

# Why the optimal requirement for Vitamin D<sub>3</sub> is probably much higher than what is officially recommended for adults<sup>☆</sup>

Reinhold Vieth\*

*Department of Laboratory Medicine and Pathobiology, University of Toronto, and Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Canada M5G 1X5*

## Abstract

The physiologic range for circulating 25-hydroxyvitamin D<sub>3</sub> [25(OH)D; the measure of Vitamin D nutrient status] concentration in humans and other primates extends to beyond 200 nmol/L (>80 ng/mL). This biologic “normal” value is greater than current population norms for 25(OH)D. Concentrations of 25(OH)D that correlate with desirable effects extend to at least 70 nmol/L, with no obvious threshold. Randomized clinical trials using 20 mcg (800 IU) per day of Vitamin D show that this suppresses parathyroid hormone, preserves bone mineral density, prevents fractures, lowers blood pressure and improves balance. Calcium absorption from diet correlates with 25(OH)D in the normal range. Health effects of Vitamin D beyond osteoporosis are mostly supported by the circumstantial evidence of epidemiologic studies and laboratory research. These include prevention of cancer and the autoimmune diseases, insulin-dependent diabetes and multiple sclerosis. One mcg per day of Vitamin D<sub>3</sub> (cholecalciferol) increases circulating 25(OH)D by about 1 nmol/L (0.4 ng/mL). A recommended dietary allowance (RDA) is the long-term daily intake level that meets the total requirements for the nutrient by nearly all healthy individuals (it would presume no sunshine). If 70 nmol/L is regarded as a minimum desirable target 25(OH)D concentration, then current recommendations of 15 mcg per day do not meet the criterion of an RDA.

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*Keywords:* Calcium; Vitamin D<sub>3</sub>; Hypertension; Evolution; Environment; Skin

## 1. Introduction

For most vitamins, dietary intakes offer a reasonable reference point for how much people might be need. For Vitamin D, we cannot use dietary intake as a guide, because except for fish, our diets do not provide enough to prevent rickets or osteomalacia. We must take a unique approach to determine a Vitamin D requirement. The first step is to accept the fact that there has never been an objective basis for currently recommended intakes of Vitamin D for adults [1–3]. We need to return to an earlier concept, and think of Vitamin D as “the sunshine vitamin”, and ask what minimal level of 25-Hydroxyvitamin D (25(OH)D) is physiologic for our species and which prevents disease; lastly, we need to decide on what Vitamin D consumption ensures that 25(OH)D level.

I begin from the perspective of the 25(OH)D levels of our closest mammalian relatives, other primates. All published 25(OH)D concentrations for healthy, non-human primates

are at or beyond the top of what we currently regard as the “normal” range for humans (Fig. 1) [4]. However, normal 25(OH)D values of modern adults are closer to concentrations in laboratory rodents [10–12]. Is this a situation we should feel comfortable with?

During our evolution, requirements for the sunshine vitamin were satisfied by the life of the naked ape in her or his tropical environment. That sun-rich environment is what our biology was effectively designed for, through evolution. Therefore, is it not possible that there might toxic consequences to the relatively sun-deprived—Vitamin D-deprived—culture of modern society that includes clothing to cover 95% of our Vitamin D-forming skin surface, avoiding time in the sun, and migration to wintery, temperate climates? The list of potential health consequences of modern life must include the diseases whose prevalence correlates with latitude and UVB exposure. These include hypertension [13], greater risk of breast, colon, and prostate cancers [14–16], multiple sclerosis [17–19], and diabetes [20]. These may even include chronic fatigue [21], and metabolic syndrome [22,23].

The preceding associations are for the most part, based on cross-sectional or case–control epidemiologic data. Many

<sup>☆</sup> Presented at the 12th Workshop on Vitamin D (Maastricht, The Netherlands, 6–10 July 2003).

\* Tel.: +1-416-586-5920; fax: +1-416-586-8628.

