Hypervitaminosis D and Systemic Manifestations: A Comprehensive Review

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Abstract: Hypervitaminosis is a rare but potentially serious condition which is manifested after mega dose replacement in addition to other sources as well. Vitamin D toxicity may also be associated with hypercalcemia. To establish a diagnosis of hypervitaminosis D there has to be a clinical and biochemical hypercalcemia along with calciuria and hypoparathyroidism with elevated serum vitamin D levels. The management primarily focuses on reduced dietary calcium intake with proper attention to hydration along with discontinuation of vitamin D therapy. Corticosteroids especially prednisolone and bisphosphonate therapy may also be useful.

INTRODUCTION

Vitamin D is likely one of the oldest hormones, having existed for at least 750 million years\(^1\). Studies have demonstrated that low levels of vitamin D represent a problem of global dimensions\(^2\). A recent Workshop Consensus for Vitamin D Nutritional Guidelines estimated that approximately 50% and 60% of the elderly in North America and the rest of the world, respectively, do not have satisfactory vitamin D levels\(^3\). But recently hypervitaminosis has also come into the limelight. Vitamin D toxicity, also called hypervitaminosis D, is a rare but potentially serious condition that occurs when we have excessive amounts of vitamin D in our body. Vitamin D toxicity is usually caused by mega doses of vitamin D supplements—not by diet or sun exposure. That’s because our body regulates the amount of vitamin D produced by sun exposure, and even fortified foods don’t contain large amounts of vitamin D. Vitamin D toxicity causes hypercalcemia and multiple other adverse effects including potentially life-threatening ones\(^4\).

There are 2 major forms of vitamin D, vitamin D\(_2\) (ergocalciferol) and vitamin D\(_3\) (cholecalciferol). Vitamin D\(_2\) is found in plants and can be consumed in fortified food products or as a supplement. Vitamin D\(_3\) is obtained from either dietary sources or through the conversion of 7-dehydrocholesterol in the skin upon exposure to ultraviolet B (UVB) radiation. Vitamin D\(_3\) from the skin is bound to the vitamin D-binding protein, whereas vitamin D\(_2\) and vitamin D\(_3\) from diet are bound to vitamin D-binding protein and lipoproteins. Both forms are hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D; D represents D\(_2\) or D\(_3\)]. However, 25(OH)D is inactive and requires hydroxylation in the kidney to form 1,25-dihydroxyvitaminD\(_3\) [1,25(OH)\(_2\)D, calcitriol]. Calcitriol [1,25(OH)\(_2\)D] maintains calcium in the blood and has an array of effects on the body’s organs. Calcitriol acts in an endocrine manner to regulate calcium metabolism by enhancing intestinal calcium absorption and mobilizing calcium from the skeleton\(^5\,\(^6\,\(^7\)\).

SERUM LEVELS OF VITAMIN D

Although 1,25(OH)\(_2\)D is considered to be the active form of vitamin D, its levels in the serum do not correlate with overall vitamin D status. Whereas the 25(OH)D levels are more clinically relevant marker\(^8\). Vitamin D activity is measured in ìg of 25(OH)D (1 ìg = 40 International Units, IU).

OPTIMUM 25(OH)D LEVELS

The vitamin D level needed to optimize intestinal calcium absorption (34 ng/mL) is lower than the level needed for neuromuscular performance (38 ng/mL)\(^9\,\(^10\). Experts however believe that the lower limit of adequate 25(OH)D levels should be 30 ng/mL\(^11\). Still others recommend a lower limit of 40 ng/mL, since impaired calcium metabolism due to low serum 25(OH)D levels may trigger secondary hyperparathyroidism, increased bone turnover and progressive bone loss\(^12\,\(^13\). The proposed 25(OH)D cut-off for optimum skeletal health is the level that reduces Parathyroid hormone (PTH) to a minimum and increases calcium absorption to its maximum\(^14\,\(^15\). A level of < 20 ng/mL is associated with suppressible levels of parathyroid hormone when challenged with pharmacologic dosages of vitamin D. Several studies have shown that PTH levels plateau at a minimum steady-state level as serum 25(OH)D levels approach and rise above approximately 30 ng/mL (75 nmol/L)\(^16\,\(^17\). The established consensus of several vitamin D cut-offs (Table 1). It is noteworthy, however, that there is a continued debate and exchange of knowledge with respect to the optimum cut-off for 25(OH)D.

Dietary sources of vitamin D are limited to fattyfish (wild or farm salmon, mackerel, tuna fish, sardines and cod liver oil) and products fortified with vitamin D which include dairy products, cereals, margarine, flour, and orange juice.

The amount of UVB radiation required for vitamin D sufficiency can be calculated from the amount of vitamin D produced from one minimal erythemal dose (MED), or 10,000–25,000 IU of oral vitamin D\(_3\). The MED can be defined as the amount of time needed to cause skin to turn pink. The length of time varies with geographical location, skin pigmentation, percent of body fat, and age. Excessive exposure to sunlight will not cause vitamin D intoxication because sunlight degrades any excess vitamin D\(^18\).

The highest recorded individual serum 25(OH)D concentration obtained from sunshine was from a farmer in Puerto Rico with a level of 225 nmol/L\(^17\). On the other hand, the highest recorded individual 25(OH)D achieved from artificial ultraviolet light treatment sessions was 275 nmol/L\(^18\). Vitamin D toxicity probably begins to occur after chronic consumption of approximately 40,000 IU/day (100 of the 400 IU capsules)\(^19\).

