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Review

What is the optimal vitamin D status for health?

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Abstract

The most objectively substantiated health-related reason for tanning is that it improves vitamin D status. The serum 25-hydroxyvitamin D concentration (25(OH)D) is the measure of vitamin D nutrition status. Human biology was probably optimized through natural selection for a sun-rich environment that maintained serum 25(OH)D higher than 100 nmol/L. These levels are now only prevalent in people who spend an above-average amount of time outdoors, with the sun high in the sky. The best-characterized criteria for vitamin D adequacy are based on randomized clinical trials that show fracture prevention and preservation of bone mineral density. Based upon these studies, 25(OH)D concentrations should exceed 75 nmol/L. This concentration is near the upper end of the 25(OH)D reference (''normal'') range for populations living in temperate climates, or for people who practice sun-avoidance, or who wear head coverings. Officially mandated nutrition guidelines restrict vitamin D intake from fortified food and supplements to less than 25 mcg/day, a dose objectively shown to raise serum 25(OH)D in adults by about 25 nmol/L. The combined effect of current nutrition guidelines and current sun-avoidance advice is to ensure that adults who follow these recommendations will have 25(OH)D concentrations lower than 75 nmol/L. Therefore, advice to avoid UVB light should be accompanied by encouragement to supplement with vitamin D in an amount that will correct for the nutrient deficit that sun-avoidance will cause.

Contents

1. Introduction

Vitamin D nutrition status is measured based upon the serum or plasma concentration of the metabolite, 25-hydroxyvitamin D [25(OH)D]. Vitamin D acquired through sun exposure or through oral consumption is

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metabolized within about 3 days, by the liver, into 25(OH)D. In temperate climates, serum 25(OH)D concentrations rise and fall throughout each year, in a pattern that parallels, with a delay of about 2 months, the intensity of UVB light (Vieth et al., 2001b; Rucker et al., 2002; Steingrimsdottir et al., 2005). When sun exposure is restricted, such as for sailors on submarine missions, or for people living in at extremely northern or southern latitudes, the decline in serum 25(OH)D progresses slowly, with a half-life of at least 2 months (Vieth, 1999).

Vitamin D is unique as a nutrient, because humans acquire it mainly through exposure of skin to light at UVB wavelengths. From all available knowledge, the oral acquisition of vitamin D is just as effective as the sunshine-derived buildup of vitamin D in the human body—this assumes that the oral dose is high enough.

The question of what an "optimal" level of vitamin D nutrition status might be is equivalent to asking what the optimal concentration of 25(OH)D in plasma or serum should be for overall health. Most of the disease consequences of sun deprivation can be corrected with the supplementation of vitamin D in amounts designed to target a 25(OH)D concentration that exceeds the minimal threshold for optimal values discussed here.

There are several considerations that relate to the issue of what might be optimal. Published, randomized clinical trials represent a high level of biomedical evidence, and the highest level of evidence is a pooled analysis (meta-analysis) of all available randomized trials. Although epidemiologic associations between serum 25(OH)D concentrations and human health are considered less powerful as evidence, many important public health messages—including those pertaining to avoidance of ultraviolet light and smoking (Doll, 1998)—will never be proven through randomized trials. Many aspects of public health can only be based upon epidemiology and laboratory investigation. The evidence that higher 25(OH)D may benefit health beyond the sphere of bone and mineral metabolism stems primarily from laboratory and epidemiologic studies. There is an ongoing debate about whether an optimal "threshold" truly exists for several relationships to health (Law and Wald, 2002; Heaney, 2005a; Vieth and El-Hajj Fuleihan, 2005). For example a threshold would be a point beyond which more 25(OH)D can no longer provide a net health benefit . In principle, such a threshold point would be the optimal level for vitamin D. A final consideration, that has been applied to other areas of nutrition, including calcium metabolism, relates to the conditions in which human biology may have been optimized through natural selection (Eaton et al., 1996) (Fig. 1).

