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"EXCESSIVE VITAMIN D – A SILENT AND LIFE-THREATENING RISK"

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ABSTRACT

Vitamin D plays an essential role in maintaining calcium and phosphorus balance in the body, which is necessary for strong bones and healthy teeth. It also supports important body functions such as metabolism, immune response, and overall physiological balance. Although vitamin D is highly beneficial, excessive intake can lead to a serious condition known as vitamin D toxicity or hypervitaminosis D. This condition mainly occurs when high-dose vitamin D supplements are taken for a long period without proper medical supervision. Vitamin D toxicity causes an increase in calcium levels in the blood, a condition called hypercalcemia. Elevated calcium levels can damage sensitive organs such as the kidneys, heart, liver, and nervous system. Common early symptoms include weakness, loss of appetite, nausea, vomiting, constipation, and fatigue. In severe cases, it may lead to kidney stones, arrhythmias, confusion, and other life-threatening complications. In children, serious conditions such as pancreatitis and severe renal damage may also occur. Diagnosis is usually confirmed when blood levels of 25-hydroxyvitamin D rise above 150 ng/mL along with increased serum calcium levels. The first step in treatment is stopping vitamin D and calcium supplements immediately. Proper hydration is important to help remove excess calcium from the body, and in severe cases, medicines may be required to lower calcium levels. As the use of supplements continues to increase, proper dosing guidelines, accurate labeling, and patient awareness have become very important. Both healthcare professionals and patients should understand the risks of excessive supplementation. Vitamin D is necessary for health, but it

should always be taken in the correct amount. Safe use, regular monitoring, and medical guidance are the best ways to prevent vitamin D toxicity and its long-term complications.

KEYWORDS: Vitamin D, Cholecalciferol, Hypervitaminosis D, Vitamin D toxicity.

1. INTRODUCTION

Vitamin D is a vital fat-soluble vitamin and hormone-like compound that plays a crucial role in maintaining overall physiological health. It is naturally obtained from dietary sources such as fatty fish, egg yolk, liver, and dairy products. Additionally, several fortified food products including milk, cereals, and nutritional supplements are enriched with vitamin D to help fulfill daily nutritional requirements. The primary natural source of vitamin D is sunlight. Upon exposure to ultraviolet-B (UV-B) radiation, the skin synthesizes vitamin D_3 (cholecalciferol), which subsequently undergoes metabolic activation in the liver and kidneys to form calcitriol, the biologically active form of vitamin D. This active metabolite regulates calcium and phosphorus homeostasis and is essential for proper bone mineralization, skeletal development, and maintenance of bone integrity.

Vitamin D deficiency is associated with several musculoskeletal disorders. In children, deficiency may lead to Rickets, characterized by impaired bone growth and skeletal deformities, whereas in adults it can result in osteopenia and Osteomalacia, causing bone pain, muscle weakness, and increased susceptibility to fractures. Beyond skeletal functions, vitamin D has significant roles in immune modulation, cardiovascular health, neuromuscular function, cellular differentiation, and regulation of inflammatory responses. Insufficient vitamin D levels have been linked with autoimmune diseases, malignancies, cardiovascular disorders, diabetes mellitus, depression, and neurodegenerative conditions. In recent years, awareness regarding vitamin D deficiency has increased considerably, leading to widespread use of supplementation and fortified foods. Although supplementation has proven beneficial in preventing deficiency-related disorders, excessive and uncontrolled intake of vitamin D may result in hypervitaminosis D, commonly referred to as vitamin D toxicity. This condition primarily occurs due to prolonged consumption of high-dose vitamin D supplements without appropriate medical supervision or laboratory monitoring. Vitamin D toxicity leads to excessive intestinal absorption of calcium, resulting in Hypercalcemia, the hallmark feature of toxicity.

It plays a major role in:

- Calcium and Phosphorus absorption, bone and teeth health, muscle function.
  Vitamin D is obtained from
- Sunlight exposure, diet (milk, fish, eggs), supplements.
  Vitamin D Toxicity, also called **Hypervitaminosis D**, is a condition caused by:
- Excessive intake of vitamin D supplements over a long period. [1]

LITERATURE REVIEW

Vitamin D is a fat-soluble secosteroid vitamin that plays an important role in calcium and phosphate regulation, bone mineralization, immune function, and metabolic health. It is obtained mainly through sunlight exposure, diet, fortified foods, and supplements. In the body, vitamin D is converted first in the liver to 25-hydroxyvitamin D [25(OH)D] and then in the kidney to its active form, calcitriol. This active form binds to vitamin D receptors and regulates calcium absorption and bone metabolism. Deficiency of vitamin D is commonly associated with rickets in children, osteomalacia in adults, muscle weakness, and increased fracture risk.