VITAMIN D TOXICITY

Supplementation and food fortification

Vitamin D as a fat-soluble vitamin raised concerns about toxicity from excessive supplementation. Wide-spread vitamin D fortification of foods and drinks from the 1930s to 1950s in the United States and Europe led to reported cases of toxicity\(^20\).

Iatrogenic

Iatrogenic vitamin D toxicity due to empirical administration of very high doses of intramuscular vitamin D injections at frequent intervals is
not uncommon, especially in elderly. It is increasingly being recognized as one of the most common causes of hypervitaminosis D and hypercalcemia.

Other causes
Endocrine disorders like primary hyperparathyroidism, MEN I & II syndrome, malignancies such as Hodgkin’s lymphoma and non-Hodgkin’s lymphoma, granulomatous diseases like sarcoidosis and tuberculosis have also been associated with hypervitaminosis D.

Hypercalcemia is responsible for producing most of the symptoms of vitamin D toxicity. Early symptoms of vitamin D toxicity include gastrointestinal disorders like anorexia, diarrhea, constipation, and vomiting. Bone pain, drowsiness, continuous headaches, irregular heartbeat, loss of appetite, muscle and joint pain are other symptoms that are likely to appear within a few days or weeks; frequent urination, especially at night, excessive thirst, weakness, nervousness and itching; kidney stones.

MECHANISM OF VITAMIN D TOXICITY
It involves increased concentration of vitamin D metabolites reaching the VDR in the nucleus of target cells and causing exaggerated gene expressions. To explain this, the three hypotheses are as follows:

I. Whenever there are increased levels of plasma 1,25(OH)2D with Vit D toxicity, and many other studies revealed that vitamin D toxicity is associated with normal or marginally elevated 1,25(OH)2D.

II. Normal physiology 1,25(OH)2D has low affinity for the transport protein DBP and high affinity for VDR making it an important ligand with access to the transcriptional signal transduction machinery. In hypervitaminosis D various vitamin D metabolites increase, compromising the capacity of the DBP and allows other metabolites to enter the cell nucleus. Among these inactive metabolites 25(OH)D has the strongest affinity for the VDR, so at high concentrations it stimulates transcription.

III. Vitamin D intake raises the concentration of many vitamin D metabolites especially vitamin D itself and 25(OH)D. In hypervitaminosis D, vitamin D metabolites such as vitamin D2, 25(OH)D2, 24,25(OH)2D2, 25,26(OH)2D2, and 25(OH)D3-26,23-lactone increase significantly. These concentrations exceed the DBP binding capacity and cause release of free 1-alpha 25(OH)D3, which enters target cells. The various studies and reports of vitamin D intoxication indicate that plasma 25(OH)D3 is a good biomarker for toxicity.

CLINICAL FEATURES OF HYPERVITAMINOSIS D
Clinical features of hypervitaminosis D are varied and mostly due to vitamin D toxicity. Early symptoms of vitamin D toxicity include gastrointestinal disorders like anorexia, diarrhea, constipation, and vomiting. Bone pain, drowsiness, continuous headaches, irregular heartbeat, loss of appetite, muscle and joint pain are other symptoms that are likely to appear within a few days or weeks; frequent urination, especially at night, excessive thirst, weakness, nervousness and itching; kidney stones.

DIAGNOSIS OF SYMPTOMATIC HYPERVITAMINOSIS D

1. Clinical features of hypercalcemia
2. Elevated serum and urine level of calcium
3. Reduced serum level of parathormone (intact)

4. Serum 25(OH)D level > 100ng/ml

MANAGEMENT OF HYPERVITAMINOSIS D

1. Hypercalcemia is usually controlled by restriction of dietary calcium and appropriate attention to hydration. Volume depletion results from uncontrolled symptoms leading to decreased intake and enhanced renal calcium loss. This tends to exacerbate or perpetuate the hypercalcemia by increasing Na+ reabsorption in the thick ascending limb of the loop of Henlé (TALH). Thus, appropriate volume repletion with isotonic sodium chloride solution is an effective short-term treatment for hypercalcemia. Once volume is restored, simultaneous administration of loop diuretics blocks Na+ and calcium reabsorption in the TALH. Replacing ongoing sodium, potassium, chloride, and magnesium losses is important if prolonged sodium chloride and loop diuretic therapy is contemplated.

2. Discontinuation of vitamin D, usually leads to resolution of hypercalcemia. Reduction of dietary calcium and vitamin D intake is effective for treating hypercalcemia due to increased intestinal calcium absorption.

3. Vitamin D stores in fat may be substantial, and vitamin D intoxication may persist for weeks after vitamin D ingestion is terminated. Such patients are responsive to glucocorticoids, which in doses of 100mg/d prednisolone or its equivalent usually return serum calcium levels to normal over several days. Prednisone may help reduce plasma calcium levels by reducing intestinal calcium absorption.

4. Hypercalcemia of vitamin D intoxication results from increased intestinal absorption of calcium and from the direct effect of 1,25(OH)2D3 to increase resorption of bone in severe cases. Therefore bisphosphonate therapy can be usefully added to the regimen.

REFERENCES


