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Review article
Pregledni članak

THE D-LIGHTFUL VITAMIN D FOR HEALTH

VITAMIN D ZA DOBRO ZDRAVLJE

Michael F. Holick

Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes
Vitamin D, Skin and Bone Research Laboratory
Boston University Medical Center, Boston, MA

Summary

Vitamin D is the sunshine vitamin that is not only important for children's and adults' skeletal health but is also important for their overall health and wellbeing. Vitamin D deficiency has been defined as a 25-hydroxyvitamin D < 20 ng/mL and vitamin D insufficiency as a 25-hydroxyvitamin D of 21–29 ng/mL. The major source of vitamin D is sensible sun exposure since very few foods naturally contain vitamin D. Vitamin D deficiency is associated with increased risk for many acute and chronic diseases including infectious diseases, autoimmune diseases, cardiovascular disease, type 2 diabetes, neurocognitive dysfunction and muscle weakness. To achieve a blood level of 25-hydroxyvitamin D >30 ng/mL children require 600–1 000 IUs and adults 1 500–2 000 IUs of vitamin D daily.

Keywords: vitamin D, cancer, sunlight, 25-hydroxyvitamin D, infectious disease, osteoporosis, rickets

Kratak sadržaj

Vitamin D je »sunčani« vitamin koji je važan ne samo za zdrave kosti dece i odraslih osoba već i za njihovo opšte zdravlje i dobro stanje. Nedostatak vitamina D definiše se kao nivo 25-hidroksivitamina D < 20 ng/mL a manjak vitamina D kao nivo 25-hidroksivitamina D 21–29 ng/mL. Glavni izvor vitamina D jeste izlaganje suncu u razumnoj meri, pošto je mali broj namirnica koje prirodno sadrže vitamin D. Nedostatak vitamina D povezan je sa povećanim rizikom za mnoge akutne i hronične bolesti, među kojima su infektivne bolesti, autoimunska oboljenja, kardiovaskularna bolest, dijabetes tipa 2, neurokognitivna disfunkcija i mišićna slabost. Da bi se dostigao nivo 25-hidroksivitamina D u krvi >30 ng/mL deci je potrebno 600–1 000 IJ a odraslim osobama 1 500–2 000 IJ vitamina D dnevno.

Ključne reči: vitamin D, kancer, sunčeva svetlost, 25-hidroksivitamin D, infektivne bolesti, osteoporoza, rahitis

Historical Perspective

Some of the earliest life forms that have existed in the Atlantic Ocean for more than 500 million years and depended on sunlight for their energy source also produced vitamin D (1). As the industrial revolution swept across Europe in the mid-1600s it brought with it the scourge of rickets (2). As early as 1822 Sniadecki realized the importance of sunlight for the prevention and cure of rickets. However, it was inconceivable how exposure of the skin to sunlight could have any impact on the bone disease. In 1889 Palm recommended sunbathing to prevent rickets, but his recommendation was also ignored. Finally, in 1919 Huldschinsky reported that children exposed to a mercury arc lamp could be cured of their bone deforming disease. Two years later, Hess and Unger reported that exposure to sunlight was effective in inducing radiologic improvement in rachitic lesions in young children (2–4). These and other observations resulted in the United States and governments in Europe recommending sensible sunbathing of children to prevent rickets (2).

Steenbock (5) introduced the concept of irradiating milk and other foods with ultraviolet radiation to impart antirachitic activity. The United States and Europe embraced this fortification not only for milk, but also many other products including custard and

Address for correspondence:

Michael F. Holick, PhD, MD
Boston University School of Medicine
85 East Newton Street, M-1013
Boston MA 02118
Tel: 617-638-4546; Fax: 617-638-8882
e-mail: mfholick@bu.edu
Web Address: DrHolick.com

even beer was fortified with vitamin D. However, in the 1950s several children were born with facial deformities and hypercalcemia and it was concluded they were vitamin D intoxicated due to overfortification of milk with vitamin D. This resulted in Europe banning the fortification not only of milk but also all other products with vitamin D (6). It is now recognized that the likely cause was a rare genetic disorder, Williams syndrome, that is associated with elfin faces and hypercalcemia. Only recently Sweden and Finland have reintroduced fortifying milk with vitamin D as a preventative measure for rickets.

