

**HOT TOPIC ON
VITAMIN D
BENEFITS AND RISKS**

**Rational Prescription of Vitamin D
In General Practice**

Prof. Than Than Aye

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UNIVERSITY OF MEDICINE 2

YANGON

21.01.2018







Available Vitamin D In Myanmar

Daily Value 400 IU

Strong bone, Teeth, Immune Health (Once a day)

Cholecalciferol - D3 1000 IU (25mcg) 250% - 100 per sf gel

Cholecalciferol - D3 2000 IU (50mcg) 500% - 42 per sf gel

Cholecalciferol - D3 5000 IU (125mcg) 1250% - 83 per sf gel

Varieties Of Vit D

Ergocalciferol(Vit D2)

Cholecalciferol (Vit D3)

Dihydrotachysterol

Alphacalcidol (1.α-hydroxy cholecalciferol)

Calcitriol (1,25 –Dihydroxycholecalciferol)

Available Vitamin D + Calcium

Calcium + D3 (D2)

Calcium 400mg + D3 200 IU 1 tablet BD to tds daily - 125

Calcium 500mg + D3 200 IU 1 tablet OD to BD daily – 50

Calcium 500mg + D3 100 IU 1 tablet OD to BD daily - 100

Calcium 600mg + D3 400 IU 1 tablet BD daily

Adult Hypervitaminosis D-A Case Series

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Received date: 10 July 2015; **Accepted date:** 14 Sept 2015; **Published date:** 18 Sept 2015.

Citation: Lodh M, Mukhopadhyay R, Jajodia N, Sen D, Roy A (2015) Adult Hypervitaminosis D-A Case Series. Int J Endocrinol Metab Disord 1(3): doi <http://dx.doi.org/10.16966/2380-548X.111>

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Abstract

Prolonged hypervitaminosis D can result in calcium deposition in the soft tissues (especially the kidneys and heart), changes in the central nervous system & **in severe cases, death**. Patients and clinicians considering supplementation above currently recommended levels should be made aware of the possible toxicities of treatment with vitamin D, and baseline calcium and parathyroid hormone and vitamin D levels should be ascertained. We report here 8 such cases, all presenting with nausea, vomiting, polyuria, polydipsia, weakness and the common history of administration of vitamin D for backache, osteoarthritis, osteoporosis, leg cramps or generalized weakness. Laboratory tests revealed hypercalcemia and hypervitaminosis D in all cases. Vitamin D intoxication from increase in vitamin D intake may have become frequent in recent years due to an understanding of the role of 25-hydroxy vitamin D in the pathogenesis of several diseases. The importance of this case series as a warning against overtreatment and unnecessary treatment with high dose vitamin D cannot be overemphasized, especially as a public health measure in a country where vitamin D deficiency in children manifesting with rickets is a risk.

Keywords: Hypervitaminosis D; Vitamin D, Cholecalciferol; Toxicity; Parathyroid; Hypercalcemia

Vitamin D Supplementation and Risk of Toxicity in Pediatrics: A Review of Current Literature

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Context: Although vitamin D toxicity is rare in children, increased use of vitamin D formulations, re-examination of optimal vitamin D levels, and use of higher doses lend potential for an increased incidence of vitamin D toxicity.

Evidence Acquisition: A PubMed search was conducted through May 2013 for cases of vitamin D intoxication and vitamin D trials in pediatrics. Safety data were collected and reviewed.

Evidence Synthesis: A small number of pediatric studies tested vitamin D doses at or above the currently recommended upper tolerable intake. In children and adolescents, vitamin D excess was rare and usually asymptomatic. Recent cases of intoxication relate to errors in manufacturing, formulation, or prescription; involve high total intake in the range of 240 000 to 4 500 000 IU; and present with severe hypercalcemia, hypercalciuria, or nephrocalcinosis. However, mild hypercalcemia and hypervitaminosis using currently recommended doses have been reported in infants with rickets.

