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| REVIEW ARTICLE

Vitamin D Supplements Overdose Toxicity: A Review Article

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ABSTRACT
Hypervitaminosis D, also known as vitamin D toxicity, is an uncommon but serious condition that occurs when the concentration of vitamin D is much higher than the body needs due to taking large doses of its supplements instead of the diet or even exposure to sunlight. The body regulates the amount of vitamin D entering it as a result of exposure to sunlight. one of serious consequences of vitamin D toxicity is accumulation of calcium in the body, which causes symptoms of nausea, vomiting, weakness, & frequent urination due to (hypercalciuria). These symptoms may develop to extend to bone pain & kidney problems such as calcium stones. This condition is treated by stopping taking the vitamin and reducing foods that contain a lot of calcium, as appropriate treatments are prescribed by the doctor and are given in the form of intravenous fluids & medications such as Corticosteroids or Bisphosphonates. When taking (60,000) IU of vitamin D daily for several months it is considered toxic because this level is much higher than the permissible and recommended limit by Recommended Dietary Allowance (RDA), which is 600 international units of vitamin D daily. In certain cases, higher doses than permitted are used to treating some medical conditions, such as severe vitamin D deficiency, but they must be taken under the supervision of a doctor and at a specific time, while monitoring calcium levels.

KEYWORDS: Vitamin D Supplements, Dietary sources , Toxicity

| ARTICLE INFORMATION

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1. Introduction
Vitamin D is a sterol hormone whose benefits extend far beyond the bones. Vitamin D deficiency has increased worldwide, so vitamin D supplements have become increasingly popular. the increasing use of vitamin D treatments has led to significant cases of vitamin D toxicity due to inappropriate & unauthorized prescriptions and high doses of over the counter supplements. Vitamin D toxicity is one of the series side effect of prescriptions .Vitamin D deficiency may also increase with rising rates of obesity, the obesity is regarded a main risk factor for vitamin D deficiency. (Taylor& Davies, 2018).
The duration of exposure to the sun, season of the year this main Factors that determine the production of vitamin D in the skin (Borel *et al*., 2015).

Skin is main site where vitamin D is manufactured 10% of the vitamin is obtained from dietary sources. The enzymatic photosynthesis by use ultraviolet light Cholecalciferol is synthesized from 7-dehydrocholesterol, This process is carefully regulated, the enzymatic hydrolysis of cholecalciferol occurs efficiently within skin, preventing the accumulation of excess cholecalciferol after which the molecule undergoes 25 hydroxylation in the liver to form 25-hydroxycholecalciferol (25OHD) which undergoes another 1 hydroxylation to form the active hormone calcitriol 1,25-dihydroxycholecalciferol (1,25OHD) This molecule acts on vitamin D receptors found throughout the body By acting on vitamin D receptors, calcitriol acts primarily on calcium homeostasis leading to increased absorption of both calcium and phosphorus from the intestine. Therefore, vitamin D deficiency is associated with decreased Calcium Absorption as well as secondary hyperparathyroidism which leads to calcium being withdrawn from the bones in order to maintain adequate plasma calcium concentrations (Norman, 2008; Holick & Slominski ,2024).

Term of "dose" is frequently used. The dose of cholecalciferol is expressed in (µg) or (UI) (where 10 µg equals to 400 IU), often (Cholecalciferol, and other compounds such as ergocalciferol, ildcalcitol, calcifediol, etc.) are associated with important clinical outcomes and are an important measure of vitamin D status as they relate to changes levels of 25OHD in the blood (Giustina *et al*,2024).

Factors affecting a given dose of(25OHD) in the blood include body weight, absorption, diet, degree of obesity, and other factors and vary widely from person to person. The optimal dose of vitamin D varies depending on which required outcome but the others suggest the upper limited of safety less than 4000 IU/day (Rizzoli,2021).

Taking 400-800 IU of vitamin D daily is considered an enough amount to averting clinical vitamin D deficiency and conserve Ca^{+2} balance in healthy human. Toxicity is associated with taking doses of the vitamin D that exceed the maximum. However, daily doses up to (10000 IU) have been used without safety attention (Fassio *et al*., 2020).

2. Dietary sources of vitamin D

Vitamin D is present in abundance in meat & meat products, while fishes are considered main food source of the vitamin, which far exceeds its intake from other sources. Food sources rich in the vitamin vary according to eating behavior and age (Bischofova,et al,2018).

Infant formula is main source of vitamin D for children who are not breastfed at the age of (4-10) years, milk and dairy products begin to enter their diet, which works alongside meat and meat products to provide them with the vitamin.
(Borel,*et al*,2015).