Sources of Vitamin D

The major source of vitamin D is sensible sun exposure (2, 3, 7). An adult in a bathing suit exposed to an amount of sunlight that causes a slight pinkness to the skin (one minimal erythemal dose) is equivalent to ingesting approximately 20,000 IUs of vitamin D (8, 9). Very few foods naturally contain vitamin D. These include wild caught salmon, herring and other oily fish, cod liver oil and sun exposed mushrooms (*Table I*). Foods fortified with vitamin D usually contain 100 IUs per serving. Both vitamin D2 and vitamin D3 when given in physiologic doses are equally effective in maintaining serum levels of 25-hydroxyvitamin D (8, 10–12).

Vitamin D Deficiency Pandemic

Vitamin D deficiency is common worldwide. In the United States approximately 32% of children and adults were found to be vitamin D deficient (13). Vitamin D deficiency is common in Europe, China, Canada, Korea, and Japan among other countries in temperate climates (7, 14–17). However, vitamin D deficiency is as common in equatorial countries including UAE, Saudi Arabia, South Africa, Thailand, Brazil and India (7, 17–23). The problem is magnified if vitamin D insufficiency (defined as a 25-hydroxyvitamin D of 21–29 ng/mL) is also included. It has been estimated that upwards of 50% of children and adults are at risk for vitamin D deficiency or insufficiency worldwide (7, 8, 17). Even in the United States where vitamin D fortification of milk and other dairy products as well as some orange juices are common it has been estimated that 50% of children aged 1–5 years and 70% of children aged 6–11 years are vitamin D deficient or insufficient (24). Pregnant and lactating women are also at very high risk (25). Pregnant women who received 600 IUs of vitamin D during their pregnancy at the time they gave birth 76% of them and 81% of their infants were vitamin D deficient (26).

Definition of Vitamin D Deficiency and Insufficiency

The Institute of Medicine defined vitamin D deficiency as a 25-hydroxyvitamin D < 20 ng/mL and based it on their evaluation of vitamin D's effect only on bone health (27). Endocrine Society defined vitamin D deficiency as a 25-hydroxyvitamin D < 20 ng/mL but concluded that to maximize bone health the blood level should be above 30 ng/mL (28). Therefore, they defined vitamin D insufficiency as a 25-hydroxyvitamin D of 21–29 ng/mL. This was based in part on several studies demonstrating that PTH plateaus between 30 and 40 ng/mL (29–31). Most importantly, a study of 675 presumed healthy German adults aged 20–70 years who met untimely deaths often due to a motor vehicle accident provided evidence for what blood level of 25-hydroxyvitamin D was essential for bone health (32). An evaluation of their bones for evidence of vitamin D deficiency osteomalacia was related to their blood level of 25-hydroxyvitamin D. The investigators reported that upwards of 36% had evidence of osteomalacia. There was also evidence for osteoidosis, i.e. osteoid buried within the mineralized bone, in approximately 35% of the healthy adults. The investigators concluded that to guarantee no evidence of osteomalacia a blood level of 25-hydroxyvitamin D should be >30 ng/mL (32).

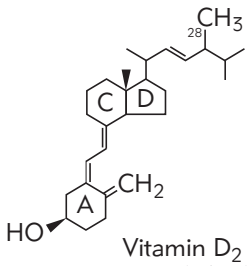
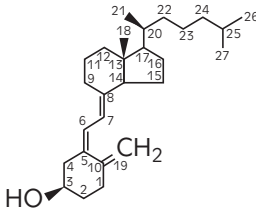
Consequences of Vitamin D Deficiency

Vitamin D deficiency results in an increase in PTH levels which induces the formation of osteoclasts (33) which results in the destruction of the matrix and mineral that leads to bone loss in both children and adults (2, 7). The secondary hyperparathyroidism causes a lowering of the blood phosphate level resulting in an inadequate calcium phosphate product causing a mineralization defect of the newly laid down matrix. In children this results in rickets and in adults causes the painful bone disease osteomalacia (2, 7, 34).

For more than 100 years there have been a variety of observations relating living at higher latitudes with increased risk for dying of cancer (7, 8). In the 1990s several reports appeared suggesting that living at higher latitudes which was associated with lower blood levels of 25-hydroxyvitamin D was the cause for the observations (35–37).

