Vitamin D

Introduction

Vitamin D is required in quantities smaller than any other fat-soluble vitamin. The major forms of vitamin D are vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Vitamin D has been described as a pro-hormone or sunshine-dependent vitamin. Some dietary vitamin D_2 comes from plants, but the largest contribution to dietary intake of vitamin D is the vitamin D_3 in fish liver oils, eggs, milk, and liver. Milk is commonly fortified with 10 μg (400 IU) of vitamin D_3 per quart. Extremely high potency (40,000 to 50,000 IU) products—sold as prescription or sometimes over the counter—often consist of vitamin D_2. Most vitamin D dietary supplements contain vitamin D_3. The conversion of international units to metric weights is extremely simple for both vitamin D_2 and D_3: 1 μg equals 40 IU; 0.025 μg equals 1 IU.

Vitamin D_3 (or D_2) from endogenous production, foods, or vitamin supplements is inert and must undergo two hydroxylation reactions in the body for activation. The first occurs in the liver and the second in the kidneys. The first hydroxylation produces 25-hydroxy vitamin D (25[OH] D) and the second produces the active hormone 1,25-dihydroxy vitamin D (1,25-di[OH]D). Because the plasma half-life of the active form 1,25-di(OH)D is short (approximately 15 hours), the best indicator of vitamin D status is 25-(OH)D (plasma half-life of 15 days or so). Because of these pharmacokinetics, most vitamin D in plasma is present as 25(OH)D, also called calcidiol, and its concentration has become the standard index of vitamin D status. 1,25-di(OH)D (calcitriol), the activated vitamin, regulates intestinal absorption and plasma concentration of calcium. As calcitriol, vitamin D is fundamentally involved in the formation of bone, and so its deficiency can lead to rickets in children or osteoporotic changes in adults.

Bioavailability

Although it can be synthesized in the body with sufficient exposure to sunlight or another ultraviolet (UV) light source, most people are not exposed to such UV light in consistent and

sufficient quantities. No extra vitamin D is required when skin exposure to UV light is ample; but without such exposure, a person is completely dependent on ingested vitamin D. The UV component of sunlight converts internally produced 7-dehydrocholesterol naturally present in the skin to cholecalciferol (vitamin D_3) (Life Sciences Research Office [LSRO] 1978; Holick 1999).

Although adequate UV light exposure can provide sufficient vitamin D, many elderly persons have limited sunlight exposure, inadequate dietary sources, and a decreased ability to activate vitamin D, making them susceptible to vitamin D deficiency (Gloth et al. 1995; Holick 1999). Elderly people are likely to have substantially increased needs for dietary vitamin D because of their decreased mobility and exposure to sun and decreased activation in the liver and kidneys.

Thus, the nutritional need for dietary vitamin D depends on the biosynthesis in the skin, which in turn is influenced by time of exposure to sunlight, season (sun intensity and clothing), latitude, skin pigmentation, and the use of sunscreens.

Safety Considerations

The formation of vitamin D in the skin is slowed once dietary vitamin D intakes are sufficient and blood levels of the activated forms are high. Therefore, excess exposure to sunlight does not lead to vitamin D toxicity (Holick 1999; Hathcock et al. 2007).

Dietary vitamin D can, however, produce toxic effects when consumed in very large quantities, especially over an extended period of time. Studies have shown that subjects with abnormally high levels of vitamin D intake can suffer from a wide range of signs and symptoms, from dehydration to permanent mineral deposits in soft tissues, including muscle, heart, kidney, and cartilage. Continued intake of toxic levels can have severe and persistent adverse consequences. The widespread occurrence of vitamin D overdoses in British children just after World War II, caused by consumption of excessively fortified milk, led health professionals to be extremely conservative in estimating safe levels for vitamin D.

