingly flat up to 250 μg (10 000 IU) vitamin D/d. To ensure that serum 25(OH)D concentrations exceed 100 nmol/L, a total vitamin D supply of 100 μg (4000 IU)/d is required. Except in those with conditions causing hypersensitivity, there is no evidence of adverse effects with serum 25(OH)D concentrations <140 nmol/L, which require a total vitamin D supply of 250 μg (10 000 IU)/d to attain. Published cases of vitamin D toxicity with hypercalcemia, for which the 25(OH)D concentration and vitamin D dose are known, all involve intake of ≥1000 μg (40 000 IU)/d. Because vitamin D is potentially toxic, intake of >25 μg (1000 IU)/d has been avoided even though the weight of evidence shows that the currently accepted, no observed adverse effect limit of 50 μg (2000 IU)/d is too low by at least 5-fold. *Am J Clin Nutr* 1999;69:842–56.

KEY WORDS Calciferol; calcidiol; cholecalciferol; calcitriol; vitamin D; 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; toxicity; safety; nutrition; environment; ultraviolet light; hyperparathyroidism; osteoporosis; osteomalacia; daily reference intake; 25(OH)D; $1,25(OH)_2D$; no observed adverse effect level; NOAEL; LOAEL; lowest observed adverse effect level

INTRODUCTION

Many arguments favoring higher intakes of calcium and other nutrients have been based on evidence about the diets of prehistoric humans (1). Likewise, the circulating 25-hydroxyvitamin D [25(OH)D; calcidiol] concentrations of early humans were surely far higher than what is now regarded as normal. Humans evolved as naked apes in tropical Africa. The full body surface of our ancestors was exposed to the sun almost daily. In contrast, we modern humans usually cover all except about 5% of our skin surface and it is rare for us to spend time in unshielded sunlight. Our evolution has effectively designed us to live in the presence of far more vitamin D (calciferol) than what most of us get now, yet there is no consensus about what vitamin D intakes are optimal or safe.

Unlike anything else used in the fortification of foods, the purpose of vitamin D is to correct for what is an environmental deficit (less ultraviolet exposure) and not to correct for lack due to classical nutritional reasons. With a few exceptions reviewed by Takeuchi et al (2), there is little or no vitamin D in the kind of foods that humans normally eat. Therefore, conclusions about the efficacy and safety of vitamin D must be in the context of the role of environmental factors.

Before 1997, the recommended dietary allowance of vitamin D (RDA; 3) for infants and children was 10 μg (400 IU). In essence, the scientific basis for this dose was that it approximated what was in a teaspoon (5 mL) of cod-liver oil and had long been considered safe and effective in preventing rickets (4). The basis for adult vitamin D recommendations has been even more arbitrary. Thirty-six years ago, an expert committee on vitamin D could provide only anecdotal support for what it referred to as "the hypothesis of a small requirement" for vitamin D in adults and it recommended one-half the infant dose, just to ensure that adults obtain some from the diet (5). In England, an adult requirement of only 2.5 μg (100 IU)/d was substantiated on the basis of 7 adult women with severe nutritional osteomalacia whose bones showed a response when given this amount (6). The adult RDA of 5 μg (200 IU)/d was described as a "generous allowance" in the 1989 version of American recommended intakes (3)—but why was this "generous" and in relation to what? It is remarkable that despite the widespread intake of 5 μg (200 IU) vitamin D/d, there is still no published data showing that this dose has any effect on the serum 25(OH)D concentration in adults.

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The objective way to assess vitamin D nutritional status is through the circulating 25(OH)D concentration (7, 8). Concentrations < 20–25 nmol/L indicate severe vitamin D deficiency (9, 10), which will lead to rickets and histologically evident osteomalacia (11). Concentrations between 25 and 40 nmol/L reflect marginal vitamin D deficiency (9, 10, 12), a situation that is common in countries north of the United States, where 40 nmol/L is a typical winter average in adults (13). Marginal concentrations of 25(OH)D are associated with mildly elevated parathyroid hormone (PTH) and diminished 1,25-dihydroxyvitamin D [1,25$(OH)_2$D; calcitriol] concentrations (2, 9, 10, 14).

According to Parfitt et al (7), "vitamin D deficiency implies the existence of an anatomic, physiological, or biochemical abnormality that can be corrected by the administration of vitamin D in nonpharmacological doses." The regression of PTH versus 25(OH)D concentrations in the elderly shows that PTH concentrations become minimal when 25(OH)D concentrations exceed 100 nmol/L (12, 15). Therefore, concentrations of 25(OH)D below this may reflect deficiency in the elderly.

A report by Adams and Lee (16) has become cited as a classic example of vitamin intoxication by individuals taking nutritional supplements. They describe 4 subjects, 1 of whom claimed a vitamin D intake of 30 μg (1200 IU)/d, who presented with hypercalciuria that moderated after vitamin D intake was stopped. The paper was accompanied by an editorial by Marriott (17) of the NIH, which reemphasized concern about vitamin D intoxication. Although moderate vitamin D supplementation may help stave off osteoporosis when it is combined with calcium (18, 19), Marriott recommended care in initiating the approach (17).

The issues surrounding vitamin D intake for adults have become confusing for both patients and physicians. For example, a 30 μg (1200-IU)/d intake in the report by Adams and Lee was a possible cause of vitamin D toxicity in one subject (16), although essentially the same intake has been reported in 2 studies to occur in some patients with distinct vitamin D deficiency (9, 20). How can 30 μg (1200 IU) vitamin D be insufficient for some and yet be implicated as mildly toxic for others? I will show that the confusion can be explained by environment because sunshine alone can bring 25(OH)D concentrations to 210 nmol/L in normal people and vitamin D intakes of 30 μg (1200 IU)/d contribute only a negligible fraction of this.

A recent review by Hathcock (21) about the efficacy and safety of vitamins and minerals did not address vitamin D. The newly revised daily reference intake (DRI) for vitamin D is 3-fold higher than the previous RDA for people > 70 y of age (19), but for most adults the DRI has remained unchanged from the 1960s RDA of 5 μg (200 IU)/d. The purpose of the present review is to assemble and interpret the substantial data now available about how vitamin D supply affects serum 25(OH)D concentrations and to relate these to issues of efficacy and safety of vitamin D.

Commentary on Methods

More than for any other analyte in the endocrine test repertoire, circulating 25(OH)D concentrations vary by geography (latitude), culture, and legislation (food fortification laws). Technical issues also arise when results from different studies are compared because assays of 25(OH)D vary. In the survey reported in 1984 by Jongen et al (22) of 19 laboratories, the mean CV for plasma 25(OH)D was 35%, much of which was attributable to the purification procedures used. Over the past 6 y, an international proficiency survey of > 30 laboratories has been available through the North West Thames, External Quality Assurance Survey (Charing Cross Hospital, London). In this ongoing quarterly survey, the one method most commonly used, the INCSTAR/Dia-Sorin radioimmunoassay (Stillwater, MN), exhibits a mean between-laboratory CV of 20–30%. The current between-laboratory CV remains essentially the same when all methods are combined (personal file of survey reports). The variability between laboratories today is only marginally better than that reported in 1984 for the various methods combined (22). For the purposes of this review, it must be assumed that differences in 25(OH)D concentration between group means in different publications reflect true differences. This assumption cannot be avoided. Any attempt to select preferential 25(OH)D methods for data inclusion would result in the omission of most of the information in the literature. Furthermore, the proficiency data available show that selection of any one method would result in only a marginal improvement in the CV of comparisons between laboratories.