Others have reported that higher intakes of vitamin D and exposure to more sunlight at lower latitudes was associated with a reduced risk for type 1 diabetes, multiple sclerosis, rheumatoid arthritis, Crohn's disease, hypertension, cardiovascular disease, Alzheimer's disease, depression, schizophrenia and cancer and cardiovascular mortality (7, 8, 38–57) *(Figure 1)*. Healthy adults who had a blood level of 25-hydroxyvitamin D ~ 38 ng/mL reduced their risk of upper respiratory tract infections by more

Table I Sources of Vitamin D_2 and Vitamin D_3 (*with permission*, copyright Holick 2007).

SOURCE	VITAMIN D CONTENT IU = 25 ng
Natural Sources	 Vitamin D_2 (Ergocalciferol)  Vitamin D_3 (Cholecalciferol)
Cod liver oil	~400–1,000 IU/tsp 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 erythemal 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	429/3.5 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	8000 IU/cc
Supplemental Sources	
Multivitamin	400, 500, 1000 IU vitamin D_3 or vitamin D_2
Vitamin D_3	400, 800, 1000, 2000, 5,000, 10,000, and 50,000 IU

* Designated calciferol which usually means vitamin D_2.

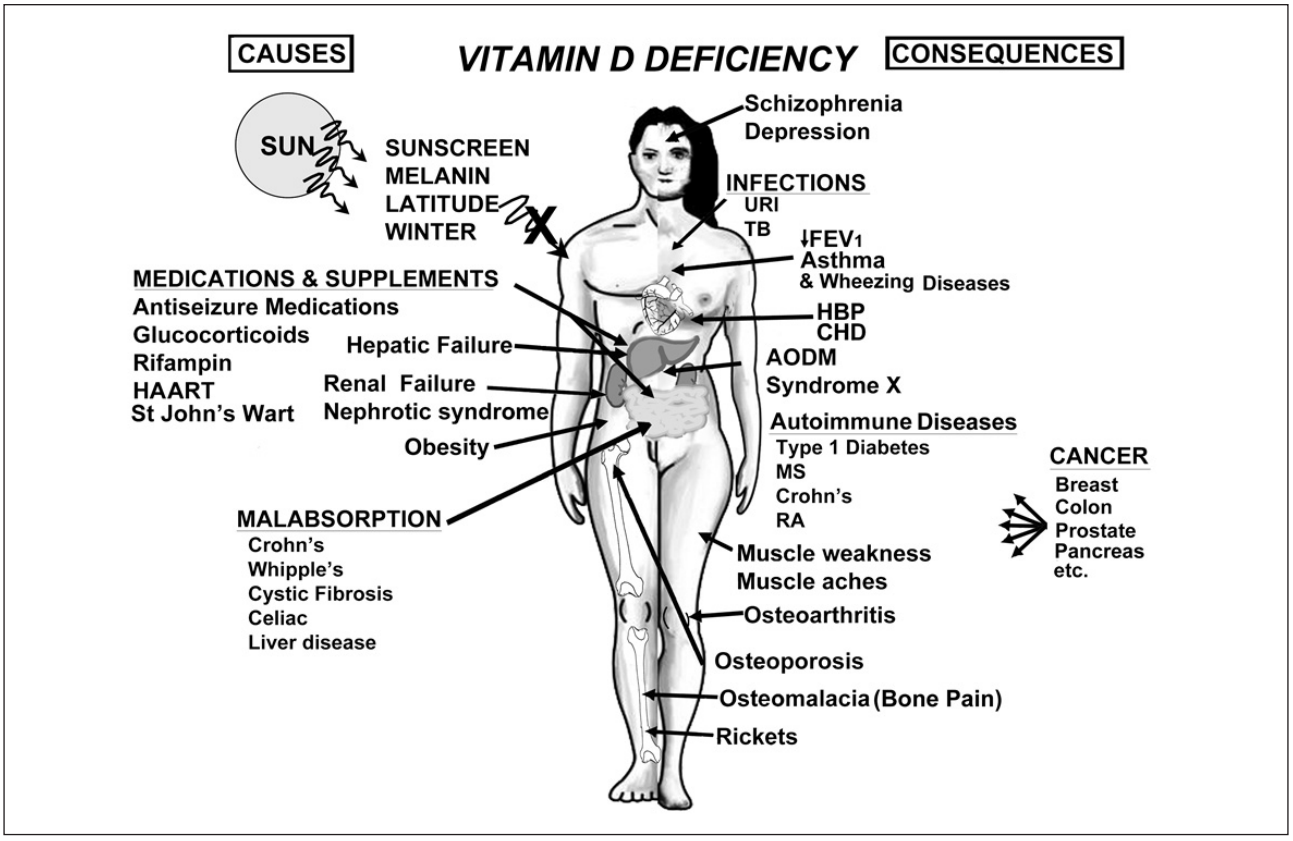


Figure 1 A Schematic representation of the major causes for Vitamin D deficiency and potential health consequences. Holick copyright 2010, *reproduced with permission*.

than 40% (58). Japanese school children who received 1200 IUs of vitamin D daily for 4 months during the winter reduced their risk of developing influenza A infection by 42% (59).

Mechanisms for the Pleotropic Effects of Vitamin D

Essentially, every tissue and cell in the body including the brain, gonads, skin, vascular smooth muscle and immune cells have a vitamin D receptor (VDR) (7, 8, 60). In addition, not only are the kidneys able to produce 1,25-dihydroxyvitamin D but also a wide variety of other cells