Conclusions: Although rare, cases of **vitamin D intoxication that present with dramatic life-threatening symptoms still occur in children.** Moreover, recent studies in infants raise a potential need for monitoring vitamin D levels when doses at or above the currently recommended upper range are used. Further studies are needed to clarify these findings. The Drugs and Therapeutics Committee of the Pediatric Endocrine Society suggests obtaining serum 25-hydroxyvitamin D levels in infants and children who receive long-term vitamin D supplementation at or above the upper level intake that is currently recommended. (*J Clin Endocrinol Metab* 99: 1132–1141, 2014)

Danger Of Vitamin D Intoxication

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Original Article

High-dose Vitamin D Supplementation Precipitating Hypercalcemic Crisis in Granulomatous Disorders

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Abstract

Background: Vitamin D supplementation precipitating hypercalcemic crisis is often the first manifestation in patients with granulomatous disorders. **Methods:** We report our experience on patients presenting with hypercalcemic crisis due to granulomatous disorder and the role of Vitamin D supplementation in the precipitation of hypercalcemic crisis in them. **Results:** The study included five patients with granulomatous disorders who presented with hypercalcemic crisis. All patients initially presented with nonspecific constitutional symptoms to other health-care centers to receive high-dose Vitamin D supplementation (60,000 U/week or 600,000 U intramuscular single dose). All of these patients presented with hypercalcemic crisis (serum calcium: 16.04 ± 0.3 mg/dl) to our centers after a period of 32.8 ± 9.62 days. Three patients were diagnosed to have sarcoidosis, and two were diagnosed to have tuberculosis. All five patients had parathyroid hormone-independent hypercalcemia with elevated serum 1,25-dihydroxy Vitamin D. Serum angiotensin-converting enzyme level was elevated in all the three patients with sarcoidosis. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography was performed in two patients with sarcoidosis which demonstrated diffusely increased tracer uptake in liver. In these two patients, liver biopsy confirmed the diagnosis. **Conclusions:** High-dose Vitamin D supplementation is most often the underlying cause of hypercalcemic crisis in patients with granulomatous disorders. Hence, high-dose Vitamin D supplementation should be used judiciously.

