【W1-2】

Circulating 25(OH)D Levels Indicative of Vitamin D Sufficiency: Implications for Establishing a New Recommended Intake for Vitamin D.

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Accepting the fact that widespread use of the sun to meet our needs with respect to nutritional vitamin D requirements is unlikely, what are we to do? Most healthcare providers would simply suggest taking a multivitamin supplement and assume it will satisfy your requirement for vitamin D. This is a dangerous assumption to make as we now know that the current AI of 400 IU/day to be grossly inadequate for the majority of the population. Let us review how the 400 IU/day AI for vitamin D was determined.

Before 1997, the RDA for vitamin D in infants and children was 400 IU (1). In essence, the scientific basis for this dose was that it approximated what was in a teaspoon of cod-liver oil and had long been considered safe and effective in preventing rickets (2). The basis for the adult vitamin D recommendation is totally arbitrary. Forty years ago, an expert committee on vitamin D provided only anecdotal support for what if referred to as "the hypothesis of a small requirement" for vitamin D in adults, and it recommended one half the infant dose to ensure that adults obtain some from the diet (3). In England, an adult requirement of only 100 IU/day was substantiated on the basis of findings in 7 adult women with severe nutritional osteomalacia whose bones showed a response when given this amount (4). The adult RDA of 200 IU/day was described as "a generous allowance" in the 1989 version of American recommended dietary allowances (1). What is truly remarkable is that the basis for these recommendations was made before it was possible to measure the circulating concentration of 25(OH)D, the indicator of nutritional vitamin D status (5,6).

Equally important with respect to daily vitamin D intakes is the lowest observed adverse effect level (LOAEL). Again, there is a lack of evidence to support statements about the toxicity of moderate doses of vitamin D. For instance, in the 1989 RDA, it is stated that five times the RDA for vitamin D may be harmful (1). This recommendation relates back to a 1963 expert committee report (3), which then refers back to the primary reference, a 1938 report in which linear bone growth was suppressed in infants given 1,800-6,300 IU vitamin D/day (7). This study was not conducted in adults, and thus, does not form a scientific basis for a safe upper limit in adults. There are many more instances of inept science being translated into recommendations relating to vitamin D intake that appear in previous reviews (8-10).

Recent reports by Vieth, et al (11), Heaney, et al (12), and Hollis and Wagner (13) have proven the previous recommendations and claims to be largely incorrect. As originally stated by Vieth (14), we have yet to find published evidence of toxicity in adults from an intake of 10,000 IU/day vitamin D that is verified by a circulating 25(OH)D concentration. Figure 1 displays the relationship between dietary vitamin D intake and circulating 25(OH)D levels. This is an historical figure prepared from previous studies (14). It clearly shows vitamin D intakes of >10,000 IU/day are required to elevate circulating 25(OH)D into a harmful range. Thus, the AI and LOAEL for vitamin D in the adult have been established with insufficient scientific evidence and require correction through sound scientific study. Such studies have recently begun to appear in the scientific literature (11-13).

A question that has intrigued our group for years is the following: How is it possible that the dietary recommendations for vitamin D is the same for a 1-kg premature infant, a 3.5-kg term infant and a 90-kg adult? The recommendation for all three of these groups is 400 IU/day! You would think that policymakers who continue to make the current recommendations would have considered this question. To answer this question, it is necessary to ascertain the effect of a daily intake of 400 IU vitamin D/day on circulating 25(OH)D levels in infants and adults. We published the results of a study in infants more than a decade ago (15). A 400 IU/day dose promoted a significant increase in circulating 25(OH)D levels that was more pronounced in the preterm infant group (15). Thus, a daily dose of 400 IU vitamin D appears to be effective in raising the 25(OH)D concentration to the normal range for infants (80-200 nmol or 32-80 ng/mL).

Conversely, what effect does a 400 IU/day dose of vitamin D for an extended time (months) have in adults? The answer is little or nothing. At this dose in an adult, the circulating 25(OH)D concentration usually remains unchanged or declines. This was first shown in both adolescent girls and young women (16,17). The most recent publication with respect to the futility of the current adult DRI for vitamin D was published by Datta, et al (18). These investigators studied 160 pregnant minority women in the United Kingdom. The women were provided with 800-1,600 IU/day vitamin D for the duration of their pregnancies. The investigators found a mean (± S.D.) increase in circulating 25(OH)D concentrations (nmol) from 14.5 ± 2.25 at the beginning of pregnancy to 28.0 ± 15.8 at term following vitamin D supplementation. In other words, mothers who were vitamin D deficient at the beginning of their pregnancies were still deficient at term after being supplemented with 800-1,600 IU vitamin D/day throughout their pregnancies. This result is precisely what the regression analysis from Heaney, et al (12), predicted would happen at this level of vitamin D intake—continued vitamin D deficiency that is a huge public health problem around the globe.