E-mail address: [rvieth@mtsinai.on.ca](mailto:rvieth@mtsinai.on.ca) (R. Vieth).

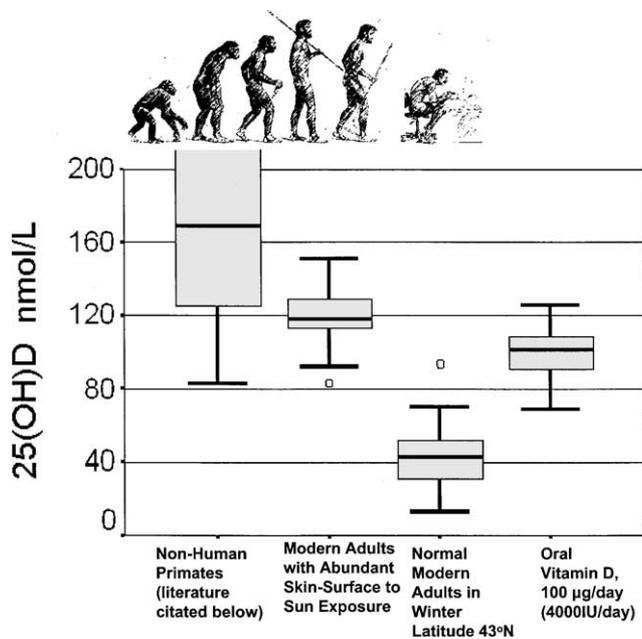


Fig. 1. Summary of historical aspects of circulating 25(OH)D concentrations in non-human primates and in modern adults, and effect of 100 mcg Vitamin D<sub>3</sub> per day. The cartoon across the top of the figure represents stages of evolution and human development for the data presented in the box plots. Since modern humans evolved in tropical regions and without clothing, early Vitamin D nutrition would have been similar to that of modern humans living under conditions of high UVB exposure. Results shown for non-human primates [5–9] and for sun-rich adults, and those given artificial tanning sessions as cited previously [2] are published mean values. Data for modern adults in winter and their responses to Vitamin D are from hospital workers in Toronto, Canada [10]. The whiskers show the lowest and highest values for the data summarized, the boxes show the range of the central 50% of the sample group, with a line indicating the median value. This figure is based on one published previously, R Vieth, in Bone Loss and Osteoporosis in Past Populations: an Anthropological Perspective. Editors Sabrina C. Agarwal and Samuel D. Stout. Publisher, Kluwer Academic Plenum, used with permission.

of these are also supported by laboratory research showing biologic mechanisms to explain why the concentration of 25(OH)D may affect disease. Various human tissues possess 25(OH)D-1-alpha-hydroxylase [24–29]. With this enzyme, 1,25(OH)<sub>2</sub>D can be produced locally, in a paracrine manner, and cells respond to this. For primary cultures of prostate cells, the antiproliferative effect of 25(OH)D occurred at 100 nmol/L, a physiologic concentration, but with 1,25(OH)<sub>2</sub>D, the effect occurred at 10 nmol/L, which is 100 times physiologic [30]. A study of adult colon biopsies by Holt et al showed that higher serum 25(OH)D concentrations were highly significantly correlated with decreased whole-crypt labeling index and the size of the proliferative compartment (phi h) for 25(OH)D ranging to 150 nmol/L (60 ng/mL). There were no correlations between serum levels of 1,25(OH)<sub>2</sub>D and the proliferative parameters [31].

