Journal of Nutritional & Environmental Medicine (2001) 11, 275–291

REVIEW

Vitamin D Nutrition and its Potential Health Benefits for Bone, Cancer and Other Conditions

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Abstract

Because humans evolved at equatorial latitudes, without modern clothing and shelter, their vitamin D supply would have been equivalent to at least 100 μg day^{-1} (4000 units day^{-1}). Thus, the human genome was selected for under conditions where the circulating 25-hydroxyvitamin D (25(OH)D) concentration was greater than 100 nmol l^{-1}. This contrasts with modern humans in whom serum 25(OH)D is typically half that. This review poses the question of whether our genome was optimized for higher levels of vitamin D nutrition than are prevalent today. Many tissues possess 25(OH)D-1-hydroxylase and they can produce 1,25-dihydroxyvitamin D (1,25(OH)2D) for local, paracrine use. Furthermore, the activity of existing 1-hydroxylase depends upon the 25(OH)D concentration in a manner different from the substrate relationships for other hormone-producing systems. The functional, in vivo Km *for 1,25(OH)2D production is higher than the concentration of substrate, 25(OH)D. That is, a doubling in 25(OH)D concentration will double the capacity for 1,25(OH)2D production* in vivo. *This applies not only to the kidney, but also to every tissue that possesses 1-hydroxylase. So far, there is little direct evidence for the health implications of this unique substrate relationship. The amounts of vitamin D that have been used in randomized clinical studies were small and do show some effect. Vitamin D supplementation with 20 μg day^{-1} (800 IU day^{-1}) is now recognized as preventing bone loss, reducing fracture risk, lowering blood pressure, and lowering circulating parathyroid hormone concentrations. However, the benefits of a higher vitamin D supply are implicated by the circumstantial evidence of epidemiological studies that reflect differences in the sun exposure that produces vitamin D in skin. These potential benefits of greater vitamin D nutrition include a reduction in the occurrence of breast, prostate, and bowel cancers and the autoimmune conditions of multiple sclerosis and insulin-dependent diabetes. Randomized clinical trials into these conditions should focus on the higher, physiological doses of nutritional vitamin D whose consumption has recently been shown to be safe for adults. Unfortunately, the term 'vitamin D' is so commonly misapplied to analogs of its hormonal form that research and side-effects relating to those analogs can be misinterpreted as being somehow related to nutrition.*

Keywords: cholecalciferol, ergocalciferol, safety, toxicity, anthropology, recommended nutrient intake, health benefits, osteoporosis, upper limit, environment.

INTRODUCTION

> How far is it 'natural' to live in this sunless climate of ours? In more 'natural' sunnier climates such [vitamin D] treatment would not be necessary. And how

ISSN 1359-0847 print/ISSN 1364-6907 online/01/040275-17 © Taylor & Francis Ltd
DOI: 10.1080/1359084012010312 0

> much of our life—our habits of clothing, shelter, artificial heating, and in fact the whole complex fabric of our artificial civilization with its incessant interference with primitive behavior—is 'natural'? Leslie J. Harris, 1935 [1]

Vitamin D, in the form of cod liver oil, has been in use for about 200 years as a folk remedy to help infants thrive. However, very little thought has been directed at determining how much vitamin D adults need. Until recently, there has been no widely held consensus about what the objective measure of vitamin D nutrition should be. The previous criterion for deciding that an individual's vitamin D supply was appropriate was simply the absence of rickets or osteomalacia. In the 1960s, there was no evidence to suggest that vitamin D might play a role in any health-related condition other than rickets or osteomalacia [2]. Despite the substantial amount of new knowledge uncovered since then, the most recent revision of North American dietary recommendations maintained a very conservative attitude when it came to making changes to dietary recommendations about vitamin D. From a vitamin D perspective, the most important outcome of the review has been that 25-hydroxyvitamin D (25(OH)D) levels are now the acceptable official criterion for characterizing the quality of vitamin D nutrition [3]. This has made it possible to evaluate the field of vitamin D nutrition more rigorously, because researchers can focus on a measurable target.

CLARIFICATIONS ABOUT THE FIELD OF VITAMIN D

Authentic vitamin D comes in two forms: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). Vitamin D2 is synthesized by exposing a fat extract of yeast to ultraviolet light. Because no metabolite of vitamin D2 is normally detectable in the blood of humans or primates [4, 5], the present discussion focuses on vitamin D3, cholecalciferol, the natural, physiological form of vitamin D in mammals. Vitamin D3 (from here on, vitamin D) is the more potent form of vitamin D in all primate species and in man [4, 5]. Based on our work comparing the two versions of vitamin D [5], and the cross-sectional analysis of studies presented below, I estimate that vitamin D3 is about four times as potent as vitamin D2, i.e. 1 μg of D3 = approximately 4 μg of D2. Nonetheless, vitamin D2 is used clinically as if it is equivalent, because official guidelines [3] and pharmacopeas say that it is. The evidence for the presumption is based on 60-year-old studies of rickets prevention in infants—evidence recognized as weak, even at the time [6, 7]. In Australia, vitamin D3 has never been licensed for use, and the only nutritional form available there is vitamin D2.