Excluded from this review are data on children, studies in which dose was not specified, and studies in which the duration of the vitamin D dose was < 4 wk (0.93 mo). 25(OH)D values presented here are either published numerical values or they were redigitized from graphical data. All 25(OH)D values are presented as nmol/L (1 nmol/L = 1 ng/mL × 2.5). Amounts of vitamin D are given in μg, each being equivalent to 40 IU or 2.6 nmol vitamin D_3. No attempt was made to distinguish between vitamin D_2 and D_3 because there was not always a distinction in the literature. However, vitamin D_2 is less effective at raising serum 25(OH)D concentrations than is vitamin D_3 (13).

THE EVIDENCE: EFFECTS OF VITAMIN D SOURCES ON SERUM 25(OH)D

Ultraviolet light

Serum 25(OH)D concentrations of people living or working in sun-rich environments are summarized in **Table 1**. The highest individual serum 25(OH)D concentration obtained from sunshine was 225 nmol/L (23); in a farmer in Puerto Rico—there is no reason to think that he was taking a vitamin D supplement. In a report showing results for 391 subjects that excluded individuals taking calcium or vitamin D supplements, Dawson-Hughes et al (14) reported 3 subjects with serum 25(OH)D concentrations > 200 nmol/L. From the data of Chapuy et al (26), as well as those of Dawson Hughes et al (12), the upper limits (+2 SDs, 97.5th percentile) were, respectively, 150 and 212 nmol/L in subjects taking only 20 μg (800 IU) vitamin D/d. Such concen-

TABLE 1
25-Hydroxyvitamin [25(OH)D] concentrations under sun-rich living conditions

Reference, year, and subjects	Location	25(OH)D
		nmol/L
Haddock et al (23), 1982	Puerto Rico	
Hospital personnel (*n* = 26)		105
Farmers (*n* = 18)		135
Haddad and Kyung (24), 1971	St Louis	
Lifeguards (*n* = 9)		163
Better et al (25), 1980	Israel	
Lifeguards (*n* = 34)		148

trations are consistent with subgroups of individuals exposed to relatively more sunshine.

The effects of artificial ultraviolet light treatment sessions on 25(OH)D concentrations are summarized in **Table 2**. The highest individual 25(OH)D concentration attained was 274 nmol/L (38). The main problem in interpreting the data was that the exact dose of ultraviolet light was ambiguous because there is variability in the surface area of skin exposed and in the frequency and duration of exposure. Had the ultraviolet treatment sessions continued, one would expect that for those given full-body exposure, serum 25(OH)D concentrations would plateau at mean values comparable with those of the farmers and lifeguards shown in Table 1.

Two studies showed that in response to a given set of ultraviolet light treatment sessions, the absolute rise in serum 25(OH)D concentration was inversely related to the basal 25(OH)D concentration. In the study by Mawer et al (34), the increase in 25(OH)D in subjects with initial 25(OH)D concentrations <25 nmol/L was double the increase seen in subjects with initial concentrations >50 nmol/L. Snell et al (27) showed that in subjects with initial 25(OH)D concentrations <10 nmol/L, ultraviolet treatments increased 25(OH)D by 30 nmol/L, but in those with initial 25(OH)D concentrations approaching 50 nmol/L, the increase was negligible.

At least 4 studies support the concept that one full-body exposure to sunlight can be equivalent to an oral vitamin D intake of 250 μg (10 000 IU). Stamp (39) compared oral vitamin D to the effects of ultraviolet light treatment sessions and found that the rise in 25(OH)D was the same in subjects treated with ultraviolet light as in those given 250 μg (10 000 IU) vitamin D/d. In a study of institutionalized elderly, Davie et al (28) exposed 600 cm^2, ≈5% of skin surface, to ultraviolet light treatments over a 2–3-mo period and compared the resulting 25(OH)D concentrations with

TABLE 2
Effects of ultraviolet light treatment sessions on serum 25-hydroxyvitamin D [25(OH)D] concentrations[1]

Reference, year, and subjects	Age	Location	Treatment	Duration	25(OH)D	
					Before	After
	y			*mo*	*nmol/L*	
Snell et al (27), 1978						
Sick, old (*n* = 12)	81	Southampton, UK	Back only	0.5	9	24
Davie et al (28), 1982						
Epileptic (*n* = 8)	22	Cambridge, UK	5% of skin	2.33	6	35
Control (*n* = 8)	21				15	35
Davies and Mawer (29), 1997						
Bone diseased (*n* = 16)	NG	Manchester, UK	5 × 1h	0.17	36	48
Chel et al (30), 1998						
Psychogeriatric (*n* = 14)	85	Netherlands	1000 cm^2	3	18	65
Reid et al (31), 1986						
Elderly (*n* = 13)	80	New Zealand	Face + hands	0.5	63	79
Falkenbach (32), 1993						
Healthy males (*n* = 24)	21–37	Frankfurt, Germany	UV	0.5	48	83
Matsuoka et al (33), 1990						
Medical students (*n* = 6)	NG	South Carolina	1 × UV	0.03	56	92
Mawer et al (34), 1984						
With psoriasis (*n* = 8)	20–57	Hamburg, Germany	UV	0.7	30	113
Stamp et al (35), 1977						
Various (*n* = 7)	Various	London	UV	0.7	20	118
Dent et al (36), 1973						
Immigrant (*n* = 1)	14	London	UV	0.5	25	124
Varghese et al (37), 1989						
Control (*n* = 7)	36	New York	10 × UV	0.5	53	124
Stone forming (*n* = 11)	36				65	129
Mawer et al (34), 1984						
Control (*n* = 5)	20–57	Hamburg, Germany	UV	0.7	53	138
Krause et al (38), 1998						
Hypertensive (*n* = 9)	26–66	Germany	3×/wk	1.4	58	151

[1]Results are ranked according to the highest 25(OH)D concentration attained and reflect full-body exposure unless indicated otherwise. NG, not given.

those achieved with oral vitamin D doses. They calculated a production of vitamin D in the skin equivalent to 0.045 nmol·d^{-1}·cm^{-2} exposed skin. This is equivalent to 10.9 μg (435 IU) vitamin D/d for 5% of skin surface. An almost identical protocol was followed recently by Chel et al (30), confirming the relative effects of light and supplementation on 25(OH)D concentration (28). If these results for the elderly are extrapolated to total body surface area, it works out to 218 μg (8700 IU) vitamin D/d that can be acquired by the elderly. More recently, Holick (40) presented data that compared blood vitamin D concentrations in subjects taking vitamin D orally with those given ultraviolet light exposure. The ultraviolet treatment produced blood vitamin D concentrations comparable with an intake of 250–625 μg (10 000–25 000 IU) vitamin D/d orally.

Ultraviolet exposure beyond the minimal erythemal dose does not increase vitamin D production further. The ultraviolet-induced production of vitamin D precursors is counterbalanced by degradation of vitamin D and its precursors. The concentration of previtamin D in the skin reaches an equilibrium in white skin within 20 min of ultraviolet exposure (41). Although it can take 3–6 times longer for pigmented skin to reach the equilibrium concentration of dermal previtamin D, skin pigmentation does not affect the amount of vitamin D that can be obtained through sunshine exposure (42). However, aging does lower the amount of 7-dehydrocholesterol in the skin and lowers substantially the capacity for vitamin D production (43, 44).

