Case Report

Vitamin D Toxicity; Stored and Released from Adipose Tissue?

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Abstract
Vitamin D is a pro-hormone that plays an important role in body calcium regulation. Vitamin D toxicity occurs rarely due to its wide therapeutic index. A 38-year-old Iranian man was admitted to our hospital with a diagnosis of vitamin D toxicity. Laboratory test revealed hypercalcemia and elevated 25-hydroxyvitamin D (25(OH)D) level. Despite the cessation of vitamin D intake and diuretic treatment, he presented four months later with high 25(OH)D level and similar clinical features. Due to the potential release of vitamin D from adipose tissue, serial monitoring of 25(OH)D level is recommended.

Keywords: Vitamin D, toxicity, adipose tissue

Cite this article as: Jenabi A, Razmjou S, Jomhouri R, Ziaie H. Vitamin D Toxicity; Stored and Released from Adipose Tissue? Arch Iran Med. 2016; 19(8): 597 – 600.

Introduction

Vitamin D is a fat-soluble vitamin with anti-inflammatory and immune-modulating properties which plays an important role in calcium homeostasis and bone mineral metabolism.1,2 Vitamin D has two distinct forms; Ergocalciferol or vitamin D2 and vitamin D3 or cholecalciferol. Vitamin D3 is present in the diet (some plants and fish) and vitamin D2 is synthesized from 7-dehydrocholesterol in the skin. Vitamin D, from diet and skin, is then transported to liver where it undergoes 25-hydroxylation, yielding 25-hydroxyvitamin D [25(OH)D].3–5 which is widely distributed in the body and is the major circulating metabolite of vitamin D.4,5

The biologically active form of vitamin D is synthesized in the kidney by conversion of 25(OH)D to 1,25-dihydroxyvitamin D [1,25(OH)2D]. 1,25(OH)2D promotes intestinal calcium absorption and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization.3,5 However, if there are enough supplies of calcium and phosphorus in the body, 25(OH)D is converted to 24,25-dihydroxyvitamin D [24,25(OH)2D] whose role is still unknown but is believed to be a potential biomarker of vitamin D catabolism, an intermediate in the inactivation-excretion process.5

Adipose tissue is considered as the major repository of vitamin D in the body; nevertheless, it is clearly distributed in other tissues like muscles.6,7 The serum concentration of 25(OH)D is an appropriate indicator of vitamin D status, reflecting both the amount of vitamin D absorbed from diet and produced cutaneously.7 This is due to its long serum half life (15 days) and high circulatory levels compared to 1,25(OH)2D (half life of 4-6 hours).3,8 However, 25(OH)D is not an indicator of stored vitamin D.1

The major source of vitamin D for most humans is exposure to sunlight. Few foods naturally contain vitamin D (oily fish such as salmon, mackerel, etc.), and nowadays vitamin D deficiency is recognized as a pandemic.9 Vitamin D deficiency will cause rickets in children and is associated with increased risk of cancer, autoimmune disease, hypertension and osteoporosis.10 The daily recommended requirement for vitamin D intake is 200 IU/day for children, 400 IU/day for adults below 50 years of age, 600 IU/day between ages 50 and 70 and thereafter 800 IU/D.1,4 The tolerable upper intake level of vitamin D likely to cause no potential harm (UL) is currently defined as 2000 IU/day both in North America and Europe.11 Because of the wide therapeutic index, vitamin D toxicity occurs rarely but there are still iatrogenic cases due to self-administered medication or, to a lesser extent, fortified food products.10,12 Hypercalcemia is mainly responsible for vitamin D toxicity symptoms. The symptoms have a wide range including headache, bone pains, arrhythmia, loss of appetite, frequent urination, nervousness, itching, kidney stones and gastrointestinal symptoms such as diarrhea, nausea, vomiting and constipation.13,14

In this paper, we present a classic case of vitamin D toxicity whose 25(OH)D level was elevated once again after four months despite the fact that supplements and vitamin D intake were ceased and the patient underwent treatment.

