

Hypercalcemia and renal function impairment associated with vitamin D toxicity: case report

Hipercalcemia e prejuízo de função renal associados à intoxicação por vitamina D: relato de caso

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ABSTRACT

Nowadays vitamin D (25-OHD) deficiency is supposed to be a global epidemic condition. Expectedly, vitamin D measurement and intake exponentially increased in Brazil in this decade. Although the benefit of vitamin D to general health is still in debate, its indiscriminate use potentially may lead to enhance the incidence of vitamin D intoxication, which is considered a rare disorder. We report a case of a 70 year old diabetic male with chronic renal disease (blood creatinine of 1.6 mg/dL) who progressed suddenly to acute kidney injury (blood creatinine of 5.7 mg/dL) associated with hypercalcemia and high blood levels of vitamin D. Vitamin D and calcitriol were discontinued and hypercalcemia was managed by hydration followed by furosemide. Thereafter, disodium pamidronate was administered and the patient did not undergo on dialysis. It took approximately 14 months to normalize 25-OHD levels and blood creatinine returned to basal levels only after 24 months. The indicated labeling dosage was 2000 IU, but most likely the vitamin D manipulated preparation was higher as the vitamin D blood levels were very high. Although rare, vitamin D intoxication is becoming more frequent as the patients use frequently manipulated preparations that could be subject to errors in the manufacturing and labeling of the tablets or capsules. The present report alerts to the potential increase in the incidence of severe vitamin D intoxication due to the frequent use of this secosteroid as a nutritional supplement. At the same time, it is necessary to improve regulation on the nutrient supplement market.

Keywords: acute kidney injury; poisoning; vitamin D.

RESUMO

Atualmente, muitos brasileiros têm utilizado vitamina D (25-OHD) como suplemento vitamínico para prevenção de diversas doenças crônicas, apesar da falta de dados científicos consistentes sobre o papel deste secosteroide na prevenção de doenças que não as do metabolismo mineral. A intoxicação por vitamina D é rara, mas devido ao seu uso indiscriminado tem ocorrido com maior frequência. Nesse relato, um homem diabético de 70 anos de idade com doença renal crônica (creatinina sérica de 1,6 mg/dL) passou a fazer uso de colecalciferol e calcitriol para recomposição dos níveis de 25-OHD, que eram de 16 ng/mL. O mesmo desenvolveu quadro de lesão renal aguda (creatinina = 5,7 mg/dL), após 45 dias. Este processo emergiu em paralelo ao surgimento de hipercalcemia e níveis circulantes elevados de vitamina D. Foram suspensas a administração de vitamina D e calcitriol, a hipercalcemia foi tratada com hidratação endovenosa, seguida de diurético de alça e posteriormente pamidronato. O paciente, que havia sido encaminhado para diálise, não necessitou desse tratamento. Os níveis de 25-OHD voltaram ao normal 14 meses após a sua suspensão, e os níveis de creatinina voltaram aos patamares anteriores 24 meses após esse evento. A dose prescrita de vitamina D correspondeu a 2000 UI/dia, a qual não é considerada inadequada segundo recomendações atuais. Existe, no entanto, na literatura controvérsia quanto à sensibilidade individual à vitamina D. Não pode ser descartado o uso inapropriado pelo paciente e nem eventual erro de manipulação. Embora raro, o quadro de intoxicação por vitamina D é grave e potencialmente pode levar a complicações clínicas irreversíveis.

Palavras-chave: envenenamento; lesão renal aguda; vitamina D.

INTRODUCTION

Parathyroid hormone and vitamin D (25-OHD) play a key role in calcium metabolism. The first acts directly on bone tissue and kidneys, increasing the flow of calcium into the bloodstream and indirectly in calcium intestinal absorption by stimulating the synthesis of 1,25-dihydroxycholecalciferol (1,25-OH₂D) in the kidneys.

Hypercalcemia may be caused by excessive bone resorption, renal calcium retention, excessive intestinal absorption, or a combination of these factors.¹ Depending on the level of renal impairment, patients with chronic kidney disease (CKD) may have normal, borderline, or below-normal serum calcium levels.