Effect of acute onset of ultraviolet light deprivation

Most of what is known about ultraviolet light deprivation is summarized in **Table 3**. The most recent data are for an American submarine crew (46), which show a percentage decline in 25(OH)D concentration comparable with that of a British crew reported 20 y earlier (45). The 30-nmol/L decline over 2 mo was despite "a standard US Navy diet which included milk and breakfast cereals fortified with vitamin D" (46). The initial mean 25(OH)D concentration was higher in the Americans than in the British, consistent with higher vitamin D supplies from diet and sun exposure in Americans.

Effect of daily vitamin D supplementation

Studies reporting a specified vitamin D intake and the resulting serum 25(OH)D concentration are summarized in **Table 4**. It is important in this kind of comparison to know whether the treatments had achieved an equilibrium concentration in terms of 25(OH)D. The half-life of 25(OH)D in the circulation is reported as ≈1 mo in humans (68), the results for the submariners suggest a 2-mo half-life (Table 3). Conventional pharmacology indicates it should take 4 half-lives before a drug's equilibrium is achieved. Unlike a conventional drug, 25(OH)D is a metabolite whose concentration can be altered through balance between its production and clearance so that an equilibrium can be achieved earlier than would be expected from the half-life. To permit some sort of comparison between the various studies in the literature, it was necessary to compromise on classical pharmacology. The data in **Figure 1** show that serum 25(OH)D is essentially at the plateau concentration by 1 mo (28, 64). Therefore, the results for 25(OH)D of studies in which the vitamin D supplementation was continued for a minimum of 4 wk (0.93 mo) are summarized in Table 4. The eventual plateau of 25(OH)D concentration may be slightly underestimated in some cases.

25(OH)D with pharmacologic doses of vitamin D and in cases of vitamin D toxicity

Reports in which pharmacologic doses of vitamin D were given for a prolonged time and in which the resulting serum 25(OH)D concentrations were provided are summarized in **Table 5**. Eventually, as 25(OH)D concentrations rise, the classic situation of hypercalcemia becomes evident. Hypercalcemia due to vitamin D intoxication per se is always accompanied by serum 25(OH)D concentrations > 220 nmol/L (70, 75, 77).

Pettifor et al (78) measured the free $1,25(OH)_2D$ concentration in 11 people intoxicated by the erroneous consumption of a vitamin D concentrate that they had used as cooking oil. The serum 25(OH)D concentrations in these patients covered the range (300–1000 nmol/L) that was required in the study of Heaney et al (79) to show a calcium-absorptive response to serum 25(OH)D itself. The mean serum free $1,25(OH)_2D$ fraction in the study group of Pettifor et al was double the mean for normal individuals, implicating free $1,25(OH)_2D$ as a contributor to toxicity when 25(OH)D concentrations match those used by Heaney et al. Not all of the subjects in Pettifor et al's study had elevated free $1,25(OH)_2D$, yet all subjects were hypercalcemic; therefore, the most likely agent causing vitamin D toxicity was a combination of inappropriate activity of both 25(OH)D and $1,25(OH)_2D$.

The data of Table 5 were incorporated into **Figure 2** to show the relation between vitamin D intake and the serum 25(OH)D concentrations achieved. Not all of the high-dose vitamin D intake data involve vitamin D intoxication. There is one case of an individual with vitamin D toxicity for which the intake was 250 μg (10 000 IU)/d.

Depot injection or intermittent large oral dosing with vitamin D

Another way to augment vitamin D nutrition has been to administer vitamin D as a single large dose, either orally or through injection. Because vitamin D has a half-life > 1 or 2 mo,

TABLE 3
Decline in 25-hydroxyvitamin D [25(OH)D] concentrations under acutely sun-deprived living conditions[1]

Reference, year, and subjects	Location	Duration	25(OH)D	
			Before	After
		mo	*nmol/L*	
Preece et al (45), 1975				
Sailors (*n* = 26)	Submarine, UK	2	35	20
Immigrant Pakistanis (*n* = 24)	UK	12	50	8
Dlugos et al (46), 1995				
Sailors (*n* = 30)	Submarine, US	2.25	78	48

[1]Data for the sailors are for the whole group; data for the immigrants are based on linear regression.

TABLE 4
Summaries of studies showing the effect of vitamin D doses on serum 25-hydroxyvitamin D [25(OH)D] concentrations[1]

Reference, year, and subjects	Location	Age	Dose	Duration	25(OH)D	
					Basal	Final
		y	*μg/d (IU/d)*	*mo*	*nmol/L*	
Ooms et al (47), 1995	Amsterdam					
(*n* = 177)		80	10 (400)	24	27	62
Lips et al (48), 1996	Amsterdam					
(*n* = 270)		80	10 (400)	12	27	62
(*n* = 96)		80	10 (400)	36	27	54
McAuley et al (49), 1997	Dunedin, New Zealand					
(*n* = 10)		76	10 (400)	6	25	43
Graafmans et al (50), 1997	Amsterdam					
(*n* = 13)		78 (BB)[2]	10 (400)	12	26	56
(*n* = 22)		78 (Bb)	10 (400)	12	28	57
(*n* = 11)		77 (bb)	10 (400)	12	31	53
Chel et al (30), 1998	Netherlands					
(*n* = 14)		85	10 (400)	3	23	60
Dawson-Hughes et al (51), 1991	Boston					
(*n* = 123 F)		61	12.5 (500)[3]	12	61	92
O'Dowd et al (52), 1993	New York					
(*n* = 86 treated, 23 control)		82	17.7 (706)[4]	Ongoing	39.75	65
Dawson-Hughes et al (53), 1995	Boston					
(*n* = 123 F)		63	20 (800)[5]	9	66	100
Sebert et al (54), 1995	France					
(*n* = 91)		83	20 (800)	6	6.75	35.25
Van Der Klis et al (55), 1996	Groningen, Netherlands					
(*n* = 29)		61	10 (400)	1	58.5	90
(*n* = 29)		61	20 (800)	1	58.5	90
(*n* = 21)	Willemstad, Curaçao	74	10 (400)	1	85	108
(*n* = 21)		74	20 (800)	1	85	108
Lips et al (56), 1988	Arnhem, Denmark					
(*n* = 47)		82	10 (400)	12	24	69
(*n* = 47)		82	20 (800)	12	24	81
Chapuy et al (26), 1992	France					
(*n* = 1634)		84	20 (800)[6]	18	40	105
Chapuy et al (57), 1996	Paris					
(*n* = 45)		86	20 (800)	6	6	41
Freaney et al (58), 1993	Dublin					
(*n* = 29)		74	20 (800)	1	13	25
McKenna et al (59), 1985	Dublin					
(*n* = 33)		80	20 (800)	16	6	79
Dawson-Hughes et al (12), 1997	Boston					
(*n* = 90, 86 M)		71[7]	22.4 (897)	36	84	112
(*n* = 184, 174 F)		72	22.5 (902)	36	61.25	112
Francis at al (60), 1996	Newcastle, UK					
(*n* = 23)		65–80	25 (1000)	6	36	61
Sorva et al (61), 1991	Helsinki					
(*n* = 14)		84	25 (1000)	9	12	57
(*n* = 5)		84	25 (1000)	9	13	57
Honkanen et al (62), 1990	Kuopio, Finland					
(*n* = 30)		69	45 (1800)	2.6	43	81
(*n* = 33)		82	45 (1800)	2.6	24	64
MacLennan and Hamilton (63), 1977	Southampton, UK					
(*n* = 11)		68–92	12.5 (500)	4	22	53
(*n* = 11)		68–92	50 (2000)	6	15	81
Himmelstein et al (64), 1990	New Jersey					
(*n* = 30)		81	50 (2000)	1.9	40	80
Nordin et al (65), 1985	Leeds, UK					
(*n* = 50)		69.8	50 (2000)	24	20	59
Papapoulos et al (66), 1980	London					
(*n* = 7)		Various	75 (3000)	5–17	5	69[8]
Tjellsen et al (67), 1986	Denmark					
(*n* = 19)		33	100 (4000)	2	75	112.5
Davie et al (28), 1982	Cambridge, UK					
(*n* = 9)		21.2	10 (400)	2.3	16.5	58

