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HYPERVITAMINOSIS D OR VITAMIN D TOXICITY

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Abstract
Vitamin D toxicity, or hypervitaminosis D is the toxic state of an excess of vitamin D. The normal range for blood concentration in adults is 20 to 50 nanograms per milliliter (ng/mL).
Fortification of food products with vitamin D was central to the eradication of rickets in the early parts of the 20th century in the United States. In the subsequent almost 100 years since, accumulating evidence has linked vitamin D deficiency to a variety of outcomes, and this has paralleled greater public interest and awareness of the health benefits of vitamin D. Supplements containing vitamin D are now widely available in both industrialized and developing countries, and many are in the form of unregulated formulations sold to the public with little guidance for safe administration. Together, this has contributed to a transition whereby a dramatic global increase in cases of vitamin D toxicity has been reported. Clinicians are now faced with the challenge of managing this condition that can present on a spectrum from asymptomatic to acute life-threatening complications. This article considers contemporary data on vitamin D toxicity, and diagnostic and management strategies relevant to clinical practice.

Keywords: Hypercalcemia; Acute Kidney Injury, Poisoning, 25(OH)D; hypervitaminosis, clinical symptoms; management; toxicity; vitamin D.

Introduction

Confusion, apathy, recurrent vomiting, abdominal pain, polyuria, polydipsia, and dehydration are the most often noted clinical symptoms of vitamin D toxicity (VDT; also called vitamin D intoxication or hypervitaminosis D). VDT and its clinical manifestation, severe hypercalcemia, are related to excessive long-term intake of vitamin D, malfunctions of the vitamin D metabolic pathway, or the existence of coincident disease that produces the active vitamin D metabolite locally. Although VDT is rare, the health effects can be serious if it is not promptly identified. Many forms of exogenous (iatrogenic) and endogenous VDT exist. Exogenous VDT is usually caused by the inadvertent or improper intake of extremely high doses of pharmacological preparations of vitamin D and is associated with hypercalcemia. Serum 25-hydroxyvitamin D [25(OH)D] concentrations higher than 150 ng/ml (375 nmol/l) are the hallmark of VDT due to vitamin D overdosing. Endogenous VDT may develop from excessive production of an active vitamin D metabolite - $1,25(OH)_2D$ in granulomatous disorders and in some lymphomas or from the reduced degradation of that metabolite in idiopathic infantile hypercalcemia. Endogenous VDT may also develop from an excessive production of 25(OH)D and $1,25(OH)_2D$ in congenital disorders, such as Williams-Beuren syndrome. Laboratory testing during routine clinical examinations may reveal asymptomatic hypercalcemia caused by the intake of vitamin D even in

doses recommended for the general population and considered safe. That phenomenon, called hypersensitivity to vitamin D, reflects dysregulated vitamin D metabolism. Researchers have proposed many processes to explain VDT. Those processes include elevated activity of 1α-hydroxylase or inhibited activity of 24-hydroxylase, both leading to increased concentration of 1,25(OH)D; increased number of vitamin D receptors; and saturation of the capacity of vitamin D binding protein. Increased public awareness of vitamin D-related health benefits might increase the risk of VDT due to self-administration of vitamin D in doses higher then recommended for age and body weight or even higher than the established upper limit intake values. Consequently, the incidence of hypercalcemia due to hypervitaminosis D might increase.

THE OTHER SIDE OF VITAMIN D THERAPY

An estimated 1 billion people worldwide are deficient or insufficient in vitamin D.[1] This staggering statistic is worrying given that vitamin D is indispensable to human health. In fact, mounting experimental, observational, and epidemiologic evidence has linked low vitamin D levels to a number of adverse health outcomes, such as all-cause mortality, cardiovascular disease, reduced bone density, fracture risk, metabolic syndrome, malignancy, autoimmune conditions, and infection.[2] Additionally, some evidence suggests that vitamin D status is a biomarker of lifestyle, given that unhealthy and sedentary lifestyles are associated with vitamin D insufficiency or deficiency, which itself represents a risk factor for adverse health outcomes.