Vitamin D is the raw material providing the substrate for synthesis of the hormone, 1,25-dihydroxyvitamin D [1,25(OH)2D, or calcitriol]. In this part of the endocrine system, vitamin D itself plays a role as a structural substrate, similar to the way cholesterol is the structural raw material for other steroid hormones. No one has ever implied that cholesterol is a 'pro-hormone' or a 'hormone', but unfortunately, those terms have been misappropriated for vitamin D. Even the US/Canadian Food and Nutrition Board [3] refers to vitamin D as a 'hormone'. My point is that because a molecule of vitamin D is not committed to becoming the hormone 1,25(OH)2D, a molecule of vitamin D is technically no more a hormone or pro-hormone than is cholesterol. The theoretically inactive intervening metabolite, 25(OH)D, is synthesized in liver mitochondria and liver microsomes. 25(OH)D has a biological half-life of about 2 months, and is thought to be inactive. However, in the healthy adult, it is the 25(OH)D concentration that correlates with parathyroid hormone (PTH) [8–11], and with the health aspects discussed below. For practical purposes, physiological amounts of 25(OH)D are non-hypercalcemic and it is the concentration of this metabolite that is associated with substantial biological effects. The health benefits discussed here are not explainable by the corresponding circulating 1,25(OH)2D level, both in the rat [12] and humans [13, 14].

The vitamin D-derived hormone 1,25(OH)2D is synthesized and released by the kidney according to the needs of calcium homeostasis. Many tissues possess classic steroid

hormone-like receptors for 1,25(OH)2D (VDR). The scientific literature often refers to 1,25(OH)2D inappropriately, calling it 'vitamin D'; this can cause confusion to those who are interested in nutrition or in the effect of ultraviolet light on the vitamin D system. The present review does not deal with 1,25(OH)2D or its analogs, which are reviewed elsewhere [15]. The present focus is on vitamin D nutrition and health benefits in the adult.

CURRENT NUTRITIONAL RECOMMENDATIONS

The terminology for recommended dietary intakes varies among the groups making recommendations in different parts of the world, but in the end the amounts recommended for vitamin D are similar. In the USA and Canada, the calcium and vitamin D recommendations fall under a new term, 'adequate intake' (AI), which is reserved for nutrients where there are not enough data to establish a recommended dietary allowance (RDA) [3]. Worldwide, nutritional recommendations specify 5–10 μg (200–400 units) day^{-1} of vitamin D for infants. But for adults under the age of 50 years the recommendation remains 5 μg (200 units) day^{-1}. For those between 51 and 70 years of age, the recommended intake is 10 μg (400 units) day^{-1} of vitamin D. For adults over the age of 70 years, the recommended intake of vitamin D has tripled to 15 μg day^{-1} (600 IU day^{-1}), in what was probably a record increase for any nutrient recommendation [3].

A conventional, milk-containing North American diet provides about 5 μg (200 IU) day^{-1} (100 units per glass), but close to half the population does not drink milk at all [16]. There is some vitamin D in ocean fish like cod and salmon, but as few adults consume much of these, they do not supply populations with much vitamin D either. Nutritional legislation assumes that we get at least 200 units from the sun, and that occasional exposure of the face and hands to sunlight is enough.

One thing that is surely a major frustration to researchers studying vitamin D nutrition is that their findings are quickly lost in the back issues of journals. Fine studies from various parts of the world have reported for many years that sunny climates, or the officially recommended intakes of vitamin D, offer surprisingly little benefit to adults. Vitamin D deficiency is common in many parts of the world, and not just in northern countries [17–20]. Nonetheless, the prevailing view continues to be that by consuming the recommended intakes of vitamin D, adults should have no concerns about low circulating 25(OH)D levels [3]. This assumption has been tested, and the overwhelming weight of evidence shows that the amounts of vitamin D currently recommended for adults do not do much good. In Finland, Lehtonen-Veromaa *et al.* asked whether 10 μg day^{-1} vitamin D given to 9–15-year-old girls would prevent them from developing 25(OH)D concentrations < 37.5 nmol l^{-1} during the winter. Their intervention study showed no preventive effect with the official recommended vitamin D intake [18]. Similar findings were obtained in cross-sectional studies. In immigrant women to Denmark, Glerup *et al.* could not uncover any prevention of 25(OH)D < 40 nmol l^{-1} when 5–15 μg day^{-1} was taken [19, 20]. In Canada, we found that adult women consuming multivitamins or vitamin D-fortified milk, whose vitamin D intake exceeded 10 μg day^{-1} (> 400 IU day^{-1}), had the same serum 25(OH)D levels as women not taking vitamin D [16]. More importantly, the women's intake of vitamin D did not change their risk of vitamin D insufficiency [serum 25(OH)D < 40 nmol l^{-1}] [16]. These things should not come as a surprise when it is recalled that the teaspoonful of cod liver oil used to prevent rickets in infants contained less than 400 units of vitamin D [6]. In other words, 10 μg (or 400 units) day^{-1} of vitamin D reflects the infant dose. This was never designed to benefit adults.

During the last 25 years, the criterion for what is an appropriate target for serum or plasma 25(OH)D concentration has evolved from an amount associated with protection against osteomalacia (adult rickets) to an intake that suppresses PTH secretion, and more recently, prevents osteoporosis [3, 21]. This evolution towards higher desirable 25(OH)D

concentrations will probably continue, because of the growing appreciation that other disease conditions are associated with low vitamin D supplies. Balancing against the evidence that vitamin D intakes should be increased for adults is the persistent notion that vitamin D is the most toxic of all vitamins [22, 23].