In individuals with end-stage renal disease, hypercalcemia may occur in association with tertiary hyperparathyroidism. Therefore, hypercalcemia in the early stages of CKD may reflect the presence of other morbidities, among which the most common are primary hyperparathyroidism and malignant tumors.^{2,3}

Other less frequent causes of hypercalcemia are sarcoidosis, tuberculosis and other granulomatous diseases, vitamin D toxicity, and immobilization.^{2,4} Concerns over serum levels of vitamin D have been the topic of reports in the media and discussions in the scientific community.

In recent years, the demand for 25-OHD testing has increased significantly, along with the use of vitamin-D supplements. Injudicious use has led to an increase in the number of cases of toxicity, caused both by patients and providers of the medication. This report describes the case of a patient with stable CKD whose renal condition worsened suddenly concomitantly to the onset of hypercalcemia associated with vitamin D toxicity.

CASE REPORT

A 70-year-old Caucasian male individual with hypertension for 18 years, diabetes type 2 for four years, and coronary artery disease had undergone conformational radiation therapy two years earlier on account of prostate cancer. His workup prior to supplementation with vitamin D was as follows: blood urea nitrogen = 70 mg/dL; creatinine = 1.6 mg/dL; hemoglobin = 15.0 g/dL; calcium = 10.2 mg/dL; phosphate = 4.2 mg/dL; parathyroid hormone (PTH) = 93 pg/mL; no proteinuria.

Forty-five days ago he was started on 2000 IU of vitamin D3 per day (his previous dosage of 25-OHD was 16 ng/mL), combined with 0.25 mcg of calcitriol. He reported weakness, nausea, and malaise, associated with worsening renal function (urea = 142 mg/dL; creatinine 5.7 mg/dL). At the time, this is what his tests showed: total calcium = 13.4 mg/mL; ionized calcium = 1.69 mmol/L; 1,25-dihydroxycholecalciferol = 59 pg/mL (normal range 18-72 pg/mL); and PTH = 15.3 pg/mL.

The patient was referred to dialysis because of the deterioration of his renal function. Biochemical assays and imaging tests ruled out multiple myeloma and other tumors. Granulomatous infections were also ruled out. Ultrasonography showed no signs of nephrocalcinosis.

After extensive testing, the only altered test result was the patient's 25-OHD level, which was exceedingly high (7.5 times greater than the normal level at 20 ng/mL; or five times the normal level of 30 ng/mL). The administration of 25-OHD and calcitriol was thus discontinued.

The patient had to be hospitalized three times for three to five days within a period of 60 days for clinical treatment. During these hospitalizations, he was given infusions of 0.9% saline solution with IV furosemide, in addition to IV infusions of pamidronate 90 mg. His renal function improved, while symptoms and calcemia subsided. This pattern of improvement was sustained after serum vitamin D levels decreased. Two years later, creatinine returned to previous levels (Table 1).

The treatment protocol elected for the patient was approved by the Research Ethics Committee of the Hospital and Clinics of the Medical School of Ribeirão Preto-USP and complied with the Declaration of Helsinki. The case report was only produced after the patient signed an informed consent term.

DISCUSSION

The patient described in this case report had CKD and was diagnosed with hypercalcemia and worsening renal function around the time when he was taking oral vitamin D3 supplements and calcitriol. The only significant findings were increased blood levels of 25-OHD and hypercalcemia. The patient progressed well and did not require dialysis once the supplements were discontinued and his calcium levels were managed; after some time, his renal function returned to previous levels.

TABLE 1 PATIENT WORKUP BEFORE AND AFTER THE DISCONTINUATION OF VITAMIN D SUPPLEMENTATION

	Blood urea nitrogen mg/dL	Creatinine mg/dL	Calcium mg/dL	Phosphorus mg/dL	PTH pg/mL	25-OHD ng/mL
Baseline test	70	1.6	10.2	4.2	93	16
Segunda avaliação	142	5.7	13.4	5.8	15.3	150
1 mês após a suspensão de vitamina D	117	4.3	12.2	5.6	8.3	-
4 months after discontinuation	46	1.9	12.3	3.4	-	384
7 months after discontinuation	79	2.2	10.6	-	-	90
9 months after discontinuation	72	2.2	9.7	3.2	55	81
14 months after discontinuation	82	2.1	8.9		58	50
18 months after discontinuation	49	1.8	10.2	-	64	47
24 months after discontinuation	59	1.6	9.7	-	-	-
36 months after discontinuation	48	1.5	9.1	2.7	-	41

In the last decade, vitamin D has been the target of great interest due to the reported association between low vitamin D serum levels and increased risk of cancer, cardiovascular disease, glucose metabolism disorders, neurodegenerative disease, and death.⁵ However, these associations have only occurred in observational studies and have not been confirmed by controlled clinical trials.^{5,6}

These findings have led large numbers of people to resort to vitamin D supplementation. Vitamin D supplements may be taken in the form of ergocalciferol or cholecalciferol, in various dosages and presentations. In this context, albeit a rare event, we found an important side effect of supplementation: vitamin D toxicity.

