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Vitamin D Toxicity, Policy, and Science

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ABSTRACT: The serum 25-hydroxyvitamin D [25(OH)D] concentration that is the threshold for vitamin D toxicity has not been established. Hypercalcemia is the hazard criterion for vitamin D. Past policy of the Institute of Medicine has set the tolerable upper intake level (UL) for vitamin D at 50 μg (2000 IU)/d, defining this as "the highest level of daily nutrient intake that is likely to pose no risks of adverse health effects to almost all individuals in the general population." However, because sunshine can provide an adult with vitamin D in an amount equivalent to daily oral consumption of 250 μg (10,000 IU)/d, this is intuitively a safe dose. The incremental consumption of 1 μg (40 IU)/day of vitamin D_3 raises serum 25(OH)D by ~1 nM (0.4 ng/ml). Therefore, if sun-deprived adults are to maintain serum 25(OH)D concentrations >75 nM (30 ng/ml), they will require an intake of more than the UL for vitamin D. The mechanisms that limit vitamin D safety are the capacity of circulating vitamin D–binding protein and the ability to suppress 25(OH)D-1-α-hydroxylase. Vitamin D causes hypercalcemia when the "free" concentration of 1,25-dihydroxyvitamin D is inappropriately high. This displacement of $1,25(OH)_2D$ becomes excessive as plasma 25(OH)D concentrations become higher than at least 600 nM (240 ng/ml). Plasma concentrations of unmetabolized vitamin D during the first days after an acute, large dose of vitamin D can reach the micromolar range and cause acute symptoms. The clinical trial evidence shows that a prolonged intake of 250 μg (10,000 IU)/d of vitamin D_3 is likely to pose no risk of adverse effects in almost all individuals in the general population; this meets the criteria for a tolerable upper intake level.
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Key words: cholecalciferol, safety, toxicity, body compartments

INTRODUCTION

THE FORMAL LIMIT for a safe intake of vitamin D is referred to as the tolerable upper intake level (UL).[1,2] This is described as the amount of vitamin D that can be consumed by adults on a long-term basis with no anticipation of harm. In both North America and Europe, the UL for vitamin D is currently 50 μg (2000 IU)/d.[3,4] The nutrition principles relating to the safety of vitamin D are summarized in Fig. 1. The "no observed adverse effect level" (NOAEL) is the highest intake of a nutrient found to have no valid, published harmful effect. In the case of vitamin D, hypercalcemia is the criterion for harm.[3] Probably a more sensitive measure of an impending adverse response, capable of detecting modest excess in vitamin D, is hypercalciuria. By definition, adults are usually in mineral balance. Therefore, any increase in net intestinal calcium absorption will raise urinary calcium excretion, which can be monitored easily by measuring the ratio of calcium to creatinine in a random morning urine sample. For those without renal insufficiency, hypercalciuria has been defined as urine calcium/creatinine >1 mmol/mmol (>0.37 mg/mg).[5] Nonetheless, hypercalcemia is the key criterion for vitamin D toxicity because it causes symptoms.

VITAMIN D EXCESS AND ITS METABOLISM

Usually, vitamin D is a bone-anabolic agent, serving as the initial substrate in a two-stage process whose hormonal product, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$; calcitriol], stimulates the active transport of calcium across intestinal mucosa. A clear understanding of the vitamin D system requires an appreciation that the principles of metabolism for the vitamin D system differ from those of the cholesterol-based steroid hormone system. Unlike all other fat-soluble signaling systems, the hormone precursor concentration, plasma 25-hydroxyvitamin D [25(OH)D; calcidiol], is rate limiting. For example, the cholesterol substrate to produce other steroids circulates in the millimolar range, at concentrations so high that the cholesterol supply is in no practical sense rate-limiting for the production of steroid hormones. In contrast, 25(OH)D circulates at concentrations in the order of a million-fold lower than cholesterol. As vitamin D supply increases, the liver also increases its rate of 25-hydroxylation of the vitamin D molecule to produce 25(OH)D.[6] The rate of this 25-hydroxylation is proportional to available vitamin D, and there is no evidence in vivo that the reaction is saturable. As the plasma 25(OH)D

