PBR
Pharmaceutical & Biomedical Research

April 2023. Volume 9. Number 2

Case Report

Secondary Hypertension Induced by Vitamin D_3: A Case Report and Literature Review

Seyyed Javad Boskabadi[1], Saeed Kargar-Soleimanabad[2], Sahar Khosravi[2], Mohammad Parsa-kondelaji[3], Farhad Gholami[4*]

1. Department Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
2. Student Research Committee, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
3. Department of Hematology and Blood Banking, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
4. Department of Internal Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.

*** Corresponding Author:**
Farhad Gholami, Assistant Professor.
Address: Department of Internal Medicine, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
Phone: +98 (11) 33364037
E-mail: f.gholami@mazums.ac.ir

Article info:
Received: 13 Jul 2022
Accepted: 11 Apr 2022

Keywords:
Vitamin D_3 poisoning, Hypercalcemia, Acute renal failure, Hypertension

ABSTRACT

Background: The effects of vitamin D on the skeletal system, biological metabolism, and immune system function are well shown. Cholecalciferol (vitamin D_2) and ergocalciferol (vitamin) are 2 major types of vitamin D. Vitamin D_3 deficiency is worldwide and the intoxication induced by it is very rare.

Conclusion: Vitamin D_3 is involved in calcium hemostasis. The effects of acute hypercalcemia on blood pressure were established. Hypercalcemia can elevate the blood pressure, and renal failure may predispose the individual to a hypertensive response. The clinical symptoms often associated with vitamin D_3 intoxication are related to acute renal failure. Hypertension without acute renal failure symptoms can emphasize the relationship between acute hypercalcemia and hypertension.

Citation Boskabadi SJ, Kargar-Soleimanabad S, Khosravi S, Parsa-kondelaji M, Gholami F. Secondary Hypertension Induced by Vitamin D3: A Case Report and Literature Review. Pharmaceutical and Biomedical Research. 2023; 9(2):163-168. http://dx.doi.org/10.32598/PBR.9.2.1043.1

http://dx.doi.org/10.32598/PBR.9.2.1043.1

Introduction

The different effects of vitamin D on physiological processes, metabolism, and immune system function have been well discussed [1]. Vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol) are 2 major forms of vitamin D. At first, cholecalciferol is hydroxylated into 25-hydroxy cholecalciferol (25(OH) D_3) in the liver and then into the activated form of vitamin D_3($1,25(OH)_2 D_3$) in the kidneys [2].

Vitamin D_3 is associated with the parathyroid hormone (PTH) and plays an important role in the mineral metabolism of bones and the skeletal system [3]. Vitamin D_3 leads to the increase of calcium concentrations in serum by affecting the gastrointestinal system, bones, and kidneys. The typical effect of the activated vitamin D_3 is on calcium transportation in gut cells. It also increases the absorption of calcium and phosphorus in the diet [4]. On the other hand, vitamin D_3 stimulates osteoblasts of the bones to produce receptor activator nuclear factor-κB (NF-κB) ligand. Then it activates the osteoclasts leading to bone demineralization and the release of calcium into the blood [5]. Most of the calcium is reabsorbed independently from vitamin D_3 in the renal system and only 1% of the filtered calcium is reabsorbed by PTH and vitamin D_3 in the distal tube. However, this percentage is significant because of the high amount of filtered calcium. According to the above functions, vitamin D_3 plays a key role in calcium homeostasis [6].

Studies have found that vitamin D_3 has a wide range of extra-skeletal biological functions, including cell growth inhibition, immune modulation, and cell differentiation. Active metabolites of vitamin D_3 downregulate the inflammatory cytokines, such as interleukin 6 [7, 8].

Vitamin D_3 deficiency is widespread in many countries and relates to the pathogenesis of auto-immune diseases, such as multiple sclerosis, and the intoxication can be seen and the number of cases has increased. Vitamin D_3 has a wide therapeutic window whose intoxication by vitamin D_3 is very rare. Vitamin D_3 intoxication is accompanied by hypercalcemia and has side effects, such as renal, neurological, and cardiac consequences [9, 10].

Hypervitaminosis may happen by the iatrogenic overuse of medication and supplements containing vitamin D_3 or the accidental increase of vitamin D_3 in the diet. The availability of vitamin D_3 or vitamin D_3 for prescribed or over-the-counter sales may cause vitamin D_3 intoxication.

Case Presentation

This study was conducted according to the Declaration of Helsinki principles. The care guidelines and methodology have also been followed. The patient is a 37-year-old male bodybuilder who was referred to the emergency department with acute headache as the major complaint. The blood pressure was measured at 180/100 mmHg during the routine examinations. Further investigations revealed that he had weekly taken vitamin , testosterone, and corticosteroid injections for a few months. He was admitted to the hospital for better control of hypertension and an investigation of renal function.