Although vitamin D is essential for health, excessive intake may lead to vitamin D toxicity, also known as hypervitaminosis D. This condition usually occurs due to prolonged use of high-dose supplements, self-medication, incorrect prescription, frequent injections, or unmonitored over-the-counter preparations. The major biochemical feature of vitamin D toxicity is hypercalcemia, which results from increased intestinal calcium absorption, increased calcium release from bones, and reduced renal calcium excretion. Serum 25(OH)D levels above 150 ng/mL are generally associated with toxicity and serious complications.

Vitamin D toxicity is considered a “silent risk” because it develops gradually and may not show early symptoms. Since vitamin D is stored in adipose tissue and has prolonged biological persistence, toxic effects may continue even after supplementation is stopped. Persistent hypercalcemia can affect several organ systems, including the gastrointestinal tract, kidneys, nervous system, and cardiovascular system.

3. Classification of Vitamin D level[2]

Table : 1 Classification of Vitamin D level

Vitamin D Level	25(OH)D (ng/mL)	Clinical Significance
Severe deficiency	< 10 ng/mL	High risk of rickets, osteomalacia, muscle weakness
Deficiency	10–20 ng/mL	Bone loss, increased fracture risk
Insufficiency	20–30 ng/mL	Suboptimal bone and immune health
Sufficiency (Normal)	30–50 ng/mL	Adequate for bone and overall health
High / Upper normal	50–100 ng/mL	Usually safe, monitoring advised
Possible toxicity	> 100 ng/mL	Risk of hypercalcemia
Vitamin D toxicity	> 150 ng/mL	Severe hypercalcemia, kidney damage

3.1 Vitamin D_2 vs Vitamin D_3[3]

Vitamin D comes in two forms: Vitamin D2 and Vitamin D3. Vitamin D2 is also known as ergocalciferol. Vitamin D3 is also known as cholecalciferol. Both Vitamin D2 and Vitamin D3 are good for calcium balance and bone health. They have sources and structures. Both Vitamin D2 and Vitamin D3 need to be changed into a form in the body to work properly. This active form helps intestines absorb calcium.

3.1.2 Vitamin D_2 (Ergocalciferol)

Vitamin D_2, also called Ergocalciferol, is mainly obtained from plant sources and fungi. It is produced when ergosterol, a natural substance present in plants and yeast, is exposed to ultraviolet (UV) light. Vitamin D_2 is commonly added to fortified foods and some medicines. After entering the body, it is converted in the liver into 25-hydroxyvitamin D.

3.1.3 Vitamin D_3 (Cholecalciferol)

Vitamin D_3, also called Cholecalciferol, is produced naturally in the skin when it is exposed to ultraviolet-B (UV-B) rays from sunlight. It is also found in animal-based foods such as fatty fish, egg yolk, and liver. Vitamin D_3 is considered more effective than Vitamin D_2 because it stays in the body longer and is more easily used by the body. Due to its better efficacy and longer duration of action, doctors usually prefer Vitamin D_3 for the treatment and prevention of vitamin D deficiency.

Table 2: Key Differences between Vitamin D_2 and D_3[3]

Parameter	Vitamin D_2 (Ergocalciferol)	Vitamin D_3 (Cholecalciferol)
1) Source	Plants, fungi	Sunlight, animal sources
2) Stability	Less stable	More stable
3) Potency	Lower	Higher
4) Duration of action	Shorter	Longer
5) Use	Fortified foods	Preferred supplement
6) Activity	Less active form	More active form
7) Initial Form (Inactive)	Ergocalciferol (inactive)	Cholecalciferol (inactive)
8) Liver Conversion	25-hydroxyvitamin D_2 (Calcidiol)	25-hydroxyvitamin D_3 (Calcidiol)
9) Kidney Conversion (Active Form)	1,25-dihydroxyvitamin D_2 (Calcitriol)	1,25-dihydroxyvitamin D_3 (Calcitriol)
10) Biological Activity	Active after conversion	Active after conversion
11) Efficacy (Potency)	Lower	Higher
12) Half-life	Shorter	Longer
13) Stability	Less stable	More stable
14) Ability to raise serum Vitamin D	Less effective	More effective
15) Clinical Preference	Rarely used	Most preferred

