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## Vitamin D toxicity

### Zatrucie witaminą D

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#### INTRODUCTION

Vitamin D is an important prohormone that plays a vital role in calcium homeostasis and bone mineralisation. Vitamin D also subserves in a wide range of fundamental biological functions, such as cell differentiation and the inhibition of cell growth, as well as immunomodulation. Vitamin D deficiency leads to a defect of bone mineralization and to increased risks of several extra skeletal complications such as cardiovascular diseases, hypertension, obesity, metabolic syndrome, chronic obstructive pulmonary disease, autoimmune diseases and cancer. Vitamin D deficiency [25-hy-

#### Summary

Vitamin D toxicity (VDT), also called hypervitaminosis D, is a rare but potentially serious condition that occurs when an individual has excessive 25(OH)D levels in the bloodstream.

Vitamin D toxicity is usually caused by extremely high doses of vitamin D supplements, not by diet or skin exposure to the sun. The main clinical consequence of VDT is elevated serum calcium level (hypercalcemia) and a variety of nonspecific symptoms. The literature reports that hypercalcemia due to overdosed vitamin D may appear if serum 25(OH)D levels are higher than 150-200 ng/ml. Many different mechanisms have been proposed to account for VDT, including the vitamin D metabolite itself, VDR number, activity of 1- $\alpha$ -hydroxylase, inhibition of vitamin D catabolism, and the capacity of VDBP. Mounting evidence that higher levels of vitamin D may have beneficial effects on bone and cellular health may predispose to enhanced administration of vitamin D and increased frequency of VDT. Hypercalcemia from VDT is rare, but a dangerous state for the organism and should receive adequate and sensible treatment.

#### Streszczenie

Zatrucie witaminą D (VDT), zwane także hiperwitaminozą D, jest rzadkim powikłaniem, będącym najczęściej następstwem podaży dużej ilości witaminy D jako suplementu, a nie skutkiem diety lub ekspozycji na promienie UVB. Następstwem klinicznym VDT może być hiperkalcemia oraz inne niespecyficzne objawy. Dane literaturowe wskazują, że do hiperkalcemii w VDT dochodzi, jeśli stężenie 25(OH)D w surowicy jest większe niż 150-200 ng/ml. Wiele różnych mechanizmów może być odpowiedzialnych za powstanie objawów VDT, w tym wzrost: stężenia metabolitów witaminy D, ilości receptorów dla witaminy D (VDR) i białka wiążącego witaminę D (VDBP). Dostępna dokumentacja wskazująca na korzystny wpływ wyższych stężeń witaminy D zarówno na tkankę kostną, jak i wiele innych komórek, zachęca niektóre osoby do przyjmowania (niekontrolowanego) większej ilości witaminy D niż zalecane, co zwiększa ryzyko wystąpienia VDT. Hiperkalcemia wskutek VDT występuje rzadko, ale jest niebezpieczna i wymaga rozważnego leczenia.

droxyvitamin D – 25(OH)D level < 20 ng/ml] and insufficiency [25(OH)D level 21-29 mg/ml] is a worldwide problem that is widely prevalent (1).

Because of the increased awareness of vitamin D deficiency in recent years, the use of vitamin D supplements by the population has increased, as well as use of high doses of vitamin D prescribed by physicians to treat vitamin D deficiency. This increased use of vitamin D supplements by the general population and the growing number of prescriptions of therapeutic doses without any monitoring may result in a greater risk of hypervitaminosis D, also known as vitamin D

toxicity (VDT) (2). This article presents some of the problems associated with VDT.

### WHAT IS VITAMIN D TOXICITY AND HOW OFTEN DOES IT OCCUR?

Vitamin D toxicity (VDT), also called hypervitaminosis D, is a rare but potentially serious condition that occurs when an individual is exposed to excessive amounts of vitamin D for prolonged period of time.

Vitamin D toxicity is usually caused by mega doses of vitamin D supplements, not by diet or exposure to the sun. This is because the human body regulates the amount of previtamin D produced by UVB, and even fortified foods do not contain large amounts of vitamin D (3).

VDT may be defined as a state when markedly elevated 25(OH)D levels ( $> 150$  ng/mL) coinciding with hypercalcemia, hypercalciuria and very low or even undetectable PTH activity. However, the major clinical worries related to VDT most often focus on elevated calcium levels (hypercalcemia) and a variety of non-specific symptoms (see below).

The literature reports that hypercalcemia due to an overdose of vitamin D may appear if serum levels of 25(OH)D reach a range of 150-200 ng/ml (3, 4). For this reason, it is generally accepted that serum 25(OH)D level above 150 ng/ml should be observed before a diagnosis of vitamin D toxicity. The lower 25(OH)D levels (up to 100 ng/mL) are considered perfectly safe for most children and adults, with the exception of individuals who have a hypersensitivity to vitamin D, such as children and adults with idiopathic infantile hypercalcemia, Williams-Beuren syndrome, granulomatous disorders and some lymphomas (5).