It has been argued that because some prostate-cancer cell lines exhibit diminished 25(OH)D-1 alpha-hydroxylase (CYP27B1) activity, therefore 1,25(OH)<sub>2</sub>D or analogs of that hormone are probably more useful therapeutic op-

tions than Vitamin D nutrition [32]. An important—and unique—feature of CYP27B1 not taken into account by this theory is that the in vivo Michaelis–Menten constant ( $K_m$ ) of the enzyme exceeds the physiologic range of 25(OH)D concentrations [33,34]. Therefore, a lower amount of CYP27A1 enzyme can be overcome by higher substrate, 25(OH)D, concentrations. Diminished enzyme in cells may be a sign that those cells require HIGHER 25(OH)D concentrations. The epidemiology of prostate cancer shows that risk of cancer is related to diminished sunshine, i.e. lower 25(OH)D (note, Vitamin D nutrition does not normally affect circulating 1,25(OH)<sub>2</sub>D levels [35]). The cellular mechanism for cancer-preventive effects involves the paracrine production and action of 1,25(OH)<sub>2</sub>D. The underlying biology points to a need for clinical trials that focus on Vitamin D nutrition [16], not just deltanoid analogs.

Why administer a paracrine hormone (1,25(OH)<sub>2</sub>D or its analogs) to the whole body, when we can facilitate local, tissue-specific production of 1,25(OH)<sub>2</sub>D simply by providing more Vitamin D? To my knowledge, research relevant to this question has not been published. This is probably because Vitamin D has had a reputation for toxicity, but in recent years concern about toxicity at physiologic doses, up to 250 mcg per day, has been overcome [2,10,36–38]. Unlike the deltanoid analogs, Vitamin D<sub>3</sub> (cholecalciferol) is remarkably non-calcemic, and safe. However, because it is a nutrient, use of Vitamin D continues to be subject to the medico-legal constraints that do not seem to have much effect on research into deltanoid drugs derived from the Vitamin D molecule; i.e. it is easier for a clinical researcher to use 1,25(OH)<sub>2</sub>D and its analogs at doses near the point where they do cause hypercalcemia, than it is to use Vitamin D at intakes that are safe. This is largely because the hypercalcemic dose of Vitamin D is still defined officially as 95 mcg per day, a value that is simply wrong [39]. According to the Food and Nutrition Board, the safety limit (no adverse effect level, NOAEL) is 60 mcg per day [40], and after applying a margin of safety, 50 mcg per day is the upper limit (UL) for intake by the general public [36]. These definitions make it difficult to use meaningful doses of Vitamin D in research studies for prevention or treatment disease. Clinical research into the use of physiologic doses of Vitamin D is also constrained by a lack of the industrial research support that flows to studies of proprietary analogs. Many physicians presume that because there is no evidence from randomized clinical trials showing efficacy of Vitamin D (cholecalciferol) for anything beyond osteoporosis, this molecule either lacks potency or it has too narrow a therapeutic window to be useful. There is no other way to explain the lack of progress in this field.

## 2. Vitamin D and osteoporosis

Osteoporosis is the one area where there is strong evidence that official recommendations for Vitamin D intake