3.1.4 Factors making Vitamin D_3 more active than Vitamin D_2

Vitamin D_3 (Cholecalciferol) is more active than Vitamin D_2(Ergocalciferol), because:

- D_3 rises level of vitamin D in blood more effectively (High Potency) than D_2.
- D_3 gives sustained action, as it remain in body for long time.
- D_3 is more efficiently converted into active form (calcitriol) as it leads to stronger biological effects.

3.2 Fat-Soluble Vitamins: Classification

Fat-soluble vitamins dissolve in fats and oils and are stored in the body's fatty tissues and liver. They are not easily removed, so excess intake may cause toxicity. These vitamins need dietary fat for proper absorption. They include Vitamin A, D, E, and K. Vitamin A supports vision, immunity, and skin health.[4]

4. ADME of Vitamin D

Pharmacokinetics is about how a drug moves through the body. It tells us how a drug is absorbed, distributed, metabolized and excreted. The body absorbs, distributes, metabolizes and excretes a drug through pharmacokinetics. Vitamin D is a type of soluble secosteroid. Vitamin D follows its special path through the body.

Vitamin D is absorbed mainly in the jejunum and ileum of the small intestine, and since it is fat-soluble, its absorption depends on dietary fats and bile salts. It is then transported by vitamin D-binding protein to the liver, adipose tissue, and muscles, where it is stored. In the liver, vitamin D is converted into 25-hydroxyvitamin D [25(OH)D], and in the kidneys, it is

further converted into 1,25-dihydroxyvitamin D (calcitriol), the active form that regulates calcium and phosphate balance.[5]

5. Physiological and Therapeutic role of Vitamin D

Vitamin D is really important for our bodies. It helps keep the amount of calcium and phosphate in our system, which is good, for our bones. Doctors like to use Vitamin D for a lot of things. They use Vitamin D to prevent people from getting sick. They use Vitamin D to help people who are already sick feel better.

5.1 Bone Disorders: Rickets and Osteomalacia

Vitamin D plays an important role in maintaining strong and healthy bones by helping the body absorb calcium and phosphate. When there is a deficiency of vitamin D, calcium absorption decreases, leading to weak and soft bones. In children, this condition is called **Rickets**, which causes bone deformities and poor growth. In adults, it leads to **Osteomalacia**, characterized by bone pain, muscle weakness, and increased risk of fractures.[6]

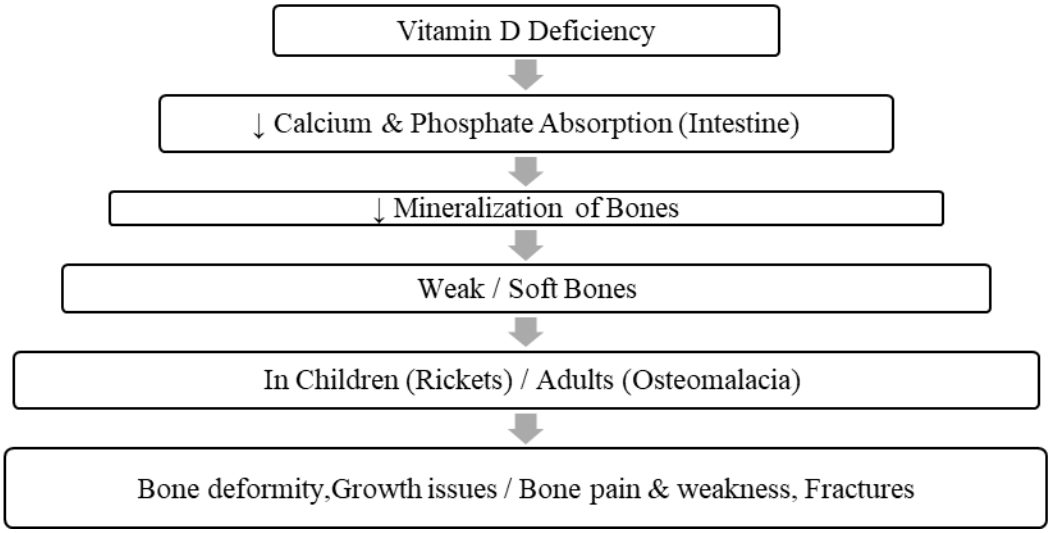

Figure: 1 Describes osteomalacia associated with Vit. D deficiency[6]