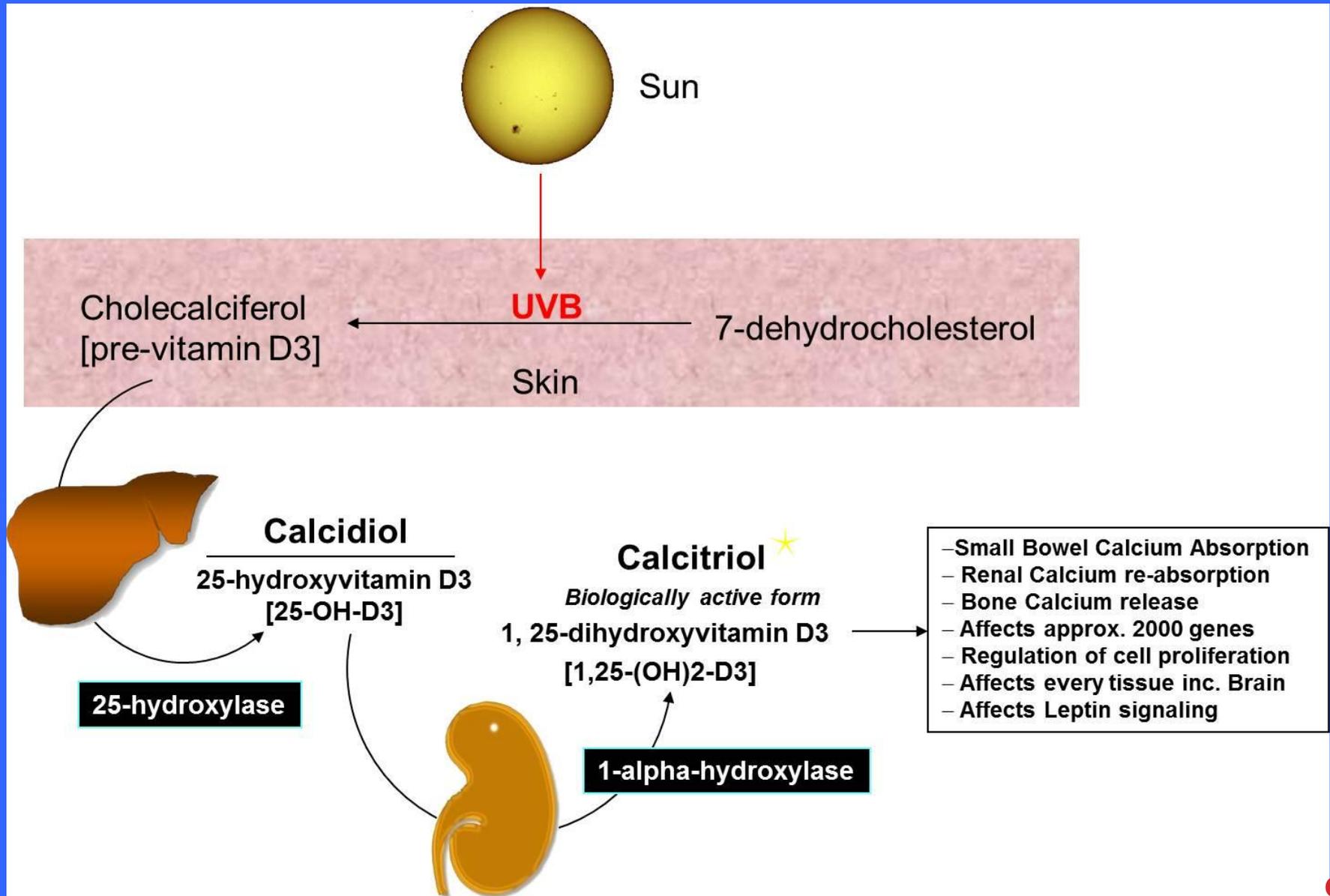
Keywords: Hypercalcemic crisis, sarcoidosis, Vitamin D



Evaluation, Treatment, And Prevention Of Vitamin D Deficiency: An Endocrine Society Clinical Practice Guideline

Michael F. Holick, Neil C. Binkley, Heike A. Bischoff-Ferrari,
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Murad, and Connie M. Weaver

Vitamin D Synthesis



Vitamin D Physiology

- 1,25(OH)₂D stimulates intestinal calcium absorption.
- 1,25(OH)₂D interacts with its vitamin D receptor in the osteoblast that changes to osteoclasts, and mobilize calcium and other minerals from the skeleton.
- In the kidney, 1,25(OH)₂D stimulates calcium reabsorption from the glomerular filtrate.
- 1,25(OH)₂D stimulates its own destruction by enhancing the expression of the 25-hydroxyvitamin into water-soluble inactive forms.

Vitamin D Biological Functions

A wide range of biological actions:

- inhibiting cellular proliferation
- inducing terminal differentiation
- inhibiting angiogenesis
- stimulating insulin production
- inhibiting renin production
- stimulating macrophage cathelicidin production
- regulating up to 200 genes

Prevalence Of Vitamin D Deficiency

- 25(OH)D of less than 20 ng/ml. (50 nmol/liter) = Vitamin D deficiency (IOM)
- 25(OH)D of more than 150 ng/ml (375 nmol/liter) = Vitamin D intoxication
- Vitamin D deficiency is common in Australia, the Middle East, India, Africa, and South America.
- 20–100% of U.S., Canadian, and European elderly men and women - vitamin D deficient.