According to the initial physical examination, weight, height, and heart rate were 120 kg, 1.83 cm, and 60 bpm, respectively. Initial laboratory tests, including blood urea nitrogen, serum creatinine, blood sugar, calcium, albumin, ionized calcium, total bilirubin, potassium, sodium, C-reactive protein, and parathyroid hormone levels were requested. All these tests were in the normal situation except for the calcium and the serum creatinine levels. Table 1 displays the biochemical test results.

Considering the increase of creatinine in serum, the estimated glomerular filtration rate (eGFR) was calculated by the modification of diet in the renal disease equation and the result was 30.6 mL/min/1.73 m². On the other hand, we calculated the eGFR by the Cockcroft-Gault equation with the adjusted body weight and the result

Table 1. Laboratory tests before hospitalization and on the day of hospitalization

Time	Calcium (8.4-10.4) mg/dL	Ionized Calcium (1.14-1.31) mmol/L	Parathyroid Hormone (12.0-65.0) pg/mL	Creatinine (0.6-1.2) mg/dL
30 days before hospitalization				4.34
14 days before hospitalization	11	1.38		3.1
Day of hospitalization	11.9	1.38	10.3	2.4

Table 2. Laboratory tests after discharge from hospital (during follow-up)

Biochemical Tests/ Month Follow-up	Calcium (8.4-10.4) mg/dL	Ionized Calcium (1.14-1.31) mmol/L	Parathyroid Hormone (12.0-65.0) pg/mL	Creatinine (0.6-1.2) mg/dL	1,25(OH)D (30-100) ng/mL
One month after discharge	9.5	1.19		1.5	
Two months after discharge	8.9	1.15	19.3	1.54	126
Five months after discharge	9.8	1.30	9.14	1.34	70
Ten months after discharge	9.8	1.30	20	1.51	88

PBR

was 46.3 mL/min/1.73 m². The patient was reported for ultrasonography and hydronephrosis grade I in both kidneys.

Acute renal failure (ARF) was initially considered because of the decrease in the eGFR, the increase in the calcium level, and the hydronephrosis diagnosed in ultrasonography; however, other symptoms of renal failure, such as fluid retention, confusion, nausea, uremia, and irregular heartbeat were not observed.

The laboratory tests for bone metabolism were inconclusive, and PTH inappropriately persisted with normal levels even with hypercalcemia. Considering that the patient had taken 300000 IU vitamin D_3 (intramuscular injection) per week for a few months before admission to the hospital, the laboratory diagnosis was probably influenced by renal failure or the possible vitamin D_3 intoxication. Therefore, the 25-hydroxy vitamin D_3 level was measured and the result was 160 ng/mL.

We used labetalol for the hypertension crisis and after controlling the blood pressure, the following managements were prescribed: Hyperhydration, administration of furosemide, and corticosteroid (prednisolone 25 mg once a day). This treatment was useful and the serum creatinine decreased slowly. We also used amlodipine (5 mg twice a day) to control hypertension during the hospitalization and the patient was discharged after 5 days by the same drug (amlodipine 5 mg once a day).

During the follow-up and the evaluation of the patient for one year, his blood pressure was controlled by amlodipine. As provided in Table 2, the laboratory results dropped and the vitamin D_3 level decreased slowly as expected because of its elimination profile. After one year, amlodipine was discontinued and the blood pres-