BENEFITS DERIVED FROM THE RDA FOR VITAMIN D

The working definition of RDA is to ensure 'levels of intake of essential nutrients considered … to be adequate to meet the known nutritional needs of practically all healthy persons' [24]. As discussed above, there is no evidence to support the assumption that if the recommended intakes of vitamin D are maintained, they will protect adults from vitamin D insufficiency. The aim of vitamin D supplementation for adults is now to minimize secretion of PTH, because that hormone initiates bone resorption. Graphs showing PTH levels vs. 25(OH)D approach a low asymptote when 25(OH)D concentrations exceed 72 nmol l^{-1} [8, 11, 25]. Recent work has shown that the normal range for PTH declines as 25(OH)D increases [9]. Thus, more recent thinking is starting to aim vitamin D supplementation at ever higher target 25(OH)D concentrations, now exceeding 72 nmol l^{-1} [26]. For adults, the value of the current RDA for vitamin D becomes trivial in this context, because it contributes only a marginal amount of the vitamin D needed to achieve the desirable target level for serum 25(OH)D.

ROLE OF VITAMIN D IN ADULT BONE HEALTH

On average, adults resorb (effectively dissolve away, through the action of osteoclasts) just under 1% of the skeleton every month, and at the same time put almost that much back. After the mid-thirties in age, we only put back about nine-tenths of what we take out of the skeleton. The calcium in our bones could be thought of as a retirement account where withdrawals exceed deposits. With this analogy, osteoporosis is a form of bankruptcy that pertains to the amount of calcium stored in the skeleton. Here, depletion results in bones that can no longer withstand some of the normal stresses of everyday living. Consequently, minor falls, unusual movements, or even a hug can result in a fracture. While treatments for osteoporosis restore bone density by a few percentage points, their long-term effect is to stabilize the condition. There is no cure for osteoporosis. However, it may be prevented.

Bone mass falls faster during the winter months, and during the summer bone density remains fairly stable. The group headed by Bess Dawson-Hughes showed that vitamin D supplements (about 800 units day^{-1}) eliminate the faster fall in bone density during the winter [27]. And when vitamin D is used along with calcium supplements, it is difficult to tell which is of greater benefit—the vitamin D or the calcium [28, 29]. They probably act together by providing calcium, and by reducing bone resorption by suppressing the secretion of PTH. That laboratory continues to publish articles on the high prevalence of low 25(OH)D levels, and its implications on the skeleton [30].

For groups of elderly people starting to take calcium and vitamin D, the occurrence of fractures is reduced by about one-third in the first year, even though bone density is not increased by enough to account for the fewer fractures [29]. What is not yet common knowledge is that vitamin D improves muscle strength and balance—it is thought that this is what reduces the occurrence of falls that cause fractures [31].

Vitamin D does not actually have to be in the stomach at the same time as the calcium. Vitamin D is the raw material for 1,25(OH)2D. After vitamin D enters the blood via the skin or the diet, conversion to 25(OH)D requires at least 1 day [32]. The 25(OH)D compound has a half-life of about 2 months, and conventional dogma regards 25(OH)D as having no activity by itself. However, 25(OH)D is the best measure of vitamin D nutritional status, and it is the main criterion for diagnosing nutritional rickets or osteomalacia. The kidney functions as an endocrine gland, using 25(OH)D to make the hormone 1,25(OH)2D.

Synthesis of 1,25(OH)2D is greatest when calcium supplies are lowest. The hormone induces the active transport of calcium through intestinal mucosa. Only minimal supplies of vitamin D are needed to maintain normal levels of 1,25(OH)2D, which is produced physiologically at a rate of about 1 μg day^{-1} (much below the physiological vitamin D supply stated below to exceed 100 μg day^{-1}). Rickets and osteomalacia usually exist despite normal 1,25(OH)2D concentrations. Increases in vitamin D will not increase 1,25(OH)2D levels [33–36]. As kidney function deteriorates, its endocrine capability also declines, and thus a low serum 1,25(OH)2D level reflects impaired renal function, not poor nutrition [37].

NON-BONE EFFECTS OF VITAMIN D

Vitamin D nutrition probably affects health beyond just bone. It does this through signaling mechanisms mediated locally, using circulating 25(OH)D as the substrate. Many tissues possess 25(OH)D-1-alpha-hydroxylase, including the skin (basal keratinocytes, hair follicles), lymph nodes (granulomata), pancreas (islets), adrenal medulla, brain, pancreas, and colon [38]. Furthermore, even a wider range of tissues possess receptors for 1,25(OH)2D (VDR) [39]. With these two key mechanistic components, vitamin D nutrition becomes essential to the local, paracrine role of 1,25(OH)2D, not necessarily reflected in the circulating level of 1,25(OH)2D. Furthermore, the 1-alpha-hydroxylase enzyme functions *in vivo* as if its substrate supply concentration is below the *Km* [40, 41]. That is, each unit of enzyme generates product at a rate directly proportional to the supply of 25(OH)D. Because the circulating 25(OH)D concentration in adults can easily vary 100-fold (2–200 nmol l^{-1}), the 1-hydroxylase in tissues must adapt to low 25(OH)D levels by compromising the way it produces and metabolizes 1,25(OH)2D—less substrate up-regulates 1-hydroxylase expression. A second mechanism for dealing with the variable substrate supply is the induction of clearance or breakdown pathways for 1,25(OH)2D. Thus, the most fundamental of the vitamin D-response elements exhibited by tissues possessing VDR is the induction of 24-hydroxylase, the first enzyme on the catabolic pathway for 25(OH)D and 1,25(OH)2D [42]. These biochemical mechanisms for tissue paracrine regulation of 1,25(OH)2D levels would partly explain the clinical and epidemiological evidence that vitamin D nutrition may affect many aspects of health.

