ACUTE AND DELAYED CONSEQUENCES OF VITAMIN D INTOXICATION: TWO CASE REPORTS

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Abstract:

Background

Vitamin D intoxication (VDI) is a rare cause of kidney injury, but it can have fatal consequences. We would like to present two cases of patients in whom high doses of vitamin D intake led to significant health problems

Case Presentation

The first case is a 68-year-old woman taking approximately 20,000 IU of vitamin D daily. On admission, laboratory tests showed elevated renal function parameters, hypercalcemia, and elevated serum vitamin D concentration. The second case was a 71-year-old man intoxicated with vitamin D two and a half years earlier, as a consequence the patient was included in the chronic hemodialysis program. Because of a potentially reversible cause of kidney disease – signs of tubulointerstitial nephritis and persistent high serum vitamin D concentration, attempt of hemodialysis withdrawal was made, steroid therapy was administered, without expected effect.

Discussion

A persistent problem is supplementing with high doses of vitamin D without medical supervision. It is estimated that a significant number of people in the U.S. population takes more than 4,000 IU of vitamin D per day. These are the doses that have been linked to numerous health benefits by unverified sources, even though in recent years scientific studies have been able to refute some of these claims. Based on the two cases we have presented, we want to emphasize how serious the consequences of vitamin D intoxication can be.

Conclusions

Vitamin D intoxication may cause acute kidney injury, and in some cases may lead to end-stage renal failure and require renal replacement therapy.

Keywords: hemodialysis, hypercalcemia, renal failure, vitamin d intoxication.

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Background

Vitamin D intoxication (VDI) is a rare cause of kidney injury even though taking higher-than-recommended doses of vitamin D supplementation is common in the general community. This is due to easy accessibility of supplements and high prevalence of unverified data on health benefits of taking these products. It is worth to ask patients carefully about the dietary supplements they are taking, especially when kidney injury is combined with hypercalcemia, because of the potentially fatal consequences of VDI [1].

We describe cases of two patients who suffered from VDI caused by excessive long-term intake of over-the--counter vitamin D supplements. Patient A presents acute consequences of VDI, while patient B presents effects of VDI years after the last oral intake of vitamin D.

Case presentation

Patient A

A 68-year-old female patient previously treated only for hypertension presented to the emergency room with

a history of progressive weakness and anemia on laboratory tests performed by a primary care physician. Laboratory tests showed elevated ionized calcium concentration of 1.75 mmol/l (normal range 1.15-1.35 mmol/l) and elevated total serum calcium concentration 13.5 mg/dl (8.6-10.2 mg/dl), significantly elevated creatinine concentration 5.4 mg/dl (0.5-0.9 mg/dl), urea concentration 98 mg/dl (15-43 mg/dl) and anemia with hemoglobin of 9.3 g/dl (11-18 g/dl). Parathyroid hormone concentration was normal. The patient was admitted to the nephrology department for further diagnostics and treatment.

On admission, the patient's main complaints were: pruritus of the whole body (persistent for six months), unintended weight loss of 4 kg in the last 8 months, abdominal pain and constipation. On physical examination: blood pressure and pulse rate were within normal limits. Lung auscultation revealed normal symmetric vesicular sound. The patient's skin presented numerous excoriations on the back. The abdomen was soft, non-tender, without peritoneal signs or pathological masses, with numerous pale striae and a small umbilical hernia. Peripheral edema was absent.

During hospitalization the patient admitted to long-term intake of high doses of vitamin D (approximately 20,000 IU per day) and calcium supplements. 25-hydroxyvitamin D serum concentration was 279.5 ng/ml (20-80 ng/ml). Hypercalcemia was treated with intensive fluid therapy, diuretics, and glucocorticosteroids. Antihistamines were used in the treatment of severe pruritus. Intravenous iron was given because of decreased serum iron concentration and anemia.

Because of suspicion of multiple myeloma, x-rays of the skull and pelvis were performed, as well as serum protein electrophoresis, urine and blood immunofixation tests and concentration of light chains of immunoglobulins, showing a kappa/lambda serum ratio of 2.171 and finding no osteolytic lesions in radiological studies. Bone marrow biopsy was not performed as indicated by a consultant hematologist.

During hospitalization abdominal ultrasound was performed with findings as follows: a few benign lesions and calcium deposits, as well as reduced parenchymal layer with a loss of corticomedullary differentiation in the right kidney. Gastroscopy was performed finding several elevated erosions in the antrum. The urease test was negative. No abnormalities were found in a colonoscopy apart from melanosis in the colon.

After 12 days of hospitalization there was an improvement in renal function, blood creatinine concentration decreased to 3.2 mg/dl, and urea concentration decreased to 82 mg/dl. We observed a consistent decrease in total serum calcium concentration to 10.9 mg/dl and ionized calcium with a final day result of 1.47 mmol/l. Despite a further drop in hemoglobin concentration, blood was not transfused due to a lack of patient consent.