Prolonged intake of excess vitamin D may lead to predictable increases in plasma 25-hydroxy vitamin D concentrations (Institute of Medicine [IOM] 2011), and the increase is directly proportional to the vitamin D dose (Barger-Lux et al. 1998). Treatment with vitamin D or 25-hydroxy vitamin D does not generally increase the serum concentrations of the active metabolite (calcitriol, 1-alpha,25-dihydroxycholecalciferol, or 1,25-dihydroxy vitamin D) (Barger-Lux et al. 1998). Nonetheless, excess vitamin D can have toxic effects, perhaps because of the increases in blood concentrations of 25-hydroxy vitamin D, a form that can overstimulate intestinal absorption of calcium and cause excessive calcium mobilization from bone and hypercalcemia (Norman 1996; Holick 1999). Although the IOM considers hypercalcemia to be the critical effect in vitamin D toxicity, no clinical trials have used levels sufficiently high to produce such high blood levels of calcium. All such evidence comes from reports of anecdotal cases of accidental massive overdoses.

The amount of daily vitamin D ingestion needed to produce adverse effects varies widely. In most adults, daily intake in excess of 50,000 IU (1.25 mg) is needed to produce toxicity (Miller and Hayes 1982). Clinical trials in the last decade or so have found no hypercalcemia in subjects in subject taking 10,000 IU (250 µg) in long-term clinical trials. In certain disease conditions such as sarcoidosis, mycobacterium infections such as tuberculosis, or idiopathic hypercalcemia, toxicity can occur at levels of vitamin D intake lower than those in healthy persons. A causal relationship between excess vitamin D intake and hypercalcemia is unlikely, although people with idiopathic hypercalcemia may be subject to adverse effects of vitamin D at lower intakes than are comfortably tolerated by healthy individuals (Expert Group on Vitamins and Minerals [EVM] 2003).

Body size matters. One study has found that in children of unspecified body weight (probably between 10 and 30 kg), the amount of dietary vitamin D causing adverse effects may be as low as 2,000 to 4,000 IU (50 to 100 µg) per day. In full-term infants, adverse effects are reported to occur with intakes as low as 1,800 IU (45 µg) per day (Chesney 1989), but no adverse effects occurred in a 6-month study of infants given 1,600 IU per day (Fomon et al. 1966). Numerous reports confirm a variety of adverse effects at very high intakes when vitamin D is used as a drug, whether administered parenterally or in activated forms (Nanji 1985; Goldman and

Wheeler 1987; Schwartzman and Franck 1987; Allen and Shah 1992; Boulard et al. 1994; Oymak et al. 1994; Matsukawa et al. 1995). These circumstances do not relate to the usual oral intakes of vitamin D from foods or dietary supplements, and such reports provide no useful information about the safety of dietary sources of vitamin D.

Official Reviews

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM did not find the data sufficiently compelling to identify a NOAEL or a LOAEL. Instead, it set a guidance level of 25 μg, based on studies by Vieth et al. (2001) at 100 μg and Johnson et al. (1980) at 50 μg. The EVM concluded that long-term use of supplements of 25 μg is "well tolerated," but did not establish a safe upper limit.

IOM (2011). The IOM has established a UL of 100 μg (4,000 IU) vitamin D, based on downward extrapolation from the NOAEL of 250 μg (10,000 IU), as derived from multiple clinical trials in a risk assessment using UL methodology (Hathcock et al. 2007). To take into account uncertainties from emerging data regarding all-cause mortality, chronic disease risk, and falls at serum 25(OH)D levels of approximately 75 to 125 nmol per L, the IOM considered the findings of Heaney et al. (2003) in establishing a UL. In this study, intakes of 5,000 IU vitamin D per day for 160 days resulted in serum 25(OH)D levels that did not exceed 150 nmol per L and serum calcium levels within normal ranges. The UL was set at 20 percent below 5,000 IU (i.e.¸4,000 IU) because of the uncertainties surrounding the data and the reliance on one study. The IOM intended "not to determine that certain levels of intake definitively cause harm, but rather to decide whether the emerging data were sufficiently compelling to warrant caution relative to vitamin D intakes."