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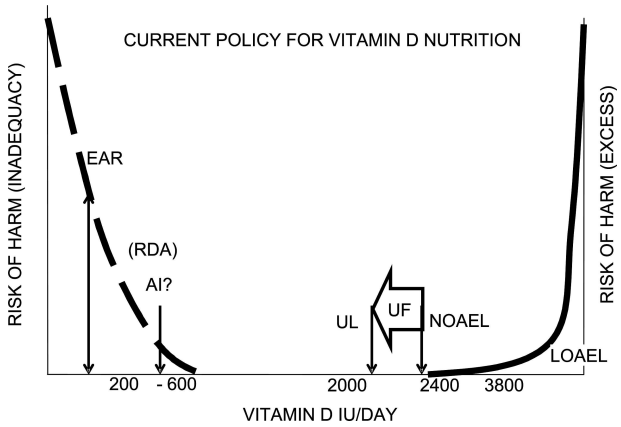

FIG. 1. Representation of nutrition terms related to formal policy for vitamin D, based on Yates et al.[1] To convert the units to micrograms per day, divide by 40 (e.g., 2000 IU/d = 50 μg/d). The abbreviations are the estimated average requirement (EAR), which suffices the average person. Nutrient guidelines aim to provide sufficiency for essentially all persons, and without suitable evidence, an adequate intake (AI) is suggested. If there is evidence on an intake that assures attainment of a measure of adequacy, the recommendation is a recommended dietary allowance (RDA). The tolerable upper intake level (UL) is calculated by dividing the no observed adverse effect level (NOAEL) by an uncertainty factor (UF). The long-term dose that is the minimum likely to cause an adverse effect is lowest observed adverse level (LOAEL).

concentration increases, the 25(OH)D-1-α-hydroxylase within kidney (CYP27A2) produces ever more $1,25(OH)_2D$ per unit of enzyme protein.[7] As the plasma 25(OH)D concentration increases in vivo, the plasma concentration of $1,25(OH)_2D$ is regulated at a fairly constant level because renal 25(OH)D-1-α-hydroxylase protein decreases and because of upregulation in the amount of 25(OH)D-24-hydroxylase, which cleaves the side-chain of both $1,25(OH)_2D$ and 25(OH)D.[8] As 25(OH)D concentrations continue to rise, a limit is reached beyond which the substrate-driven output of $1,25(OH)_2D$ can no longer be regulated appropriately.

When the vitamin D system is driven to excess, hypercalcemia results because of increased intestinal calcium absorption and by the induction of bone resorption.[9] This increased resorption with vitamin D excess is opposite to the relationship between bone resorption when vitamin D supplies are insufficient, because as one proceeds from low 25(OH)D concentrations, rising 25(OH)D concentrations are associated with declining concentrations of bone turnover markers.[9,10] The classic symptoms of vitamin D toxicity are entirely attributable to hypercalcemia, and they include nausea, dehydration, and lethargy.[11,,12] Without laboratory testing, these signs of hypercalcemia have been mistaken for gastroenteritis.[13]

BODY COMPARTMENTS

One concern expressed about consumption of higher doses of vitamin D is that, if adipose tissue was to break down, a sudden influx of vitamin D from adipose might be toxic.[14,15] When excessive or toxic doses of vitamin D are administered, the most severe effects will be manifest during the period of administration. Although adipose tissue is indeed the most concentrated storage site of vitamin D in humans, there is no evidence that sudden weight loss can release enough stored vitamin D from adipose tissue to cause a recurrence of vitamin D toxicity at some time long after vitamin D is stopped. Storage in adipose does not proceed indefinitely, and even in that tissue, there is turnover of vitamin D with time, reflecting the average whole body half-life for vitamin D molecules of 62 days, based on the disappearance of radioactivity after radioactively labeled vitamin D_3 was injected into 60 adults.[16] In adults, there is no evidence that the amount of adipose tissue affects vitamin D, aside from affecting the overall volume of distribution for vitamin D. In adults, the storage of vitamin D occurs in both adipose and muscle (Fig. 2). This explains why women, even though they average a percent of body mass comprised of adipose tissue that is 50% greater than in men, exhibit no fundamental difference from men in any aspect of the pharmacokinetics of vitamin D or its metabolites.