The level of evidence needed to make a health claim that can be sanctioned officially involves more than the circumstantial evidence of laboratory experiments and epidemiology. It requires direct intervention, the controlled administration of the agent to many healthy people, and showing an effect that stands up to statistical analysis. While all the effects in Table 1 are statistically significant, most of the evidence for a role of vitamin D is circumstantial. Epidemiological studies show that higher serum 25(OH)D, and/or environmental ultraviolet exposure, is associated with lower rates of breast, ovarian, prostate, and colorectal cancers [61–68]. More recent statistical analyses have also shown significant relationships, including non-Hodgkin's lymphoma, and cancer of the bladder, esophagus, kidney, lung, pancreas, rectum, stomach and corpus uteri [56]. Multiple sclerosis is more prevalent in populations having lower levels of vitamin D nutrition or ultraviolet exposure [51, 66, 69, 70], and it has been proposed that vitamin D intake ranging from 1300 to 3800 units day^{-1} helps to prevent the disease [51]. Established osteoarthritis progresses more slowly (is less severe) in adults with a higher vitamin D nutritional status, with serum 25(OH)D exceeding 75 nmol l^{-1} [47, 48]. The prevalence of hypertension increases with population distance, north or south, from the equator [43]. Blood pressure goes down in subjects whose 25(OH)D levels are raised to over 100 nmol l^{-1} by tanning [44], and there is now one randomized intervention study showing that vitamin D supplementation at 20 μg day^{-1} (800 IU day^{-1}) lowers blood pressure in elderly women [71]. Vitamin D deficiency impairs immune function in animals [72], and in children there is a strong association between pneumonia and nutritional rickets [50]. The concept that there is a connection

TABLE 1. Diseases known to be, or implicated as being, prevented by greater vitamin D nutrition or skin ultraviolet light exposure

Disease	Type of evidence supporting the association	Reference
Rickets	Long established, causal and preventive	
Osteomalacia	Long established, causal and preventive	
Osteoporosis	Direct, controlled studies that vitamin D prevents loss of bone density, and lessens fracture risk	[27–29]
Blood pressure regulation	Epidemiological and randomized interventional data	[31, 43, 44]
Risk of diabetes	Epidemiological and case-control data	[45, 46]
Progression osteoarthritis	Epidemiological, cross-sectional studies	[47, 48]
Diminished intrauterine growth	Presumed effect	[49]
Resistance to pneumonia	Epidemiological association with rickets	[50]
Multiple sclerosis (occurrence and progression)	Epidemiological data, and laboratory effects on tissue	[51–53]
Prevention of tuberculosis	Epidemiological data, and laboratory effects on tissue	[54, 55]
Protection against breast cancer	Epidemiological data, and laboratory effects on tissue	[56, 57]
Protection against prostate cancer	Epidemiological data, and laboratory effects on tissue	[56, 58–60]
Protection against large bowel cancer	Epidemiological and cross-sectional data, based on latitude and serum 25(OH)D	[56, 57]

25(OH)D, 25-hydroxyvitamin D.

between vitamin D nutrition and immune function is further supported by the apparent protective effect of improved vitamin D nutrition during infancy and childhood against type I diabetes mellitus [46, 70]. If any of these non-traditional effects of vitamin D were taken into account, they would result in a substantial upward revision of the RDA for vitamin D.

A few years ago Goodwin and Tangum [73] described the attitude of conventional academic medicine about micronutrients (and one might include ultraviolet light among these). They described a bias that ignores evidence of benefit and exaggerates evidence of harm [73]. Vitamin D and ultraviolet light are clear examples of this. For both there has been an intense focus on harmful effects, and few are aware of the evidence of benefit. If any of the disease correlations with vitamin D or ultraviolet light in Table 1 were the opposite of what was observed (i.e. if more of either were harmful for the conditions listed), there is no doubt that the bad news would have spread quickly across the front pages of newspapers.

What is missing in this area are randomized intervention trials to take this knowledge beyond the pre-clinical basic research showing mechanisms, and beyond the circumstantial epidemiological or cross-sectional evidence leading to plausible hypothesis. Yes, there are ongoing 'vitamin D'-related randomized trials relating to cancer, multiple sclerosis, and osteoporosis. However, they are dealing with analogs of 1,25(OH)2D. Simple vitamin D nutrition (cholecalciferol itself) has been overlooked for all practical purposes. There are three reasons for this. First, the financial incentive lies with the patented analogs, which are endowed with private research support that diverts the focus of investigators able to do such studies. Second, because an optimized vitamin D dose has never been established for adults, it should not come as a surprise that 'plain' vitamin D compares poorly with 1,25(OH)2D analogs, whose dose is more thoroughly optimized [74]. Third, because of the official misrepresentation that vitamin D2 and vitamin D3 are equal, all efficacy studies using vitamin D doses greater than 25 μg day^{-1} actually used vitamin D2, which comprises the high-dose commercial preparations of vitamin D. A key example of this is the work looking at whether vitamin D2 supplementation might be able to prevent bone loss in steroid-treated patients [75, 76]; the treatment results were marginal, but as vitamin D3 was never part of the picture, the issue remains unresolved.