Toxicity is caused mostly by the prescription of high doses of vitamin D unsupported by a sound diagnosis of vitamin D deficiency or rickets. In addition, patients often take more vitamin D than they were prescribed.^{7,8}

The recommended daily dose of vitamin D varies from 400 IU (during the first year of life), 600 IU (from 1-70 years), and 800 IU in people over 70 years of age.⁹ However, much higher doses are required to cause

renal toxicity. Experimental studies have suggested that exposure to sunlight for at least 20 minutes by an adult equals an oral dose of 10,000 IU of vitamin D.¹⁰

Despite our great endogenous vitamin D production capacity, prolonged or frequent exposure to sunlight does not lead to toxicity. Ex Mechanisms modulate vitamin D synthesis and lead to the production of inactive compounds by thermoregulation.⁶ However, these regulatory processes do not affect exposure to exogenous vitamin D.

In addition, genetics may induce increased susceptibility to exposure to vitamin D and affect vitamin metabolism in the liver and kidneys. Thus, sensitivity to vitamin D toxicity may be genetically determined.¹¹ Most reports of vitamin D toxicity have cited intakes of a minimum of 20,000 to 30,000 IU per day or 100,000 IU per day for at least a month.¹⁰

The prescription held by the patient read 2000 IU per day, a dose unlikely to cause the clinical manifestations and workup alterations seen in this case. No genetic testing was performed on the transport proteins or enzymes involved in the metabolism of vitamin D. Issues pertaining to supplement manipulation could not be ruled out.

The dose in the manipulated supplement might have been greater than the dose prescribed, as reported in similar cases in the literature. Two cases were reported in which one patient ingested 1,864,000 IU (46.6 mg) and another 970,000 IU (24.3 mg) of vitamin D per day, which translated into a dose 1,000 times greater than the one on the label of the administered supplement.¹ In another report, the patient was taking 7.5 mg (300,000 IU) instead of 7.5 IU (300 IU);¹² and in another study the capsules the patient took were labeled as containing 2000 IU, but dosing analysis revealed he was actually taking 4,000,000 IU (100 mg) also due to errors in manipulation.¹³

Hypervitaminosis D increases intestinal calcium absorption and causes hypercalcemia, which in turn may cause several side effects, particularly of a neurological, gastrointestinal and renal nature.¹⁴ Acute hypercalcemia may lead to acute kidney injury by direct renal vasoconstriction and by decreases in extracellular fluid volume (due to anorexia, nausea, vomiting, and decreased ability to concentrate urine). In addition, chronic hypercalcemia may lead to the formation of calculi and to the onset of nephrocalcinosis.^{2,4,15}

The main complaints of the patient described in this case were weakness, nausea, and vomiting. After the discontinuation of vitamin D supplementation, the symptoms subsided within two months, and renal function stabilized after four months. Meanwhile, it took longer - 14 months - for 25-OHD levels to normalize.

The sequestration of 25-OHD in adipose tissue has been traditionally accepted as true. In such setting, adipose tissue functions as storage for 25-OHD with a half-life of approximately two months. However, it is unclear in the literature whether vitamin D clearing in cases of toxicity varies with age. Hypercalcemia may continue for more than six months after the onset of toxicity. Thus, patients should be followed up until 25-hydroxyvitamin D and calcium levels return to normal, due to the risk of recurrence.^{6,16}

As in the cases described above, our patient was taking a manipulated supplement. Therefore, he may have ingested doses greater than the one he was prescribed. However, we could not measure the content of cholecalciferol in the remaining capsules. The general population and health care workers should be advised of the risks inherent to the indiscriminate use of vitamin D alone or in combination with other nutritional supplements.

In addition, stronger supervision is required over the production of manipulated vitamin products and nutritionally enhanced foods. Controlled studies are being developed in several countries to assess ideal serum 25-OHD levels and the potential benefits of using it in the prevention of various chronic diseases.

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