Table (5) Baseline Biochemical Parameters Of Calcium And Placebo Group (Myanmar 20-73 yrs, BMI >23) ye myint et al,2016

Variables	Calcium group (n=50) Mean (SD)	Placebo group (n=50) Mean (SD)	P value
Insulin (μ U /ml)	21.9(15.56)	19.9(12.86)	0.485
HOMA-IR	5.14(3.71)	4.51(2.93)	0.352
FiCa (mg/dl)	2.64(1.19)	3.01 (1.58)	0.190
PTH (pg/ml)	57.88(17.05)	61.14 (13.86)	0.297
25(OH)Vit D (ng /ml)	29.13(14.08)	27.91(18.29)	0.709



Vitamin D Deficiency

At risk populations

- Breastfed infants
- Older adults
- People with limited sun exposure
- Darker skin pigments
- Certain religious groups



Causes Of Vitamin D Deficiency

- The major source - natural sunlight.
- There is an inverse association of serum 25(OH)D and obesity.
- Fat mal absorption syndromes and bariatric patients, nephrotic syndrome.
- Anticonvulsants and AIDS/HIV drugs, enhance the catabolism.
- Lymphomas, and primary hyperparathyroidism increased metabolism

Consequences Of Vitamin D Deficiency

- Vitamin D deficiency results in abnormalities in calcium, phosphorus, and bone metabolism.
- Rickets.
- Osteomalacia
- Isolated or generalized aches and pains in bones and muscles.
- Muscle weakness;
 - Children - difficulty standing and walking,
 - Elderly - increasing sway and frequent falls, thereby increasing their risk of fracture.

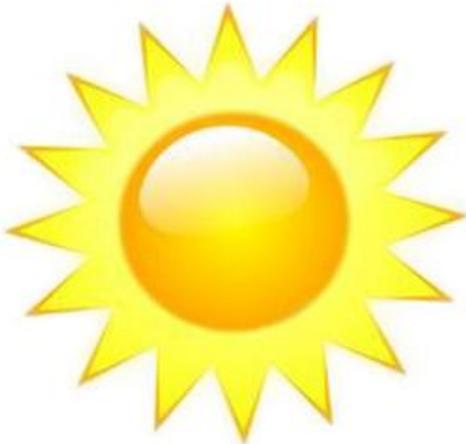
Vitamin D intoxication

The main consequence of vitamin D toxicity

- **Hypercalcaemia**
- **poor appetite,**
- **Nausea**
- **Vomiting.**
- **Weakness**
- **Frequent urination**
- **Abdominal cramps**
- **Nervousness**
- **Itching**
- **kidney failure**

Sources Of Vitamin D

Sources of vitamin



Sunlight



Cheese



Milk



Eggs



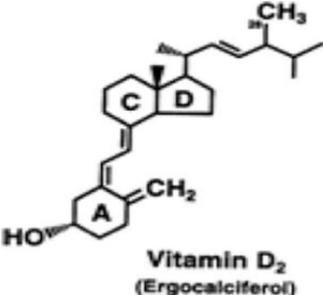
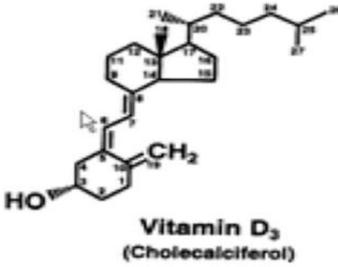
Salmon