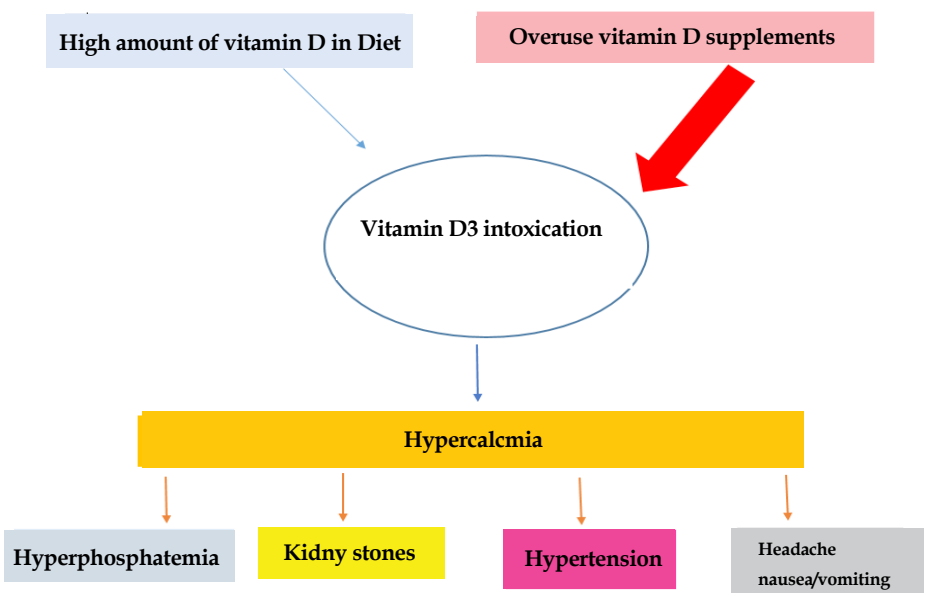

Figure 1. The schematic effect of vitamin D_3 toxicity

PBR

sure was in the normal range for 2 months following the drug discontinuation.

Discussion

The concentration of intracellular calcium has been found to increase in primary and various forms of secondary hypertension [11]. The effect of acute hypercalcemia on blood pressure was evaluated. The observations showed that acute hypercalcemia can cause an elevation in blood pressure, and renal failure may predispose the individual to such a hypertensive response [12]. When renal failure can predispose hypertension to acute hypercalcemia, rising blood pressure can be found in every vitamin D_3 intoxication patient.

A wide range of vitamin D_3 supplements is easily available to buy for the general population in pharmacies. Nowadays, various types of vitamin D_3 supplements are prescribed for all infants and pregnant women. It is also used to increase the level of calcium absorption in the body and decrease the risk of skeletal diseases, such as osteoporosis and rickets [13]. Recent studies have demonstrated that a low level of vitamin D_3 is accompanied by an increased risk of different kinds of cancers, cardiovascular diseases, and autoimmune and inflammatory diseases [14].

Humans have 2 main ways of providing vitamin D_3. The first way is the ability of the body to produce vitamin D_3 in association with exposure to sunlight, and the second one is through food. If the body does not have enough exposure to sunlight, the amount of vitamin , which is provided by food is insufficient; therefore, supplementations become necessary in this situation. If the level of vitamin D_3 exceeds 100 ng/mL, it is considered hypervitaminosis. If this level exceeds 375 nmol/L (150 ng/mL), it is defined as vitamin D_3 intoxication [15]. The level of vitamin D_3 in our patient was 160 ng/mL; therefore, he had intoxication.

While vitamin D_3 intoxication is reported to be rare, the potential toxicity of high-dose vitamin D_3 is not well understood or recognized among the general population. Vitamin D_3 intoxication can usually occur when the vitamin D_3 supplementation is overused, just like our patient [16].

Symptoms of vitamin D_3 intoxication include hypercalcemia (as in this case), hypercalciuria, hyperphosphatemia, kidney stones, nausea, vomiting, hypertension, and headache [10, 17]. Hypertension and headache were the main symptoms of the presented case which were caused by hypercalcemia (Figure 1). Hypercalcemia causes an increase in vascular resistance, especially in renal vascular. This mechanism is related to the direct effects of calcium on the calcium channel in vascular smooth muscle. Also, calcium induces hypercatecholaminemia. This condition can eventually lead to hypertension [18].

Screening for the secondary causes of hypertension is necessary for new-onset hypertension in adults. If there are more specific clinical characteristics present, screening for uncommon causes of secondary hypertension is indicated.

At the beginning of vitamin D_3 intoxication, tests show an elevated calcium level and an undetectable level of PTH. As over 100 ng/mL of the level of vitamin D_3 in serum confirms intoxication, the major step in the treatment of vitamin D_3 intoxication is to stop the intake of vitamin D_3 and proscribes all foods, including calcium, such as milk. Patients with asymptomatic or mild symptomatic hypercalcemia (calcium <12 mg/dL [3 mmol/L]) do not require immediate treatments. However, additional therapy depends mostly on the cause of hypercalcemia. Hypercalcemia is caused by the excess vitamin D_3 lasting long; therefore, more aggressive therapies, such as glucocorticoids, zoledronic acid, or other bisphosphonates may be necessary [19].

Conclusion

Clinical conditions that are often associated with vitamin D_3 intoxication are related to ARF. Signs and symptoms of an acute kidney injury differ from fatigue, confusion, and nausea. Unusual presentations, such as hypertension without ARF symptoms can emphasize the relationship between acute hypercalcemia and hypertension.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interests.

Acknowledgments

The authors thank the patient and his family for their cooperation to publish this case report.

