Delaware Valley Institute of Fertility & Genetics
Conceptions
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The Many Faces of Vitamin D

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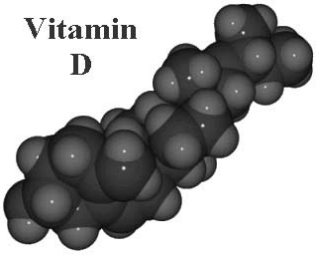


History: In 1941 the recommended dietary allowance (RDA) of vitamin D was established incidentally from the observation that a teaspoon of cod liver oil could guard against rickets and that 400 units of vitamin D was present in that amount of cod liver oil. It was also noted that exposure to sunlight, not necessarily dietary intake of vitamin D, was the first line of defense against vitamin D deficiency and maintenance of a healthy skeleton. In 1997 the Institute of Medicine (IOM) identified the serum 25 hydroxylase vitamin D (25 (OH) D) as the functional indicator of vitamin D status since it takes into account both cutaneous photoconversion of ultraviolet beta radiation (UVB) and the orally ingested vitamin D.

It was known then that this vitamin has an important function for calcium absorption and prevented rickets in children. What had remained unknown was the exact amount of vitamin D required to optimize calcium absorption, in order words, what was the normal vitamin serum concentration to achieve that in the absence of adequate sunlight exposure, how much dietary or supplemental vitamin D was required. The other non-calciotropic functions of vitamin D were unknown as well.

Present Status: Sixty years later in its publication of the Dietary Reference Intake (DRI) for nutrients, the IOM recommendation for daily vitamin D requirements remained unchanged.

DIETARY REFERENCE INTAKE (DRI) FOR VITAMIN D

Age	AI* IU/d	UL** IU/d
Birth to 12 months	200	1,000
1-50	200	2,000
51-70	400	2,000
71+	600	2,000

*AI = Adequate Intake **UL = Upper Limit

The extreme low and extreme high levels of vitamin D for patients to develop clinical manifestations are known. Rickets occur at a vitamin D serum level of less than 10 ng/mL and vitamin D toxicity occurs at levels exceeding 160 ng/mL, but as was stated previously, the optimal level of vitamin D in the serum has not been exactly defined. The physiological normal range for vitamin D was based on the observation that its levels are inversely related to parathyroid hormone levels until vitamin D reaches a serum concentration between 30 and 40 ng/mL. It was also observed that the intestinal absorption of calcium transport increases to 65% from 45% when vitamin D levels arrive to 32 ng/mL from 20 ng/mL. Taking this data into account, it follows that a level of vitamin D over 30 ng/mL must represent sufficient or normal concentration for that vitamin.

25 (OH) D		
Rickets	<10 ng/ml	(25 nmol/L)
Deficiency	20 ng/ml	(50 nmol/L)
Insufficiency	21-29 ng/ml	(51-74 nmol/L)
Sufficiency	30-40 ng/ml	(75-100 nmol/L)
Intoxication	>160 ng/ml	(>400 nmol/L)

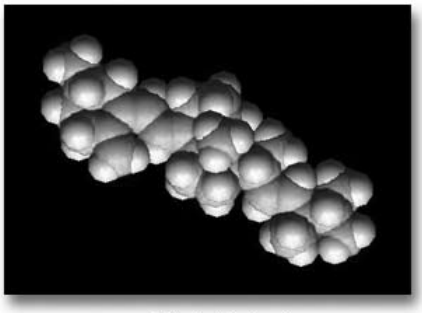
Based on those estimates, one billion people worldwide suffer from either deficiency or insufficiency and 50% of postmenopausal women in the United States taking medication for osteoporosis have insufficient levels of vitamin D. Forty-two percent of black girls and black women 15 to 45 years of age have deficient levels of vitamin D by the end of winter. One out of three healthy students, residents and physicians in a Boston hospital were deficient for vitamin D serum levels, despite eating salmon at least once a week, taking multivitamins, and drinking a glass of milk daily. Studies in six countries not deprived of adequate sunlight (Australia, Lebanon, Turkey, United Arab Emirates, Saudi Arabia, and India) showed that 30-50% of children and adults have vitamin D deficiency. **In another study, 73% of pregnant women were found to have vitamin D deficiency and 80% of their infants at birth were vitamin D deficient in spite of the fact that 70% of them took prenatal vitamins, 90% of them ate fish as recommended, and 93% drank at least two glasses of milk a day.**