2. The 25(OH)D concentration desirable for human health

The classic perspective of vitamin D requirements and 25(OH)D concentrations has focused upon mineral homeostasis and prevention of rickets, osteomalacia, and osteoporosis. It is a long-established principle that adequate vitamin D is necessary to regulate active transport of calcium across intestinal mucosa in response to dietary calcium intake. Serum 25(OH)D concentrations correlate with intestinal calcium absorption (Heaney et al., 1997, 2003b), but this effect reaches a plateau at 80 nmol/L, beyond which there is no further rise in calcium absorption (Fig. 2). The evidence about the relationship between 25(OH)D concentration and calcium absorption suggests that when 25(OH)D concentrations are below 80 nmol/L, the body's ability to absorb calcium is impaired. Recent research suggests that the serum 25(OH)D concentration may be more important than a high calcium intake in maintaining the desired values of serum PTH and calcium metabolism. As long as the 25(OH)D concentration is greater than 45 nmol/L (18 ng/mL) more than 800 mg/day of calcium may be unnecessary for maintaining calcium metabolism (Steingrimsdottir et al., 2005). If a population were provided with enough sun exposure or vitamin D supplement to ensure that the lower tail of the distribution of 25(OH)D concentrations is 75 nmol/L, all available evidence shows that the top end of the distribution will still be safe, with no increased risk of hypercalciuria (Vieth et al., 2001a, 2004; Barger-Lux and Heaney, 1994; Heaney et al., 2003a).

The fracture-prevention trials of vitamin D supplementation, with or without calcium, for which 25(OH)D concentrations were available have been evaluated in a recent meta-analysis (Bischoff-Ferrari et al., 2005a). For each clinical trial, fracture risk for subjects receiving vitamin D supplement was compared to the fracture risk for subjects receiving placebo. The combined data from these studies show a downward trend in fracture risk as 25(OH)D concentrations in the treatment group increase. Fractures become progressively less, toward at least 100 nmol/L (Bischoff-Ferrari et al., 2005b).

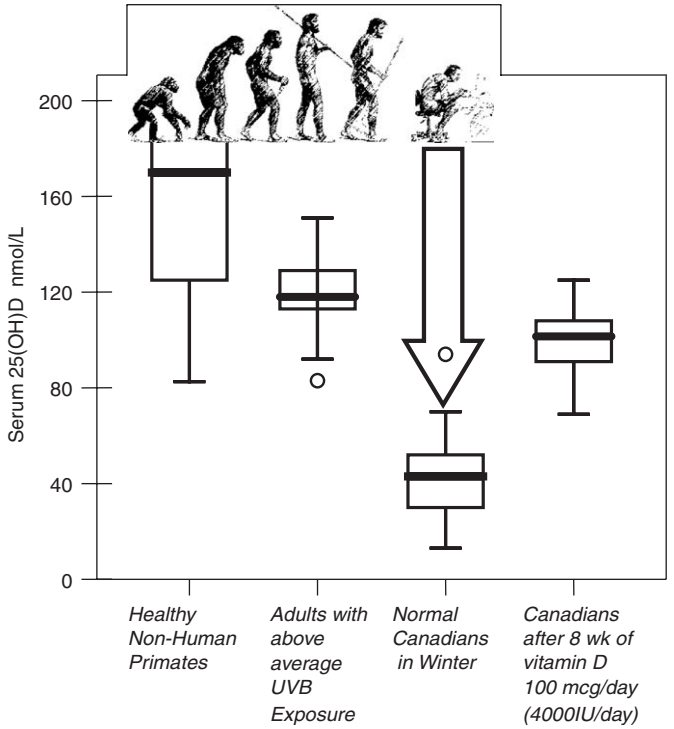

Fig. 1. Circulating 25(OH)D concentrations through primate and human evolution, the effect of UVB exposure and vitamin D supplementation. Estimates of Paleolithic human 25(OH)D concentrations are based on data for farmers, lifeguards, and adults exposed to artificial UVB light. Concentrations "normal" for modern adults are shown, along with their response to supplementation with 100 mcg Vitamin D3 per day. The icons across the top represent stages of primate and human development for the data presented below. Whiskers show extremes and boxes show quartile values for 25(OH)D. Results shown for non-human primates (Vieth et al., 1987; Marx et al., 1989; Adams et al., 1985; Kewenig et al., 1999; Gacad and Adams, 1992) and for sun-rich adults, those given artificial tanning sessions as cited previously (Vieth, 1999) are published mean values. Data for modern adults in winter and their responses to Vitamin D are from hospital workers in Toronto, Canada (Vieth et al., 2001a).

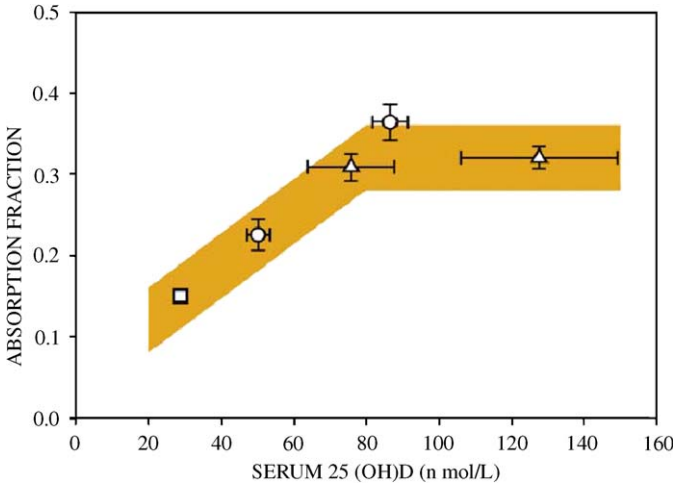

Fig. 2. Relationship between serum 25(OH)D concentration and the fractional absorption of calcium from the gut. The pairs of symbols represent data from various studies that involve subjects treated with and without Vitamin D, as explained previously (Heaney, 2005b). (Copyright Robert P. Heaney, 2003. Used with permission.)