(Continued)

TABLE 4 *(Continued)*
Summaries of studies showing the effect of vitamin D doses on serum 25-hydroxyvitamin D [25(OH)D] concentrations[1]

Reference, year, and subjects	Location	Age	Dose	Duration	25(OH)D	
					Basal	Final
		y	*μg/d (IU/d)*	*mo*	*nmol/L*	
Davie et al (28), 1982	Cambridge, UK					
(*n* = 9)		21.4	25 (1000)	2.3	13.3	62
(*n* = 8)		22.5	250 (10000)	2.3	13.2	125
Stamp et al (35), 1977	London					
(*n* = 13)		Various	45 (1800)	0.9	12	62.5
(*n* = 14)		Various	250 (10000)	0.9	24	112.5
(*n* = 15)		Various	500 (20000)	0.9	24	157.5
(*n* = 16)		Various	1000 (40000)	0.9	60	307.5

[1]Studies are listed in order of increasing dose used. Criteria for inclusion of study: adult subjects, 25(OH)D means given, baseline values for the study group or for a comparable reference group given data concerning the age of subjects, sex, sample size, vitamin D dose, and duration of treatment given.
[2]Genotype for vitamin D receptor, where "b" indicates susceptibility to cleavage by *Bsm1* enzyme.
[3]Represents total vitamin D intake: mean basal intake from diet was reported as 2.5 μg/d (100 IU/d), plus 10 μg (400 IU) as supplement.
[4]Represents total vitamin D intake: the sum of ≈7.5 μg (300 IU) from diet plus 400 IU as supplement.
[5]Results are data for 2 treatment groups taking a total of 5 μg (200 IU) or 20 μg (800 IU) vitamin D_3/d; untreated baseline 25(OH)D data not given.
[6]For subgroups of 73 control and 69 treated subjects, taken from the larger placebo or treatment groups.
[7]Represents total intake of ≈5 μg (200 IU/d, basal) from diet plus 700 IU/d as supplement.
[8]Final value after taking vitamin D given as "less than 70".

a large dose should suffice for the better part of a year. The approach is often called stoss therapy (from the German for *to bump*) and it is most common in Europe. One Finnish study, by Heikinheimo et al (80), concluded that annual injection of vitamin D_2 in the autumn (3750–7500 μg, or 150 000–300 000 IU) can lower the probability of osteoporotic fractures by ≈25%. Note that before treatment, the mean 25(OH)D concentration in the untreated control subjects was only 16 nmol/L, and thus, much of the fracture prevention appears to have been attributable to raising 25(OH)D concentrations out of the osteomalacic range.

The effects of single large doses of vitamin D are summarized in **Table 6**. Only a few studies monitored serum 25(OH)D concentrations during the days, weeks, or months after administration of large doses of vitamin D. Both Davie et al (28) and Weisman et al (87) showed that with oral dosing, there was a relatively rapid peak in serum 25(OH)D concentration, with concentrations falling progressively afterward. When doses were administered intramuscularly, there was a longer-lasting response in terms of serum 25(OH)D. However, in some cases it took ≈2 mo for the peak concentration to be achieved. In the study by Heikinheimo et al (80), serum 25(OH)D concentrations after injection remained higher than those of the control group for the entire year.

Reliability of intermittent dosing was poor because of wide variability in the serum 25(OH)D concentrations achieved, both between individuals and in each individual over time. Consequently, the dose-response graph of Figure 2 does not include results from groups given single large injections.

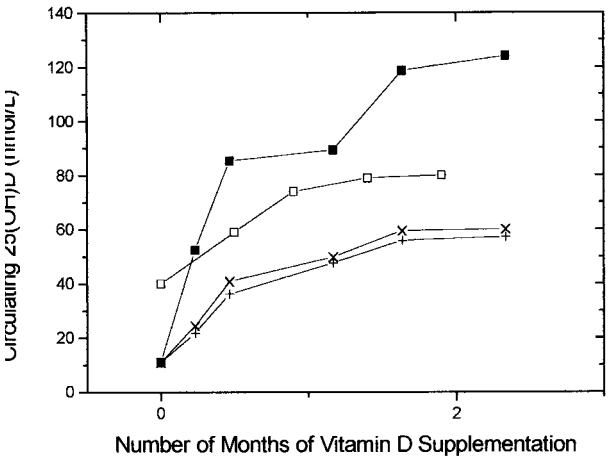

FIGURE 1. Effect of the duration of vitamin D supplementation on the mean serum 25-hydroxyvitamin D [25(OH)D] concentration achieved. Vitamin D intakes for the groups were as follows: 10 μg (400 IU)/d (+; 28), 25 μg (1000 IU)/d (X; 28), 50 μg (2000 IU)/d (□; 64), 250 μg (10 000 IU)/d (■; 28).

ASSESSMENT OF EVIDENCE

Objectives achieved with vitamin D intake recommendations

If the objective of vitamin D supplementation is simply to avoid severe osteomalacia, then the 2.5 μg (100 IU)/d requirement suggested by Dent and Smith (89) might be adequate for some individuals. Supplementation with 10 μg (400 IU) vitamin D/d raises 25(OH)D by ≈45 nmol/L (28, 30, 47, 56, 90). By extrapolating downward, it appears that the commonly consumed amount of 5 μg (200 IU)/d may be sufficient, as a sole source of vitamin D, to maintain average serum 25(OH)D concentrations at 25 nmol/L, but there are no data to verify this.

There is a prevalent view that occasional exposure of the face and hands to sunlight is "sufficient" for vitamin D nutrition. Indeed, this exposure can provide 5–10 μg (200–400 IU) vitamin D during those months when the appropriate sunlight is available. However, a 5% skin exposure produces a mean 25(OH)D concentration of only 35 nmol/L (28), which would leave more than half of the population vitamin D insufficient. Gloth et al (20) found that in homebound, American elderly, the mean vitamin D intake was 12.9 μg (517 IU)/d, resulting in a mean 25(OH)D concentration of 40 nmol/L. Interestingly, for subjects with

TABLE 5
Serum 25-hydroxyvitamin D [25(OH)D] concentrations associated with pharmacologic or toxic vitamin D intakes[1]

