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Resistant Hypertension and Renal Injury Related to High-Dosage Vitamin D Intake: A Case Report.

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KEYWORDS

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ABSTRACT:

The use of vitamin D in outpatient care has increased exponentially in recent years. The replacement for vitamin D deficiency (lower than 30nmol/l) for enhanced bone health is consensual in the literature. The real benefits of supplementing vitamin D for extra-skeletal or articular disease are unclear. Although there is no evidence, an off-label use of massive doses for joint disease treatment is observed, with an obvious risk of toxicity. Misuse by iatrogenic or self-medication can lead to toxicity, which may occur with plasma concentrations above 150ng/ml. There is a report of a 1600% elevation in the exposition to toxicity in the past decade in the United States. Vitamin D toxicity features are often related to hypercalcemia, with neuropsychiatric, gastrointestinal, cardiovascular, and renal findings. We describe a case of a 57-year-old man who presented with resistant hypertension and acute kidney injury. He had edema, flushing, headache, and recent elevation of a former well-controlled hypertension. Laboratory findings were high creatinine levels, proteinuria, and a vitamin D dosage of 156ng/ml. He had an ankylosing spondylitis diagnosis and tried to relieve its symptoms by using vitamin D, 10000ui, once daily in the last six months, prescribed by a nutritional specialist. The blood pressure levels, and glomerular filtration rate were near average three months after suspension, but vitamin D levels remained high (>100ng/ml) for 12 months. Clinicians and the population should be aware of these risks.

1. Introduction

Vitamin D is a steroid hormone whose primary function is the regulation of bone metabolism, both calcium and phosphorus.[1] It acts in almost all tissues by controlling hundreds of genes in several body functions.[2] The two primary forms of vitamin D are D2, which is disposable in plants (ergosterol), and D3, which is endogenously synthesized in the skin tissues after sun exposure, as well as obtained by the intake of cod fish liver and oily fishes, as salmon.[3]

There is an essential role of both types in the feedback mechanism of parathyroids for calcium regulation reaching narrowed concentrations (8.9–10.1 mg/dL); low calcium concentrations trigger an increase in parathyroid hormone (PTH) secretion, which leads to increased tubular reabsorption of calcium by kidneys and resorption of calcium from bone; there is more renal 1,25(OH)2D production, with enhanced intestine calcium absorption; these homeostatic mechanisms work for calcium homeostasis.[4]

Vitamin D deficiency is a common medical finding with many causes and consequences; the leading causes are low solar exposition, winter and air pollution, drugs and supplements (antiepileptic, corticoids, antiretroviral, rifampicin), renal injury/failure, liver failure, obesity, and intestinal absorption; main consequences are neuropsychological effects, hypertension, autoimmune and allergic disorders, type-2 diabetes, skin ichthyosis, low cancer vigilance and bone diseases (osteoporosis, osteomalacia, and osteoarthritis).3 Given these consequences, the 25(OH)-vitamin D supplementation to reach normal levels (20-

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40 ng/ml) is consensual in literature, especially in patients with high risk for consequences.[5]

Although there is some circumstantial evidence [6] and reports of the safety of high-dosage intake of vitamin D for immunological diseases [7,8], toxicity by vitamin D is now a concern for physicians because its occurrence is often related to over supplementation, either by iatrogenic or self-medication, which can lead to plasma concentrations above 150ng/ml, and, according to National Poison Data System data, the average, which was 196 exposures per year from 2000 to 2005, increased by 1600% between 2005 and 2011, reaching an annual average of 4,535 exposures.[9]

Cardiovascular and renal complications have been associated with vitamin D toxicity, such as hypertension, QT interval enlargement, renal injury, and renal lithiasis.[10]

2. Objective

Since vitamin D supplementation is a world-spread current practice and its indication enlarged with some high-dosage protocols, the risk of toxicity is a real problem, the objective is to report a case of vitamin D toxicity.Submit your manuscript electronically for review.

3. Case Report

A 57-year-old man presented to the medical office complaining of non-controlled hypertension.

He was a regular patient with well-controlled hypertension for many years, with Olmesartan 20mg/day, Amlodipine 5mg/day, and Hydrochlorothiazide 25mg/day. His medical history included ankylosing spondylitis, more than ten years from diagnosis, with many episodes of pain crisis in his life, and he had been in treatment with various clinicians; he used phenylbutazone, diclofenac, adalimumab, prednisone, pregabalin, and other non-steroidal anti-inflammatory agents, in a non-regular basis. There was also gastric peptic disease, with omeprazole irregular use, and hypothyroidism, using levothyroxine 50mcg/day, well controlled.