Two clinical trials were reported last year that failed to demonstrate a fracture prevention effect with vitamin D and calcium. One trial was not placebo controlled, but it involved a comparison between the provision of free calcium and vitamin D to one group, versus a control group of subjects who were advised to obtain these on their own. Since 25(OH)D concentrations were not measured, the study offers no guidance about 25(OH)D concentrations (Porthouse et al., 2005). The other trial, the RECORD study (Grant et al., 2005), was fundamentally different from earlier clinical trials of vitamin D and fracture prevention because it dealt with the secondary prevention of fracture (treatment of patients who had suffered a previous fracture). Patient compliance was poor, and the serum 25(OH)D concentrations for those in the RECORD study receiving 20 mcg/day of vitamin D_3 was 62 nmol/L, well below the average 25(OH)D concentrations shown to prevent fractures in other studies. Furthermore, the RECORD study produced no difference in serum PTH concentration between placebo and vitamin D groups, although addition of calcium supplement did lower PTH modestly compared to placebo or vitamin D treated patients. When viewed together with the data of the meta-analysis of Bischoff-Ferrari et al., the data from the RECORD study are in full agreement with the conclusion that for fracture prevention, 25(OH)D concentrations should exceed 75 nmol/L (Bischoff-Ferrari et al., 2005b).

Beyond bone, data from randomized clinical trials show that higher vitamin D nutrition is associated with improved muscle strength, balance and fewer falls (Pfeifer et al., 2001b). Furthermore, clinical trials data show that blood pressure is diminished by UVB exposure (Krause et al., 1998) and by vitamin D supplementation (Pfeifer et al., 2001a).

Epidemiological studies suggest that low serum 25(OH)D concentrations pose a variety of risks to public health. Data for bone-mineral density in American women declines progressively as serum 25(OH)D levels fall below 100 nmol/L (Bischoff-Ferrari et al., 2004). Responsiveness to insulin deteriorates progressively as 25(OH)D decline below 100 nmol/L (Chiu et al., 2004). Periodontal attachment declines progressively in the US population as serum 25(OH)D concentrations declines below 85 nmol/L (Dietrich et al., 2004). Two prospective, case-control studies reveal a several fold increase in risk of colon and rectal cancer as 25(OH)D concentrations decline below 50 nmol/L (Garland et al., 1989; Feskanich et al., 2004). Based upon the epidemiologic data that relate low serum 25(OH)D concentrations to disease, it would seem prudent from the perspective of public health, to maintain 25(OH)D concentrations in all adults within the range associated with improved health outcomes, >75 nmol/L.

3. Does an optimal "threshold" level even exist?

In other areas of disease prevention and health, Law and Wald have discussed epidemiologic relationships between disease related parameters such as the serum cholesterol, blood pressure, and bone density (Law and Wald, 2002). For all of these, they showed a trend toward linear reduction in probability of disease event with logarithmic improvement in risk factor.

For the vitamin D system, the question of an optimal threshold concentration of risk factor—a low 25(OH)D concentration—has focused mainly upon the relationship between serum parathyroid hormone (PTH) and serum 25(OH)D concentrations (Heaney, 2005a; Vieth and El-Hajj Fuleihan, 2005). If the goal is to establish a consensus value for a desirable 25(OH)D concentration, then the criterion of an apparent flattening of the PTH concentration (a marker for disease burden) versus 25(OH)D curve seems to have intuitive support in the range of 40–80 nmol/L (Heaney, 2005a; Chapuy et al., 1996; Lips, 2004). Furthermore, based upon the well-characterized goal of preventing fractures in older adults, the consensus of evidence points toward 25(OH)D concentrations should exceed 75 nmol/L (Bischoff-Ferrari et al., 2005b; Vieth, 2005b; Dawson-Hughes et al., 2005).