Reference, year, and daily dosage	Duration	Final 25(OH)D concentration	Indication
	wk	*nmol/L*	
Mason et al (69), 1980			
1250 μg (50000 IU)	> 52	717 [6]	Hypoparathyroidism
Haddock et al (23), 1982			
1875 μg (75000 IU)	>100	1707.5 [14]	Hypoparathyroidism
Gertner and Domenech (70), 1977			
500 μg (20000 IU)	12–52	442 [6]	Various
1000 μg (40000 IU)	12–52	647 [7]	Various
1375 μg (55000 IU)	12–52	723 [4]	Various
2000 μg (80000 IU)	12–52	1022 [4]	Various
Counts et al (71), 1975			
2500 μg (100000 IU)	12	1550	Anephric
Hughes et al (72), 1976			
6250 μg (250000 IU)	>52	1480	Not stated
3750 μg (150000 IU)	>52	1000	Not stated
2500 μg (100000 IU)	>52	1600	Not stated
Streck et al (73), 1979			
2500 μg (100000 IU)	200	707.5	Hypoparathyroidism
Davies and Adams (74), 1978			
3750 μg (150000 IU)	364	1125	Paget disease
2500 μg (100000 IU)	520	1000	Thyroidectomy
Mawer et al (75), 1985			
1875 μg (75000 IU)	520	568	Hypoparathyroidism
5000 μg (200000 IU)	520	1720	Hypophosphatemic rickets
2500 μg (100000 IU)	520	995	Carpal tunnel syndrome
1250 μg (50000 IU)	1248	632	Celiac disease
4285 μg (171429 IU)	26	908	Chilblain
2500 μg (100000 IU)	520	856	Thyroidectomy
2500 μg (100000 IU)	312	778	Arthritis
1250 μg (50000 IU)	1040	903	Hypoparathyroidism
Allen and Skah (76), 1992			
1875 μg (75000 IU)	19 y	267	Hypoparathyroidism
Rizzoli et al (77), 1994			
15000 μg (600000 IU)	96	221	Osteoporosis
7500 μg (300000 IU)	3	801	Osteoporosis
7500 μg (300000 IU)	74	1692	Hypoparathyroidism
1075 μg (43000 IU)	12	374	Osteoporosis
7500 μg (300000 IU)	4	650	Osteoporosis
7500 μg (300000 IU)	4	621	Osteoporosis
250 μg (10000 IU)[2]	390	608	Osteomalacia

[1]Criteria for inclusion of study: adult subjects, vitamin D dose given, dose given for > 1 mo, and 25(OH)D concentration given. Supplements were generally vitamin D_2 (ergocalciferol). *n* in brackets if >1.
[2]Subject received 7500 μg (300000 IU) once monthly.

serum 25(OH)D concentrations < 25 nmol/L, the mean vitamin D intake was 11.7 μg (467 IU)/d. Apparently, some people require more vitamin D than others to reach a given concentration of 25(OH)D in serum. More recent reports show that dietary vitamin D intake correlates poorly with 25(OH)D concentrations (2, 9) and that 25(OH)D concentrations can hover around what is considered to be marginal deficiency (38 nmol/L) despite consumption of the recommended amount of vitamin D (9). Ultraviolet exposure and time spent outdoors are better predictors of 25(OH)D concentration than is dietary vitamin D intake (9). Obviously, the current, arbitrarily set vitamin D intakes play a minor role in the total economy of vitamin D for most adults.

If the objective is to optimize the probability of good health, then it seems reasonable that the daily vitamin D supply should be >20 μg (800 IU)/d. In both of the well-accepted studies showing osteoporosis fracture prevention with vitamin D and calcium, mean 25(OH)D concentrations exceeded 100 nmol/L (12, 26). The osteoporosis studies of Chapuy et al (26) and Heikinheimo et al (86) have been interpreted as evidence that the value of the vitamin supplement is simply to raise 25(OH)D concentrations out of the osteomalacic or insufficient range. However, patients in the recent study of Dawson-Hughes et al (12) started off with perfectly acceptable basal 25(OH)D concentrations of 61 nmol/L and still derived benefit. Target 25(OH)D concentrations exceeding 100 nmol/L would also minimize PTH concentrations because the decrease in 25(OH)D with age has a greater effect on the secondary hyperparathyroidism of aging than does the decline in renal function (10).

For most drugs and hormones, the relevant serum concentration attained is more important than is the actual intake of the agent. The recent increase in the DRI for vitamin D for adults >50 y of age was based on evidence of fracture prevention with vitamin D

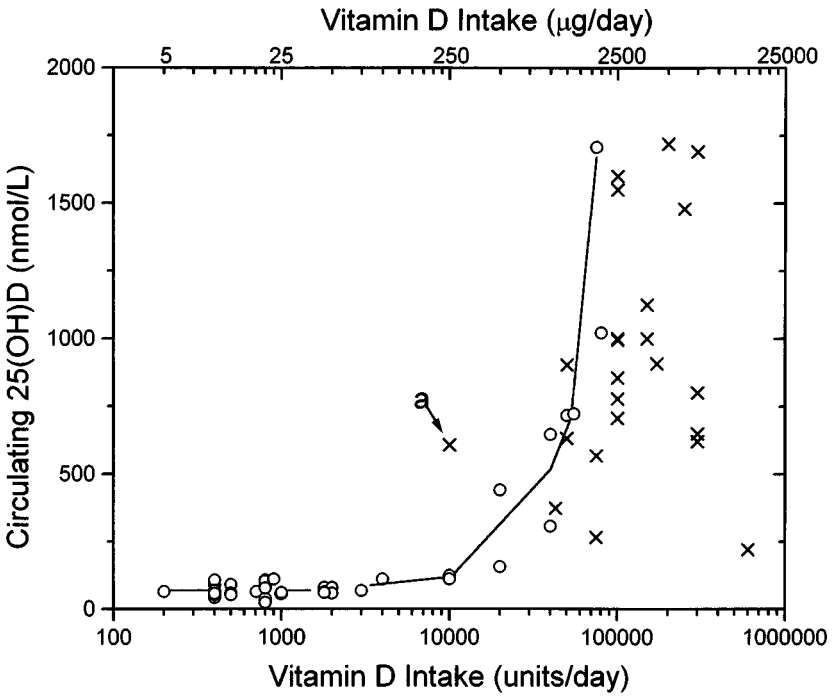

FIGURE 2. Dose response for vitamin D intake versus final serum 25-hydroxyvitamin D [25(OH)D] concentration reported. Circles indicate group means from Tables 4 and 5. Points indicated by "X" represent single values from Table 5 for people reported as intoxicated with vitamin D. The arrow indicates the lowest dose reported as causing hypercalcemia, but which is an outlier because vitamin D was given as a single dose of 7500 μg (300 000 IU)/mo, instead of 250 μg (10 000 IU)/d (77). If authors reported 25(OH)D for several time points, only the final serum 25(OH)D is shown in the figure. The line representing the dose response passes through the points that represent group data.

and calcium, as shown by Dawson-Hughes et al (12) and Chapuy et al (26). In both of those studies, mean serum 25(OH)D concentrations exceeded 100 nmol/L, which was unusual. Of the 21 groups summarized in Table 4 to whom vitamin D was given at doses between 20 and 75 μg (800 and 3000 IU)/d, it was only the subjects in these 2 studies that attained average 25(OH)D concentrations > 100 nmol/L (12, 26), except for subjects who lived near the equator (55). Calcium supplementation would not account for the unusual results because calcium by itself does not affect serum 25(OH)D in elderly women (91). A glance at Table 4 will show that to ensure the desirable objective of mean 25(OH)D concentrations > 100 nmol/L, the total vitamin D supply from dietary and environmental sources must be 100 μg (4000 IU)/d. This view is also based on the results of recent unpublished work (R Vieth, 1998) and on reference 67.