Signs and symptoms

An excess of vitamin D causes abnormally high blood concentrations of calcium, which can cause overcalcification of the bones, soft tissues, heart and kidneys. In addition, hypertension can result.[1] Symptoms of vitamin D toxicity may include the following:

- Dehydration
- Vomiting
- Diarrhea
- Decreased appetite
- Irritability
- Constipation
- Fatigue
- Muscle weakness
- Metastatic calcification of the soft tissues
- Insomnia

Symptoms of vitamin D toxicity appear several months after excessive doses of vitamin D are administered. In almost every case, a low-calcium diet combined with corticosteroid drugs will allow for a full recovery within a month. It is possible that some of the symptoms of vitamin D toxicity are actually due to vitamin K depletion. One animal experiment has demonstrated that co-consumption with vitamin K reduced adverse effects, but this has not been tested in humans.[2] However the interconnected relationships between vitamin A, vitamin D, and vitamin K, outlined in a 2007 paper[3] published in the journal Medical Hypotheses, describes potential feedback loops between these three vitamins that could be elucidated by future research.

A mutation of the CYP24A1 gene can lead to a reduction in the degradation of vitamin D and to hypercalcemia.

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Recommended supplement limitsThe U.S National Academy of Medicine has established a Tolerable Upper Intake Level (UL) to protect against vitamin D toxicity ("The UL is not intended as a target intake; rather, the risk for harm begins to increase once intakes surpass this level."). These levels in microgram (mcg or µg) and International Units (IU) for both males and females, by age, are:

(Conversion : 1 µg = 40 IU and 0.025 µg = 1 IU.)

0–6 months: 25 µg/d (1000 IU/d)
7–12 months: 38 µg/d (1500 IU/d)
1–3 years: 63 µg/d (2500 IU/d)
4–8 years: 75 µg/d (3000 IU/d)
9+ years: 100 µg/d (4000 IU/d)
Pregnant and lactating: 100 µg/d (4000 IU/d)
The recommended dietary allowance is 15 µg/d (600 IU per day; 800 IU for those over 70 years). Overdose has been observed at 1,925 µg/d (77,000 IU per day).[citation needed] Acute overdose requires between 15,000 µg/d (600,000 IU per day) and 42,000 µg/d (1,680,000 IU per day) over a period of several days to months.
Suggested tolerable upper intake level
Based on risk assessment, a safe upper intake level of 250 µg (10,000 IU) per day in healthy adults has been suggested by non-government authors. Blood levels of 25-hydroxyvitamin D necessary to cause adverse effects in adults are thought to be greater than about 150 ng/mL, leading the Endocrine Society to suggest an upper limit for safety of 100 ng/mL
Long-term effects of supplementary oral intake
Excessive exposure to sunlight poses no risk in vitamin D toxicity through overproduction of vitamin D precursor, cholecalciferol, regulating vitamin D production. During ultraviolet exposure, the concentration of vitamin D precursors produced in the skin reaches an equilibrium, and any further vitamin D that is produced is degraded.[9] This process is less efficient with increased melanin pigmentation in the skin. Endogenous production with full body exposure to sunlight is comparable to taking an oral dose between 250 µg and 625 µg (10,000 IU and 25,000 IU) per day.
Vitamin D oral supplementation and skin synthesis have a different effect on the transport form of vitamin D, plasma calcifediol concentrations. Endogenously synthesized vitamin D3 travels mainly with vitamin D-binding protein (DBP), which slows hepatic delivery of vitamin D and the availability in the plasma. In contrast, orally administered vitamin D produces rapid hepatic delivery of vitamin D and increases plasma calcifediol.
It has been questioned whether to ascribe a state of sub-optimal vitamin D status when the annual variation in ultraviolet will naturally produce a period of falling levels, and such a seasonal decline has been a part of Europeans' adaptive environment for 1000 generations. Still more contentious is recommending supplementation when those supposedly in need of it are labeled healthy and serious doubts exist as to the long-term effect of attaining and maintaining serum 25(OH)D of at least 80 nmol/L by supplementation.
Current theories of the mechanism behind vitamin D toxicity (starting at a plasmatic concentration of ≈750 nmol/L propose that:

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Intake of vitamin D raises calcitriol concentrations in the plasma and cell

Intake of vitamin D raises plasma calcifediol concentrations which exceed the binding capacity of the DBP, and free calcifediol enters the cell

Intake of vitamin D raises the concentration of vitamin D metabolites which exceed DBP binding capacity and free calcitriol enters the cell

All of this affect gene transcription and overwhelm the vitamin D signal transduction process, leading to vitamin D toxicity

Cardiovascular disease

Evidence suggests that dietary vitamin D may be carried by lipoprotein particles into cells of the artery wall and atherosclerotic plaque, where it may be converted to active form by monocyte-macrophages. This raises questions regarding the effects of vitamin D intake on atherosclerotic calcification and cardiovascular risk as it may be causing vascular calcification. Calcifediol is implicated in the etiology of atherosclerosis, especially in non-Whites.

The levels of the active form of vitamin D, calcitriol, are inversely correlated with coronary calcification. Moreover, the active vitamin D analog, alfacalcidol, seems to protect patients from developing vascular calcification. Serum vitamin D has been found to correlate with calcified atherosclerotic plaque in African Americans as they have higher active serum vitamin D levels compared to Euro-Americans. Higher levels of calcidiol positively correlate with aorta and carotid calcified atherosclerotic plaque in African Americans but not with coronary plaque, whereas individuals of European descent have an opposite, negative association. There are racial differences in the association of coronary calcified plaque in that there is less calcified atherosclerotic plaque in the coronary arteries of African-Americans than in whites.

Among descent groups with heavy sun exposure during their evolution, taking supplemental vitamin D to attain the 25(OH)D level associated with optimal health in studies done with mainly European populations may have deleterious outcomes. Despite abundant sunshine in India, vitamin D status in Indians is low and suggests a public health need to fortify Indian foods with vitamin D. However, the levels found in India are consistent with many other studies of tropical populations which have found that even an extreme amount of sun exposure, does not raise 25(OH)D levels to the levels typically found in Europeans.

Recommendations stemming for a single standard for optimal serum 25(OH)D concentrations ignores the differing genetically mediated determinates of serum 25(OH)D and may result in ethnic minorities in Western countries having the results of studies done with subjects not representative of ethnic diversity applied to them. Vitamin D levels vary for genetically mediated reasons as well as environmental ones.

Ethnic differences

Possible ethnic differences in physiological pathways for ingested vitamin D, such as the Inuit, may confound across the board recommendations for vitamin D levels. Inuit compensate for lower production of vitamin D by converting more of this vitamin to its most active form.

A Toronto study of young Canadians of diverse ancestry applied a standard of serum 25(OH)D levels that was significantly higher than official recommendations These levels were described to be 75 nmol/L as "optimal", between 75 nmol/L and 50 nmol/L as "insufficient" and <50 nmol/L as "deficient". 22% of individuals of European ancestry had 25(OH)D levels less than the 40 nmol/L cutoff, comparable to the values observed in previous studies (40 nmol/L is 15 ng/mL).

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78% of individuals of East Asian ancestry and 77% of individuals of South Asian ancestry had 25(OH)D concentrations lower than 40 nmol/L. The East Asians in the Toronto sample had low 25(OH)D levels when compared to whites. In a Chinese population at particular risk for esophageal cancer and with the high serum 25(OH)D concentrations have a significantly increased risk of the precursor lesion.

Studies on the South Asian population uniformly point to low 25(OH)D levels, despite abundant sunshine. Rural men around Delhi average 44 nmol/L. Healthy Indians seem have low 25(OH)D levels which are not very different from healthy South Asians living in Canada. Measuring melanin content to assess skin pigmentation showed an inverse relationship with serum 25(OH)D.[37] The uniform occurrence of very low serum 25(OH)D in Indians living in India and Chinese in China does not support the hypothesis that the low levels seen in the more pigmented are due to lack of synthesis from the sun at higher latitudes.