His blood pressure had been well-controlled, except for rare episodes of elevation associated with non-steroidal anti-inflammatory drugs' eventual use, with rapid return to normal levels after diuretic or amlodipine transient dose elevation. He never had cardiac or renal repercussions.

His psychosocial profile included professional and pain-related stress, but he was not using anti-depressive medication.

He wasn't in cardiology assessment for the past three years. Six months before, he, searching for back pain relief, initiated, with a medical prescription, a new treatment with 10000 UI/day cholecalciferol orally, with partial pain relief.

This time, the symptoms and signs were different; he had leg edema, flushing, and headache, with persistent high blood pressure (BP) levels and weight gain (Table 1). His general practice had duplicated olmesartan, amlodipine, and hydrochlorothiazide dosages but failed. Nebivolol, 5mg/day, was initiated, and his BP was 160/92mmHg, heart rate (HR) was 56 bpm, weight was 78kg (BMI= 27,6kg/m2), and 5 kg over the habitual weight. There was a +++/4 soft edema in both legs, under the knees.

Table 1. Symptoms and signs presented in the patient assessment over time.

,	2018 Jun	2021 Apr	2022 Jul	2023 Aug
Timing	Baseline	Toxicity	1 y after	2 y after
Drugs for hypertension	3 (medium dosage)	4 (high dosage)	4 (medium dosage)	4 (medium dosage)
BP (mmHg)	132/68	160/92	142/80	120/78
HR (bpm)	68	56	52	56
BMI ($kg/cm^{2)}$	24.4	27.6	25.4	25.0
Edema	0	+++/4 Under Kness	+/4 Ankle	+/4 Ankle

y= years, BP: blood pressure, HR: heart rate; BMI: body mass index. Source: authors

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Laboratory findings at the toxicity moment (2021, pandemic) showed high levels of plasmatic creatinine and calcium and low levels of plasmatic parathyroid hormone. Urinary protein was also detectable. Electrocardiogram (ECG) had no changes. The abdominal image showed renal lithiasis bilateral after toxicity (Table 2). The treatment included interruption of vitamin D intake, high water intake, and antihypertensive drug adjustment. After the acute toxicity phase, the patient presented hypokalemia and persistent proteinuria.

Table 2. Laboratory and Image findings.

Date	2018Jun	2021Apr	2022Jul	2023Aug
Timing	Baseline	Toxicity	1 y after	2 y after
Plasmatic Creatinine (RV= 0,6-1,2 mg/dl)	1,00	1,55	0,98	1,04
GFR (MDRD) ml/min/ 1,73m^2	82,8	49,4	83,8	78,0
Plasmatic Calcium (RV=8,8-10,4 mg/dl)	8,7	10,9	9,9	9,2
Plasmatic Potassium (RV= 3,5-5,5 mEq/l)	4,3	3,5	3,3	3,6
Plasmatic Parathyroid hormone (RV= 12-88 pg/ml)	-	4,30	-	14,30
1,25(OH) Vitamin D (RV= 20-40 ng/ml)	28	156	106	36
Urinary Protein (150mg/24h)	0	1205	446	2443
ECG	Normal	Normal	Normal	Normal
Abdominal Image	Normal	-	-	Renal lithiasis bilateral

Y: years, GFR: glomerular filtration rhythm, MDRD: modification of diet in renal disease formula, RV: reference value, ECG: electrocardiogram. Source: authors

The dosage of 1,25(OH) Vitamin D decreased slowly in 2 years after the patient stopped the vitamin D use (Figure 1). The patient is now using olmesartan 40mg/day, amlodipine 10mg/day, spironolactone 25mg/day, and nebivolol 5mg/day. The change for spironolactone occurred because hypokalemia occurred. He has persistent and reduced ankle edema and BP levels on control with four drugs. A rheumatologist treats the ankylosing spondylitis with secukinumab, an interleukin-17 blocker. A renal team works on residual nephropathy (persistent proteinuria).

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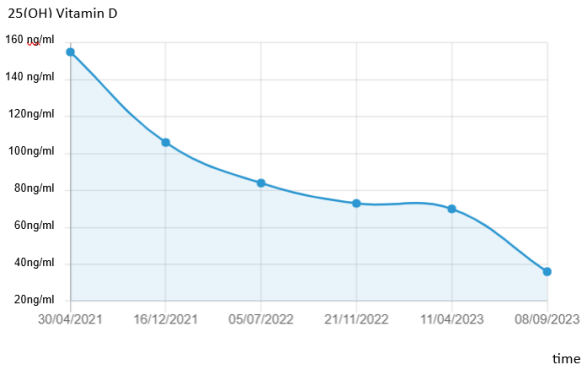

Figure 1. 1,25(OH) VD decreasing levels after stopping intake.