The objective of vitamin D supplementation should be to compensate for insufficient ultraviolet light exposure. Studies in submariners offer a reasonable way to estimate the decrement in vitamin D. A low estimate for the vitamin D decrement of submariners is 15 μg (600 IU) vitamin D_2/d. This was inferred by Holick on the basis of a small (n = 11) unpublished study done in 1984 that compared supplemented and unsupplemented sailors. Unfortunately, neither the actual 25(OH)D concentrations nor statistical significance were provided, and the summary includes the unreasonable observation that final 25(OH)D concentrations were 23% higher in subjects not taking any vitamin D (92). Studies with more complete data are summarized in Table 3. One way to estimate the serum 25(OH)D that may have been lost in the submariners reported on by Dlugos et al (46) is to determine the level of vitamin D supplementation that would sustain their initial 25(OH)D concentration of 78 nmol/L. Data in Table 4 show that an additional supplement of 10–25 μg (400–1000 IU) may be required to sustain the sailors' initial 25(OH)D concentrations. This is probably an underestimate because none of the vitamin D–supplemented subjects were totally sun deprived. Another approach to estimating the submariners' vitamin D decrement could be based on the amount of vitamin D required to produce the opposite effect on serum 25(OH)D within the same time period. In Table 4, it can be seen that MacLennan and Hamilton (63) reported in 1977 that 50 μg (2000 IU) vitamin D/d increased 25(OH)D concentrations from basal values of 15 to final values of 81 nmol/L. This was verified by Himmelstein et al (64), who showed that 2 mo of 50 μg (2000 IU) vitamin D/d raised serum 25(OH)D concentrations from the initial 40 to 80 nmol/L (Figure 1). On this basis, the sailors were deprived of ≈50 μg (2000 IU) environmental vitamin D/d during the time they were confined to the submarine.

Other reasons to consider increasing vitamin D nutrition

There are nonclassical and less well substantiated reasons to consider increasing vitamin D nutrition. As discussed above, the biochemical criterion of PTH suppression suggests that 25(OH)D concentrations > 100 nmol/L are desirable in elderly subjects (12, 15). Epidemiologic studies show that higher serum 25(OH)D concentrations or environmental ultraviolet light exposure are associated with lower rates of breast, ovarian, prostate, and colorectal cancers (93–100). There is impressive circum-

TABLE 6
Effects of single large doses of vitamin D[1]

Reference, year, and subjects	Location	Age	Dose	Duration after dose	25(OH)D concentration	
					Before	After
		y	*μg (IU)*	*mo*	*nmol/L*	
Davies (81), 1985	Manchester, UK					
(*n* = 10)		Elderly	2500 (100000) po	1	4	52
(*n* = 10)		Elderly	2500 (100000) po	2	4	35
(*n* = 10)		Elderly	2500 (100000) po	6	4	21
Matsuoka et al (82), 1992	Philadelphia					
(*n* = 18)		25	1250 (50000) po	0.03	46	49
Whyte et al (83), 1979	St Louis					
(*n* = 5 M)		Young	6000 (240000) po	1.6	45	70
(*n* = 3 M)		Young	6000 (240000) sc	1.6	33	93
(*n* = 3 M)		Young	6000 (240000) im	1.6	33	118
(*n* = 4 M)	London	Young	6000 (240000) iv	1.6	27.5	62.5
(*n* = 4)			6000 (240000) D_2 iv	1.6	37.5	45
(*n* = 5 M)		Young	15 000 (600000) iv	0.9	80	95
(*n* = 4)			6000 (240000) D_3 iv	1.6	35	52.5
Stern et al (84), 1982	Indianapolis					
(*n* = 24)		21–56	4 × 2500 (4 × 100000) po	0.13	45	97.5
(*n* = 12)		21–56	4 × 2500 (4 × 100000) po	0.13	62.5	85
Scragg et al (85), 1995	Cambridge, UK					
(*n* = 95)		70	2500 (100000) po	1.2		52.5
Heikinheimo et al (80), 1992	Tampere, Finland					
(*n* = 13)		85	3750 (150000) im	12	31	49
(*n* = 13)		75–84	3750 (150000) im	12	14	45
Heikinheimo et al (86), 1991	Tampere, Finland					
(*n* = 7)		75–84	3750 (150000) im	3	17	60
(*n* = 7)		75–84	3750 (150000) im	12	10	33
Weisman et al (87), 1986	Tel Aviv, Israel					
(*n* = 10)		72–94	2500 (100000) po	0.5	28	89
(*n* = 10)		72–94	2500 (100000) po	5	28	51
(*n* = 17)		72–94	2500 (100000) po	0.5	25	78
(*n* = 17)		72–94	2500 (100000) po	4	25	38
Burns and Peterson (88), 1985	Dundee, UK					
(*n* = 10)		75–94	15000 (600000) im	2	5	55
(*n* = 10)		75–94	15000 (600000) im	6	5	66

[1] po, by mouth; sc, subcutaneous; im, intramuscular; iv, intravenous; D_2, as vitamin D_2 (ergocalciferol); D_3, as vitamin D_3 (cholecalciferol).

stantial evidence that multiple sclerosis is more prevalent in populations having lower concentrations of vitamin D or ultraviolet exposure (98, 101), and there are suggestions that vitamin D intake ranging from 32.5 to 95 μg (1300 to 3800 IU)/d helps prevent the disease (101). The probability that established osteoarthritis will progress to a more severe stage is reduced with better vitamin D nutritional status, based both on serum 25(OH)D concentrations and diet history. On the basis of these results, McAlindon et al (102) recommended that serum 25(OH)D should exceed 75 nmol/L in persons with osteoarthritis of the knee. The prevalence of hypertension in a population increases with distance north or south of the equator (103), and it was reported recently that hypertension becomes less severe in subjects whose 25(OH)D concentrations are increased to >100 nmol/L through ultraviolet exposure (38). Vitamin D deficiency impairs immune function in animals (104), and in children there is a strong association between pneumonia and nutritional rickets (105). Vitamin D nutrition probably affects major aspects of human health other than its classical role in mineral metabolism; however, the evidence is not conclusive enough yet to warrant considering these other potential health benefits as objectives in nutritional guidelines. If any of this evidence were taken into consideration it would require substantial upward revision of the current DRI.

Some investigators found no statistically significant relations between serum 25(OH)D concentrations in archived tissue samples and eventual prostate cancer death (106, 107). Two points seem to have been missed in these studies. First, 25(OH)D concentrations vary with season and this will confound conventional approaches to cancer follow-up. Second, modern society in general is vitamin D–deprived compared with prehistoric humans. The concentrations of 25(OH)D observed today are arbitrary and based on contemporary cultural norms (clothing, sun avoidance, food choices, and legislation) and the range of vitamin D intakes being compared may not encompass what is natural or optimal for humans as a species.

Dose-response curve of 25(OH)D concentration versus vitamin D intake

The serum 25(OH)D concentration is maintained within a narrow range (Figure 2), ≈75–220 nmol/L across vitamin D supplies from 20 μg (800 IU) to the physiologic limit of 250–500 μg (10 000–20 000 IU)/d. The most reasonable explanation for this kind of relation is that there are homeostatic control systems to

regulate serum 25(OH)D and to buffer against variability in vitamin D supply. The metabolic points at which serum 25(OH)D can be regulated include the concentration of 25-hydroxylase in the liver (108), the catabolism of 25(OH)D by the liver into breakdown products excreted into bile (109), and the catabolism of 25(OH)D via the side-chain cleavage pathway initiated by 24-hydroxylase present in tissues throughout the body (110). Beyond the vitamin D supply limit, which is comparable with that attainable with sunshine, there is a classic rise in the dose-response curve. The sharp rise reflects the introduction of vitamin D and 25(OH)D at rates that exceed the capabilities of the various mechanisms to regulate 25(OH)D.