References

[1] Hanel A, Carlberg C. Vitamin D and evolution: Pharmacologic implications. Biochem Pharmacol. 2020; 173:113595. [DOI:10.1016/j.bcp.2019.07.024] [PMID]

[2] Lips P. Vitamin D physiology. Prog Biophys Mol Biol. 2006; 92(1):4-8. [DOI:10.1016/j.pbiomolbio.2006.02.016] [PMID]

[3] Durá-Travé T, Gallinas-Victoriano F, Chueca-Guindulain MJ, Berrade-Zubiri S, Urretavizcaya-Martinez M, Ahmed-Mohamed L. Assessment of vitamin D status and parathyroid hormone during a combined intervention for the treatment of childhood obesity. Nutr Diabetes. 2019; 9(1):18. [DOI:10.1038/s41387-019-0083-z] [PMID] [PMCID]

[4] Gil A, Plaza-Diaz J, Mesa MD. Vitamin D: Classic and novel actions. Ann Nutr Metab. 2018; 72(2):87-95. [DOI:10.1159/000486536] [PMID]

[5] Fumoto T, Takeshita S, Ito M, Ikeda K. Physiological functions of osteoblast lineage and T cell-derived RANKL in bone homeostasis. J Bone Miner Res. 2014; 29(4):830-42. [DOI:10.1002/jbmr.2096] [PMID]

[6] DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr. 2004; 80(6 Suppl):1689S-96S. [DOI:10.1093/ajcn/80.6.1689S] [PMID]

[7] Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: A double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006; 83(4):754-9. [DOI:10.1093/ajcn/83.4.754] [PMID]

[8] Silberstein M. Vitamin D: A simpler alternative to tocilizumab for trial in COVID-19? Med Hypotheses. 2020; 140:109767. [DOI:10.1016/j.mehy.2020.109767] [PMID] [PMCID]

[9] Feige J, Moser T, Bieler L, Schwenker K, Hauer L, Sellner J. Vitamin D supplementation in multiple sclerosis: A critical analysis of potentials and threats. Nutrients. 2020; 12(3):783. [DOI:10.3390/nu12030783] [PMID] [PMCID]

[10] Haridas K, Holick MF, Burmeister LA. Hypercalcemia, nephrolithiasis, and hypervitaminosis D precipitated by supplementation in a susceptible individual. Nutrition. 2020; 74:110754. [DOI:10.1016/j.nut.2020.110754] [PMID]

[11] Villa-Etchegoyen C, Lombarte M, Matamoros N, Belizán JM, Cormick G. Mechanisms involved in the relationship between low calcium intake and high blood pressure. Nutrients. 2019; 11(5):1112. [DOI:10.3390/nu11051112] [PMID] [PMCID]

[12] Simonini M, Casanova P, Citterio L, Messaggio E, Lanzani C, Manunta P. Endogenous ouabain and related genes in the translation from hypertension to renal diseases. Int J Mol Sci. 2018; 19(7):1948. [DOI:10.3390/ijms19071948] [PMID] [PMCID]

[13] Bhattarai HK, Shrestha S, Rokka K, Shakya R. Vitamin D, calcium, parathyroid hormone, and sex steroids in bone health and effects of aging. J Osteoporos. 2020; 2020:9324505. [DOI:10.1155/2020/9324505] [PMID] [PMCID]

[14] Muscogiuri G. Vitamin D: Past, present and future perspectives in the prevention of chronic diseases. Eur J Clin Nutr. 2018; 72(9):1221-5. [DOI:10.1038/s41430-018-0261-4] [PMID]

[15] Sintzel MB, Rametta M, Reder AT. Vitamin D and multiple sclerosis: A comprehensive review. Neurol Ther. 2018; 7(1):59-85. [DOI:10.1007/s40120-017-0086-4] [PMID] [PMCID]

[16] Galior K, Grebe S, Singh R. Development of vitamin D toxicity from overcorrection of vitamin D deficiency: A review of case reports. Nutrients. 2018; 10(8):953. [DOI:10.3390/nu10080953] [PMID] [PMCID]

[17] Ferreira C, Khan I, Badshah A, Singhal P. Hyper-Vitaminosis D. Med Clin Res. 2019; 4(9):1. [Link]

[18] Zhu Y, Qu J, He L, Zhang F, Zhou Z, Yang S, et al. Calcium in vascular smooth muscle cell elasticity and adhesion: Novel insights into the mechanism of action. Front Physiol. 2019; 10:852. [DOI:10.3389/fphys.2019.00852] [PMID] [PMCID]

[19] Houghton CC, Lew SQ. Long-term hypervitaminosis D-induced hypercalcaemia treated with glucocorticoids and bisphosphonates. BMJ Case Rep. 2020; 13(4):e233853. [DOI:10.1136/bcr-2019-233853] [PMID] [PMCID]

This Page Intentionally Left Blank