5.2 Supplementation in Deficiency

Vitamin D supplements are a must for people who're at high risk of deficiency. These include individuals, people who do not get much sunlight and those with certain digestive issues. There are two types of Vitamin D supplements: cholecalciferol (D_3) and ergocalciferol (D_2). It also helps avoid problems, like hypercalcemia that can happen if there is much Vitamin D. Doctors recommend regular blood tests to check 25-hydroxyvitamin D levels. This way they can make sure the person is getting the amount of Vitamin D.[7]

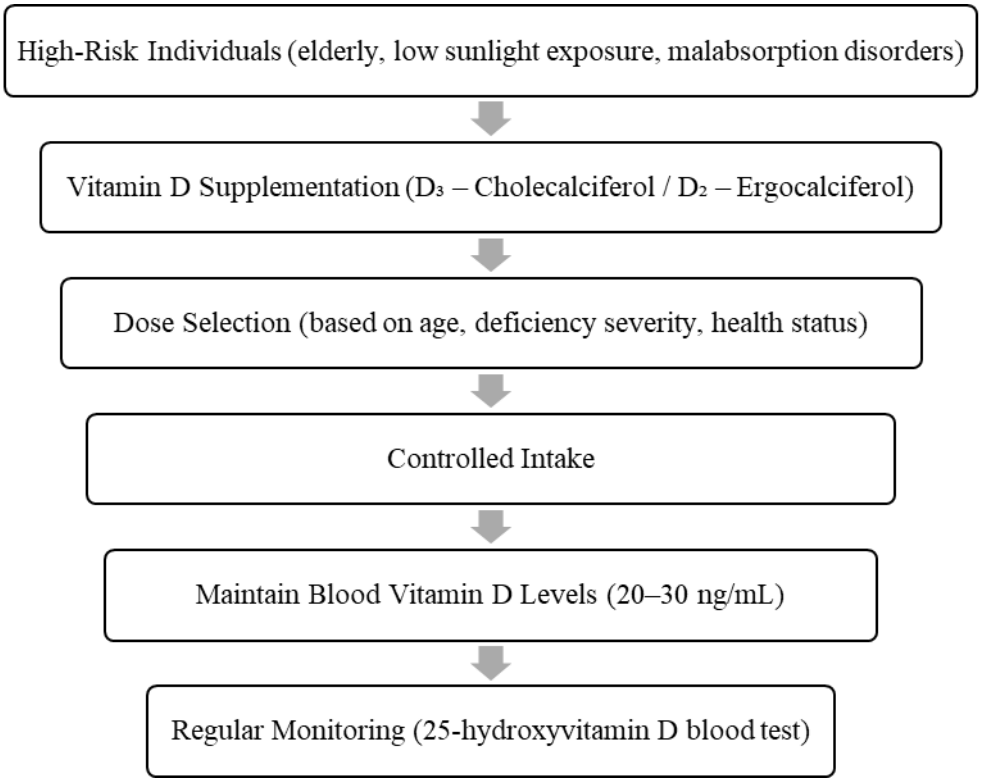

Figure 2: Recommendation of suitable supplements in view of risk[7]

6. Dose, Dosage Forms and Preparations

Vitamin D comes in forms to help prevent and treat a lack of it in the body. You have to be careful with the dose because not having Vitamin D and having too much can both cause serious health issues. Vitamin D is important, for our health. We need to make sure we get the right amount.