including prostate, skin, brain, macrophages, colon and breast have the capacity to produce 1,25-dihydroxyvitamin D (7, 8, 60–62). It is believed that the local production of 1,25-dihydroxyvitamin D by these tissues and cells is for the purpose of regulating a wide variety of metabolic processes as well as controlling cellular growth and preventing malignancy (7, 8, 60–68). The production of 1,25-dihydroxyvitamin D by macrophages is important for helping macrophages fight infections including TB by increasing the expression of cathelicidin, a defensin protein that helps kill bacteria and other infectious agents (69) *(Figure 2)*.

1,25-dihydroxyvitamin D increases the expression of transcription factors that can downregulate cellular growth including p21 and p27 (7, 63). It has been estimated that as many as 2000 genes may be directly or indirectly regulated by 1,25-dihydroxyvitamin D (7, 70). In addition, 1,25-dihydroxyvitamin D can also affect the epigenetics of the cell adding an additional method for influencing cellular activity.

Treatment and Prevention of Vitamin D Deficiency

The Institute of Medicine made its recommendations using a population model and recommended for most children and adults up to the age of 70 years that 600 IUs of vitamin D daily will prevent vitamin D deficiency (27) *(Table II)*. The Endocrine Society made its recommendations for the treatment and prevention of vitamin D deficiency and insufficiency and recommended that children of one year and over receive 600–1000 IUs of vitamin D daily and adults 1500–2000 IUs of vitamin D daily (28) *(Table II)*. There are a variety of patients including those with obesity, malabsorption syndromes and on medications that would enhance the destruction of vitamin D and its metabolites who require at least 2–3 times more vitamin D. Patients with sarcoidosis should be