Yogurt

Healthbring.com

TABLE 1. Sources of vitamin D₂ and vitamin D₃

Source	Vitamin D content	
Natural sources		
	 Vitamin D₂ (Ergocalciferol)	 Vitamin D₃ (Cholecalciferol)
Cod liver oil	~400–1,000 IU/teaspoon vitamin D ₃	
Salmon, fresh wild caught	~600–1,000 IU/3.5 oz vitamin D ₃	
Salmon, fresh farmed	~100–250 IU/3.5 oz vitamin D ₃ , vitamin D ₂	
Salmon, canned	~300–600 IU/3.5 oz vitamin D ₃	
Sardines, canned	~300 IU/3.5 oz vitamin D ₃	
Mackerel, canned	~250 IU/3.5 oz vitamin D ₃	
Tuna, canned	236 IU/3.5 oz vitamin D ₃	
Shiitake mushrooms, fresh	~100 IU/3.5 oz vitamin D ₂	
Shiitake mushrooms, sun-dried	~1,600 IU/3.5 oz vitamin D ₂	
Egg yolk	~20 IU/yolk vitamin D ₃ or D ₂	
Sunlight/UVB radiation	~20,000 IU equivalent to exposure to 1 minimal erythral dose (MED) in a bathing suit. Thus, exposure of arms and legs to 0.5 MED is equivalent to ingesting ~3,000 IU vitamin D ₃ .	
Fortified foods		
Fortified milk	100 IU/8 oz, usually vitamin D ₃	
Fortified orange juice	100 IU/8 oz vitamin D ₃	
Infant formulas	100 IU/8 oz vitamin D ₃	
Fortified yogurts	100 IU/8 oz, usually vitamin D ₃	
Fortified butter	56 IU/3.5 oz, usually vitamin D ₃	
Fortified margarine	429 IU/3.5 oz, usually vitamin D ₃	
Fortified cheeses	100 IU/3 oz, usually vitamin D ₃	
Fortified breakfast cereals	~100 IU/serving, usually vitamin D ₃	
Pharmaceutical sources in the United States		
Vitamin D ₂ (ergocalciferol)	50,000 IU/capsule	
Drisdol (vitamin D ₂) liquid	8,000 IU/cc	
Supplemental sources		
Multivitamin	400, 500, 1,000 IU vitamin D ₃ or vitamin D ₂	
Vitamin D ₃	400, 800, 1,000, 2,000, 5,000, 10,000, and 50,000 IU	

IU = 25 ng. [Reproduced with permission from M. F. Holick: *N Engl J Med* 357:266–281, 2007 (3). © Massachusetts Medical Society.]

Food Sources Of Vitamin D

3 oz smoked salmon = 583 IU



3 oz light tuna, canned in oil = 229 IU



1 large, whole egg = 29 IU



Foods Fortified With Vitamin D

8 oz skim milk = 115 IU



8 oz orange juice = 100 IU



1 cup Cheerios = 40 IU



1/2 cup yogurt = 40 IU



1.0 Diagnostic Procedure

1.1 We recommend screening for vitamin D deficiency in individuals at risk for deficiency.

We do not recommend population screening for vitamin D deficiency in individuals who are not at risk (1|QQQQ).

1.0 Diagnostic Procedure

1.2 : We recommend using the serum circulating 25-hydroxyvitamin D [25(OH)D] level, measured by a reliable assay, to evaluate vitamin D status in patients who are at risk for vitamin D deficiency.

▪We recommend **against using the serum 1,25-dihydroxyvitamin D [1,25(OH)₂D] assay** for this purpose and are in favor of using it only in monitoring certain conditions, such as acquired and **inherited disorders of vitamin D and phosphate metabolism (1|QQQQ)**.

TABLE 2. Indications for 25(OH)D measurement
(candidates for screening)

Rickets
Osteomalacia
Osteoporosis
Chronic kidney disease
Hepatic failure
Malabsorption syndromes
 Cystic fibrosis
 Inflammatory bowel disease
 Crohn's disease
 Bariatric surgery
 Radiation enteritis
Hyperparathyroidism
Medications
 Antiseizure medications
 Glucocorticoids
 AIDS medications
 Antifungals, e.g. ketoconazole
 Cholestyramine
African-American and Hispanic children and adults
Pregnant and lactating women
Older adults with history of falls
Older adults with history of nontraumatic fractures
Obese children and adults (BMI > 30 kg/m²)
Granuloma-forming disorders
 Sarcoidosis
 Tuberculosis
 Histoplasmosis
 Coccidiomycosis
 Berylliosis
Some lymphomas

Diagnostic point

- 25(OH)D of less than 20 ng/ml (50 nmol/l) = deficiency
- 25(OH)D of 21–29 ng/ml (52.5–72.5 nmol/l) = insufficiency
- 25(OH)D more than 150 ng/ml (375 nmol/l) = intoxication
- Up to 100 ng/ml (250 nmol/l) = safe

2.0 Recommended Dietary Intakes Of Vitamin D For Patients At Risk For Vitamin D Deficiency

2.1 : Aged 0 to 1 yr - 400 IU/d

▪ Aged 1 yr to 18yrs - 600 IU/d

▪ To raise the blood level of 25(OH)D consistently above 30 ng/ml (75 nmol/liter) may require at least **1000 IU/d of vitamin D** (2|Q|Q|Q|Q).

