

Vitamin D: An Overview

Purpose: This course will look at the many health conditions associated with vitamin D as well as the diagnosis and treatment of vitamin D deficiency.

Objectives

1. Discuss two ways the body can attain vitamin D
2. List three functions of vitamin D
3. Identify three cardiovascular benefits of vitamin D
4. List three neurological diseases associated low vitamin D levels
5. Identify adequate amounts of vitamin D in different populations

Vitamin D is a fat soluble vitamin that has been linked to many health problems. It has been known to be critical to bone health for years, but recently a lot of research has linked it to many other health conditions and diseases.

Traditionally, deficiencies of vitamin D were well known to lead to rickets in children and osteomalacia in adults. Rickets is a softening of bones in kids that puts the child at high risk of fracture and deformity. It is much more common in developing countries.

Osteomalacia is a reduction in bone mineral content and presents with muscle weakness, bone pain and weak bones.

Physiology

Vitamin D is a precursor to a hormone. It comes in two forms: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). While both forms can be used to supplement, vitamin D3 is the most common form found in vitamin supplementation. Vitamin D3 is made by the skin in response to sunlight as well as found in some fatty fish. Vitamin D2 is most commonly found in yeast.

Vitamin D₃ is made from the skin and is transported to the liver where it is hydroxylated to 25(OH)D. This is the inactive form. It is then transported to the kidneys where it is transformed to its active form, 1,25(OH)D.

Sunlight makes vitamin D through ultraviolet B rays. In the upper latitudes, vitamin D is most effectively synthesized at midday. In the winter, vitamin D production is low in the northern parts of the United States. Ultraviolet B rays do not penetrate clouds well and therefore overcast days are not optimal for the creation of vitamin D. Sunscreen significantly reduces the production of vitamin D as does advanced age.

Older adults are more prone to vitamin D deficiencies because their bodies do not make it as well in response to sunlight. Obesity is another factor that reduces vitamin D production. Dark skin inhibits the synthesis of vitamin D and therefore vitamin D deficiencies are more common in dark skinned individuals.

The amount of vitamin D that the sun makes depends on a number of factors including the time in the sun, the amount of pigment in the skin and the strength of the UVB rays.

The Role of Vitamin D

Vitamin D has important functions throughout the body (1). In the small intestine it controls calcium absorption. It helps mediate bone mineralization and helps maintain calcium and phosphorous levels in the blood. It provides anti-inflammatory effects and immune modulating properties.

Vitamin D has an important role in many disease states. Many of these conditions will be discussed below. Some of the conditions have good evidence suggesting their link, others need more research before a correlation can be proven.

Vitamin D and Death

Vitamin D is effective at reducing death rates in a variety of people. It does this through multiple possible mechanisms including its immune-modulating effects, its anti-inflammatory effects or its effect on certain disease states (1).

Research shows that dialysis patients have reduced death rates when they are supplemented with vitamin D (2). Similarly, those with chronic kidney disease and low vitamin D levels have increased death rates (3).

Death rates are not just improved in kidney patients. Those with coronary heart disease and a low vitamin D level have a higher cardiovascular and overall mortality than those with normal vitamin D levels (4).

The exact mechanism of how vitamin D affects death rates is unclear but a link has been noted between all-cause mortality and supplementation of vitamin D (5).

Osteoporosis

Osteoporosis is a common bone disease that increases the risk of fractures. It has been shown that a low level of vitamin D is a risk factor for osteoporosis (1). Low levels of vitamin D affect the ability of calcium to enter the bone. When vitamin D in doses of over 700 IU a day is given with calcium bone loss is reduced (6).

There is question to the benefit of vitamin D alone. Most of its benefit (in osteoporosis) comes when combined with calcium (1). Doses of vitamin D of at least 400 IU is needed to reduce the risk of non vertebral fractures (1).

Osteoporosis is significantly more risky when individuals fall. Vitamin D has some benefit in reducing the risk of falls. This may occur because vitamin D is linked to improved muscle function (1). One study suggested that 800 IU every day reduces the risk of falls. When doses were less than 800 IU there was no reduction in falls (7).