We observed a significant reduction in pruritus. The patient was released home with a recommendation of withdrawal of vitamin D and calcium supplementation.

Patient B

A 71-year-old male patient with a history of end-stage chronic kidney disease secondary to VDI was admitted to the hospital for a re-assessment of the purposefulness of further hemodialyses. The patient had become intoxicated with vitamin D two and a half years earlier, at which time intermittent hemodialysis was initiated. With stable renal function parameter results and normal diuresis, it was possible to discontinue hemodialysis for six months. About a year and a half earlier, the patient was put back on a chronic hemodialysis program because of increasing symptoms of chronic kidney disease.

The patient also presented a history of hypertension, permanent atrial fibrillation, dilated cardiomyopathy, hypertensive retinopathy, spondylosis, obesity, restless legs syndrome, benign prostatic hyperplasia and hemodialysis-catheter-related sepsis five months earlier. The patient denied kidney disease before the VDI episode.

On the initial examination the patient presented with irregular heartbeat, hypertension, and pain in the shoulders, lumbar and cervical spine but denied any abdominal tenderness, muscle weakness or signs of infection.

The patient was admitted to the hospital to start treatment - findings of tubulointerstitial nephritis with nephrocalcinosis on kidney biopsy indicated a potentially reversible cause of the disease. Persistently high blood concentration of vitamin D were noted, even though the patient had not taken vitamin D supplementation for more than two and a half years.

Initially hemodialyses were discontinued and the patient received intravenous diuretic therapy. He had a serum total calcium concentration in the normal range of 9.1 mg/dl (8.6-10.2 mg/dl), with a parathyroid hormone concentration of 78.7 pg/ml (15-65 pg/ml) and elevated 25OHD serum concentration of 91.3 ng/ml (20-80 ng/ml). A test for active vitamin D (1,25 (OH)2) was also taken, and its concentration was low: 19.2 pg/ml (20-63 pg/ml).

The patient received 125 mg of methylprednisolone on days 6-8. Steroid therapy was continued orally with prednisone. Due to low diuresis despite high dose intravenous diuretic therapy and increasing peripheral edema, hyperkalemia and increasing creatinine and urea concentration, the patient underwent hemodialysis on day 7 of hospitalization. Tests were performed for other possible causes of tubulointerstitial nephritis: tuberculosis, syphilis and multiple myeloma, all turned out to be negative.

After 11 days of hospitalization, the patient was released from the hospital with recommendations for further renal replacement therapy and steroid therapy. A date has been set for another hospitalization to assess the effects of implemented treatment, at which the patient did not appear.

Discussion

Various non-medical sources attribute remarkable health benefits as an effect of taking high doses of vitamin D. In recent years, many randomized controlled clinical

trials and meta-analyses have been published that do not support some of these claims. Increasing serum 25 OHD concentration does not significantly affect the risk of cancer, cardiovascular incidents, type 2 diabetes, falls or fractures. While taking doses above 4,000 IU daily is associated with a risk of hypercalcemia and hypercalciuria [2]. Due to widespread access to unverified medical knowledge on the internet and easy access to vitamin D supplements, many people take supplements on their own without medical supervision. It is estimated that in 2013-2014, more than 3% of the U.S. adult population took supplements containing 4,000 IU (100 µg) or more vitamin D [3]. There are over-the-counter preparations on the market that contain very high unit doses of cholecalciferol up to as much as 50,000 IU (1,250 µg) per capsule. A significant problem is also the content of vitamin D in unlicensed supplements, in many reports exceeding many times the dose declared on the package [4].

Symptoms of VDI depend on vitamin D metabolism and function. Vitamin D is lipophilic, in the body it is stored in adipose tissue with an elimination half-life of approximately 2 months. Both 25OHD and 1,25 (OH)2D circulate bound to vitamin D binding protein (DBP), while the free form of 1,25 (OH)2D is considered the metabolically active form. Although it is 1,25OH2D that is the active form of vitamin D, toxicity may also result from the high concentration of circulating 25OHD through direct activation of vitamin D receptors and dissociation of 1,25OH2D from DBP associated with excess circulating 25OHD[5, 6].

Vitamin D is involved in the regulation of more than 1000 genes [7]. The clinical manifestations of VDI can be varied but are closely related to hypercalcemia and include weakness, nausea, vomiting, polyuria, dehydration, abdominal pain and anorexia [8]. Hypercalcemia is the leading cause of AKI in VDI. There are three potential causes of AKI in hypercalcemia: spasm of the afferent arteries resulting in decreased glomerular filtration rate, decreased antidiuretic hormone reactivity resulting in dehydration and tubular damage, and fibrosis due to long-term calcium deposition in the kidney [9].