2.0 Recommended Dietary Intakes Of Vitamin D For Patients At Risk For Vitamin D Deficiency

2.2 : Aged 19 to 50 yr - 600 IU/d

It is unknown whether 600 IU/d is enough to provide all the potential non skeletal health benefits associated with vitamin D. However, to raise the blood level of 25(OH)D consistently above 30 ng/ml may require at least **1500–2000 IU/d of vitamin D** (2|QQQQ).

2.0 Recommended Dietary Intakes Of Vitamin D For Patients At Risk For Vitamin D Deficiency

2.3 We suggest that all adults aged 50–70 and 70 yr require at least 600 and 800 IU/d, respectively, of vitamin D.

Whether 600 and 800 IU/d of vitamin D are enough to provide all of the potential nonskeletal health benefits associated with vitamin D is not known at this time.

However, to raise the blood level of 25(OH)D above 30 ng/ml may require at least **1500–2000 IU/d** of supplemental vitaminD(2|QQQQ).



2.0 Recommended Dietary Intakes Of Vitamin D For Patients At Risk For Vitamin D Deficiency

2.4 We suggest that **pregnant and lactating women** require at least 600 IU/d of vitamin D and recognize that at least **1500–2000 IU/d of vitamin D** may be needed to maintain a blood level of 25(OH)D above 30 ng/ml (2|QQQE).

2.0 Recommended Dietary Intakes Of Vitamin D For Patients At Risk For Vitamin D Deficiency

2.5 : We suggest that obese children and adults and children and adults on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and medications for AIDS be given at least **two to three times** more vitamin D for their age group to satisfy their body's vitamin D requirement (2|QQQQ).

2.0 Recommended Dietary Intakes Of Vitamin D For Patients At Risk For Vitamin D Deficiency

2.6 : We suggest that the maintenance tolerable upper limits (UL) of vitamin D, **which is not to be exceeded without medical supervision**, should be

1000 IU/d for infants up to 6 months,

1500 IU/d for infants from 6 months to 1 yr,

2500 IU/d for children aged 1–3yr,

3000 IU/d for children aged 4–8yr, and

4000 IU/d for everyone over 8yr.

However, higher levels of 2000 IU/d for children 0–1 yr, 4000 IU/d for children 1–18yr, and 10,000 IU/d for children and adults 19yr and older may be needed to correct vitamin D deficiency (2|QQQQ).

3.0 Treatment And Prevention Strategies

3.1 We suggest using either vitamin D2 or vitamin D3 for the treatment and prevention of vitamin D deficiency (2|QQQQ).

3.0 Treatment And Prevention Strategies

3.2 For infants and toddlers **aged 0–1 yr** who are vitamin D deficient,

we suggest treatment with **2000 IU/d** of vitamin D2 or vitamin D3, or

with **50,000 IU** of vitamin D2 or vitamin D3 **once weekly for 6 wk** to achieve a blood level of 25(OH)D above 30 ng/ml,

followed by **maintenance** therapy of **400-1000 IU/d** (2|QQQQ).

3.0 Treatment And Prevention Strategies

3.3 For children **aged 1–18 yr** who are vitamin D deficient, we suggest treatment with **2000 IU/d** of vitamin D2 or vitamin D3 for at least 6 wk or

with **50,000 IU** of vitamin D2 **once a week** for at least **6 wk** to achieve a blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 600-1000 IU/d (2|QQQQ).