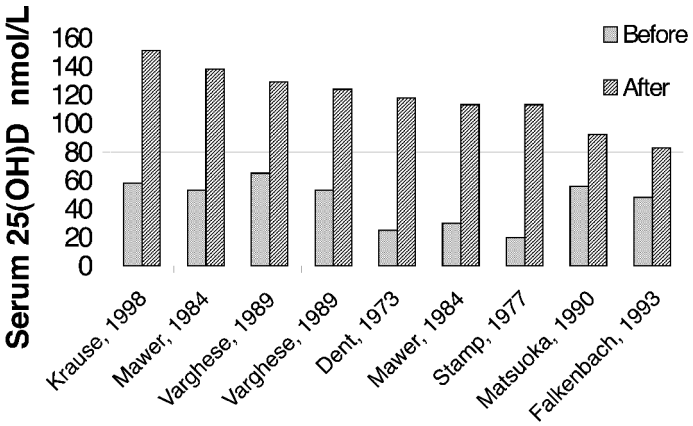

FIG. 1. Exposure of groups of adults to artificial ultraviolet light treatments, and its effect on their mean circulating 25-hydroxyvitamin D (25(OH)D) concentrations. Bars show concentrations before and after periods of treatment that were typically 2 weeks, and sorted according to the final 25(OH)D concentration attained. This is a graphical representation of 25(OH)D data extracted from the literature and converted to nmol l^{-1}, with the publication identified below the respective data [44, 86–92].

ULTRAVIOLET LIGHT, VITAMIN D INTAKE, AND EFFECTS ON 25(OH)D

The synthesis of vitamin D is a self-limiting chemical reaction whereby equilibrium is achieved between the production of precursors that will become vitamin D and the photo-catalytic breakdown of these precursors and vitamin D into inactive molecules [77]. Skin color does not affect the amount of vitamin D that can be generated. However, darker skin requires longer exposure. Very black skin requires about 1.5 hours, or six times longer than white skin, to reach the equilibrium for vitamin D production [78]. At least four studies have shown that ultraviolet light exposure of the full skin surface of an adult is equivalent to a vitamin D consumption of about 250 μg (10,000 IU) day^{-1} [79–82]. Lifeguards in the USA and Israel, as well as farmers in the Caribbean, exhibit serum 25(OH)D concentrations greater than 100 nmol l^{-1} [83–85]. Furthermore, even regular short periods in sun-tan parlors consistently raise serum 25(OH)D to beyond 80 nmol l^{-1} [86] (Fig. 1). The highest 25(OH)D concentrations in the groups of adults acquiring vitamin D physiologically (via ultraviolet light exposure) range up to 235 nmol l^{-1} [44, 83], and none of these studies implies that such 25(OH)D levels have caused hypercalcemia. Because humans evolved as naked apes at latitudes lower than 30 degrees from the equator, I contend that our genome was selected under conditions of such abundant vitamin D supplies [93]. As such, the substantially lower levels of 25(OH)D prevalent among modern humans must be accompanied by biological compromises, such as increased PTH secretion, and altered cellular metabolism of vitamin D metabolites. These compromises may have had long-term consequences on the health of modern humans.

If one relates the ultraviolet light-induced levels of 25(OH)D to the amount of vitamin D needed to achieve such levels (Fig. 2, Table 2), then lifeguards and farmers acquire the equivalent of at least 250 μg (10,000 IU) day^{-1} (or 0.25 mg day^{-1}) [92]. The official safety limit for vitamin D intake is properly referred to as the upper limit [122, 123], and this specifies 2000 IU day^{-1} [3]. However, the weight of published evidence on this point shows that the lowest dose of vitamin D proven to cause hypercalcemia in some healthy adults is 40,000 units day^{-1} [92]. This translates to 1000 μg (or 1 mg) taken daily for many months. If a consumer wanted to achieve this toxic dose, he or she would need to take 40

TABLE 2. Mean circulating 25-hydroxyvitamin D (25(OH)D; nmol l^{-1}) for groups of adults consuming specified amounts of vitamin D*