The existing knowledge related to VDT is based on case reports, series courses and animal experiments. The experimental analysis of VDT in humans is impossible due to ethical problems. In the 1930s to the 1950s, public health officials in USA and Great Britain recommended the routine fortification of milk and other foods with vitamin D initially as prophylactic for rickets in children and later to improve the general condition of adults. In the 1940s, massive doses of vitamin D (200,000 to 300,000 IU/D) were considered as an effective treatment strategy for many chronic illnesses from tuberculosis to rheumatoid arthritis. In 1950s, the incidence of hypercalcemia significantly increased, mainly in Great Britain as well as in some other countries in Europe. This unexpected and unexplained (at that time) increase of incidence of hypercalcemia resulted in the discontinuation of the fortification of food with vitamin D. Because hypercalcemia was observed at early stages of treatment, the therapy was discontinued and symptoms of vitamin D intoxication disappeared after a few months. This experience alerted physicians to the potential of vitamin D toxicity, and that concern persists to this day (5, 6). During the 1930s to the 1950s, there was no reliable assay for vitamin D and its metabolite, so symptoms of hyper-

calcemia in some children were based on a survey of dietary intake.

### MECHANISM OF VITAMIN D TOXICITY

Vitamin D toxicity involves an increased concentration of vitamin D metabolites reaching the VDR in the nucleus of target cells and causing exaggerated gene expressions. The three mechanisms are suggested to explain vitamin D toxicity (3, 7):

1. Toxicity mediated by the increased levels of plasma  $1,25(\text{OH})_2\text{D}$  (active hormonal form of vitamin D) leads to its increased intracellular concentration. This hypothesis is not strongly supported, as only Mewar et al. reported elevated  $1,25(\text{OH})_2\text{D}$  levels at VDT, and many other studies revealed that  $1,25(\text{OH})_2\text{D}$  levels were only marginally elevated or normal.
2.  $1,25(\text{OH})_2\text{D}$  has low affinity to the vitamin D binding protein (DBP, transport protein) and high affinity to VDR making it an important ligand with access to the transcriptional signal transduction machinery. At the state of hypervitaminosis D, the levels of various vitamin D metabolites are markedly increased compromising the capacity of the DBP, and in term enable other vitamin D metabolites to enter the cell nucleus. Among these inactive metabolites 25(OH)D has the strongest affinity to the VDR, so at high concentrations 25(OH)D itself may stimulate transcription.
3. 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  $\text{D}_3$ ,  $25(\text{OH})\text{D}_3$ ,  $24,25(\text{OH})_2\text{D}_3$ ,  $25,26(\text{OH})_2\text{D}_3$  and  $25(\text{OH})\text{D}_3$ -26,23-lactone increase significantly. These concentrations exceed the DBP binding capacity and cause release of free 1-alpha  $25(\text{OH})_2\text{D}_3$ , the latter one enters target cells. The various studies and reports of vitamin D intoxication indicate that plasma  $25(\text{OH})\text{D}_3$  is a good biomarker for toxicity.

### CLINICAL FEATURES OF VITAMIN D TOXICITY

The clinical manifestation of hypervitaminosis D is varied and mostly results from hypercalcemia and reflects the essential role of calcium in many tissues and targets, including bone, cardiovascular system, nerves and cellular enzymes.

Initial signs and symptoms of hypervitaminosis D may be similar to other hypercalcemic states and include generalized weakness and weight loss (6, 8-11).

Central nervous system features may include confusion, difficulty in concentration, drowsiness, apathy and coma. Neuropsychiatric symptoms include depression and psychosis, both of which are resolved following improvement of the hypercalcemia.

Hypercalcemia can affect the gastrointestinal tract and cause recurrent vomiting, abdominal pain, polydipsia, anorexia, and constipation. Hypercalcemia may

also be observed due to induced hypergastrinemia results peptic ulcers and pancreatitis.

In the heart, hypercalcemia may result in a shortened Q-T interval, ST segment elevation, and bradyarrhythmias with first-degree heart block on the electrocardiogram (EKG).

Kidney function is affected because hypercalcemia alerts the action of vasopressin on the renal tubules. The net result is reduced urinary concentrating ability and a form of nephrogenic diabetes insipidus. This usually presents as polyuria, but rarely is the volume as high as that association with central diabetes insipidus. Symptoms may include polydipsia, which is an accepted consequence of polyuria. The hypercalcemia also results in vasoconstriction that can cause hypertension.

Hypercalciuria is one of the earliest signs of vitamin D toxicity and precedes the occurrence of hypercalcemia. The increased excretion of urinary calcium is due to a decrease in the parathyroid hormone (PTH) production. When the kidneys are not able any longer keep up with the amount of calcium entering into the circulation from dietary calcium and bone calcium mobilization, the serum calcium begins to rise (6). The decrease in PTH also causes a decrease in phosphate excretion by the kidneys. The elevated levels of 25(OH)D directly interact with the VDR in the intestine increasing intestinal calcium and phosphate absorption (6). This results in an increase in both serum calcium and serum phosphate resulting in a supra saturating calcium phosphate product which is deposited (ectopic soft tissue calcification) in the kidneys resulting in nephrocalcinosis and in atherosclerotic plaques in blood vessels leading to vascular calcification (6). Ectopic soft tissue calcification as a result of both hypercalcemia and hypophosphatemia can be a particular problem in VDT. It is documented (on experimental VDT toxicosis in rats) that the pathological processes of vitamin D toxicity were related to dosage, length of time between doses and duration of exposure (3, 6).