The IOM approach, however, did not take into account the ample caution built into the NOAEL and the UL method in the peer-reviewed literature (Hathcock et al. 2007). In addition, the IOM examined the data related to several endpoints but based their UL of 4,000 IU on only one of several different adjustments of the data on all-cause mortality in several different age, gender, and disease groups (Visser et al. 2006).

For example, Figure 6-1 of the IOM report graphs the hazard ratio of all-cause mortality against serum 25(OH)D (nmol per L), with adjustments for various health and age factors. All risk curves are high when vitamin D status is low and progress downward to low points as vitamin D status increases. Although the two right side points are equal, there is no hint of a reverse J-shape to the curves—and thus no indication that that vitamin D status up to 82 nmol per L causes any harm.

Figure 6-2 plots relative risk of death in elderly people against baseline serum 25(OH)D, graphed with four different adjustments for factors that could influence health. Only Model 4 shows definite increases in risk as serum 25(OH)D reaches 75+ nmol per L. This model adjusts the data for gender, age, education, chronic disease, serum creatinine concentration, and lifestyle variables including smoking status, alcohol consumption, and physical activity; it adjusts for all these plus frailty indications including physical activity, low serum albumin concentration, and low serum total cholesterol concentration.

Figure 6-3 displays the results of adjustment to the data similar to that in Figure 6-2's Model 4, and there is no increase in risk with serum 25(OH)D concentrations up to 80.3+. There was no discussion of the likelihood of a random "significant" effect when more than 20 adjustments are made to the primary data.

EFSA (2012). EFSA considered that a daily vitamin D dose of 250 µg per day reflects a NOAEL, based on two studies in which doses of 234 to 275 µg vitamin D_3 per day for 8 weeks to approximately 5 months did not result in hypercalcemia in healthy young men (Barger-Lux et al. 1998; Heaney et al. 2003). A UF of 2.5 was applied to account for the variation in the sensitivity of the population to potential adverse effects of long-term vitamin D exposure, the short duration of the studies, as well as the small number and characteristics (healthy young men with minimal sun exposure) of the individuals studied. The UL was therefore estimated to be 100 µg per day.

CRN Recommendations

The traditional—but not data-based—conservatism of vitamin D recommendations is rapidly being corrected to evidence-based assessments. These assessments indicate that larger amounts are now considered safe for most persons.

The data by Heaney and coworkers (2003) indicate that the NOAEL for vitamin D is at least 250 µg (10,000 IU). Thus, from the available data, the LOAEL is greater than 250 µg per day in relation to its hypercalcemic effects. The IOM and EVM estimate vitamin D intakes from all nonsupplement sources to be in the range of 360 IU (9 µg) or less. Many dietary supplements that include vitamin D contain 10 µg (labeled in the U.S. as 400 IU) or less, although some recent formulations contain 600 to 800 IU. There are no reports of adverse effects at these levels of intake. It is noteworthy that hypercalcemia has never been observed in a causal relationship to vitamin D in a randomized clinical trial. All the evidence for vitamin D causing hypercalcemia comes from anecdotal reports of accidental or misinformed consumption of much higher amounts.

With recent clinical trial data in mind, the CRN UL for supplements is identified as 250 µg (10,000 IU), based on the absence of adverse effects at this level of supplementation in clinical trials of sufficient size and duration and under a variety of conditions (Hathcock et al. 2007; IOM 2011). Having confidence in the safety of the 250 µg intake level, CRN does not consider this NOAEL µg to need adjustment by application of a UF (i.e., a UF of 1.0 is applied). Thus, CRN sets the UL for supplements at 250 µg (10,000 IU).

Quantitative Summary for Vitamin D

CRN UL, supplemental intake	250 µg (10,000 IU)/day
IOM UL, total intake	100 µg (4,000 IU)/day
EFSA UL, total intake	100 µg (4,000 IU)/day
EC supplement maximum	Not determined
EVM, guidance level, supplemental intake	25 µg (1,000 IU)/day

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