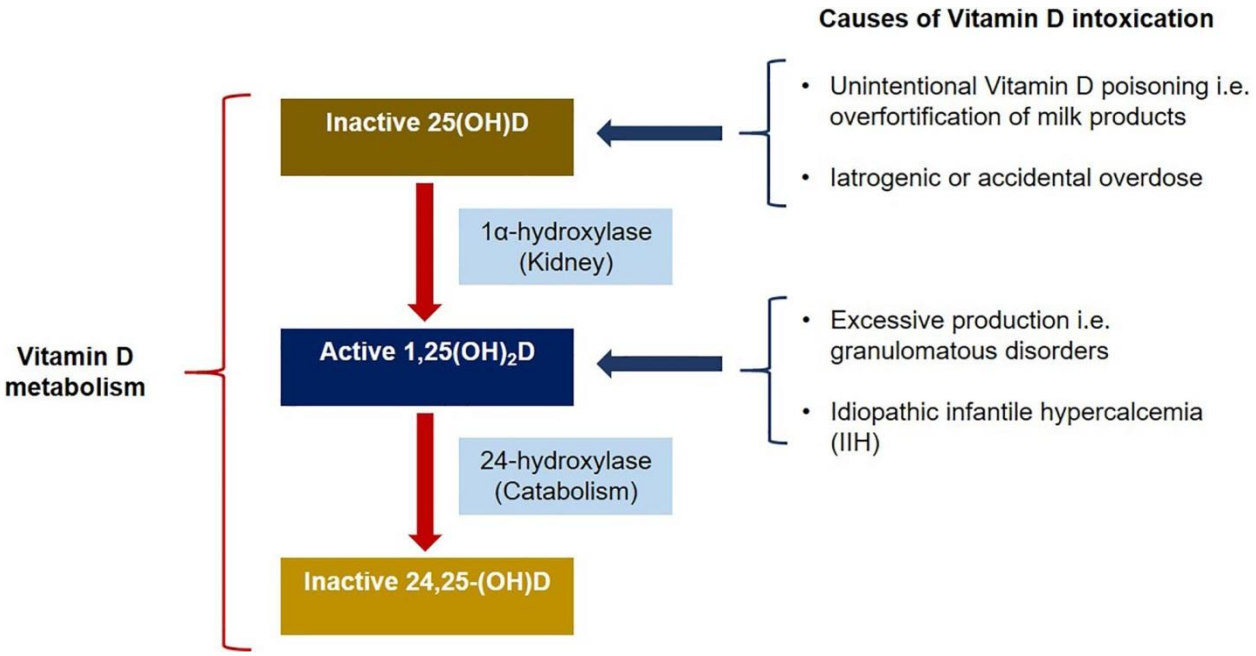
Premature aging

Complex regulatory mechanisms control metabolism. Recent epidemiologic evidence suggests that there is a narrow range of vitamin D levels in which vascular function is optimized. Animal research suggests that both excess and deficiency of vitamin D appears to cause abnormal functioning and premature aging.

ComparVitamin D compounds, specifically cholecalciferol (D3) and ergocalciferol (D2), are used in rodenticides due to their ability to induce hypercalcemia, a condition characterized by elevated calcium levels in the blood. This overdose leads to organ failure and is pharmacologically similar to vitamin D's toxic effects in humans.

Concentrations used in these rodenticides are several orders of magnitude higher than the maximum recommended human intake, with acute baits containing 3,000,000 IU/g for D3 and 4,000,000 IU/g for D2. This leads to hypercalcemia in the rodents and subsequent death several days after ingestion ative Toxicity: Use of Vitamin D in Rodenticides

PATHOPHYSIOLOGY OF VITAMIN D TOXICITY



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The Institute of Medicine (IOM) Report in 2011 highlighted the upper limits for vitamin D intake on the basis of the effects of acute, short-term administration of high-dose vitamin D preparations and those that can occur secondary to chronic administration over years of supplementation.18 Acute vitamin D toxicity is usually caused by doses of vitamin D above 10,000 IU/day resulting in serum 25(OH)D concentrations >150ng/mL. Chronic vitamin D toxicity can potentially occur with administration of doses above 4,000 IU/day for extended periods, likely in the region of years resulting in 25(OH)D concentrations in the 50-150 ng/mL range.