Case Report

A 38-year-old Iranian male was admitted to our hospital because of bloodshot eyes, arthralgia, ostealgia, and weight loss for 18 months. The patient was first presented to his clinician with a complaint of non-itchy red eye without discharge or any other effect on his vision. He had received treatment for conjunctivitis several times. Two months later, the patient experienced generalized pruritus without any other dermatological symptoms, unresponsive to common medication. After three months, he complained of a progressive ostealgia, starting at lower extremities, particularly in the plantar regions, and fatigue,
weakness, arthralgia and hypohidrosis. He also mentioned a significant weight loss, 16.5 kilograms over the past 18 months. No sign of arthritis was observed. He also mentioned a mild hearing loss for a couple of months prior to his admission.

The patient is a professional bodybuilder since early adolescence. He has consumed various types of minerals, vitamins and protein supplements. Remarkably, he gave a history of weekly intramuscular (IM) injections of vitamin D (300,000 IU) for 10 years, which subsequently increased to two IM injections per week as his symptoms aggravated.

On physical examination, he was conscious and well-oriented. His vital signs were normal as follows: blood pressure 132/78 mmHg, pulse rate 72 per minute, respiratory rate 16 per minute and temperature 36.8°C. His conjunctiva was slightly pale. Heart, chest and abdomen were found normal. Extremities were also normal on neurological examination with no sign of edema or clubbing.

On ECG, he had short QT intervals (Figure 1). In ophthalmology assessment, keratopathy band was observed (Figure 2). Myringosclerosis, conductive hearing loss and type E tympanometry were reported in his ENT consultation. The CT scan of temporal bone showed no pathology.

CT scan without contrast was performed and several nephrolithiasis and nephrocalcinoses were found (Figure 3). He was treated with transurethral ureterolithotripsy (TUL) because of further obstructive symptoms.

On laboratory investigation, hypercalcemia and high levels of BUN and creatinine were reported (Table 1). On further assessment, the 25(OH)D level was reported at 310 ng/mL (normal range: 20–100 ng/mL). Therefore, a diagnosis of vitamin D toxicity induced acute kidney injury and hypercalcemia was stated for him. The intake of all supplements and vitamin D was stopped and he was treated with intravenous fluid (2/3 of his urine output) and furosemide 40 mg three times per day. After 25 days, his creatinine and calcium levels gradually declined and his symptoms improved. The 25(OH)D level was reported at 105 ng/mL and he was discharged. He was advised not to take any supplements or vitamin D injections afterwards.

Despite discontinuing vitamin D intake, the patient presented four months later with severe ostealgia, 25(OH)D level of 500 ng/mL, and high creatinine and calcium levels (Table 1). He was admitted once again and further work up was done. Hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus antibody were negative. Skull X-ray was normal. Urine and blood protein electrophoresis were normal without spike. A thorough panel of the rheumatologic tests was performed with no
abnormality found (Table 2).

His second hospital stay lasted 27 days and he was treated with intravenous fluid (2/3 of his urine output) and furosemide 40 m three times per day. The 25(OH)D level declined to 263 ng/mL and the calcium level to 10.2 mg/dL. He was discharged with a prescription of calcium-restricted diet, and furosemide 40 mg three times per day. Further follow up was recommended.

### Discussion

Vitamin D is a principal pro-hormone in body which is affected by many factors including dietary intake, supplement, latitude, skin color and sun exposure. Vitamin D toxicity rarely happens due to the wide therapeutic index, tightly regulated synthesis of 1,25(OH)2D and the characteristics of adipose tissue as a depot for storage and release of vitamin D. In this case report, a patient with classic symptoms of hypervitaminosis D is presented whose 25(OH)D level was reduced after cessation of all supplements and proper treatment; however, after four months, the 25(OH)D level was remarkably elevated and the patient’s symptoms returned.