Vitamin (D3 & 25OHD3) are present primarily in foods of animal origin and vitamin (D2 & 25OHD2) are found in foods that plant origin & yeast. Generally, the fat content in food determines the presence of vitamin D because this vitamin is fat-soluble, as well as on the feed that the animals are fed, and the extent of exposure of the food to UVB radiation (Jakobsen & Christensen,2021).

There are few foods that are regarded abundant source of vitamin D3 or D2 and such foods are rarely eaten, so that get of vitamin D is obtained from foods that contain less of the vitamin regularly and in larger quantities. The meat of some fishes as salmon & wild tuna, fishes' liver oils are among best food sources of vitamin D specifically vitamin D3. (Spiro & Buttriss,2014; Roseland *et al*,2018).

Vitamin D content depends on the origin of food which be eaten and many factors enter and cause large differences in the vitamin D3 content of animal foods. For most animals, vitamin D3 content is positively correlated with fat content. In fishes, however, the presence of the vitamin is not related to the fat content. A high vitamin D3 content has been present in some fishes with low fat content as halibut (Kühn *et al*,2014).

3. Dietary supplements of vitamin D

Vitamin D deficiency has recently become main concern for people to take vitamin supplements to compensate for this deficiency. Therefore, increasing numbers of its formulas have been included in the local and global market and used regularly (Rizzoli, 2021). Vitamin D3 is manufactured pharmaceutically when 7-dehydrocholesterol from lanolin is irradiated and cholesterol is chemically converted, while vitamin D2 is manufactured pharmaceutically by irradiating ergosterol with ultraviolet light in fungi and yeast(Holick, 2007).

The variety forms of vitamin D in oral supplements, whether tablets, capsules or liquid preparations as oral drops or as sprays, has led to widespread controversy over the effectiveness of these formulations, but recent research has shown no difference in effectiveness between these vitamin-containing on this formulations, in addition, there is no difference in the effectiveness and safety of taking (1000 IU) of vitamin D daily, weekly or monthly (Žmitek,et al,2020;Takács,et al,2017).

All forms (vitamin D3, vitamin D2) increase serum (25OHD) concentrations more efficiently and faster, vitamin D3 maintains these high concentrations to a greater extent and for a longer period than vitamin D2 (Guo et al,2018;Tripkovic et al,2012)

Vitamin D3 is still the preferred and most relevant option for vitamin D deficiency and in selected patients 25(OH)D3 is used because it is too expensive (Sosa & Gómez , 2020).

Dietary supplements are available in variety of over the counter formulations that are more strictly regulated and give content values within standard limits (Garg et al,2013; Žmitek et al,2021).

4. Upper Limit of Vitamin D Intake

Neuropsychiatric manifestations such as confusion, stupor & lethargy, gastrointestinal symptoms such as anorexia, vomiting & constipation, cardiovascular manifestations, polyuria & renal colic resulting from the passage of kidney stones are all clinical Symptomas of vitamin D toxicity resulting from hypercalcemia & hyperuria. Vitamin D & calcium supplementation has increase the risk of kidney stones (Jackson,2006; Tebben *et al*.,2016).

Suggested upper limit of vitamin D daily doses that can be taken over a lifetime without significant health risks are summarized by several health authorities in **Table 1.**

Table 1. Acceptable upper limit of vitamin D intake stated by various health bodies.*

Age	ESPG	SACN	IOM	EFSA
Infant	0–6 m: 1000 IU (25 µg)/d	1000 IU (25 µg)/d	0–6m: 1000 IU (25 µg)/d	1000 IU (25 µg)/d
	6–12 m: 1500 IU (37.5 µg)/d		6–12 m: 1500 IU (37.5 µg)/d	
1–10 y	1–3 y: 2500 IU (62.5 µg)/d	2000 IU (50 µg)/d	1–3 y: 2500 IU (62.5 µg)/d	2000 IU (50 µg)/d (children and adolescents)
	4–8 y: 3000 IU (75 µg)/d		4–8 y: 3000 IU (75 µg)/d	
11–17 y	>8 y: 4000 IU (100 µg)/d	4000 IU (100 µg)/d	9–18 y: 4000 IU (100 µg)/d	
Adult	4000 IU (100 µg)/d	4000 IU (100 µg)/d	19->70 y: 4000 IU (100 µg)/d	4000 IU (100 µg)/d

*The upper limit does not apply to persons with certain medical conditions such as normal hyperparathyroidism, granulomatous conditions (sarcoidosis, tuberculosis) or those with hereditary conditions such as familial hypocalcemia that increase the risk of hypercalcemia. Hypercalcaemia , Endocrine Society Practice Guideline (ESPG);Scientific Advisory Committee on Nutrition (SACN); Institute of Medicine (IOM) ; European Food Safety Authority(EFSA).