Authors (year)	Ref.	No. of subjects	Age (years)	Dose (mg day^{-1})	25(OH)D concentration	
					Initial	Final
Ooms *et al.* (1995)	[94]	177	80	10	27	62
Lips *et al.* (1996)	[95]	270	80	10	27	62
		96	80	10	27	54
McAuley *et al.* (1997)	[96]	10	76	10	25	43
Graafmans *et al.* (1997)	[97]	13	78	10	26	56†
		22	78	10	28	57†
		11	77	10	31	53†
Chel *et al.* (1998)	[81]	14	85	10	23	60
Dawson-Hughes *et al.* (1991)	[27]	123	61	13	42	63‡
O'Dowd *et al.* (1993)	[98]	23, 86	82	18	40	65
Dawson-Hughes *et al.* (1995)	[99]	123	63	20	46	69‡
Sebert *et al.* (1995)	[100]	91	83	20	7	35
Vanderklis *et al.* (1996)	[101]	29	61	10	59	90
		29	61	20	59	90
		21	74	10	85	108
		21	74	20	85	108
Lips *et al.* (1988)	[102]	47	82	10	24	69
		47	82	20	24	81
Chapuy *et al.* (1992)	[28]	1634	84	20	28	72‡
Chapuy *et al.* (1996)	[103]	45	86	20	6	41
Freaney *et al.* (1993)	[104]	29	74	20	13	25
McKenna *et al.* (1985)	[105]	33	80	20	6	79
Prestwood *et al.* (1999)	[106]		>70	20	50	52
Krieg *et al.* (1999)	[107]	50	62–90	22	30	66
KyriakidouHiminas *et al.* (1999)	[108]	10	>50	20	24	63
Dawson-Hughes *et al.* (1997)	[29]	90, 86	71	22	58	77‡
		184,174	72	23	42	77‡
Francis *et al.* (1996)	[109]	23	65–80	25	36	61
Sorva *et al.* (1991)	[110]	14	84	25	12	57
		5	84	25	13	57
Honkanen *et al.* (1990)	[111]	30	69	45	43	81
		33	82	45	24	64
MacLennan and Hamilton (1977)	[112]	11	68–92	13	22	53
		11	68–92	50	15	81
Himmelstein *et al.* (1990)	[34]	30	81	50	40	80
Nordin *et al.* (1985)	[113]	50	69.8	50	20	59§
Papapoulos *et al.* (1980)	[114]	7	various	75	5	69
Tjellsen *et al.* (1986)	[115]	19	33	100	75	113
Malabanan *et al.* (1998)	[116]		D2	175	43	88§
Davie *et al.* (1982)	[80]	9	21.2	10	17	58
		9	21.4	25	13	62
		8	22.5	250	13	125
Arthur *et al.* (1990)	[117]	6	>60	350	53	90§
Adams *et al.* (1999)	[118]	12	>50	350	25	60§
Stamp *et al.* (1977)	[88]	13	various	45	12	63
		14	various	250	24	113
		15	various	500	24	158
		16	various	1000	60	308
Mason *et al.* (1980)	[119]	6	various	1250		717
Barger-Lux *et al.* (1998)	[120]	13	<30	25	67	79
		10	<30	250	67	204
		14	<30	1250	67	942
Haddock *et al.* (1982)	[83]	14	various	1875		1708
Gertner and Domenech (1977)	[121]	6	various	500		442
		7		1000		647
		4		1375		723
		4		2000		1022

* Mean 25(OH)D concentrations in nmol l^{-1} (ng ml^{-1} = nmol l^{-1}/2.5) prior to, and after, consumption of vitamin D at the doses indicated (IU day^{-1} = mg day^{-1} × 40). Inclusion criteria are: adult subjects whose vitamin D intake was stated, and 25(OH)D concentration determined after at least 4 weeks of supplementation.

† Results for the three vitamin D receptor BSM1 genotypes.

‡ Results for 25(OH)D assay obtained by binding assay, without purification, and thus adjusted downward, multiplying by 0.69, as discussed elsewhere [122].

§ Vitamin D2 used, instead of vitamin D3. Note, vitamin D2 is less effective than vitamin D3.

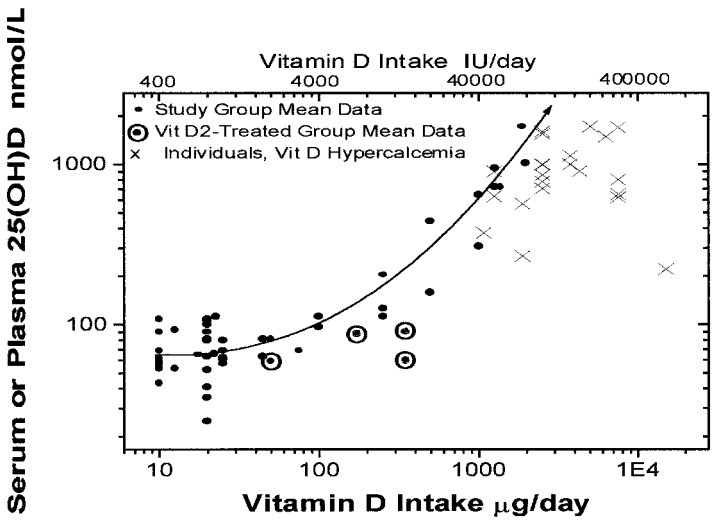

FIG. 2. Dose–response relationship between daily vitamin D intake and mean 25-hydroxyvitamin D (25(OH)D) concentration. Both axes are log scale. The solid points show the mean results for groups of adults consuming the indicated doses of vitamin D (Table 1), usually vitamin D3. The results for groups of adults who unambiguously consumed vitamin D2 are shown by the circled points. Vitamin D3 is about four times as potent as vitamin D2, based on tracing the circled points for subjects consuming vitamin D2 back to the trend line based on vitamin D3. The results represented by Xs are for individuals showing the classic hypercalcemic response to toxic levels of prolonged vitamin D consumption, as summarized elsewhere [11]. Note that the toxic intakes were in the form of vitamin D2, not D3.

of the 1000 unit pills (the highest dose available in North America without a prescription) every day for many months.