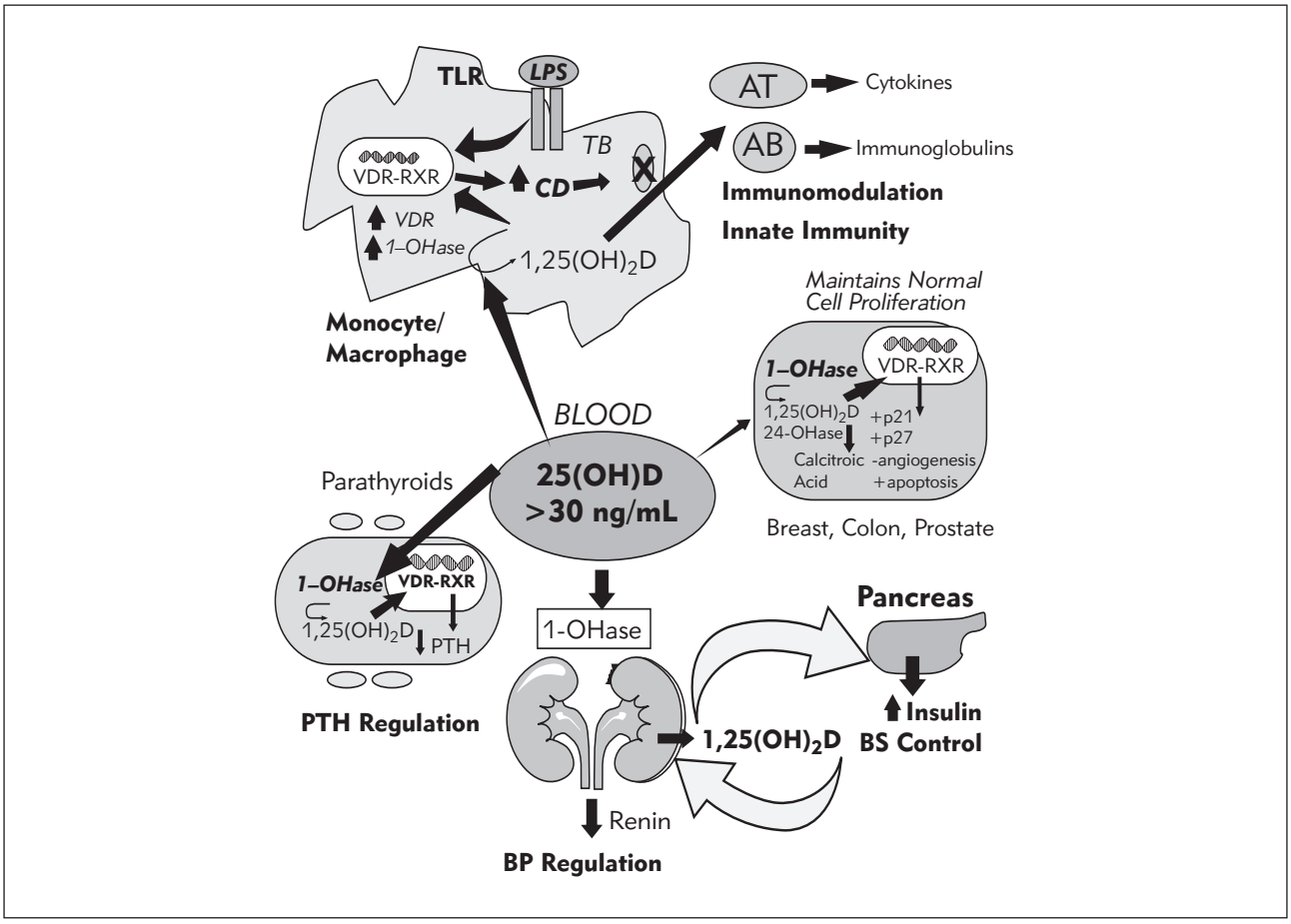


Figure 2 Metabolism of 25-hydroxyvitamin D [25(OH)D] to 1,25 dihydroxyvitamin D $1,25(OH)_2D$ for non-skeletal functions. When a monocyte/macrophage is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infective agent such as Mycobacterium tuberculosis (TB), or its lipopolysaccharide (LPS) the signal upregulates the expression of vitamin D receptor (VDR) and the 25-hydroxyvitamin D-1-hydroxylase (1-OHase). A 25(OH)D level >30 ng/mL provides adequate substrate for the 1-OHase to convert it to 1,25(OH)2D. $1,25(OH)_2D$ returns to the nucleus where it increases the expression of cathelicidin (CD) which is a peptide capable of promoting innate immunity and inducing the destruction of infective agents such as TB. It is also likely that the $1,25(OH)_2D$ produced in the monocytes/macrophage is released to act locally on activated T (AT) and activated B (AB) lymphocytes which regulate cytokine and immunoglobulin synthesis respectively. When 25(OH)D levels are ≈ 30 ng/mL, it reduces risk of many common cancers. It is believed that the local production of $1,25(OH)_2D$ in the breast, colon, prostate, and other cells regulates a variety of genes that control proliferation including p21 and p27 as well as genes that inhibit angiogenesis and induced apoptosis. Once $1,25(OH)_2D$ completes the task of maintaining normal cellular proliferation and differentiation, it induces the 25-hydroxyvitamin D-24-hydroxylase (24-OHase). The 24-OHase enhances the metabolism of $1,25(OH)_2D$ to calcitroic acid which is biologically inert. Thus, the local production of $1,25(OH)_2D$ does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity and the local production of $1,25(OH)_2D$ inhibits the expression and synthesis of PTH. The production of $1,25(OH)_2D$ in the kidney enters the circulation and is able to downregulate renin production in the kidney and to stimulate insulin secretion in the β-islet cells of the pancreas. Holick copyright 2007, *reproduced with permission*.

carefully monitored because of their hypersensitivity to vitamin D because of the granulomas producing 1,25-dihydroxyvitamin D that can cause hypercalciuria and hypercalcemia (7, 28).