One case illustrates the physiologic limit well. The patient, who had primary hypoparathyroidism, is indicated by the arrow in Figure 2. This data point is an outlier because it is clearly the highest serum 25(OH)D concentration within the physiologic range of vitamin D intake. Although this subject did not take a remarkably large dose of vitamin D daily, the effect was toxic because the dose was taken as a single monthly dose of 7500 μg (300 000 IU) (77). This exceeded by 30-fold the physiologic range and resulted in the production of more 25(OH)D than the body had the capacity to clear from the system at one time—hence toxicity with one form of stoss therapy.

Aside from the vitamin D supply itself, endocrine and dietary factors affect circulating 25(OH)D. In rats, both low (109, 111) and excessively high calcium intakes (111) can lower serum 25(OH)D concentrations. The calcium-raising hormones each tend to lower serum 25(OH)D. In hypoparathyroid humans, $1,25(OH)_2D$ treatment speeds up the metabolic clearance of 25(OH)D from the circulation (68). In hyperparathyroid humans, there is accelerated clearance of 25(OH)D (112).

The preceding discussion highlights the fact that $1,25(OH)_2D$ is not the only metabolite that is regulated in the vitamin D endocrine system. The purpose of the mechanisms to regulate 25(OH)D concentrations may be to optimize the availability of 25(OH)D for tissues that require it, either for its direct action (79), or as the source of substrate for nonrenal, paracrine 1-hydroxylase (calcidiol 1-monooxygenase, EC 1.14.13.13) (113).

Lowest dose causing harm

The recent paper by Adams and Lee (16) about mild vitamin D toxicity defined elevated 25(OH)D as anything >125 nmol/L, which was the upper limit of the reference range stated by their referral laboratory. Their subject with the highest concentration of urinary calcium had a serum 25(OH)D concentration of 140 nmol/L, and this was on only one occasion. When this subject's serum 25(OH)D fell to 102 and then to 75 nmol/L, the urinary ratio of calcium to creatinine remained unchanged at its highest value, suggesting some other metabolic cause of the hypercalciuria. The other cases in the report more closely resemble those given milk excessively supplemented with vitamin D reported by Jacobus et al (114) or those in the poisoned household reported by Pettifor et al (78).

Except for the report by Adams and Lee (16), all instances of vitamin D toxicity have involved serum 25(OH)D concentrations in excess of 200 nmol/L (Table 5). Adams and Lee came across their putative cases of vitamin D intoxication by checking urinary calcium concentrations in patients screened in an osteoporosis evaluation. Certainly, the first sign of vitamin D excess would involve an increase in urinary calcium, but whether this occurs with physiologic 25(OH)D concentrations in healthy individuals is by no means established by their study (115, 116). Furthermore, Adams later stated that the subjects had consumed amounts of vitamin D "at least one order of magnitude greater than" what was on the label (ie, ≥10 times 30 μg or 1200 IU/d) (117).

Dawson-Hughes et al (14) found 25(OH)D concentrations comparable with those of Adams and Lee's subjects in ≈20 healthy elderly men and women who were not taking vitamin D supplements. Likewise, presumably healthy farmers in Puerto Rico and lifeguards also had such 25(OH)D concentrations (Table 1). Although not strictly within the "normal" range for a clothed, sun-avoiding population, serum 25(OH)D concentrations ≤220 nmol/L are consistent with certain environments, are not unusual in the absence of vitamin D supplements, and should be regarded as being within the physiologic range for humans.

The report of Adams and Lee (16), together with its accompanying editorial, suggest that serum 25(OH)D concentrations as low as 140 nmol/L are harmful. This is alarmist. Are we to start avoiding the sun for fear of raising urine calcium or increasing bone resorption? The question has never been addressed objectively. My view is that there is no harm in the 25(OH)D concentrations associated with sun exposure and that such concentrations are probably optimal for human health.

Higher rates of osteoporosis and arteriosclerosis have been attributed to virtually any vitamin D intake (118). Furthermore, the US National Academy of Sciences (3) indicated in 1989 that the toxic dose of vitamin D can be as low as "five times the RDA." This view now seems to have been carried forward to the latest set of vitamin D recommendations, in which the tolerable upper intake level is indicated as 50 μg (2000 IU)/d (19).

Throughout my preparation of this review, I was amazed at the lack of evidence supporting statements about the toxicity of moderate doses of vitamin D. Consistently, literature citations to support them have been either inappropriate or without substance. The statement in the 1989 US nutrition guidelines that 5 times the RDA for vitamin D may be harmful (3) relates back to a 1963 expert committee report (5), which then refers back to the primary reference, a 1938 report in which linear bone growth in infants was suppressed in those given 45–157.7 μg (1800–6300 IU) vitamin D/d (119). The citation is not related to adult nutrition and it does not form a scientific basis for a safe upper limit in adults. The same applies to the statement in the 1987 Council Report for the American Medical Association that "dosages of 10,000 IU/d for several months have resulted in marked disturbances in calcium metabolism…and, in some cases, death." Two references were cited to substantiate this. One was a review article about vitamins in general, which gave no evidence for and cited no other reference to its claim of toxicity at vitamin D doses as low as 250 μg (10 000 IU)/d (120). The other paper cited in the report dealt with 10 patients with vitamin D toxicity reported in 1948, for whom the vitamin D dose was actually 3750–15 000 μg (150 000–600 000 IU)/d, and all patients recovered (121). If there is published evidence of toxicity in adults from an intake of 250 μg (10 000 IU)/d, and that is verified by the 25(OH)D concentration, I have yet to find it.

The issue of poorly substantiated claims of toxicity extends even to the most recent, 1997, revision for vitamin D intakes published by the National Academy of Sciences (19). The only study cited to address the question of critical endpoint doses for vitamin D (potential adverse effect levels) was an esoteric article by Narang et al (122). The basis for the current no observed adverse effect level (NOAEL) of 50 μg (2000 IU)/d is that Narang et al reported a mean serum calcium concentration >11 mg/dL(2.25 mmol/L) in

the 6 normal subjects given 95 μg (3800 IU) vitamin D/d. That intake was then defined as the lowest observed adverse effect level (LOAEL). The next lowest test dose used by Narang et al, 60 μg (2400 IU)/d, with 20% less as the safety margin, became the NOAEL. Narang et al reported only serum electrolyte changes, the doses of vitamin D were not verified, and 25(OH)D concentrations were not reported. The National Academy committee missed evidence showing the safety of larger doses of vitamin D. Directly comparable with the protocol of Narang et al (122) is the study by Tjellesen et al (67), in which 19 normal subjects were given 95 μg (3800 IU) vitamin D_2 or 110 μg (4400 IU) vitamin D_3/d (these doses were validated by direct assay) (Table 4). Serum calcium increased by a minute, but statistically significant, 0.05 mmol/L (0.12 mg/dL) with 110 μg (4400 IU) vitamin D_3 and there was an increase in urinary calcium, as one should expect with improved intestinal calcium absorption. Another report indicative of the safety of larger doses is by Stern et al (84), who administered vitamin D_2 at 2500 μg (100 000 IU)/d for 4 d (Table 6). This represented a far greater stress to the vitamin D system because it delivered in 4 d a total vitamin D dose equivalent to what Narang et al used over 3 mo. Nonetheless, Stern et al (84) detected no significant effects on serum calcium in the 24 normal adult subjects they treated in this way.