CONFLICTS BETWEEN CURRENT POLICY AND THE SCIENCE

The current NOAEL is a vitamin D intake of 60 μg/d (2400 IU/d), an intake value based on a report by Narang et al.,[17] which showed a statistically significant increase in serum calcium, but not quite into the hypercalcemic range. An uncertainty factor of 1.2 was applied by the United States Food and Nutrition Board to the NOAEL, and this produced a UL of 50 μg/d (2000 IU/d).[3] This intake had been mentioned as a safe limit for vitamin D since the 1960s.[18] When newer data were published, indicating that 100 μg (4000 IU)/d produced no ill effect, the European Commission applied an uncertainty factor of 2, to specify a UL of 50 μg/d.[4] Recent evidence in men shows that 8 wk of supplementation with 275 μg (12,500 IU)/d of vitamin D does not affect circulating calcium concentration (urine results were not reported).[19] In other words, the dose is noncalcemic and safe by the criteria applied both to drug studies of vitamin D analogs[20–22] and to nutrient recommendations.[3,4]

Concentrations of $1,25(OH)_2D$ are not increased much by vitamin D intoxication. This reflects the high level of regulation of the circulating concentrations of this hormone through both synthesis and catabolism. Nonetheless, vitamin D toxicity is the result of excessive levels of "free" $1,25(OH)_2D$ displaced from its carrier protein, vitamin D–binding protein (DBP), when there is a vast excess of other vitamin D metabolites.[23] This excess was confirmed by studies using centrifugal ultrafiltration isodialysis to measure the "free" $1,25(OH)_2D$ concentrations in vitamin D–intoxicated individuals[24] (Fig. 3). This physiochemical saturation of binding capacity is also confirmed by the high total of vitamin D and 25(OH)D concentrations (19,500 nM; 7800 ng/ml) in patients intoxicated after consuming over a million IU (>25,000 μg) daily for many months.[13]

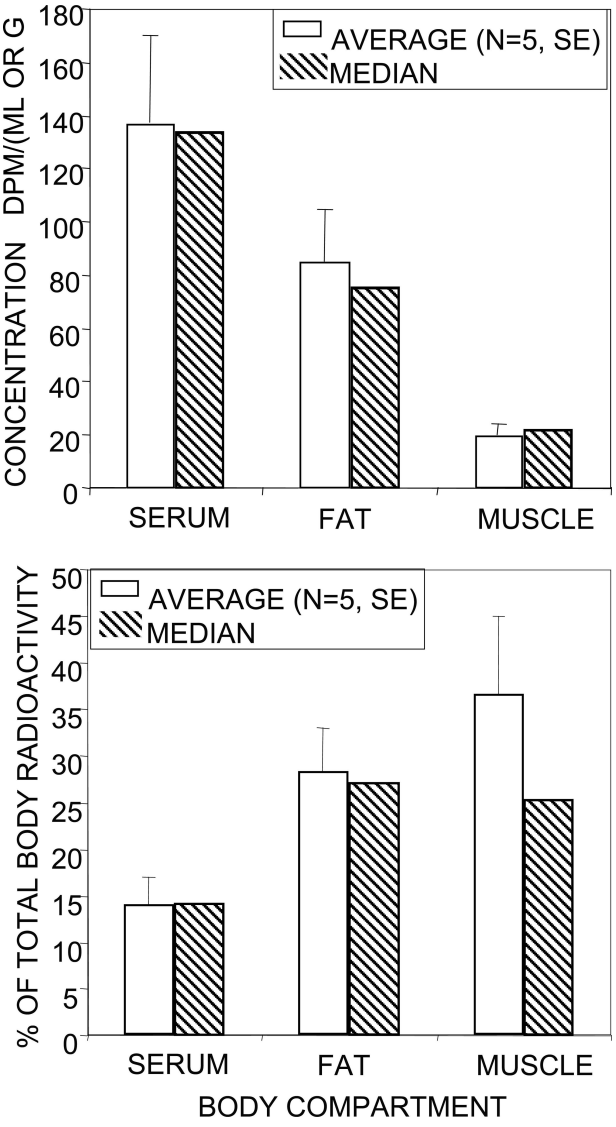

FIG. 2. Distribution of radiolabeled vitamin D_3 among tissues of the body in human adults. The data for these graphs were transcribed from Mawer et al.[16] Vitamin D_3 labeled with either ^{14}C or ^{3}H had been injected between 16 and 90 days before the death of terminally ill patients, and tissues were harvested after death. The white bars show the mean with SE; the cross-hatched bars show the median. The concentration of radioactivity in each tissue is shown in the top panel. For the entire human body, the proportions of total vitamin D and metabolites in each tissue compartment, as reported by Mawer et al., are shown in the bottom panel.