VITAMIN D TOXICITY AND SAFETY ISSUES

Like anything that has an effect on living things, vitamin D can be harmful if it is taken in excess. The margin of safety for vitamin D is similar to the safety margin of many other nutrients (including even water). I contend that the reason why vitamin D is thought of as toxic is that daily ingestion in the milligram range has caused harm, while milligram amounts of other nutrients are benign. Toxicity in normal adults requires intake of more than 1 mg day^{-1} (40,000 IU day^{-1}), which reflects amounts of vitamin D that are four times more than can be produced naturally by sunshine [92]. On the other hand, the current RDA for adults under the age of 50 years represents only about 2% of what people with white skin would be making if they lay in the summer sun for 20 min. Ten years ago, a dairy in the Boston area, servicing 10,000 households, made prolonged, gross errors in fortifying milk with hundreds of thousands of units (several milligrams) per quart. The case was published quickly [124] and covered by the media. The rigorous epidemiological follow-up was published later. That showed that the situation contributed to the deaths of two susceptible elderly people [125]. While hypercalcemia did occur, it was not widespread. By far the most susceptible group to the excess vitamin D was women over the age of 65 years, suggesting that diminished renal function may play a role. The average 25(OH)D concentration of the confirmed cases of vitamin D toxicity was 900 nmol l^{-1} (214 ng ml^{-1}) [125]; in comparison, physiologically attained 25(OH)D concentrations reach 235 nmol l^{-1} safely without hypercalcemia. When physiologically higher vitamin D

nutrition is associated with hypercalcemia, it reflects aberrant control of 25(OH)D-1-hydroxylase. This would reflect either primary hyperparathyroidism [126] or granulomatous disease [92].

If people with abundant sun exposure acquired an additional physiological amount of vitamin D (100 μg day^{-1}), their serum 25(OH)D concentrations would already exceed 150 nmol l^{-1} without the additional amount. Under these conditions, the pre-supplement supply of vitamin D would already be equivalent to about 250 μg day^{-1} [92]. The 25(OH)D response to a vitamin D dose behaves in a log-dose manner as presented in Fig. 2. As a further example, we reported that 25 μg day^{-1} of vitamin D resulted in average 25(OH)D concentrations of 69 nmol l^{-1}, while four times that amount increased 25(OH)D concentrations by only another 27 nmol l^{-1} [13] (Fig. 3). The increment with each additional amount of vitamin D becomes progressively smaller as the pre-dose 25(OH)D level increases. Thus, a further 100 μg day^{-1} would add marginally to what I regard as the inconsequential risk due to the 250 μg day^{-1} vitamin D supply that is physiological because it is obtainable through sun exposure. Because a long-term vitamin D consumption of at least 1000 μg day^{-1} would be needed to cause hypercalcemia, there is a large margin of safety with 100 μg day^{-1}. (I would welcome any discussion of evidence implicating harm with vitamin D3 (not D2) in adults at doses below 1000 μg day^{-1}. There is simply nothing published about this, except on infants.)

It is thought that because vitamin D is a fat-soluble vitamin, it must accumulate in adipose tissue. Thus, if adipose tissue was to break down, there is a theoretical possibility of a vitamin D influx. In our study, we could not detect a correlation between weight and the effect of a vitamin D dose on serum 25(OH)D [13]. In rats administered enough vitamin D to raise circulating 25(OH)D into the toxic range, it is possible to detect vitamin D in fat tissue [127]. Pharmacological amounts of vitamin D are toxic because they pre-occupy circulating vitamin D-binding protein (DBP) and the percentage of vitamin D that is free and unbound increases [92, 128]. At toxic doses, the freely circulating vitamin D and its metabolites accumulate not only in adipose [127] but also in muscle [129]. The 100 μg day^{-1} vitamin D we have used is physiological and far below the amount that could change the free fraction of its circulating metabolites due to saturation of DBP [130]. Thus, the deposition of vitamin D in adipose tissue would be no more than what will occur for people getting a lot of sun exposure.

We recently completed what could be regarded as a safety evaluation of vitamin D3 supplementation of normal adults, involving daily consumption of 100 μg (4000 IU). Contrary to what was reported by the Narang *et al.* study [131] used by the Food and Nutrition Board to establish the 50 μg day^{-1} (2000 IU day^{-1}) upper limit for vitamin D intake, there was no detectable change in serum or urine calcium [13, 123]. Figure 3 presents the 25(OH)D results obtained throughout the safety study. The 25(OH)D results for this kind of study are best looked at from the context of the lowest and the highest level attained with each dose, because the objectives for establishing nutritional guidelines focus on the lowest level of 25(OH)D 'ensured' by the given dose, while avoiding the possibility of risking an excess [24, 132]. When the results in all three figures presented in this review are compared, it is evident that consumption of vitamin D3 in an amount equivalent to 10–20 times the current AI or RDA recommendations [3] results in 25(OH)D concentrations that approach the upper range of what should be regarded as physiologically normal for adults.

CONCLUDING COMMENTS

The adult recommended dietary intake (be it RDA or AI) for vitamin D stems from an educated guess made in the 1960s, before its metabolism was clarified, and before it could be measured in the bloodstream [2]. Furthermore, dietary recommendations were aimed at preventing the childhood disease of rickets, and directed at nothing related to adults.

