

Vitamin D Toxicity: A Comprehensive Review

Barakat Wathiq Alawadi¹, Zahraa Jasim Abed²

¹Department of Pharmacology and Toxicology, College of Pharmacy, Ahl Al-Bayt University, Karbala 56001, Iraq
Barakatwathiqbarakat@abu.edu.iq

²Department of Pharmacognosy, College of Pharmacy, Ahl Al-Bayt University, Karbala 56001, Iraq
Iraq.zahraa19932021@gmail.com

Article Info.

Article history:

Received 2 June 2025
Revised 15 June 2025
Accepted 20 August 2025
Published 30 December 2025

Keywords:

Vitamin D toxicity;
Hypervitaminosis D;
Hypercalcemia; Vitamin D
overdose; Calcium metabolism

How to cite:

Barakat Wathiq Alawadi, Zahraa
Jasim Abed. Vitamin D Toxicity:
A Comprehensive Review. Aca.
Intl. J. Med. U. 2025; 3(2) 28-33.

DOI:

<https://doi.org/10.59675/U324>

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Abstract

Although very infrequent, vitamin D toxicity is an important clinical issue that has serious clinical implications. This is a disease mainly caused by overdosing on the supplement and is expressed through hypercalcemia and the related complications. Clinical manifestation extends from very mild gastrointestinal symptoms to cardiovascular and renal dysfunction that is life-threatening. Healthcare providers need to understand the pathophysiology, risk factors, clinical presentation, and treatment measures. This review will analyze the existing data on vitamin D toxicity with a focus on its biochemical pathways, diagnostic skills, and treatment care.

Introduction

Vitamin D is important in calcium homeostasis, bone metabolism, and many other physiological functions [1]. As the deficiency of vitamin D has been widely examined and is still widespread worldwide, the clinical issue of vitamin D toxicity poses an opposite challenge [2]. This is because vitamin D is fat-soluble and thus accumulation occurs when large volumes are ingested, consequently resulting in hypervitaminosis D [3].

Vitamin D toxicity has become more common over the past few years, which is associated with the popularity of supplementation and the sale of high doses of the vitamin [4]. In contrast to water-soluble vitamins, which are easily disposed of, vitamin D is simply stored in adipose tissue and liver, forming a lengthy half-life, which causes a problem of maintaining toxicity [5].

Pathophysiology

Vitamin D toxicity is a complicated phenomenon with a complicated biochemical pathway that is focused on calcium imbalance. Vitamin D is first hydroxylated into 25-hydroxyvitamin D [25(OH)D] in the liver and then hydroxylated into the active metabolite, 1,25-dihydroxyvitamin D [1,25(OH)₂D] in the kidney [6]. The excessive amount of vitamin D saturates the carefully controlled conversion process, leading to an increase in levels of the 25(OH)D and 1,25(OH)₂D [7].

Active metabolite 1, 25(OH) ₂D stimulates intestinal calcium absorption by increasing calcium-binding proteins and calcium channels in enterocytes [8]. It also encourages osteoclastic bone resorption, which raises serum calcium levels further [9]. The kidneys usually counteract it by a greater calcium loss, but prolonged hypercalcemia may result in nephrocalcinosis and progressive renal failure [10].

Hypercalcemia causes pathological effects that are cascading and occur in various organ systems. The cardiovascular changes encompass shortening of the QT interval, cardiac arrhythmias, and high chances of sudden cardiac death [11]. Neurological alterations are associated with a change in neuronal excitability and neurotransmitter activity [12]. The GIT reacts with reduced motility and higher secretion of gastric acid [13].

Clinical Manifestations

Depending on the level and the duration of hypercalcemia, the clinical manifestation of vitamin D toxicity differs significantly. Initial symptoms tend to be nonspecific as they include fatigue, weakness, and malaise [14]. GIT-related symptoms, such as nausea, vomiting, constipation, and abdominal pain, are common [15].

The development of polyuria and polydipsia is a result of hypercalcemia weakening the concentrating ability of the kidney by reducing the expression of aquaporin-2 channels [16]. Further dehydration can develop, worsening hypercalcemia and causing acute kidney failure [17]. Nephrolithiasis and nephrocalcinosis are serious complications of the kidney, which may cause chronic kidney disease [18].

The neurological signs of the disease are confusion, cognitive change, and depression, and occasionally, in serious cases, a change in consciousness or coma [19]. The heart complications include high blood pressure, heart rhythm disorders, and myocardial calcification [20]. Musculoskeletal Symptoms Bone pain occurs, but it is rather ironic that too much vitamin D can affect the bone mineralization by reducing the parathyroid hormone [21].