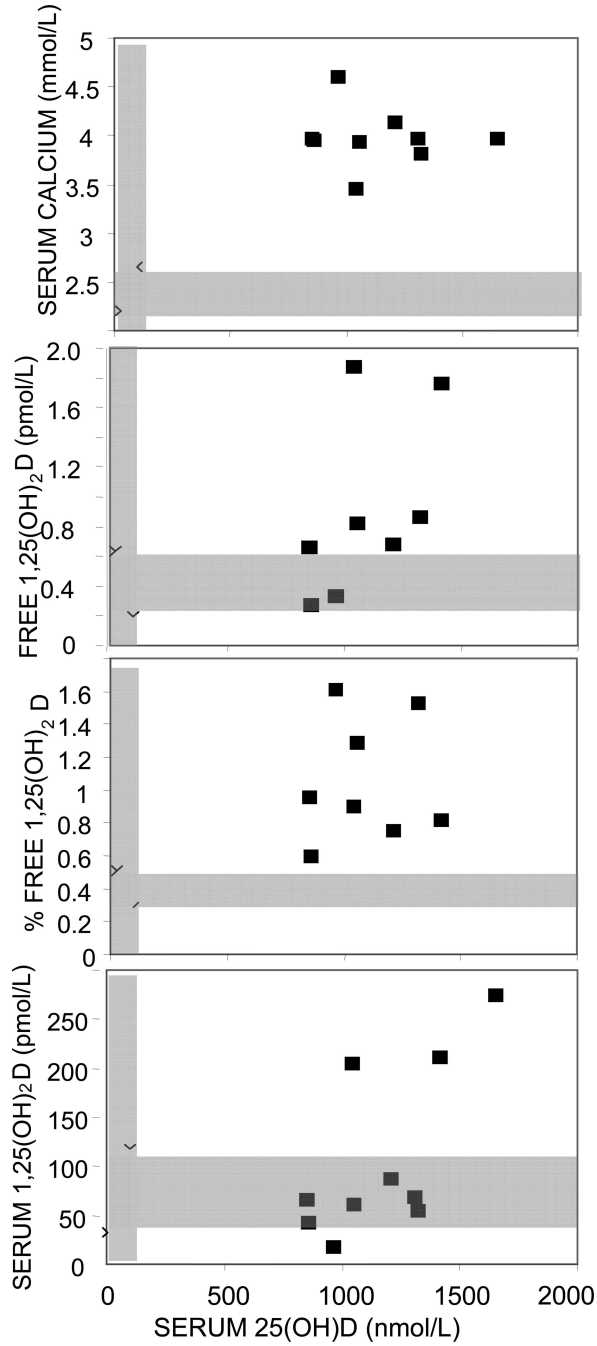

FIG. 3. Ten cases of adult vitamin D toxicity and the concentration of $1,25(OH)_2D$ free and unbound to vitamin D–binding protein. The horizontal shaded zones show reference ranges for plasma calcium and three pertinent parameters of $1,25(OH)_2D$. The vertical shaded zones show the reference range for plasma 25(OH)D. Each point shows a value for one household member intoxicated by the inappropriate use of a vitamin D_3 oil concentrate as cooking oil. The data were transcribed from Pettifor et al.[24] To convert the SI units in these figures to mass units: calcium, 1 mM = 2.5 mg/dl; $1,25(OH)_2D$, 1 pM = 0.4 pg/ml; 25(OH)D, 1 nM = 0.4 nM.

In laboratory rats, the capacity of DBP is 5800 nM.[25] In laboratory rats, hypercalcemia is detected only once the total of all vitamin D metabolites exceeds ~20% of the binding capacity of DBP.[6] A further mechanism for toxicity may be possible if high concentrations of 25(OH)D can bind to the vitamin D receptor and trigger a response.[26]

In contrast to the hypercalcemia reported in normal adults by Narang et al.,[17] which was used by the Food and Nutrition Board, Institute of Medicine, to establish the 50 μg/d (2000 IU/d) UL for vitamin D intake, confirmatory studies using 100 μg (4000 IU)/d with more subjects and for longer periods have produced no detectable change in serum or urine calcium.[5,27,28]