One strategy to treat vitamin D deficiency is to give 50,000 IUs of vitamin D once a week or its equivalent about 6000 IUs of vitamin D daily for 2 months (71). To prevent recurrence 50,000 IUs vitamin D once every 2 weeks or an equivalent of 3000 IUs of vitamin D daily is suggested. This has been effective for up to 6 years without any untoward toxicity. Vitamin D toxicity is usually not seen in adults until they ingest more than 10,000 IUs of vitamin D daily for at least several months (7, 71) *(Figure 3)*.

Conclusion

Vitamin D deficiency and insufficiency is a global health problem for children and adults. Health

Table II Vitamin D dietary reference intakes.

IOM Recommendations					Committee Recommendations	
Life Stage Group	AI	EAR	RDA	UL	Daily Allowance (IU/d)	RUL (IU)
Infants						
0 to 6 mo	400 IU (10 μg)	---	---	1,000 IU (25 μg)	400–1,000	2,000
6 to 12 mo	400 IU (10 μg)	---	---	1,500 IU (38 μg)	400–1,000	2,000
Children						
1–3 y	---	400 IU (10 μg)	600 IU (15 μg)	2,500 IU (63 μg)	600–1,000	4,000
4–8 y	---	400 IU (10 μg)	600 IU (15 μg)	3,000 IU (75 μg)	600–1,000	4,000
Males						
9–13 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000	4,000
14–18 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000	4,000
19–30 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
31–50 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
51–70 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
> 70 y	---	400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
Females						
9–13 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000	4,000
14–18 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000	4,000
19–30 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
31–50 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
51–70 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
> 70 y	---	400 IU (10 μg)	800 IU (20 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
Pregnancy						
14–18 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000	4,000
19–30 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
31–50 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
Lactation*						
14–18 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	600–1,000	4,000
19–30 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000
31–50 y	---	400 IU (10 μg)	600 IU (15 μg)	4,000 IU (100 μg)	1,500–2,000	10,000

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

Note: AI = Adequate Intake; EAR = Estimated Average Requirement; IU = International Units; RDA = Recommended Dietary Allowance; UL = Tolerable Upper Intake Level.