Vitamin D intoxication occurs as a result of a vitamin D metabolite reaching the vitamin D receptor (VDR) in the nucleus of target cells and causing exaggerated gene expression.19

Three hypotheses to explain vitamin D toxicity have been previously put forward:

- Increased vitamin D intake increases serum

concentrations of the active form of vitamin D, 1,25(OH)2D (1,25-dihydroxyvitamin D).19 1,25(OH)2D has a high affinity for VDRs and is a critical ligand with access to transcriptional signal transduction machinery in the cell.20

- Vitamin D intake increases inactive plasma

25(OH)D (25-hydroxyvitamin D) and saturates the binding capacity of vitamin D binding protein (VDBP).19 25(OH)D at higher

concentrations has a greater affinity for VDRs (in a dose-dependent effect) compared to other vitamin D metabolites, that enter cells where it has direct effects on gene expression.20

- Increased vitamin D intake raises the concentrations

of many vitamin D metabolites, particularly 25(OH)D.19 In states of hypervitaminosis D, the concentrations of various vitamin D metabolites, including 25(OH)D, 24,25(OH)2D, 25,26(OH)2D, and 25(OH)D-26,23-lactone, increase significantly.21 These metabolites exceed the VDBP capacity and cause the release of "free" 1,25(OH)2D, which enter target cells by diffusion and subsequently stimulates the VDR.

CLINICAL FEATURES AND DIAGNOSIS OF VITAMIN D TOXICITY

The presentation of vitamin D toxicity can range from asymptomatic to severe neuropsychiatric and life-threatening features. Vitamin D toxicity is largely characterized by severe hypercalcemia that may persist for a prolonged time. Clinical manifestations of vitamin D toxicity are varied, but largely related to hypercalcemia and include neuropsychiatric (such as confusion, psychosis, stupor, or coma), gastrointestinal (abdominal pain, vomiting, polydipsia, anorexia, constipation, pancreatitis), cardiovascular (hypertension, shortened QT interval, ST segment elevation, bradyarrhythmias, first degree heart block), and renal (hypercalciuria, acute kidney injury (AKI), dehydration and nephrocalcinosis) complications.15 Additional complications of hypercalcemia include band keratopathy, hearing loss, and painful periarticular calcinosis.

In animal studies, hypervitaminosis D has been shown to cause widespread vascular calcification.22

Serum inactive 25(OH)D levels >100 ng/mL (250 nmol/L) have been defined as hypervitaminosis D,

whereas serum levels >150 ng/mL (375 nmol/L) have been proposed to define vitamin D intoxication by the Endocrine Society. (14) Other laboratory findings include hypercalcemia, hypercalciuria, and very low or undetectable parathyroid hormone (PTH) levels. The $1,25(OH)_2D$ concentration, which is the active form of vitamin D, may be within the reference range, slightly

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increased or reduced. The latter finding is secondary to inhibition of 1a-hydroxylase activity responsible for synthesizing active $1,25(OH)_2D$ and enhancement of 24-hydroxylase activity involved in its catabolic pathway.[23] Exogenous administration of active vitamin D metabolite or increased endogenous production can result in elevated $1,25(OH)_2D$ concentrations, and normal or decreased 25(OH)D levels.