3.0 Treatment And Prevention Strategies

3.4 : We suggest that **all adults** who are vitamin D deficient be treated with **50,000 IU** of vitamin D2 or vitamin D3 **once a week** for **8 wk** or

its equivalent of **6000 IU** of vitamin D2 or vitamin D3 **daily** to achieve a blood level of 25(OH)D above 30 ng/ml,

followed by maintenance therapy of 1500–2000 IU/d (2|QQQQ).

3.0 Treatment And Prevention Strategies

3.5 In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of 3000–6000 IU/d (2|QQQQ).

3.0 Treatment And Prevention Strategies

3.6 : In patients with extra renal production of $1,25(\text{OH})_2\text{D}$, we suggest **serial monitoring of 25(OH)D levels** and serum calcium levels during treatment with vitamin D to **prevent hypercalcemia** (2|QQQQ).

3.0 Treatment And Prevention Strategies

3.7 : For patients with primary hyperparathyroidism and vitamin D deficiency, we suggest treatment with vitamin D as needed. Serum calcium levels should be monitored (2|QQQQ).

4.0 Non calcemic Benefits Of Vitamin D

4.1 : We recommend prescribing vitamin D supplementation for fall prevention. **We do not recommend** prescribing vitamin D supplementation **beyond recommended daily needs for the purpose of preventing cardiovascular disease or death or improving quality of life (2|QQQQ).**

TABLE 3. Vitamin D intakes recommended by the IOM and the Endocrine Practice Guidelines Committee

Life stage group	IOM recommendations				Committee recommendations for patients at risk for vitamin D deficiency	
	AI	EAR	RDA	UL	Daily requirement	UL
Infants						
0 to 6 months	400 IU (10 μ g)			1,000 IU (25 μ g)	400–1,000 IU	2,000 IU
6 to 12 months	400 IU (10 μ g)			1,500 IU (38 μ g)	400–1,000 IU	2,000 IU
Children						
1–3 yr		400 IU (10 μ g)	600 IU (15 μ g)	2,500 IU (63 μ g)	600–1,000 IU	4,000 IU
4–8 yr		400 IU (10 μ g)	600 IU (15 μ g)	3,000 IU (75 μ g)	600–1,000 IU	4,000 IU
Males						
9–13 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μ g)	800 IU (20 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
Females						
9–13 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	600–1,000 IU	4,000 IU
14–18 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
51–70 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
>70 yr		400 IU (10 μ g)	800 IU (20 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
Pregnancy						
14–18 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
Lactation ^a						
14–18 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	600–1,000 IU	4,000 IU
19–30 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU
31–50 yr		400 IU (10 μ g)	600 IU (15 μ g)	4,000 IU (100 μ g)	1,500–2,000 IU	10,000 IU

AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

^a Mother's requirement, 4,000–6,000 IU/d (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

Take home message



Diagnostic point

- 25(OH)D of less than 20 ng/ml (50 nmol/l) = deficiency
- 25(OH)D of 21–29 ng/ml (52.5–72.5 nmol/l) = insufficiency
- 25(OH)D more than 150 ng/ml (375 nmol/l) = intoxication
- Up to 100 ng/ml (250 nmol/l) = safe

Recommended Dose Vit D

0-1 year 400-1000 IU/d

8-older 400-4000 IU/d

infants deficient 2000 IU/d or 50,000 IU/wk for 6 wk

Adult Deficient 6000 IU/d or 50,000 IU /wk for 8 wk

Maintenance therapy 400–2000 IU/d

Contradication For Vit D

High Calcium Levels ARE a Vitamin D Contraindication

High blood calcium levels or conditions that can lead to high calcium levels such as:

- * High Calcium Levels
- * Sarcoidosis
- * Tuberculosis
- * Parathyroid disease

are 'relative' Vitamin D Contraindications.

THANK YOU



Two white dice with rounded corners are placed on a light brown wooden surface. The die on the left shows a large black letter 'Q' and a smaller black letter 'q' in the bottom right corner. The die on the right shows a large black letter 'A' and a smaller black letter 'a' in the bottom right corner.

Q

q

A

a