4. Anthropologic perspective

For all adults, the only way to achieve a 25(OH)D concentration of 75 nmol/L without a prescription for vitamin D is by spending time in the sun. Without UVB exposure, the amount of vitamin D in diet sources and supplements is not enough to produce this level in adults (Vieth, 2005a). Human skin production of vitamin D is proportional to the size of the area of skin exposed to sunshine. In the context of human biology, regular

exposure of virtually 100% of skin surface would have been normal during the evolution of our species, because we evolved in hot tropical climes and latitudes without clothing. In modern times, the median serum 25(OH)D concentration of clothed outdoor workers is 122 nmol/L (Barger-Lux and Heaney, 2002). It is only in the last few thousand years—a timeframe too short to change the fundamental nature of our biology—that we have started to shield ourselves from the sunshine in which humans have been effectively designed to live through the processes of evolution (Jablonski and Chaplin, 2000; Vieth, 2003).

The human species could not have evolved in a way that would make sun avoidance necessary. However, it is the very process of sun avoidance that has made the skin of some sub-populations unusually susceptible to the burning and cancer-causing effects of sunshine. Natural selection for lighter skin pigment was a way for human populations to adapt to migration away from equatorial latitudes—both northwards and southwards, independently (Relethford, 1997; Jablonski and Chaplin, 2002; Diamond, 2005). Lighter skin made production of vitamin D more efficient when UVB light was limited. Lighter skin provides the survival benefit of preventing rickets and its mis-shapen pelvis that makes normal childbirth impossible (Vieth, 2001). Lighter skin color has come at the cost of greater susceptibility to damage by UVB light. Similarly, avoidance of sunshine comes at the cost of greater risk of musculoskeletal disease, cancers, diabetes, multiple sclerosis and osteoporosis that are discussed elsewhere in this symposium.

One plausible clue for what may be an "optimal" 25(OH)D concentration, would be the serum concentration of 25(OH)D for which our genome might have been effectively designed for through evolution and natural selection. As a reference point, one should consider the 25(OH)D concentrations in other primate species, and in humans who live under conditions that provide sunshine exposure comparable to what existed during our early development as a species. Anthropologists accept that humans originated in the region known as the Horn of Africa. The evidence for anatomically modern humans dates to approximately 100,000 years ago, and our biology has not undergone any fundamental change since then. Therefore, one should consider humans as naked apes effectively designed, and optimized within their genome, to inhabit equatorial latitudes.

Given those circumstances, the circulating 25(OH)D concentrations normal for humans are in the order of 150 nmol/L (Fig. 1). Furthermore, these concentrations would have been stable in populations near the equator, with none of the seasonal fluctuations seen in populations where there is winter (Vieth et al., 2001b; Rucker et al., 2002; Steingrimsdottir et al., 2005). Lifelong fluctuations in 25(OH)D concentrations may be problematic, because the changes to 25(OH)D-1-hydroxylase and 25(OH)D-24-hydroxylase that must occur to adapt to the prevailing 25(OH)D concentration are probably not optimally complete so long as 25(OH)D concentrations are changing. Thus, the combination of both low and fluctuating concentrations of 25(OH)D at temperate latitudes may contribute to seasonal health-related phenomena that include: seasonality in the time of birth and risk of multiple sclerosis (Willer et al., 2005), seasonality of birth and risk of schizophrenia (Davies et al., 2003), seasonality in the rate of rise in prostate specific antigen in men with recurring prostate cancer (Vieth et al., 2005), and the seasonal pattern to lesions in patients with multiple sclerosis (Embry et al., 2000).

5. Conclusion

Public health would probably not be served well by the encouragement of greater sunshine exposure as a way to raise serum 25(OH)D concentrations. The obvious problem with skin exposure to sunshine is that climate makes this is unreliable, skin exposure is not culturally acceptable to many, and exposure can harm the skin. Furthermore, reliance on sunshine for vitamin D will cause substantial annual fluctuations in 25(OH)D concentrations that may be harmful in themselves (Vieth, 2004). The goal of raising 25(OH)D concentrations can be achieved efficiently and simply by providing vitamin D through food supplementation. The doses of vitamin D needed to target specific serum 25(OH)D concentrations have been reviewed elsewhere (Heaney et al., 2003a; Vieth, 2005a). In short, adult humans should be consuming at least 50 mcg (2000 IU)/day of vitamin D. This will raise serum 25(OH)D by about 50 nmol/L. Currently, the major legislative barrier to improving vitamin D status for the general public is that 50 mcg/day is the current upper limit (UL) for this nutrient (Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, 1997; Health Consumer Protection Directorate-General, 2002), and it is double the guidance level in the United Kingdom

(Expert Group on Vitamins and Minerals, 2003). The evidence for the preceding safety limits needs to be reassessed. Guidelines to avoid ultraviolet radiation should be accompanied by a meaningful strategy to compensate for the lower 25(OH)D concentrations that will happen in people who follow those guidelines.

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