Vitamin D, regardless of origin, is an inactive pro-hormone. It is transported to the liver by vitamin D binding protein (DBP).
and it is metabolized to 25(OH)D by a cytochrome P450 (CYP) enzyme, likely CYP2R1.\textsuperscript{5,16} The further hydroxylation reaction occurs in the kidney and is tightly regulated by the induction of CYP27B1 enzyme.\textsuperscript{15} The production of CYP27B1 is stimulated by parathyroid hormone (PTH) which is secreted in response to hypocalcemia. CYP27B1 is suppressed by calcitriol (1,25(OH)\textsubscript{2}D) and hyperphosphatemia.\textsuperscript{16} This metabolic step constitutes the basis of vitamin D regulation that is central to calcium and phosphate homeostasis.

Vitamin D is a fat soluble vitamin and it is primarily excreted in bile; however, the exact mechanism or the related excretion products are not clear.\textsuperscript{17} Adipose tissue is the predominant storage site for vitamin D. Following vitamin D intake, it is rapidly distributed in adipose tissue and then slowly released into systemic circulation. These characteristics of accumulation and release could have the potential as a protective mechanism against toxicity, maintaining the balance of plasma concentration of vitamin D level.\textsuperscript{8,19} The issue of storage could be confirmed by the fact that inducing a deficiency state in a laboratory animal takes time.\textsuperscript{20} Furthermore, the literature states an estimation of four months for biological activity of vitamin D in human plasma after cessation of large doses.\textsuperscript{21}

Adiposity is inversely associated with 25 (OH)D level and obese people have lower 25(OH)D level which might be due to decreased bioavailability of vitamin D after it is deposited in fat tissue.\textsuperscript{19} Vitamin D is a fat soluble vitamin stored and sequestered in adipose tissue.\textsuperscript{22} Conversely, Blum et al.\textsuperscript{23} found a positive correlation between serum and fat tissue D3 levels using liquid chromatography mass spectrometry (LC/MS). Heaney et al.\textsuperscript{23} indicated that the amount of vitamin D in adipose tissue is too small to affect 25(OH)D level during weight loss. In another study conducted by Pramyothin et al.,\textsuperscript{24} despite remarkable loss of fat mass after Roux-en-Y gastric bypass surgery, vitamin D in adipose tissue did not contribute significantly to serum 25(OH)D level. Conversely, Lin et al.\textsuperscript{25} observed a positive association between adipose tissue and systemic 25(OH)D concentration, suggesting adipose tissue as a storage site that releases vitamin D during weight loss. Therefore, further investigation is warranted to ascertain whether vitamin D is stored in body and then released or it is sequestered in adipose tissue in obese individuals.

Vitamin D supplements are available over the counter and obese people have lower 25(OH)D level which might be due to decreased bioavailability of vitamin D after it is deposited in fat tissue.\textsuperscript{19} Vitamin D is a fat soluble vitamin stored and sequestered in adipose tissue.\textsuperscript{22} Conversely, Blum et al.\textsuperscript{23} found a positive correlation between serum and fat tissue D3 levels using liquid chromatography mass spectrometry (LC/MS). Heaney et al.\textsuperscript{23} indicated that the amount of vitamin D in adipose tissue is too small to affect 25(OH)D level during weight loss. In another study conducted by Pramyothin et al.,\textsuperscript{24} despite remarkable loss of fat mass after Roux-en-Y gastric bypass surgery, vitamin D in adipose tissue did not contribute significantly to serum 25(OH)D level. Conversely, Lin et al.\textsuperscript{25} observed a positive association between adipose tissue and systemic 25(OH)D concentration, suggesting adipose tissue as a storage site that releases vitamin D during weight loss. Therefore, further investigation is warranted to ascertain whether vitamin D is stored in body and then released or it is sequestered in adipose tissue in obese individuals.

Vitamin D supplements are available over the counter and nowadays, there is a growing concern regarding “vitamin D deficiency” and the consequent potential issues, as in this case report, the patient consumed vitamin D supplements for approximately 10 years without any medical problem. Thus, careful dosing of vitamin D is important. Furthermore, considering the role of adipose tissue as the main storage site that releases vitamin D, serial monitoring of 25(OH)D level could be a good indicator of vitamin D status in patients treated for vitamin D toxicity.

References