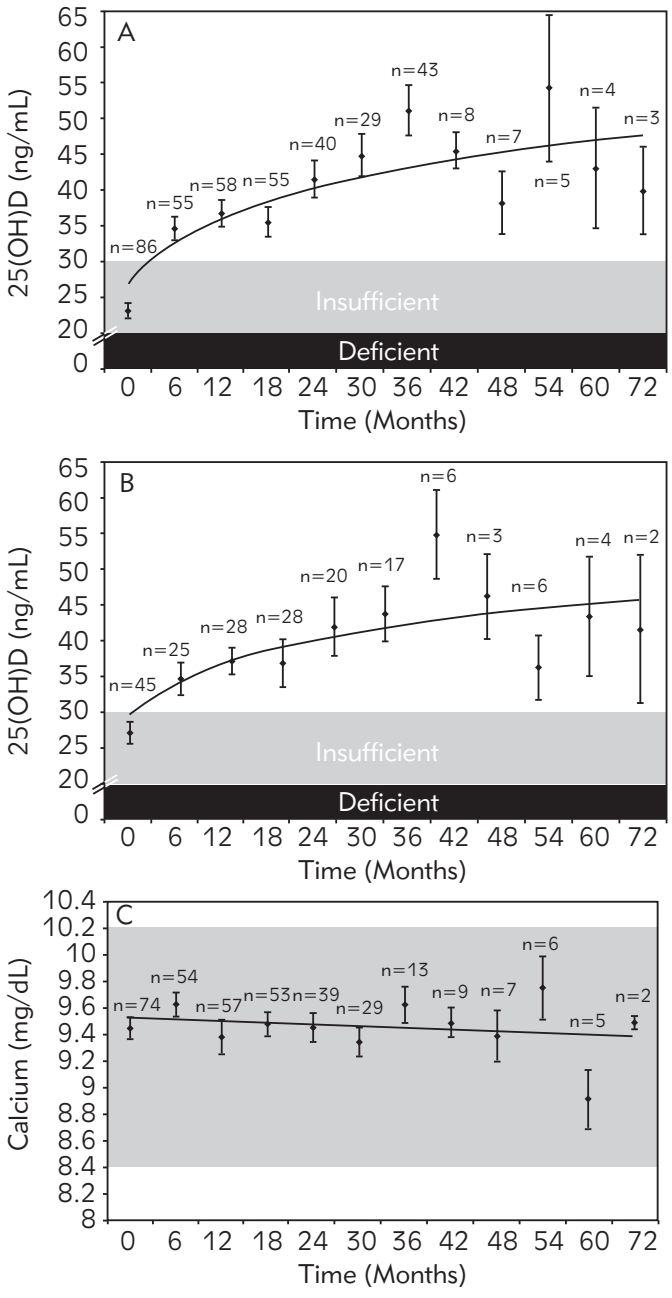


Figure 3 A. Mean serum 25-hydroxyvitamin D [25(OH)D] levels in all patients: Includes patients treated with 50,000 IU vitamin D_2 every 2 weeks (maintenance therapy, N=81), including those patients with vitamin D insufficiency who were initially treated with 8 weeks of 50,000 IU vitamin D_2 weekly prior to maintenance therapy (N=39). Error bars represent standard error of the mean, mean result over 5 years shown. Time 0 is initiation of treatment, results shown as mean values averaged for 6-month intervals. When mean 25[OH]D in each 6-month group was compared to mean initial 25[OH]D, $p<0.001$ up until month 43; $p<0.001$ when all remaining values after month 43 were compared to mean initial 25(OH)D.
B. Mean serum 25[OH]D levels in patients receiving maintenance therapy only: Levels for 37 patients who were vitamin D insufficient (25[OH]D levels < 30 ng/mL) and 5 patients who were vitamin D sufficient (25[OH]D levels ≥ 30 ng/mL) who were treated with maintenance therapy of 50,000 IU vitamin D_2 every two weeks. Error bars represent standard error of the mean, mean result over 5 years shown. Time 0 is initiation of treatment, results shown as mean values averaged for 6-month intervals. When mean 25(OH)D in each 6-month group were compared to mean initial 25[OH]D, $p<0.001$ up until month 37; $p<0.001$ when all remaining values after month 43 were compared to mean initial 25[OH]D.
C. Serum calcium levels: Results for all 81 patients who were treated with 50,000 IU of vitamin D_2. Error bars represent standard error of the mean. Time 0 is initiation of treatment, results shown as mean values averaged for 6-month intervals. Normal serum calcium: 8.5–10.2 mg/dL. *Reproduced with permission*.

Table III Conditions When 25(OH)D measurement is indicated.

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
Older adults with history of falls
Older adults with history of non-traumatic fractures
Obese children and adults (BMI>30)
Granulomatous disorders
Sarcoidosis
TB
Histoplasmosis
Coccidiomycosis
Berylliosis
Some lymphomas

care professionals worldwide should be aware of the insidious health consequences of vitamin D deficiency. However, this does not mean that everyone should be screened for their 25-hydroxyvitamin D level. Both the Institute of Medicine and the Endocrine Society recommend sensible sun exposure, eating foods that naturally contain or are fortified with vitamin D along with taking a vitamin D supplement to ensure both children and adults are vitamin D sufficient (27, 28). There is no need to be screening every one for their vitamin D status but only those who are at risk *(Table III)*. Although there is great concern about sun exposure and risk for skin cancer, it should be realized that sensible sun exposure especially of the arms, legs, abdomen and back to suberythemal doses of sunlight a few times a week will not significantly increase risk for non-melanoma skin cancer (72). The concern, of course, is melanoma, which is the most deadly form of skin cancer. However, often it is not appreciated that most melanomas occur on the least sun exposed areas and occupational sun exposure decreases risk for this deadly disease (73). Even Australia, the skin cancer capital of the world, recognizes that upwards of 40% of their children and adults are vitamin D deficient and now recommends sensible sun exposure as a means of preventing this disease of neglect.

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