6.1 Marketed Formulations

Vitamin D is available in different dosage forms to help prevent and treat deficiency while improving patient convenience and treatment effectiveness. Common forms include tablets, capsules, softgel capsules, sachets, oral drops, syrups, and oral solutions, which are easy to use for both treatment and maintenance therapy. Vitamin D is mainly available as Ergocalciferol (Vitamin D_2) and Cholecalciferol (Vitamin D_3), with Vitamin D_3 being preferred because of its better efficacy and longer duration of action. High-dose preparations like 60,000 IU sachets and softgel capsules are commonly used for deficiency treatment, while lower-dose tablets and drops are used for daily maintenance. A newer dosage form is the Vitamin D_3 oral thin film strip, which dissolves quickly on the tongue without water and improves patient compliance, especially in children and elderly patients.[8]

6.2 Recommended Daily Allowance (RDA)

The recommended daily allowance (RDA) of vitamin D varies according to age, sunlight exposure, and health condition. According to the Institute of Medicine, infants from 0 to 12 months require 400 IU per day, while children and adults from 1 to 70 years need 600 IU daily. People above 70 years of age require 800 IU per day because of reduced vitamin D synthesis and increased bone health needs. These recommended amounts help maintain blood vitamin D levels at or above 20 ng/mL in healthy individuals. People with limited sunlight exposure or certain medical conditions may require higher doses under medical supervision.[9]

Table 3: RDA and age groups[9]

Group	Typical recommended intake
Infants (0–12 month)	400 IU/day
1–70 years	600 IU/day
>70 years	800 IU/day

6.3 Therapeutic vs Toxic Dose

The therapeutic dose of vitamin D for adults is usually 800–2000 IU per day to maintain normal levels and support bone health. In cases of deficiency, higher doses such as 6000 IU daily for a few months or 50,000 IU once weekly for 6–8 weeks may be prescribed, followed by maintenance therapy of 800–2000 IU daily. Vitamin D toxicity is rare but can occur when high doses are taken for a long time. Intake of more than 10,000 IU per day may increase the risk of toxicity and raise blood levels of 25(OH)D above 150 ng/mL, leading to hypercalcemia. Very high doses such as 50,000 IU daily for several months can cause serious problems like vomiting, dehydration, kidney damage, confusion, weakness, and high calcium levels in the blood. [10]

7. Vitamin D Toxicity (Hypervitaminosis D)

7.1 Definition and Types

Vitamin D toxicity, also called hypervitaminosis D, occurs when there is too much vitamin D in the body, usually due to excessive supplement intake. Since vitamin D is fat-soluble, it gets stored in body tissues and is removed slowly, causing its effects to last for a long time. This increases blood levels of 25-hydroxyvitamin D and calcium, leading to hypercalcemia.

7.2 Causes

The main cause of vitamin D toxicity is excessive use of supplements rather than sunlight or diet. Common causes include overdose of high-dose supplements for a long time, self-medication without medical advice, incorrect prescriptions, dosing errors, and frequent high-dose injections. After the COVID-19 pandemic, the use of vitamin D supplements increased greatly, which also raised the number of toxicity cases. This shows that uncontrolled supplementation can become harmful.

7.3 Risk Factors'

Some people are more likely to develop vitamin D toxicity due to certain health conditions or age-related factors. Major risk factors include excessive supplementation without monitoring, chronic kidney disease, granulomatous diseases that increase calcitriol production, and long-term use of high-dose therapy. These factors increase the chances of calcium imbalance and complications such as hypercalcemia, kidney damage, and cardiovascular problems.[11]

8. Mechanism of Toxicity (Core Pharmacology)

8.1 Mechanism of Development of Hypercalcemia

Vitamin D toxicity mainly occurs due to excessive intake of vitamin D supplements, which increases the level of calcitriol, the active form of vitamin D. High calcitriol increases calcium absorption from the intestine, releases more calcium from bones, and reduces calcium excretion by the kidneys. As a result, calcium accumulates in the blood, causing hypercalcemia. Hypercalcemia is the main reason for symptoms such as nausea, vomiting, weakness, kidney problems, and damage to major organs like the kidneys, heart, brain, and blood vessels. This makes careful monitoring of vitamin D intake very important.