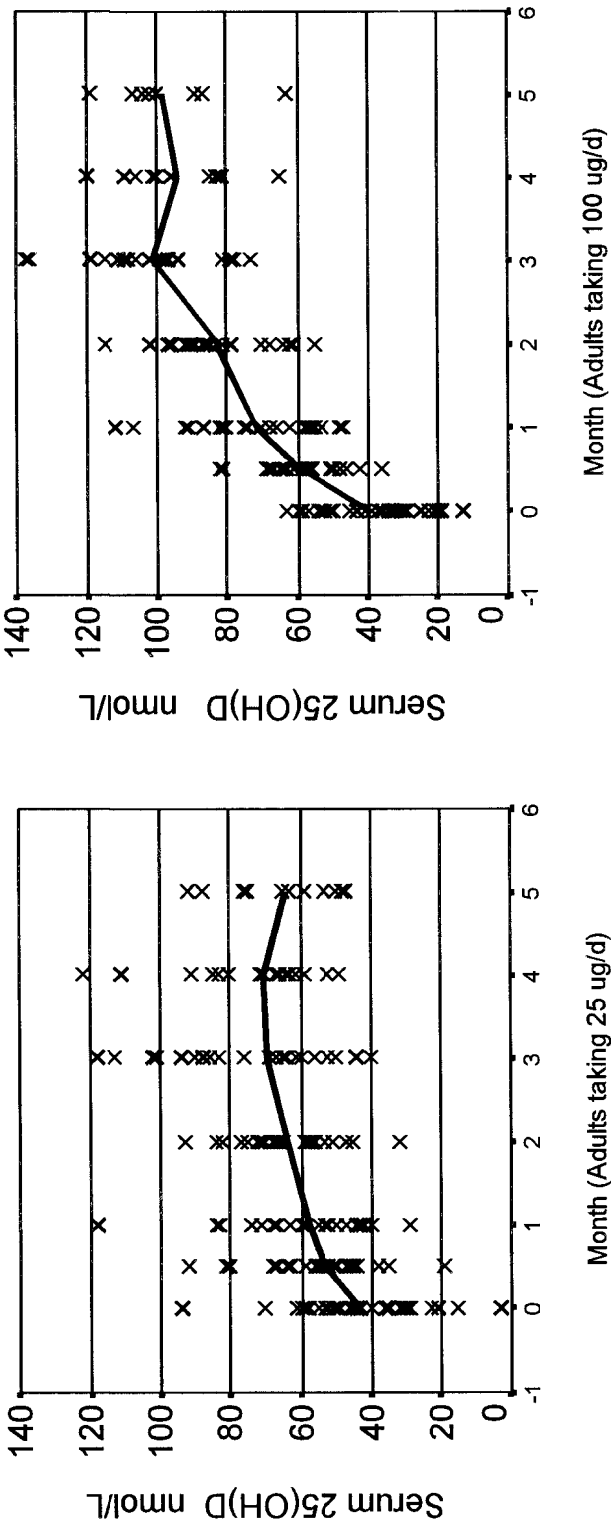

FIG. 3. Serum 25-hydroxyvitamin D (25(OH)D) concentrations of Canadian adults before and during vitamin D3 supplementation, beginning in January. Left panel, 25 mg day^{-1}; right panel, 100 mg day^{-1}. The study ended in June, and for co-workers not in the study, summertime mean 25(OH)D levels were 47 nmol l^{-1}.

TABLE 3. The clinical interpretation of serum 25-hydroxyvitamin D (25(OH)D) levels and the estimated intakes of vitamin D needed to ensure these levels (note the new units for vitamin D, where 1 μg = 40 IU)

	Deficiency (rickets and osteomalacia)	Insufficiency (increased PTH secretion, osteoporosis)	Sufficiency	Desirable (ensures 25(OH)D to match levels implicated in other health effects and suppress PTH)	Toxic/therapy (could increase urine and serum calcium)
Serum 25(OH)D nmol l^{-1}	0–25	25–40	40–100	75–160	> 220
Vitamin D3 mg day^{-1} needed to reach the 25(OH)D above					
Dietary guidelines [3]	0	5–10	5–20	not stated	≥ 95
From evidence reviewed [13, 92]	0–5	10–15	25–100	100–250	> 1000 (> 40,000 IU)

PTH, parathyroid hormone.

Long-standing, mild insufficiency of vitamin D is now recognized as one cause of osteoporosis, and low amounts of vitamin D probably increase the risk of a wide variety of diseases. We can now quantify vitamin D nutrition by testing circulating 25(OH)D concentrations, and it is obvious that the guesses about adult vitamin D requirements made almost 40 years ago are far too low for adults. Still, they remain the dogma for current nutritional guidelines around the world. Table 3 summarizes two views of the relationship between long-term vitamin D intake and the anticipated range of 25(OH)D concentration associated with it.

Another complication entering the vitamin D picture is our cultural response towards sunlight. We are becoming progressively more sun-avoiding because of the fear of skin cancer, and a cultural preference by some of us to prevent skin from darkening. For older adults, sunlight is more harmful, and of less value in terms of vitamin D, because less of it is produced when skin is exposed to the sun.

The solution to the problem of diminished vitamin D nutritional status is to supplement with more vitamin D than we have been—with at least 25 μg day^{-1} (1000 IU day^{-1}) not just during the winter, but all year. Vitamin D is safe, inexpensive and, with calcium, of proven effectiveness for bone health.

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