4. Discussion

Vitamin supplements are disposable in the market, acquired with no medical prescription, and there is a disseminated belief that vitamin D has no side effects with many healthy effects, such as immunity gain, skin and hair health enhancement, bone strength, and heart disease prevention. Some of these have a scientific basis, some of them do not. Although the well-recognized vitamin D replacement role in preventing various diseases, this use is not guided by previous laboratory dosage or risk assessment so this self-medication could lead to toxicity.[1]

Iatrogenic toxicity is concerning because it counteracts the medical principle of "do not harm." Physicians who prescribe vitamin D replacement for a deficiency detected in laboratory exams need to explain to patients the use period and monitor this replacement with sequential dosages once some patients prolong its use indefinitely.[10]

Another type of medical prescription of vitamin D is in expansion in practice, which is the high dosage, orally or injectable, for multiple diseases, as seen in recent literature publications, which advocate the vitamin D resistance hypothesis for many autoimmune diseases; this hypothesis considers gene polymorphism, environmental effects, use of corticosteroids, and exacerbating factors, as age and low sun exposition.[6] The most studied of these diseases are multiple sclerosis and psoriasis.[6-8] Some authors reported that the high dosage vitamin D intake has biological plausibility and, if parathormone levels don't fall on high dosage prescription, this would confirm the resistance hypothesis.6 However, the research only recently described the metabolism, mechanism of action and pleiotropic effects.[11] Most randomized controlled studies carried out for vitamin D effect assessment did not restrict their study to vitamin D deficiency, and there were no significant effects on the primary outcomes.[12] A five-year Finish study, randomized, placebo-controlled, with 2495 men, published last year, failed to demonstrate differences in the hard objectives of cancer, cardiovascular events, and mortality.[13] There is a need for better, well-designed studies to answer if supplementation for deficiency or high dosages for the immune disease is safe and effective and determine the dose-response relationship for each medical condition; for now, if there is a medical decision for its use, this should be shared with the patient, with a clear explanation of the risks, and followed by near monitoring and experienced physicians.[8] In a systematic review, Pantoja et al. (2023) reported that many toxicity cases were related to dosage or follow-up neglect.

The present case had a moderate and partially reverted toxicity caused by high dosage intake for an impairing autoimmune disease, ankylosing spondylitis, with a half-preconized dosage.[6] The patient presented renal injury, proteinuria, edema, and resistant or secondary hypertension; he was treated as an outpatient. The hypercalcemia and hypercalciuria effects, however, could be more aggressive, with neuropsychiatric findings from lethargy to coma; gastrointestinal, such as anorexia, vomiting, and constipation; cardiac arrhythmia and large QT interval; and renal injury, failure, nephrolithiasis, and nephrocalcinosis.[1,10,14].

Two remarkable findings after the acute toxicity phase were proteinuria and hypokalemia. Although there are conflicting studies and case reports on the reduction of proteinuria with vitamin D supplementation in type-2 diabetic patients, there is a recommendation for deficiency correction in patients with proteinuria.[15-18] Mild hypokalemia has been reported in vitamin D toxicity.[19] This case presents proteinuria, probably after a glomerular impairment; nephrologists haven't performed a renal biopsy yet since there was a clinically good response. The mild and transient hypokalemia after the toxicity phase, quickly corrected with spironolactone, could also be attributed to the thiazide diuretic therapy he used before.

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Patients with rheumatic or immunologic disease, in association with hypertension or other cardiovascular risk factors, should be followed by specialists since inflammatory activation is itself a risk factor for significant complications for the heart, kidneys, and mortality; this should be more intensive if the patient has symptoms and signs of resistant or secondary hypertension.[20]

5. Conclusion

Vitamin D toxicity is a real possibility once supplementation and treatments with high dosages are expanding. There is a need for better population education about risks, dosage, and period of using vitamin D supplements. High-dosage vitamin D therapy for autoimmune diseases should be followed closely by experienced physicians. Prospective randomized, placebo-controlled trials are needed to clear the role of supplementation and high dosage protocols. Renal function, metabolic exams, cardiologic assessment, and neurologic vigilance are justified medical cautions when patients are on vitamin D replacement or treatment. Medical workup of resistant hypertension in patients with associated inflammatory diseases, with or without vitamin D prescription, must be conducted by specialists.

Vitamin D toxicity has potential high-risk complications, such as neuropsychiatric, cardiovascular, renal, and metabolic. The population and physicians must be aware of these risks.

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