Another study showed that those supplemented with vitamin D have a 22% decrease in fall risk. Fifteen people need to be treated to prevent one fall. This study recommended the use of 800-1000 IU each day to prevent falls (8).

The Heart and Vitamin D

Vitamin D has been linked to many problems with the heart. Vitamin D has been correlated directly with heart problems and with many risk factors associated with heart disease.

Recent evidence suggests that there is an association between blood pressure and vitamin D status. More research is needed to determine more specifically what level of vitamin D and in what sub-populations it has its effect on blood pressure (9).

Those with the lowest levels of vitamin D in the blood are at highest risk for a cardiovascular event (10). Men with vitamin D levels below 15 ng/ml are at increased risk for a heart attack (11).

Strokes are also related to vitamin D levels. Those with the lowest level of vitamin D are at increased risk for fatal stroke. In addition, vitamin D supplementation may reduce the risk of a future stroke (12).

Another cardiovascular risk factor – diabetes - is also linked to low vitamin D levels. This will be discussed in the next section.

Diabetes

One way that vitamin D may reduce the risk of heart disease is in its effect on diabetes. Vitamin D has a role in the management of blood glucose and the development of diabetes. Low levels of early life exposure to vitamin D may be linked to type I diabetes (13) and intake of vitamin D supplementation is theorized to reduce the risk of type I diabetes (14).

Vitamin D level is also linked to type 2 diabetes. Vitamin D may be instrumental in many processes critical to glucose metabolism such as beta-cell function, insulin secretion and

insulin sensitivity (1). Low levels of vitamin D and calcium have a negative effect on glucose control. When vitamin D and calcium are supplemented there may be improvement in glucose control (15).

Cancer

Vitamin D affects cell differentiation and growth and is therefore linked to cancer. Some research shows a link between vitamin D and total cancer death rates and some research shows no relationship (16, 17, 18).

Some specific cancers have demonstrated a link between cancer and vitamin D levels. Those with a high level of serum 25(OH) have a significantly reduced rate of colorectal cancer. One study showed that those with a level over 33 ng/ml had more than a 50% reduction in colorectal cancer over those with a level lower than 12 ng/ml (19). The authors of this study suggested that a daily intake of 1000-2000 IU is appropriate to help in the prevention of colon cancer.

Studies show that those with higher levels of vitamin D have a lower level of breast cancer. Women with a blood level of vitamin D above 50 ng/ml have a 50% lower rate of breast cancer than those with low vitamin D levels (20).

Vitamin D and the Nervous System

Vitamin D has been linked to multiple sclerosis (MS) and memory loss. Despite this link, the evidence linking vitamin D to these neurological diseases is not definitive.

Research suggests that children exposed to sun early in life are at reduced risk for developing MS (21). Another study demonstrated an inverse relationship between MS and vitamin D levels (22). There is also evidence that degree of disability is correlated with vitamin D levels. Patients with MS and the lowest levels of vitamin D levels have the most disability (23).

Can vitamin D intake reduce the risk of MS? The Nurses' Health Study showed that those who took vitamin D as a supplement had a 40% reduced risk of MS (24). Although some have argued this finding as the study design had some weaknesses (25).

It has not been proven that vitamin D is linked to dementia, but there is some evidence. Low levels of vitamin D are associated with an increased risk of many risk factors of dementia such as diabetes, depression, periodontal disease, cardiovascular disease and dental cavities (26). Also, vitamin D is involved in protecting the brain and lowering inflammation, which may be linked to dementia (26). Some research suggests that individuals with Alzheimer's disease have lower levels of vitamin D (27).

Vitamin D and the Musculoskeletal System

Vitamin D helps with bone and muscle health and through this mechanism may help with chronic pain because much chronic pain is related to bones and muscles. Results on this are mixed with some research showing a correlation and some research showing no correlation.