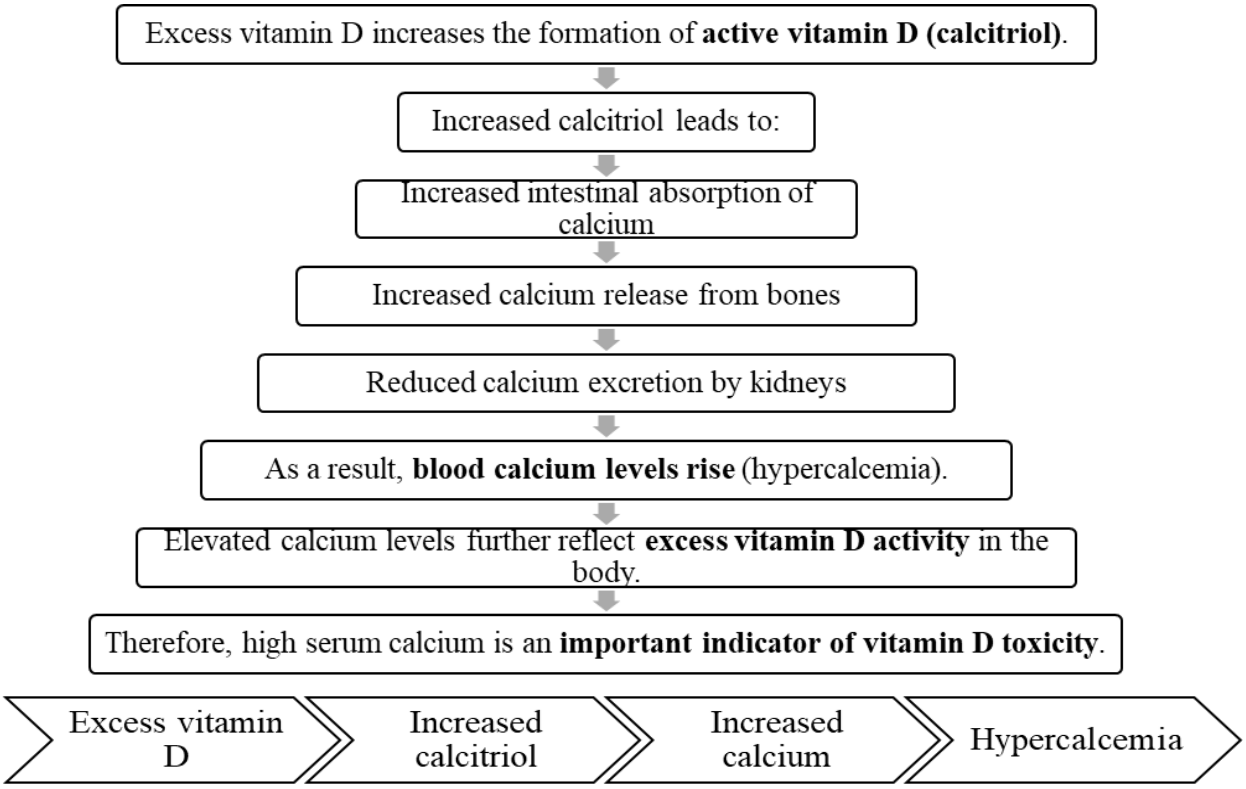

Figure 12: Cascade of Calcium \ Hypervitaminosis.

8.2 Cellular and Organ Damage

Persistently high calcium levels cause deposition of calcium in soft tissues, leading to organ damage such as-

- **Kidneys:** Nephrocalcinosis and renal failure
- **Heart:** Arrhythmias and vascular calcification
- **Brain:** Confusion and neurological disturbances
- **Blood vessels:** Calcification leading to reduced elasticity[12]

8.3 Vitamin D is a Silent Risk

Vitamin D is called a silent risk because toxicity develops gradually and causes serious damage before symptoms appear.

Vitamin D is called a “silent risk” because its toxicity develops slowly and often shows no early warning signs. Being a fat-soluble vitamin, it gets stored in body fat and liver. This leads to:

- Increased calcium absorption from the intestine
- Increased release of calcium from bones
- Reduced excretion of calcium by kidneys

As a result, calcium starts building up in the blood, causing Hypercalcemia. This condition may not show symptoms initially, but over time it can damage important organs like kidneys, heart, and brain.

"Vitamin D toxicity is silent because damage begins before symptoms appear."