The mechanism causing vitamin D toxicity involves the unbridled expression of 1,25$(OH)_2$D-like activity. Whether 1,25$(OH)_2$D or 25(OH)D is the main signaling molecule causing vitamin D toxicity remains a point of contention. There is a growing likelihood that 25(OH)D has biological activity in its own right. The concentration of 25(OH)D is often reported to be better correlated with absorption of calcium from the gut than is serum 1,25$(OH)_2$D (123, 124). Recently, Heaney et al (79) showed that the circulating 25(OH)D concentration affects intestinal calcium absorption. However, to show this, it was necessary to raise serum 25(OH)D concentrations into the range of 300–1000 nmol/L, and this is well beyond what could be considered physiologic.

As vitamin D doses increase, the mechanisms to explain the toxic responses are 3-fold: *1*) a possible conversion of vitamin D_3 to 5,6-*trans*-vitamin D_3, which contains a pseudo-1-α group; *2*) a direct action of 25(OH)D at the 1,25$(OH)_2$D receptor (79); or *3*) an unbridled production of 1,25$(OH)_2$D with inappropriate maintenance of its total concentration in the circulation despite its displacement from vitamin D binding protein to increase free 1,25$(OH)_2$D (78, 125). The opinion that 95 μg (3800 IU) vitamin D/d is the LOAEL (19) is not consistent with these current theories of why vitamin D is toxic and is not consistent with the amounts of vitamin D needed to raise 25(OH)D concentrations to the hypercalcemic levels reported in all studies in which serum 25(OH)D is related to toxicity.

Fraser (126) speculated that orally acquired vitamin D might be particularly toxic because it enters the body via an unnatural route for this nutrient. This hypothesis has never been put to the test. It does seem reasonable that the metabolism of vitamin D acquired through the skin might be more finely regulated than that of vitamin D obtained orally. Haddad et al (127) showed that the transport of vitamin D in the circulation is different for vitamin D acquired by dermal and oral routes. Oral vitamin D is primarily transported along with chylomicrons and lipoproteins until it is cleared by the liver within hours, whereas dermal vitamin D is transported on vitamin D binding protein and takes days to clear. We recently observed that the apparent self-regulation of 25-hydroxylase first observed for vitamin D generated in skin (27, 34) pertains equally well to vitamin D acquired orally. Oral vitamin D supplementation produced the greatest increase in 25(OH)D in those who initially had the lowest 25(OH)D concentrations (13). From what is known now, there is no practical difference whether vitamin D is acquired from ultraviolet exposed skin or through the diet.

Hypersensitivity to vitamin D

Hypersensitivity to vitamin D can occur (128). Primary hyperparathyroidism is probably the most common example. It would be simplistic to avoid or minimize vitamin D intake because of this. Before the occurrence of hyperparathyroidism, vitamin D nutrition is preventive because it reduces parathyroid secretion and lowers the likelihood of parathyroid hyperplasia (129–131). Once primary hyperparathyroidism exists, production of 1,25$(OH)_2$D is persistently up-regulated by the high PTH concentrations, and 1,25$(OH)_2$D concentrations correlate directly with serum 25(OH)D (132). In hyperparathyroid individuals, vitamin D exaggerates hypercalcemia because of the connection between vitamin D nutrition and 1,25$(OH)_2$D production. Vitamin D deficiency can mask primary hyperparathyroidism (132) and this could account for the occasional cases of hypercalcemia that occur when large groups of elderly people are given vita min D supplements (133). Some patients with sarcoidosis, tuberculosis, or lymphoma become hypercalcemic in response to any increase in vitamin D nutrition (122, 134, 135). For these persons, it may be prudent to avoid any dietary or environmental sources of vitamin D.

Efficacy and safety

Although the new DRI for vitamin D for most adults is 5 μg (200 IU)/d (19), the beneficial amount is more likely to be 10–12.5 μg (800–1000 IU)/d, on the basis of bone density measurements and fracture prevention in the elderly (12, 18, 26). For this reason, DRIs have been increased for those >70 y of age to 600 IU/d. This intake will also lessen the chance of vitamin D deficiency–induced secondary hyperparathyroidism and will bring serum 25(OH)D concentrations closer to those associated with other health benefits. Even if all adults consumed 12.5 μg (1000 IU)/d, it would be difficult to detect an increase in the number of individuals with 25(OH)D concentrations >140 nmol/L because ≥90% of the vitamin D contributing to such concentrations would be from sunshine exposure, not oral intake.

The assignment of a NOAEL, as defined by Hathcock (21), or allowable "tolerable upper intake level," as defined by the Food and Nutrition Board, Institute of Medicine (19), is especially difficult for vitamin D. Because of environmental input, the concentration referred to must be that of 25(OH)D in the circulation and not simply dietary vitamin D. Another consideration is that rare individuals are hypersensitive to vitamin D. There is no simple answer here because the primary disease may be made more likely to occur by previous vitamin D deficiency (129). The following discussion disregards the possibility of vitamin D hypersensitivity. If it exists, hypersensitivity would appear to negate the value of any vitamin D intake or sunshine exposure.

For vitamin D, a NOAEL could define the highest 25(OH)D concentration not suspected to cause hypercalciuria in healthy subjects. As discussed above, it could be difficult to prove that vitamin D is the cause of hypercalciuria because the condition is commonly caused by other things and it is a mild and nonclassicl criterion for vitamin D intoxication. Nonetheless, because of the hypothesized predisposition to hypercalciuria of the Israeli

lifeguards (25) and of the subjects in the study of Adams and Lee (16), 140 nmol 25(OH)D/L could be regarded as a very conservative limit for the NOAEL because the concentrations in those reports were higher than this. In the absence of sunshine, all available evidence indicates that this would require prolonged intake of ≈250 μg (10 000 IU)/d to achieve. All of the reports of vitamin D toxicity showing the convincing evidence of hypercalcemia involve serum 25(OH)D concentrations well above 200 nmol/L (Table 5), which requires a daily intake of ≥1000 μg (40 000 IU), and which could thus be conservatively considered the LOAEL.

The current adult DRI for vitamin D approximates half the amount in the teaspoon of cod-liver oil that was a 19th-century folk remedy. Today, new drugs are passed through dose-finding studies before their efficacy is evaluated in clinical trials. This principle is not strictly applicable to nutrient recommendations because the bulk of what humans consume of them is from unfortified foods and this consumption is what recommended intakes tend to match. In contrast, vitamin D is a special case; the bulk of our dietary vitamin D intake is determined by legislation. I contend that this practice amounts to the dosing of populations with a drug, vitamin D, that is not present in the foods humans normally consume. If vitamin D is similar to a drug, then dose-finding studies are needed to use it properly, especially if nonclassical benefits are potentially relevant. Alternatively, if by analogy with other nutrients, vitamin D supplementation is intended to make up for what some people may not be getting from its natural source, in this case the sun, then the current adult DRI of 5 μg (200 IU)/d is woefully inadequate.

This work is dedicated to my retired teachers, particularly Donald Fraser and Sang-Whay Kooh, for the pleasurable times we shared trying to understand the vitamin D system. I also thank Fraser for his thoughtful review of this manuscript.

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