Further complications of VDI can be serious. Patients with chronic kidney disease are much more prone to complications [10]. Elevated vitamin D concentrations may persist long after supplementation is discontinued due to its long half-life [11]. This may be partly related to the accumulation of fat-soluble vitamin D in adipose tissue, as well as to the effect of parathormone itself, prolonging the half-life of vitamin D, as has both been reported in the past [12, 13].

Patient A, although she originally arrived at the hospital due to anemia, presented with symptoms of hypercalcemia, such as abdominal pain, constipation, fatigue, as well as worsening renal function and nephrolithiasis in ultrasonography. Due to taking high doses of vitamin D supplements, her serum 25OHD concentration was as high as 279.5 ng/ml (698.75 nmol/l) while concentrations above 150 ng/ml (375 nmol/l) are already a sign of VDI [14]. However, it is worth mentioning that high vitamin D concentrations correlate neither with serum calcium concentration nor with clinical symptoms [15]. The applied treatment of hypercalcemia had the expected effect, the symptoms reported by the patient significantly decreased. The blood calcium concentration decreased, and a reduction in creatinine and urea concentration was achieved.

Patient B presents with renal failure associated with hyperparathyroidism as well as VDI years ago. Despite ending supplementation of vitamin D two and a half years earlier, the patient presented with high serum 25OHD concentration at the time. Also despite a long time since the cessation of vitamin D supplementation, steroid treatment was attempted. Immediately in the hospital, the expected effect was not obtained, and it was necessary to continue intermittent hemodialysis. There are no data on the patient's further course of the disease because he did not appear for a scheduled visit.

Conclusion

Vitamin D intoxication can cause both acute and delayed health problems so, due to the prevalence of patient use of dietary supplements, it is worth to remember VDI as a possible cause of hypercalcemia and renal failure.

References

1. Kaur P, Mishra SK, Mithal A. Vitamin D toxicity resulting from overzealous correction of vitamin D deficiency. Clin Endocrinol (Oxf), 2015; 83 (3): 327-331
2. Bouillon R, Manousaki D, Rosen C et. al. The health effects of vitamin D supplementation: evidence from human studies. Nat Rev Endocrinol, 2022; 18 (2): 96-110
3. Rooney MR, Harnack L, Michos ED et al. Trends in Use of High-Dose Vitamin D Supplements Exceeding 1000 or 4000 International Units Daily, 1999-20JAMA, 2017; 317 (23): 2448-2450
4. Taylor PN, Davies JS. A review of the growing risk of vitamin D toxicity from inappropriate practice. Br J Clin Pharmacol, 2018; 84 (6): 1121-1127
5. Bell DA, Crooke MJ, Hay N, Glendenning P. Prolonged vitamin D intoxication: presentation, pathogenesis and progress. Intern Med J, 2013; 43 (10): 1148-1150
6. Deluca HF, Prahl JM, Plum LA. 1,25-Dihydroxyvitamin D is not responsible for toxicity caused by vitamin D or 25-hydroxyvitamin D. Arch Biochem Biophys, 2011; 505 (2): 226-230
7. Carlberg C. Vitamin D: A Micronutrient Regulating Genes. Curr Pharm Des, 2019; 25 (15): 1740-1746
8. Ozkan B, Hatun S, Bereket A. Vitamin D intoxication. Turk J Pediatr, 2012; 54 (2): 93-98
9. Aihara S, Yamada S, Oka H, et al. Hypercalcemia and acute kidney injury induced by eldecalcitol in patients with osteoporosis: a case series of 32 patients at a single facility. Ren Fail, 2019; 41 (1): 88-97
10. Hsu RK, Hsu CY. The Role of Acute Kidney Injury in Chronic Kidney Disease. Semin Nephrol, 2016; 36 (4): 283-292
11. Araki T, Holick MF, Alfonso BD, et al. Vitamin D intoxication with severe hypercalcemia due to manufacturing and labeling errors of two dietary supplements made in the United States. J Clin Endocrinol Metab, 2011; 96 (12): 3603-3608
12. Ziaie H, Razmjou S, Jomhouri R et al. Vitamin D Toxicity; Stored and Released from Adipose Tissue?. Arch Iran Med, 2016; 19 (8): 597-600
13. Taskapan H, Vieth R, Oreopoulos DG. Unusually prolonged

vitamin D intoxication after discontinuation of vitamin D: possible role of primary hyperparathyroidism. Int Urol Nephrol, 2008; 40(3): 801-805
14. Marcinowska-Suchowierska E, Kupisz-Urbańska M, Łukaszkiewicz J et al. Vitamin D Toxicity-A Clinical Perspective. Front Endocrinol (Lausanne), 2018; 9: 550
15. Lee JP, Tansey M, Jetton JG et al. Vitamin D Toxicity: A 16-Year Retrospective Study at an Academic Medical Center. Lab Med, 2018; 49 (2): 123-129