Physiology: Few foods naturally contain vitamin D. Humans get vitamin D mainly from exposure to sunlight, but also from dietary supplements and fortified food products. Solar ultraviolet beta radiation (WV 290-315 nm) converts a precursor of cholesterol (7-dehydrocholesterol) to previtamin D, which is rapidly converted by heat to vitamin D. Adequate sunlight exposure provides sufficient vitamin D, which is stored in the body fat from where it is released during the winter. The adipose tissue sequestrates vitamin D. Obesity leads to a decrease in vitamin D blood concentration. There is an inverse relationship between vitamin D and Body Mass Index (BMI). People living near the equator who are exposed to sunlight have robust levels of vitamin D. Excessive amounts of previtamin D or vitamin D are destroyed by sunlight and no intoxication of vitamin D can occur by exposure to sunlight. Although in Europe very few foods are fortified with vitamin D, in the United States several food products contain vitamin D. Vitamin D from either the skin or the diet goes to the liver where it becomes 25 (OH) D, the functional indicator of vitamin D sufficiency in the serum. The 25 (OH) D undergoes an additional change at the kidney to become the active form of vitamin D, 1,25 $(OH)_2$ D.

The Many Faces Of Vitamin D: Vitamin D controls more than 200 genes, including genes regulating the growth, differentiation and death of the body cells along with the creation of blood vessels. Several functions of vitamin D have been identified and vitamin D effects have been studied.

A reduction of nonvertebral fracture ranging from 58% to 29% was observed in three studies when 700 to 800 units of vitamin D were used daily with or without calcium supplements. There was no benefit with a daily supplemental dose of 400 units. Supplementation of vitamin D improves muscular strength and performance speed and reduces the risk of falls.

Colon, breast, ovarian, prostate and pancreatic cancer along with Hodgkin's lymphoma and other cancers have been associated with vitamin D deficiency. These cancers occur with higher frequency to individuals living at higher latitudes as compared to those that reside at lower latitudes. Not only the frequency, but the mortality rate from these cancers is also increased. Appropriate blood levels of circulating vitamin D are required at the local (cellular) level for vitamin D to exert its protective effect. It has been suggested



Vitamin D molecule

that when a cell becomes malignant, 1,25 $(OH)_2$ D can induce death of this cell (apoptosis) and prevent blood vessel formation (angiogenesis) that reduces the survival of a malignant cell.

Vitamin D deficiency is associated with the increase of inflammatory proteins, congestive heart failure and hypertension. Treatment with UVB radiation almost doubled the serum levels of vitamin D and normalized the blood pressure.

Living below 35 degrees of latitude, ingesting more than 400 units of vitamin D daily, or maintaining sufficient serum concentration of vitamin D reduces the risk for multiple sclerosis, rheumatoid arthritis, and osteoarthritis by 50% and protects against other autoimmune diseases such as diabetes mellitus type 1. A large cross-sectional study of St. Thomas Hospital in London, UK, focused on the effect of vitamin D on inflammation and longevity. The difference between women with the highest and lowest vitamin D concentration was equivalent to five years. Vitamin D deficiency has been linked to increased

incidence of schizophrenia and depression. **Maintaining vitamin D sufficiency in utero and during early development in life may be important for brain development as well as maintenance of mental function.**

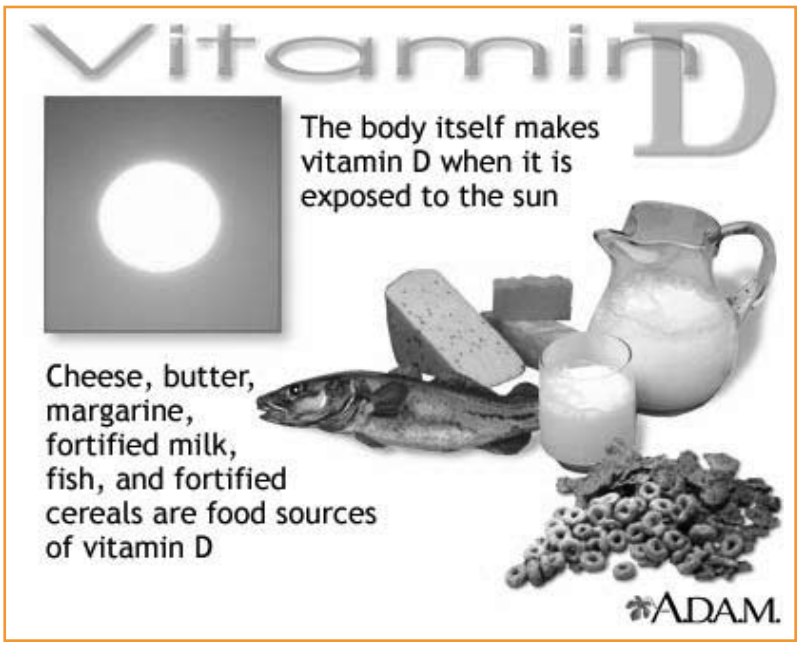
Vitamin D given during pregnancy reduces the development of pancreatic islet autoantibodies in the offspring and by prescribing 2,000 units daily during the first year reduces the risk of developing type 1 diabetes mellitus by 80%. On the other hand, deficiency of vitamin D in children increases this risk by 200%. Metabolic syndrome is associated with vitamin D deficiency as is insulin resistance and reduction of insulin production. Appropriate daily doses of vitamin D and calcium (800 units and 1,200 mg respectively) reduce the risk for type 2 diabetes by 33%.

