Vitamin D: Can we use higher doses for wider indications?

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Vitamin D is a unique substance with properties of both a vitamin and a hormone. Over many decades it has been considered an essential vitamin for bone mineral homeostasis. In the recent past there has been growing appreciation for its role in many other areas of human health including immune regulation, metabolic and cell proliferation and differentiation (1). These pleiotropic effects of vitamin D are called non-classic actions of vitamin D.

In response to the awareness of these recently recognised health benefits there has been a continuous debate about vitamin D's safety and efficacy. Most of these benefits related to the classic actions of vitamin D occur with much higher doses than what is considered safe and nutritionally sufficient dose, a long ago.

Before 1997, adequate daily intake of vitamin D as advocated by the Food and Nutrition Board (FNB) was 200 IU, which is similar to half the amount found in a teaspoon of cod liver oil. According to Vieth, however, there is no adequate evidence to prove that this dose of vitamin D has any effect on the serum 25(OH) D concentrations which is the correct and objective way of determining vitamin D status in the body (2).

Although most people believe that the daily intake of vitamin D is 200 IU, in 1997 the tolerable upper limit of (UL) vitamin D was increased up to 2000 IU / day by the FNB (3). Subsequently, there have been many well designed human clinical trials where the safety and tolerability of higher vitamin D doses were established.

The method of calculating the safe tolerable UL of vitamin D by the FNB consists of three steps; identification of hazards, dose response evaluation and derivation of UL.

Identification of hazards includes evaluation of data regarding the substance in relation to its adverse effects towards human. Type and severity of adverse effects are identified in this step. In dose response evaluation, oral intake and adverse effects that result from the substance are evaluated quantitatively. This step identifies the No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effects Level (LOAEL) and degree of uncertainty assigned by a numerical value. If someone is selecting vitamin D dose as the NOAEL, which has been tested in one or more adequately designed randomised control trial/s that is free of adverse effects we can use 1 as the uncertain factor (UF).

FNB used the following equation to calculate the UL.

UL = NOAEL / UF

FNB selected 60 microgram as the NOAEL from the clinical trial by Narang et al (4). They considered 1.2 as the UF which gave the UL as 50 micrograms.

Vit D UL = 60 μg / 1.2 = 50 μg = 2000 IU

Using the same method European Commission Scientific Committee on Food (SCF) considered NOAEL 100 micrograms from the study by Vieth et al and considered 2 as the UF (5). So the UL declared by SCF was 50 micrograms (6).

Vit D UL = 60 μg / 1.2 = 50 μg = 2000 IU

After formulating these levels many clinical trials have shown that vitamin D oral intake can be increased to a higher level without causing harm to human. Current recommendations have obtained UL of vitamin D using a higher uncertainty factor because of unwarranted fear towards vitamin D. It has, restricted its health benefits. If NOAEL and UF are taken from the recently published literature the UL will invariably be higher than 2000 IU / day.

Trivedi et al (2003) in a randomised control trial on elderly adults reported no acute toxicity or adverse outcomes after giving 100,000IU bolus dose once every four months. Duration of this trial was 5 years (7).

Barber Lux et al (1998) administered vitamin D_3 of 25, 250, 1250 micrograms (50,000 IU) per day to healthy men for eight weeks and reported no adverse effects (8). In this clinical trial mean (SD) baseline serum calcium was 9.58 (0.29) mg/dL. After receiving 1250 micrograms of vitamin D_3 per day for eight weeks serum calcium level increased up to 9.7 (0.19) mg/dL. This increase was not statistically significant.

Stern et al, (1981) used vitamin D3 100,000 IU as a single morning dose for four days in 24 adults and no adverse effects were observed (9). These are only few to illustrate the point that the much higher doses of vitamin D can be safely used without any evidence of toxicity.

The fact that toxic signs of vitamin D are primarily meadiated through elevation of serum calcium was known for a long time. These include fever, chills, vomiting, anorexia, conjunctivitis, thirst and polyuria. There is, however, no consensus on the dose of vitamin D which causes these symptoms. Considering the reports on the adverse effects of vitamin D, many of them were due to accidental consumptions in which the exposures were far above those given in human clinical trials. These are good examples to support that acute toxic potential of increased serum calcium concentrations could occur only with very large doses of vitamin D.

Mixing of vitamin D_3 in its crystalline form into the table sugar resulted in an intake of 42,000 micrograms per day and continuing this dose for several months produced symptoms of hypercalcaemia in two people (10). Administrating 2.4 million IU of vitamin D over days to a two year old boy produced toxic symptoms due to hypercalcaemia (11).

Therefore scientists are continuously challenging the current UL of vitamin D of 2000 IU, as weight of evidence support for a much higher dose (10,000 IU / day) as the UL of vitamin D.

Recognition of the traditional therapeutic dose as the safe UL of vitamin D can potentially restrict research efforts and prevent obtaining additional health benefits of vitamin D.

References

1. Nagpal S, Na S, and R. R., Non calcaemic actions of vitamin D receptor ligands. *Endocr Revision* 2005; **26**: 662-87.
2. Vieth R., Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. *Am J Clin Nutr* 1999; **69**(5): 842-56.
3. Food and Nutrition Board. Institute of Medicine. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC. National Academy Press, 1997.
4. Narang NK, Gupta RC, and J. MK., Role of vitamin D in pulmonary tuberculosis. *J Assoc Physicians India* 1984; **32**: 185-8.
5. Vieth R, Chan PC, and M.G. Efficacy and safety of vitamin D_3 intake exceeding the lowest observed adverse effect level. *Am J Clin Nutr* 2001; **73**: 288-94.
6. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of vitamin D. Brussels, Belgium: European Commission, 2002.
7. Trivedi DP and e.a. R. Doll. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003; **326**(7386): 469.
8. Barger-Lux MJ, et al. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. *Osteoporos Int* 1998; **8**(3): 222-30.
9. Stern PH, T.A., Bell NH, Epstein S. Demonstration that circulating 1 alpha, 25-dihydroxyvitamin D is loosely regulated in normal children. *J Clin Invest* 1981; **68**: 1374-7.
10. Vieth R, et al. Vitamin D poisoning by table sugar. *Lancet* 2002; **359**: 672.
11. Barrueto F, et al. Acute vitamin D intoxication in a child. *Pediatrics* 2005; **116**: E4536.