So, the question is, what vitamin D intake is required to maintain or preferably improve the nutritional vitamin D status in adults, including those who are pregnant or lactating? This is a complex scientific question, yet recent, well-controlled studies have provided some provisional answers (11-13). Remember from the previous discussion that humans evolved utilizing sun exposure to endogenously generate tens of thousands of IU's of vitamin D_3/day. So, in light of the above facts, an AI of 400 IU/day is woefully inadequate and basically insignificant with respect to maintaining normal circulating concentrations of 25(OH)D in adults with minimal solar exposure.

On the basis of 25(OH)D concentrations in sun-replete adults, what vitamin D intake is required to sustain an adequate nutritional status of vitamin D? In Caucasians who experience significant solar exposure to the body routinely, this is not an important question. As a population, however, our unprotected exposure to the sun is declining rapidly because of the fear of skin cancer and premature aging resulting from public education campaigns. For persons of color, the problem is obvious. What do we do? The answer is, we modernize the AI for vitamin D so that the intakes actually have physiologic meaning.

The first study to address this topic of modernization was published by Vieth, et al (12) in 2001. In this study, the investigators supplemented healthy adults with up to 4,000 IU/day vitamin D_3 for a period of 5 months. Circulating 25(OH)D levels increased substantially into a mid-normal range and not a single adverse event or episode of hypercalciuria was observed. In an even more detailed report, Heaney, et al (11), studied 67 men divided into 4 groups that received 200, 1,000, 5,000 or 10,000 IU/day vitamin D_3 for 5 months. The results from this study are displayed in Figure 2. The 200 IU/day group failed to maintain circulating 25(OH)D concentrations during the study period. The remaining 3 groups responded in a dose-response fashion with respect to elevations in circulating 25(OH)D concentrations. From the data in Figure 10, using regression analysis, it has become possible to calculate a response of circulating 25(OH)D from a given oral intake of vitamin D. The data show that for every 40 IU of vitamin D intake, circulating 25(OH)D increases by 0.70 nmol (0.28 ng/mL) over 5 months on a given regimen. Note that a steady-state appears to be achieved after ~90 days of each dose tested (11,12). Thus, doses of 400, 1,000, 5,000 and 10,000 IU/day for 5 months will result in theoretical increases in circulating concentrations of 7, 17.5, 70, and 175 nmol 25(OH)D, respectively. Again, no adverse events were noted.

Our laboratory has conducted similar studies in lactating women (13). The data from this study is displayed in Figure 3. The results are similar to the Vieth, et al (11), and Heaney, et al (12) studies. We noted that the breastfeeding infants of the mothers receiving 4,000 IU/day vitamin D_2 had a substantially improved nutritional vitamin D status due to their transfer of vitamin D into the mothers' milk (Figure 4). No adverse effects have been noted.

Given the results of these recent scientific studies that evaluated high-dose vitamin D supplementation, it appears that the current AI and LOAEL for adults are woefully inadequate, misleading and potentially harmful. Again, it is important to point out that when I refer to high-dose vitamin D supplementation, it is high compared to the current AI of 400 IU/day, which is extraordinarily low compared to endogenous production during sun exposure. In truth, the actual AI for vitamin D in the adult could exceed 2,000 IU/day. Only future research will provide us with the answer.

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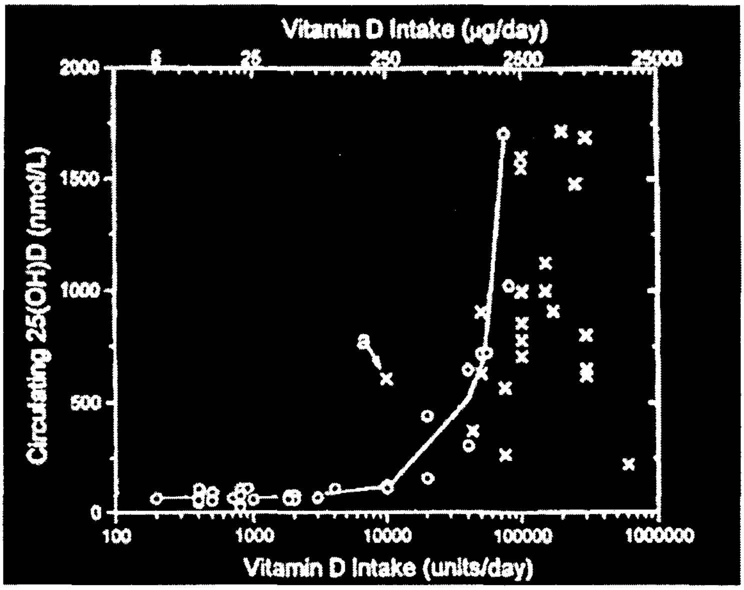

Figure 1. Dose response for vitamin D intake vs. final 25(OH)D concentrations reported. Circles indicate group means from previous studies. Points indicated by "x" represent single values for people reported as intoxicated with vitamin D. The arrow indicates the lowest dose reported causing hypercalcemia, but which is an outlier because vitamin D was given as a single dose of 300,000 IU/month instead of 10,000 IU/day. From reference (14).