### DIAGNOSIS OF SYMPTOMATIC HYPERVITAMINOSIS D

The diagnosis of VDT can be made on clinical grounds. Detailed clinical and drug history are of paramount importance in order to make early diagnosis. Most patients who are suffering from VDT take vitamin D for osteoporosis, hyperparathyroidism, hypophosphatemia, osteomalacia, or renal osteodystrophy in excessive dosages or at too frequent dosing intervals. With the recent idea that vitamin D is protective of many diseases, vitamin D therapy became very widespread in otherwise normal subjects. Therefore, general practitioners should be suspicious in cases where patients are being treated with pharmacological dosages of vitamin D or its metabolites.

Patients with granulomatous diseases or lymphoma have a widespread active disease when hypercalcemia develops. In such cases, the diagnosis is obvious at the time of presentation.

With modern assays for calcitropic hormones, PTH, 25(OH)D, 1,25(OH)<sub>2</sub>D, one can readily differentiate VDT from other causes of hypercalcemia.

Laboratory tests in patients with symptomatic VDT will show an elevated serum and urine level of calcium and reduced serum level of parathormone (intact), serum 25(OH)D<sub>3</sub> level > 100 ng/ml, and normal or decreased 1,25(OH)<sub>2</sub>D levels (3, 4, 6, 10).

### TREATMENT OF VITAMIN D TOXICITY

Vitamin D toxicity may occur in patients due to any one of the three forms of vitamin D, as previously mentioned in the mechanisms of vitamin D toxicity. Vitamin D (D<sub>2</sub> or D<sub>3</sub>) toxicity is more difficult to manage than toxicity due to its metabolites [25(OH)D or 1,25(OH)<sub>2</sub>D]. In part, this due to the extensive lipid solubility of the parent compound in liver, muscle and fat tissues and corresponding large storage capacity. Thus, the hypercalcemia of parent vitamin D overdose theoretically can last for as long as 18 months, long after dosing is discontinued because of its slow release from fat deposits. An overdose of 25(OH)D can persist for weeks, but excessive levels of 1,25(OH)<sub>2</sub>D will last only for few days.

Treatment of the underlying disease process is essential. It consists of (3, 4, 10, 12):

1. Discontinuation of vitamin D, reduction of dietary calcium (due to decreased intestinal calcium absorption), avoidance of exposure to sunlight and other ultraviolet light sources should be advised to the patients at high risk to develop vitamin D metabolite – hypercalcemia (granulomatous diseases and lymphoma).
2. Treatment of hypercalcemia is usually controlled by restriction of dietary calcium intake and appropriate attention to hydration. Volume depletion results from uncontrolled symptoms leading to decreased intake and enhanced renal sodium loss. This tends to exacerbate or perpetuate the hypercalcemia by increasing Na<sup>+</sup> reabsorption in the thick ascending limb of the loop of Henley (TALH). Thus, appropriate volume repletion with isotonic sodium chloride solution is an effective short-term treatment for hypercalcemia. Once the volume is restored, simultaneous administration of loop diuretics blocks Na<sup>+</sup> and calcium reabsorption in the TALH. Replacing on going sodium, potassium, chloride, and magnesium losses is important if prolonged sodium chloride and loop diuretic therapy is contemplated (4).
3. Therapy with glucocorticoids (GS) may help reduce plasma calcium levels by reducing intestinal calcium absorption by decreasing the synthesis of calcium-binding protein and may down regulate intestinal VDRL and decrease active transcellular transport, increase urinary excretion of calcium and may alter hepatic vitamin D metabolism. GS with doses of 100 mg/d hydrocortisone or its

equivalent usually return serum calcium levels to normal over several days.

4. Bisphosphonate therapy can be useful in severe cases where hypercalcemia of vitamin D intoxication results from decreased osteoplastic bone resorption due to direct effect of  $1,25(\text{OH})_2\text{D}_3$  increase resorption of bone.

## CONCLUSIONS

Vitamin D toxicity (VDT) is not a common cause of hypercalcemia, but can be life-threatening if not identified promptly. There are many forms of exogenous (iatrogenic) and endogenous VDT. Inadvertent excessive use of pharmaceutical

preparations is the most common aetiology of exogenous vitamin D toxicity. Endogenous aetiologies may result from ectopic production of  $1,25(\text{OH})_2\text{D}_2$  in granulomatous diseases, such as sarcoidosis and tuberculosis, or in lymphoma. Many different mechanisms have been proposed to account for VDT, including the vitamin D metabolite itself, VDR number, and activity of 1  $\alpha$ -hydroxylase, inhibition of vitamin D metabolism, and the capacity of VDBP. Mounting evidence that higher levels of vitamin D may have beneficial effects on bone and cellular health predispose to enhanced administration of vitamin D and increased incidence of VDT.

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