5. Toxicity

Vitamin D has a broad therapeutic range & its toxicity only occurs at very high doses, although it affects all age groups, there are few known cases of vitamin D toxicity (Galior et al,2018;Marcinowska et al,2018).

There is no evidence a dose of vitamin D that causes toxicity or a safe upper limit for serum /plasma 25(OH)D3 levels (Bouillon, 2017).

Populations are affected differently by factors such as geography, lifestyle, and genetics. When serum 25OHD3 concentrations are higher than (150 ng/ml) or (375 nmol/L) that mean hypercalcemia, but the concentration accepted by the Endocrine Society is 100 ng/ml (Lim & Thadhani, 2020 ; Holick et al,2011).

Individuals with juvenile idiopathic hypercalcemia, lymphoma and many other vitamin D-related diseases are more sensitive to excess vitamin D from various sources, making them more susceptible to vitamin D toxicity, the elevated active form of vitamin D in juvenile idiopathic hypercalcemia patients is associated with a defective CYP24A1 enzyme, while in lymphoma patients are not fully understood causes of vitamin D toxicity (Marcinowska et al,2018).

There are large scientific reports on the benefit of vitamin D in treating a number of diseases. Vitamin D supplements have become easily available without a prescription, so it is necessary to provide conditions for their use and determine the acceptable and permissible limits (Lim & Thadhani, 2020; Temova & Roškar, 2018).

Taking an overdose of vitamin D and the subsequent toxicity it causes mainly linked to several factors, including incorrect doses taken by mistake, either due to errors in the medical prescription or the use of unlicensed products, in addition to medical factors (Taylor & Davies,2018).

As a result of the failure of quality control of manufactured supplements, cases of chronic vitamin D poisoning have been recorded, where the actual vitamin levels were (1000) times higher than acceptable daily dose level announced by the manufacturer (Galior et al,2018; Taylor & Davies,2018).

5.1 Cases of Toxicity

Prescription errors and high doses of vitamin D supplements have caused cases vitamin D poisoning. Several cases have been recorded, including after a 73-year-old person took (10000 IU) of vitamin D daily for several years, he developed vitamin D poisoning. This case was recorded in 2020(Sharma et al,2020).

In another case recorded in the same year 2020, a 56-year-old woman developed symptoms of nausea, vomiting and muscle weakness. She was then transferred to the hospital. It was later found that she had taken an average of (130000 UI) of vitamin D daily for 20 months, thinking that it would improve her symptoms of multiple sclerosis. The amount of vitamin she had taken was 30 times the maximum generally allowed limit of 4000 UI daily (De Vincentis et al,2020).

Not understanding the medication instructions, a 64-year-old man accidentally took (200000 IU) of vitamin D daily. This man suffered from confusion and disorientation due to an altered mental state associated with hypercalcemia. His condition gradually improved after 10 days of his hospital stay with decreased calcium levels. After about 18 days, his calcium levels returned to the permissible normal limit. This case was recorded in 2021 (Nguyen et al,2021).

An 89-year-old man in the UK died after taking vitamin D supplements for 9 months. The patient was admitted to hospital due to high blood calcium levels and the laboratory showed that his vitamin D levels were high and at the maximum that can be recorded in the laboratory. This patient died 10 days later due to kidney and heart failure, high calcium levels and vitamin D toxicity. It is important to know the daily dose of vitamin D for adults up to age of 70 is (15 µg) or (600 IU) and increases to (20 µg) or (800 IU) after the age of 70 years(Lindsey,2024).

An 18-month-old child was given approximately (50,000 IU) of vitamin D3 for 3 months. The child developed diarrhea and stomach pain but these symptoms disappeared after the child stopped taking the vitamin supplements, while the maximum allowable limit for a child of this age is 2,000 IU (50 mcg)/day (Talarico et al,2016).

6. Vitamin D supplement safety

People with severe vitamin D deficiency take high doses of (50000 IU) weekly for 8 weeks, and when their levels reach 30 ng/ml they take doses of (2000 IU) daily. The doctor is the one who decides the most appropriate doses based on his monitoring of vitamin levels to ensure that these doses are appropriate for the actual vitamin levels of the person (Sizar et al.,2021).

Conclusion

The endogenous synthesis of vitamin D is insufficient, so its sever to achieve adequate levels of vitamin D in the body through diet alone, so it is necessary to take vitamin supplements in a regular manner with monitoring the quality of vitamin supplements. People with vitamin D deficiency should take supplements at levels much higher than the permissible limit to achieve optimal levels of the vitamin, but for limited periods to prevent possible toxicity due to the vitamin.

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