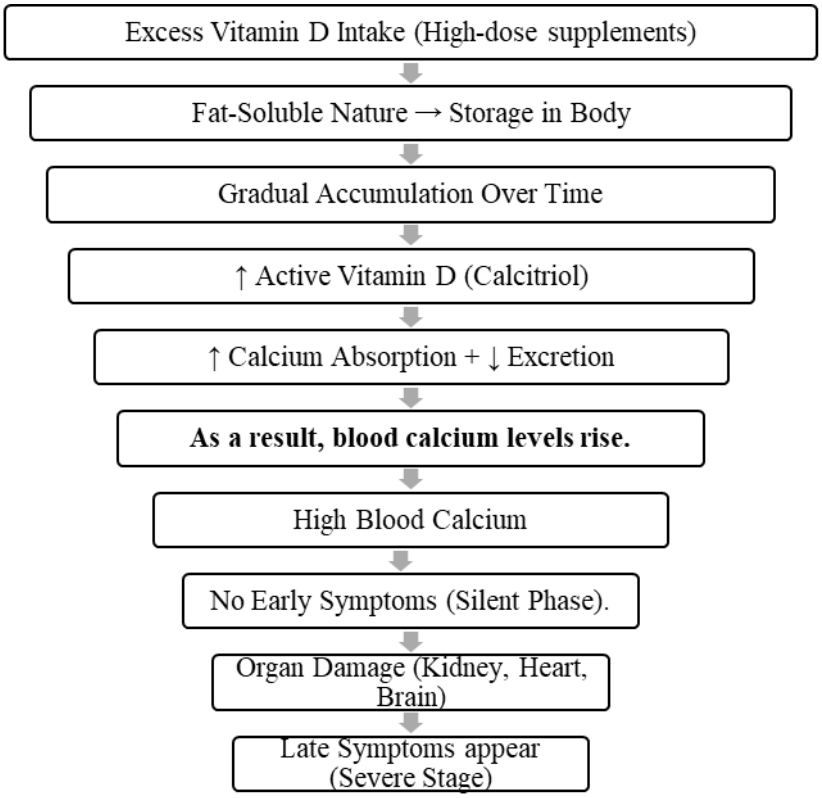

Figure 13 : Silent causes, effects of Excess Vitamin D.

- The danger is that by the time symptoms appear (nausea, confusion, weakness), significant internal damage may already have occurred.[11]

9. Clinical Manifestations of Vitamin D Toxicity

Vitamin D toxicity mainly causes hypercalcemia, which means high calcium levels in the blood. This affects many body systems. Common gastrointestinal symptoms include nausea, vomiting, loss of appetite, constipation, and abdominal pain. The kidneys may develop frequent urination, increased thirst, kidney stones, nephrocalcinosis, and even renal failure due to calcium deposition. Neurological symptoms include weakness, fatigue, confusion, headache, and drowsiness. The cardiovascular system may also be affected, causing hypertension, arrhythmias, vascular calcification, and increased risk of heart complications due to calcium imbalance and tissue damage..[13]

Table 4: Evidence snapshot[13]

System	Typical manifestations you listed
Gastrointestinal	Nausea, vomiting, anorexia, constipation, abdominal pain
Renal	Polyuria, polydipsia, nephrolithiasis, nephrocalcinosis, renal failure
Neurological	Weakness, fatigue, confusion, irritability, drowsiness, coma
Cardiovascular	Hypertension, arrhythmias, vascular calcification, cardiac complication

10. Toxicokinetics of Vitamin D

Vitamin D is fat-soluble, so it is stored in fatty tissues, liver, and muscles after repeated doses and is not removed quickly from the body. It is slowly released into the bloodstream over time, which keeps vitamin D and calcium levels high even after stopping supplements. The main stored form, 25-hydroxyvitamin D, has a long half-life of about 2 to 3 weeks, while the active form, calcitriol, acts strongly for a shorter time. Persistent hypercalcemia may continue for weeks and can damage important organs such as the kidneys, heart, and blood vessels, making early detection and regular monitoring very important.[14]

Table 5: Half-life and Persistence.[14]

Compound	Approx. plasma Half life	Notes
Vitamin D(D_2/D_3)	2 days (plasma)	Biologic persistence 2-3 months via storage
25(OH)D	15 days – 2 weeks	Overdose may persist for weeks
1,25$(OH)_2$D	12-15 hours	Short, but very potent

11. Management of Vitamin D Toxicity

The main goal in managing vitamin D toxicity is to lower high calcium levels in the blood (hypercalcemia) and prevent further complications. The first step is to immediately stop vitamin D and calcium supplements. Hydration therapy is very important, where doctors use isotonic saline to correct dehydration and help the kidneys remove excess calcium through urine. This helps reduce blood calcium levels and protects the kidneys from damage. In some cases, diuretics are also given after proper hydration to increase calcium excretion. Early treatment and proper medical care are essential to control vitamin D toxicity safely.[15]