The weight of published evidence on toxicity shows that the lowest dose of vitamin D causing hypercalcemia in some healthy adults is 1000 μg (40,000 IU)/d of the vitamin D_2 form.[29] This translates to 1000 μg, or 1 mg, taken daily for many months. Few studies have looked at effects of high doses of vitamin D on hypercalciuria, probably a more sensitive indicator of vitamin D excess.[5]

A rigorous epidemiological analysis of a community population of ~10,000 households intoxicated by grossly excessive fortification of milk with vitamin D concluded that the situation contributed to two deaths of susceptible elderly.[11] Although hypercalcemia did occur, it was not widespread. The most susceptible group to the excess vitamin D was women >65 yr of age. The authors suggested diminished renal function may play a role in the toxic response, although with renal impairment, $1,25(OH)_2D$ production should be diminished, with a smaller response to vitamin D [in this context, the nutrient, distinct from $1,25(OH)_2D$ therapy]. The average 25(OH)D concentration of the confirmed cases of vitamin D toxicity was 535 nM (214 ng/ml).[11]

People with abundant exposure to sunlight can easily exhibit a serum 25(OH)D >150 nM (60 ng/ml), which would be a physiologic presupplement input of vitamin D equivalent to >100 μg (4000 IU)/d.[30] An additional oral intake of 100 μg/d of vitamin D would still be less than the dose of 1250 μg (50,000 IU)/d vitamin D shown to be noncalcemic.[28]

Amounts of vitamin D much greater than physiologic (i.e., pharmacologic amounts much higher than 250 μg [>10,000 IU]/d) eventually become toxic once they occupy a meaningful proportion of circulating DBP. High circulating concentrations of vitamin D metabolites displace $1,25(OH)_2D$ into the unbound, free phase.[24,29] At toxic doses, the freely circulating vitamin D, along with its metabolites, accumulate not just in adipose[31] but also in muscle.[16,32] The 100 μg (4000 IU)/d doses of vitamin D used in adults should be regarded as physiologic—comparable to the amount of vitamin D acquired through natural sun exposure—and far below the doses required to cause physiochemical displacement of metabolites from DBP.[33] The average capacity of human plasma DBP to bind vitamin D and its metabolites is 4700 nM (1888 ng/ml)[33]; this exceeds by 20 times the physiologic total concentration of its vitamin D–derived ligands, and it is the saturable factor that limits the safe range for vitamin D dosing in most adults.

RENAL DISEASE

It is often mentioned that patients with chronic renal failure are more sensitive to vitamin D toxicity than are healthy subjects. This concern almost certainly stems from experience with $1,25(OH)_2D$—not with nutrient vitamin D. To my knowledge, there is no scientific evidence that the margin of safety for the hormone precursor, vitamin D_3, is any less for patients with renal disease than it is for the rest of the population. Unfortunately, the nephrology community has tended to refer to $1,25(OH)_2D$ as "vitamin D," and this has caused much confusion.

A comparison between rates of soft tissue calcification among clinical centers that have implemented very different background dosages of vitamin D suggests that a combination of higher-dose vitamin D along with $1,25(OH)_2D$ may be preferable.[34,35] It is now accepted that activated metabolites of vitamin D improve survival of dialysis patients compared with survival of patients given no vitamin D of any kind.[36] What is unresolved is whether that survival benefit may be the result of nontraditional actions of the vitamin D system, in which case, greater provision of nutrient vitamin D_3 could raise the concentration of 25(OH)D in plasma and facilitate local, nonrenal production of $1,25(OH)_2D$ in various tissues.[37,38] Comparison of data reported by Briese et al.[34] with that of Oh et al.[35] suggests that, if patients with chronic renal failure receive enough vitamin D_3, there may be less need to administer $1,25(OH)_2D$ in doses high enough to cause coronary and valvular calcification.

CONCLUSION

The absence of hypercalcemia and hypercalciuria in well-conducted trials of vitamin D leads to the conclusion that the current UL of 50 μg (2000 IU)/d has been excessively conservative. The overwhelming bulk of clinical trial evidence supports the conclusion that a prolonged intake of 250 μg (10,000 IU)/d of vitamin D_3 likely poses no risk of adverse effects in almost all individuals in the general population. These conclusions are more fully supported in a formal risk assessment for vitamin D by Hathcock et al.[39]

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