Diagnosis

Vitamin D toxicity can only be diagnosed by a clinical suspicion with biochemical confirmation. The main diagnostic predictor is Serum 25(OH) D, and these levels above 150 ng/mL (375 nmol/L) would be considered as toxic [22]. Nevertheless, at lower concentrations, toxicity effects can be experienced in people who are vulnerable [23].

The hallmark biochemical abnormality is hypercalcemia, which is defined as serum calcium above 10.5mg/dL (2.6mmol/L) [24]. Other lab results are suppressed parathyroid hormone, high serum phosphate, and high urinary levels of calcium excretion [25]. Serum creatinine and estimated glomerular filtration rate are renal function tests that must be tested to assess kidney involvement [26].

On imaging, nephrocalcinosis can be seen in ultrasound or computed tomography images, and in bone radiographs, which can be osteopenia or vascular calcifications [27]. Electrocardiography is required to evaluate cardiac conduction anomalies, especially the shortening of the QT interval [28].

Risk Factors

There are a number of conditions that predispose one to vitamin D toxicity. Overdosing is the main reason and is usually caused by the misconception of the use of the dosage or self-medication [29]. There have also been manufacturing errors, and the supplements have been found to contain the levels of vitamin D that are much higher than indicated [30].

The vulnerability of some populations increases. Patients with granulomatous diseases, including sarcoidosis and tuberculosis, display excessive extrarenal synthesis of 1, 25(OH)₂D by stimulated macrophages, which augments toxicity even in the case of standard supplementation [31]. Primary hyperparathyroidism and a small number of malignancies may also increase susceptibility [32].

Liver disease or genetic variations in the metabolism of enzymes can impair the metabolism or clearance of vitamin D and extend the exposure to vitamin D [33]. The hypercalcemia is aggravated by concomitant use of drugs that influence the calcium homeostasis, e.g., thiazide diuretics or calcium supplements [34].

Management and Treatment

Treatment of vitamin D toxicity aims at terminating the consumption of vitamin D and treating hypercalcemia. The intensity of treatment is defined by the severity of hypercalcemia. Milder cases can be treated by withdrawal of supplementation, higher fluid intake, and dietary restriction of calcium [35].

Moderate to severe hypercalcemia needs a vigorous intravenous hydration using normal saline, which enhances calcium loss and salvages volume contraction caused by dehydration [36]. When patients have been sufficiently hydrated, loop diuretics like furosemide can be used to increase calciuresis, but care should be taken to avoid aggravation of the dehydration [37].

Glucocorticoids have a beneficial effect on the absorption of calcium into the intestines and reduce the production of 1,25(OH)₂D, especially in granulomatous diseases [38]. Bisphosphonates suppress bone resorption by osteoclastic cells and may be useful in patients with a refractory case [39]. Calcitonin is a rapid, but temporary, calcium-lowering effect that can be applied in case of acute severe hypercalcemia [40].

Calcimimetic agents, which enhance the calcium-sensing receptor responsiveness, are a new therapeutic agent [41]. Severe cases of hemodialysis may need low-calcium or calcium-free dialysate in the case of life-threatening hypercalcemia or severe renal impairment [42].

Vitamin D has a long half-life and thus requires a long period of monitoring, especially when hypercalcemia is noted and can occur a week to months after intoxication [43]. Serial levels of serum calcium and 25(OH)D determine the length and severity of treatment [44].

Prevention

Vitamin D toxicity should be prevented by educating about the proper use of supplementation. The adult levels of 600-800 IU/day are recommended dietary intake, and the set tolerable upper intake level is 4,000 IU/day in adults [45]. The clinicians ought to evaluate the status of vitamin D thoroughly before deciding to administer high-dose therapy and follow-up patients under chronic supplementation [46].

The quality of products is paramount because cases of toxicity have been associated with the contamination or mislabelling of the supplements [47]. Patients ought to be educated on the dangers of overdose of vitamin D and the need to take prescriptions as scheduled [48].

Certain special populations, such as patients with granulomatous diseases or malabsorption syndromes, should receive a specific monitoring strategy [49]. Risk mitigation involves awareness of any possible drug interaction and other underlying conditions that can influence calcium metabolism [50].

Conclusion

Vitamin D overdose is a rare condition, but it poses serious clinical problems that must be identified and treated in a timely manner. The disease is mainly caused by excess supplementation, which causes hypercalcemia with multisystem complications. Diagnosis is based on high levels of serum 25(OH)D and hypercalcemia with decreased levels of parathyroid hormone. The treatment includes the withdrawal of vitamin D, the introduction of vitamin D-minimizing measures, and providing supportive treatment. With more people taking vitamin D supplements, healthcare providers should be highly alert to toxicity, teach patients to take vitamin supplements properly, and monitor the high-risk groups. Future studies need to be conducted on defining the best supplementation protocol, determining genetic vulnerabilities, and formulating effective treatment regimens in severe cases of toxicity.

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