Table 6: Core management steps.[15]

Step	Description
1)Stop Vitamin D &Calcium	Immediate discontinuation of supplements/dietary excess
2)IV isotonic saline	First-line to correct dehydration, ↑ renal Ca excretion
3)Add loop diuretic after hydration	Furosemide to promote calciuresis; monitor electrolytes

11.2 Pharmacological Treatment (Diuretics, Steroids)

Loop diuretics such as furosemide are used in vitamin D toxicity to help remove excess calcium from the body through urine, but they are given only after proper hydration to prevent dehydration. These medicines act on the kidneys and help lower blood calcium levels, while electrolyte levels must be closely monitored. They help reduce calcium levels by decreasing intestinal calcium absorption, increasing renal calcium excretion, and reducing the production of active vitamin D (calcitriol), which helps control serum calcium effectively.[16]

12. Vitamin D Deficiency

Vitamin D deficiency is a common health condition that occurs when the level of vitamin D in the blood becomes too low. Vitamin D is essential because it helps the body absorb calcium, which is necessary for strong bones and teeth. Severe deficiency can cause rickets in children and osteomalacia in adults. Treatment mainly includes vitamin D_3 supplementation, calcium supplementation, increased sunlight exposure, a balanced diet, and regular monitoring of vitamin D and calcium levels to prevent complications.[17]

13. Role in Immunity and Diseases

Vitamin D is not only important for bone health but also plays a significant role in regulating the immune system and influencing various disease conditions. It acts as an immunomodulatory agent and helps maintain a balance between innate and adaptive immunity. Vitamin D plays an important role in immune modulation by supporting both innate and adaptive immunity through activation of immune cells such as macrophages and T-lymphocytes. Vitamin D deficiency is also linked to chronic diseases such as Diabetes Mellitus, cardiovascular diseases, and certain cancers. It helps in insulin secretion, improves insulin sensitivity, and reduces inflammation and oxidative stress, which are major factors in chronic disease development.[18]

14. Safety Monitoring

Safety monitoring is an essential part of vitamin D therapy because it helps prevent both deficiency and toxicity. Since vitamin D is fat-soluble, it can accumulate in the body and increase the risk of hypercalcemia if taken in excess. Patient counseling is equally important to prevent misuse. Patients should avoid self-medication, follow prescribed doses, maintain a balanced diet with proper sunlight exposure, and undergo regular blood tests. Proper monitoring and guidance ensure safe, effective, and successful vitamin D therapy. [19]

Table 8: Healthcare team responsibilities[19]

Role	Examples mentioned in literature
Dose & formulation choice	Match dose to indication; avoid unnecessary high-dose/empiric use
Lab monitoring	25(OH)D, calcium (± PTH, creatinine) in at risk or high dose patients
Toxicity prevention	Avoid prescribing/dispensing errors, track all supplements

15. Recent Advances in Pharmacology

Advancements in pharmacology have shown that vitamin D acts not only in bone health but also like a hormone affecting immunity, metabolism, and many body functions. Nutrigenomics studies how nutrients interact with genes and how genetic differences influence the body's response to vitamin D. Personalized dosing is a modern approach where vitamin D supplementation is adjusted according to age, body weight, lifestyle, genetic profile, and existing vitamin D levels. This helps prevent both deficiency and toxicity, improves treatment outcomes, and makes vitamin D therapy safer and more effective.[20]

CONCLUSION

Vitamin D is essential for strong bones, calcium balance, and overall health, but too much of it can become dangerous. Unlike deficiency, vitamin D toxicity often develops silently when people take high-dose supplements without proper medical advice. Since vitamin D is fat-soluble, it gets stored in the body and can slowly build up over time. Excess vitamin D increases calcium levels in the blood (hypercalcemia), which can damage the kidneys, heart, brain, and blood vessels. Early symptoms such as nausea, weakness, tiredness, and confusion are often ignored, making it a hidden health risk. This is why vitamin D toxicity is called a "silent threat." Regular monitoring, proper dosage, and avoiding self-medication are the best ways to stay safe. Vitamin D is beneficial only when taken in the right amount—because in medicine, more is not always better.

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