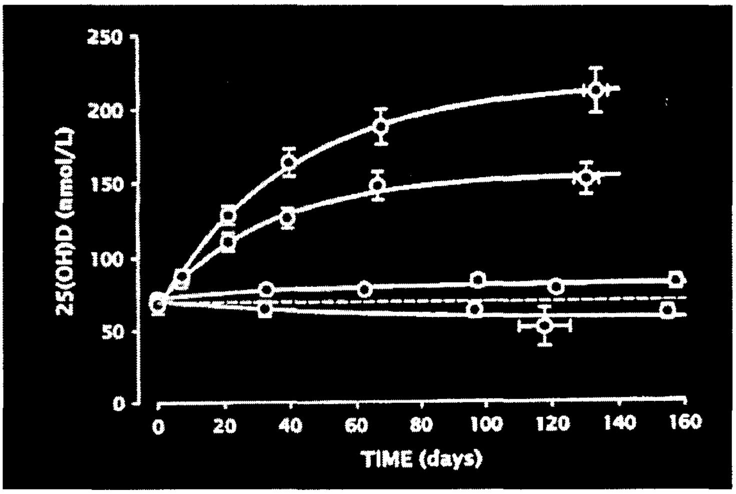

Figure 2. Time course of circulating 25(OH)D concentration for the 4 dosage groups. The curves, from the lowest upward, are for 0, 1,000, 5,000 and 10,000 IU vitamin D_3/day. The horizontal dashed line reflects zero change from baseline. From reference (12).

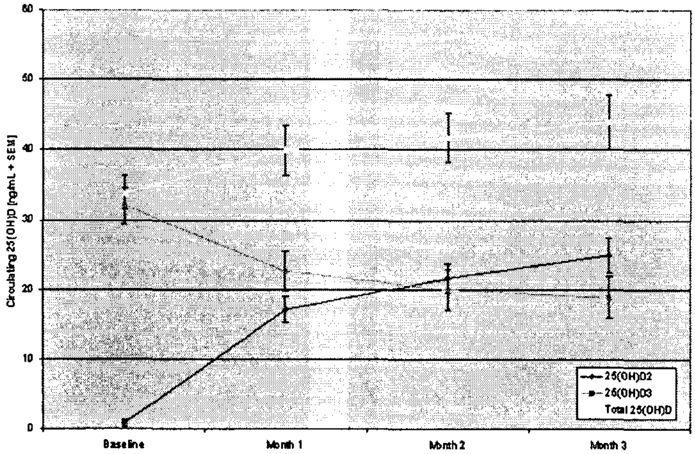

Figure 3. Circulating 25(OH)D concentrations (mean ± SEM) over time in lactating mothers receiving 3,600 IU/day vitamin D_2 and 400 IU/day vitamin D_3. The diamonds denote circulating 25(OH)D_2, squares denote circulating 25(OH)D_3 and triangles denote total circulating 25(OH)D. From reference (13).

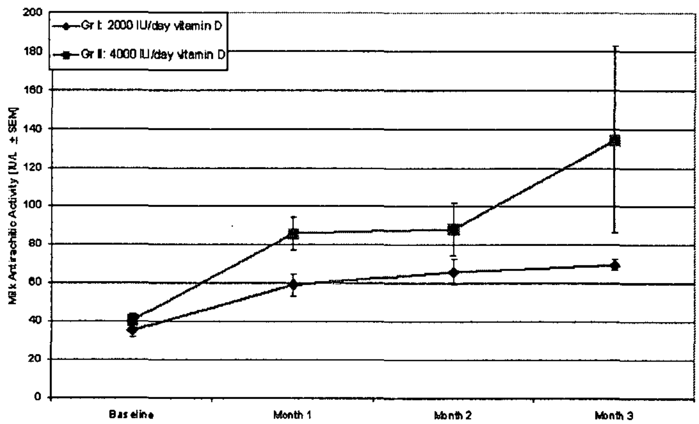

Figure 4. Milk antirachitic activity (mean ± SEM) over time in lactating mothers receiving 2,000 (diamonds) or 4,000 (squares) IU/day vitamin D. From reference (19).