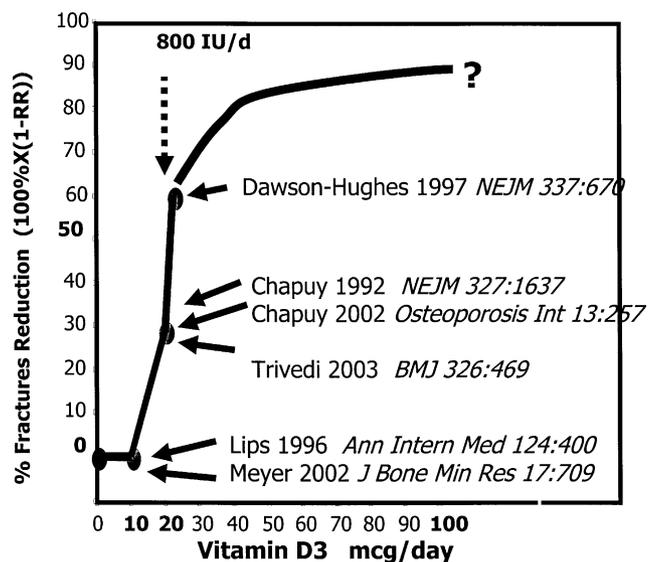


Fig. 2. Dose–response curve, summarizing randomized-control clinical trials of fracture-prevention using Vitamin D, with or without calcium. None of the studies using doses of Vitamin D<sub>3</sub> providing less than 20 mcg per day was effective in reducing fracture risk [41,42]. However, all the studies in which there was a reduction in fracture risk used approximately 20 mcg per day of Vitamin D<sub>3</sub> [43–46]. This dose includes the known background intake; for the work by Dawson-Hughes background intake, this was 5 mcg per day [44]. The question mark is included in the figure to emphasize that there have been no studies looking at effects of Vitamin D<sub>3</sub> beyond 20 mcg per day.

are too low. Fig. 2 summarizes randomized control trials of Vitamin D, with or without calcium on fracture prevention in older adults. There are no studies showing efficacy of Vitamin D at less than 20 mcg (800 IU) per day, yet official recommendations for Vitamin D intake by adults continue to be lower than this [40]. The studies using less than 20 mcg per day failed to prevent fractures [42,47]. Two randomized, controlled studies show that Vitamin D<sub>3</sub> given by itself in doses of 2500 mcg (100,000 IU) every 4 months [46], or 750 mcg annually [48] reduces the occurrence of fractures. Three studies now show that the combination of calcium and 20 mcg Vitamin D together lower fracture risk in adults older than age 65 [43–45]. Fracture risk appears to be reduced by about a third even without detectable changes in bone density to account for the fewer fractures [44]. The explanation appears to be that 20 mcg per day of Vitamin D improves muscle strength and balance [49,50]. Cross-sectional work shows similar benefits of Vitamin D nutrition in elderly attending a falls-clinic. Those with serum 25(OH)D levels <28 nmol/L had impaired balance, reflexes, and more falls than those with 25(OH)D over 44 nmol/L (>17.5 mcg/L) [51]. Unfortunately, there have been no randomized control trials of any condition involving Vitamin D<sub>3</sub> dosages beyond 20 mcg per day (Fig. 2).

Several reports show that active absorption of calcium through the gut correlates better with 25(OH)D concentrations than it does with 1,25(OH)<sub>2</sub>D [52–54]. This relationship does not appear to reach a plateau, so that an “optimal”

25(OH)D concentration cannot be determined from this. This suggests that the dietary requirement for calcium may decrease as 25(OH)D concentrations increase. Likewise, a recent cross-sectional study showed that the correlation between BMD and 25(OH)D concentrations is linear, and without a threshold, i.e. “BMD continued to rise beyond 94 nmol/L” [55].

### 3. Conclusion

The perspectives of evolution, epidemiology, molecular and cellular biology all point to 25(OH)D concentrations higher than 70 nmol/L as being natural, and beneficial to various aspects of human health. Recommendations for adult Vitamin D intake in Europe range from 0–10 mcg per day, depending on country [56] and in the North America, they range from 5–15 mcg per day, depending age [40]. Since it is well established that 1 mcg per day increases 25(OH)D by an average of 1 nmol/L (0.4 ng/mL) [10,38], it is impossible to imagine that Vitamin D intakes of 5–15 mcg per day can have more than a marginal effect on the health of adults [57–60]. Recently, the Osteoporosis Society of Canada recommended that all adults should be consuming at least 20 mcg/d of Vitamin D [61]. This may be the first recommendation for Vitamin D intake by a national group that is consistent with published randomized controlled clinical trials. A recent meeting aimed at defining a consensus for Vitamin D intake for osteoporosis concluded (with one dissention) that the 25(OH)D concentration should exceed 70 nmol/L and that this would require an average Vitamin D intake of 20–25 mcg per day [62]. Optimal amounts of Vitamin D for other aspects of human health are probably higher still, and their definitions await the appropriate clinical research data.

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