Treatment: The IOM recommendations fall short of what the experts currently agree is necessary as a daily intake of vitamin D when inadequate sun exposure is present. For any adult at this category, 800 to 1,000 units of vitamin D per day are required. Natural sources rich in vitamin D provide no more than 300 units per ounce and most of them have 30 units per ounce. Most fortified foods provide even less, approximately 15 units per ounce. Therefore, vitamin D supplementation is required. There are two sources for orally ingested vitamin D. Vitamin D_2 is manufactured from yeast ergosterol (ergocalciferol) and vitamin D_3 from lanolin 7-dehydrocholesterol (cholecalciferol). When the label says vitamin D or calciferol, the product usually contains vitamin D_2. The vitamin available through prescription in the United States usually is vitamin D_2. Since ergocalciferol (vitamin D_2) is approximately 30% as effective as cholecalciferol (vitamin D_3), three times the amount of the former should be prescribed. If vitamin D deficiency has been documented, then 50,000 units of vitamin D_2 capsules can be given once a week for eight weeks and thereafter every two to four weeks. Fifty thousand units of vitamin D_2 per week for two years did not result in any clinical evidence of toxicity, hypercalcemia, or abnormally elevated vitamin D serum levels. Another approach is to either prescribe 1,000 units of vitamin D_3 (cholecalciferol) or 3,000 units of vitamin D_2 (ergocalciferol) daily.

Vitamin D_2 (ergocalciferol)	**Vitamin D_3** (cholecalciferol)
Yeast	Fish liver oil
Mold	Salmon
	Sardines
	Herring
	Egg Yolks

Many sunscreen products have a sun protection factor (SPF) of 30% to 50%. Even if only SPF 8 was applied, the photosynthesis of vitamin D is reduced by 92.5% while a SPF 15 effectively reduces vitamin D production by 99%. Skin pigment has a 99% vitamin D photosynthesis reduction. Very little or no amount of vitamin D is synthesized between November and February. Exposure of the arms and legs between 10 a.m. and 3 p.m. for 5 to 30 minutes twice a week, depending on the season, latitude, and skin pigmentation, is considered to be adequate. Sunbathing with a swimsuit causing minimal erythema to the exposed skin surfaces is equivalent to 20,000 units of vitamin D_2 ingested. For patients that suffer from malabsorption, exposure to a tanning bed for 30% to 50% of the recommended time for tanning, with sunscreen on the face, is an excellent means of preventing and treating vitamin D deficiency.

Breast milk contains approximately 20 units (IU) of vitamin D per liter and women with vitamin D deficiency provide even less. A daily dose of 4000 IU of vitamin D_3 (cholecalciferol) increased the serum level of vitamin D to 30 ng/ml and was sufficient to satisfy the infant's needs for this vitamin. Although the American Academy of Pediatrics' (AAP) current recommendation provides for a 200 IU of vitamin D daily requirement in the breastfed infant, the Canadian Pediatric Society, after reconsidering the scientific evidence that vitamin D deficiency in childhood is associated with an increased risk of several chronic conditions, recommends 400 IU per day for all neonates.



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Happy Birthday to . . .

Eibhleann Greer, born March, 20, 2007, to Audrey Poe and Campbell Knox.
Caiden Alexander, born May, 1, 2007, to Allison and Brian Spinelli.
Michelle Rachel and Annelise Rebecca, born August, 22, 2007, to Becky and Mike Meidt.
Nolan Kien, born September, 14, 2007, to Elise Do and David McClintock.
Anthony Patrick, born September, 21, 2007, to Amanda Negro and Patrick Witts.
Alysa Rose, born September, 23, 2007, to Alexis and Joseph Rivel.
Adrienne Lily, born September, 24, 2007, to Diane and Edward Magram.
Gabrielle and Matthew, born September, 27, 2007, to Rebecca Metzger and Kimberly Cyganik.
Cody and Cole, born October, 3, 2007, to Melissa and Adam Walker.
Cooper and Abgail, born October, 9, 2007, to Christie and Jeff Willoughby.
Chad Colby Blase, born October, 19, 2007, to Belinda and Aaron Ogitis.
Jack Tyler, born November, 7, 2007, to Patricia and John Watkins.
Viggio, born December, 10, 2007, to Sigrid Strybol and Olaf Babinet.

All of the babies and parents are doing well. Thank you, DVIF&G!

George S. Taliadouros, M.D., FACOG, medical director of DVIF&G. For more on this topic, please click on ***www.dvifg.com****.*