It should be noted that serum $1,25(OH)_2D$ has been reported to be falsely elevated in patients with vitamin D intoxication with certain laboratory assays, particularly radioimmunoassay due to significant cross-reactivity of very high levels of 25(OH)D.[24] Additionally, circulating levels of 25(OH)D may not always reflect its true values and activities, in part due to many extrarenal tissues expressing signaling components for vitamin D including the 1a-hydroxylase enzyme that is responsible for synthesizing biologically active $1,25(OH)_2D$. For example, vascular smooth muscle cells (VSMCs) express a functional VDR and the 1a-hydroxylase enzyme, enabling arteries to synthesize bioactive vitamin D and establish an autocrine/paracrine hormonal system to regulate cardiovascular health locally.[2,25]. This suggests that the endocrine, autocrine, and paracrine functions of vitamin D may not always be reflected from its serum 25(OH)D levels.[26] Additionally, circulating 25(OH)D concentrations are influenced by many factors such as race, pigmentation, age, season, latitude, weather conditions, dietary habits, and exposure to sunlight. Many peripheral tissues are able to convert circulating 25(OH)D to active $1,25(OH)_2D$ to meet local requirements and this may not be reflected by its serum levels

MANAGEMENT OF VITAMIN D TOXICITY

The main goal of treatment during vitamin D toxicity is emergent resuscitation in an unstable patient and correction of hypercalcemia. Hypercalcemia due to vitamin D overdose theoretically can last up to 18 months following discontinuation of administration. This is due to the slow release of stored vitamin D from fat deposits

Therefore, sustaining normocalcemia is just as pivotal as acute treatment of hypercalcemia. Additionally, vitamin D2 or D3 has a high lipid solubility in liver, muscles, and fat tissues and a long half-life in the body. However, 25(OH)D and 1,25(OH)2D have shorter half-lives at 15 days and 15 hours, respectively. Therefore, overdose of 25(OH)D can persist for weeks.

Therapeutic strategies for vitamin D toxicity can be categorized into 1) stabilization and supportive treatment; 2) correction of hypercalcemia, and 3) other therapies to reduce vitamin D levels as illustrated in Figure 2.

Adequate concentrations and dosing of vitamin D

Vitamin D status is determined by measuring 25(OH)D concentrations. Unfortunately, there remains controversy as to the definitions of vitamin D deficiency, sufficiency, and recommended dietary allowance (RDA) to help guide optimal supplementation. In the 2011 dietary reference intake (DRI) report by the IOM, bone health was reported to be the only outcome whereby causality has been established by available evidence. The evidence for other extraskeletal chronic disease outcomes was deemed to be inconsistent or inconclusive to establish causality and insufficient to serve as a basis for DRI. A 25(OH)D level of 16 ng/mL (40 nmol/L) has been suggested by the 2011 IOM report to meet the needs of approximately half the population (median population requirement) and levels of 20 ng/mL (50 nmol/L) meet the needs of at least 97.5% of the population.[18] However, the UK Department of Health and Scientific Advisory Committee on

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Nutrition (SACN) define vitamin D deficiency as <25 nmol/L (10 ng/mL). Additionally, others have argued that the deficiency threshold should be significantly higher, at 50 nmol/L (20 ng/dL)

CONCLUSIONS

Both underdosing and overtreatment with vitamin D can have considerable health consequences. Vitamin D toxicity remains an ongoing issue and its incidence is likely to continue increasing, owing to the widespread availability of over-the-counter preparations and public interest.7 Measures to help prevent and manage cases of vitamin D excess are critically needed and is of substantial public health importance. We suggest the following considerations in regard to the prevention of vitamin D toxicity:

1. Clear physician-patient communication should be emphasized when prescribing vitamin D-containing formulations and the risks associated with excess administration should be communicated.
2. Health care providers and community pharmacists should be aware of the various vitamin D preparations, their variability, safety profile, and risks associated with supratherapeutic dosing to help in clinical- decision making and provision of appropriate recommendations. Appropriate education of health professionals will assist in preventing inappropriate prescribing or dispensing.
3. High dose vitamin D administration should be avoided until serum 25(OH)D and calcium levels have been assessed. This will help assess the need for high dose vitamin D and avoid potential toxicity by empiric treatment.
4. One case report described that a single dose of 2,000,000 IU of vitamin D was given in error to two nursing home residents.28 This suggests the need to regulate the availability of multiple use bottles with more conventional dose formulations in line with current IOM and other published guidelines.
5. Consideration of vitamin D toxicity or excess should be made in patients presenting with hypercalcemia or hypercalciuria.

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