Osteomalacia is characterized by diffuse pain. It is not commonly diagnosed, but some people can have dramatic improvements in pain after being treated with vitamin D; partially because it reverses osteomalacia.

One review study showed a correlation between vitamin D deficiency and musculoskeletal pain. When those with a vitamin D deficiency were treated, there was a reduction in back and lower limb pain. There was also an improvement in muscle strength (28).

More data is needed before a strong conclusion can be made linking vitamin D to chronic pain.

Testing

There are no standard guidelines to help clinicians determine who to test and how to treat vitamin D levels. Routine screening is not recommended, but it is also not discouraged. Those at high risk should be tested.

It is reasonable to recommend treatment of almost everyone with vitamin D. This does not mean giving high doses to everyone, but recommending that patients get at least the recommended daily allowance (RDA) of vitamin D. Individuals who do not get adequate vitamin D, should be encouraged to supplement.

In order to test high risk individuals it is important to know who is at high risk. The following groups of people are considered high risk for vitamin D deficiency:

- Older individuals (greater than 65 years-old)
- Dark skinned individuals
- Institutionalized adults (those in nursing homes)
- Those who live a sedentary lifestyles
- Those with a body mass index greater than 30 (obese patients need more vitamin D)
- Individuals with liver or kidney disease
- Those with malabsorption syndromes such as Crohn's disease or cystic fibrosis
- Kids who are exclusively breastfeed without vitamin D supplementation
- Those who take anticoagulants, corticosteroids and some seizure medications

The best test for vitamin D is the serum 25-hydroxy vitamin D level. When levels are less than 20 ng/ml, than the person is deficient.

The optimal level is unknown, but many agree that levels should be above 30 ng/ml. Levels over 30 ng/dl optimize intestinal calcium transport and parathyroid hormone levels plateau when vitamin D is somewhere between 30-40 ng/dl (29).

Toxicity cannot be caused by sunlight, but it can occur from over consumption of vitamin D supplementation. Toxicity is noted at levels over 150 ng/ml and symptoms may include nausea, vomiting, fatigue and weakness. With vitamin D, levels of calcium rise in the blood. Toxic blood calcium levels have the potential to lead to cardiac arrhythmias.

Prevention and Treatment of Vitamin D Deficiency

Sunlight exposure is an easy way to get vitamin D. Individuals who get 10-30 minutes of sunlight between 10 am and 3 pm, two times a week will most often have enough vitamin D. It does not require full body sunbathing to get vitamin D. Exposing the arms and face allows the body to acquire adequate vitamin D in most individuals.

Getting vitamin D is more difficult in the winter (especially in the north). Adding dietary sources of vitamin D becomes more critical. Food sources of vitamin D include fortified milk and other dairy products, fortified juice, cereal, tuna, salmon, sardines, cod liver oil and egg yolk. It is difficult to get enough vitamin D through the diet alone as vitamin D is not found abundantly in the diet and no food contains high amounts of vitamin D.

Another way to get vitamin D is through supplementation. Multivitamins typically contain the RDA, but many experts now agree that individuals need more than the RDA to get maximal benefit of vitamin D. Over the counter products contain doses of vitamin D of up to 5000 IU.

Patients who are free of liver or kidney disease are unlikely to become toxic with supplementation if directions on the bottle are followed. None-the-less, limited data is available to recommend the upper tolerable daily limits.

The adequate intake of vitamin D is 200 IU for those under the age of 51 years-old (30). The levels increase to 400 IU for those 51 years-old to 70 years-old. The adequate intake amount assumes that the individual does not get sunlight exposure.

Older adults have reduced absorption of vitamin D and therefore need higher levels to counteract this decreased absorption. The adequate intake amount for individuals over the age of 70 is 600 IU, but this may not be high enough. One expert recommends that adults get 1000 IU of vitamin D per day in addition to a multivitamin and at least a glass of milk (29).

The American Academy of Pediatrics recommends that all pediatric patients and adolescents get 400 IU of vitamin D a day (31).

Vitamin D is not associated with many side effects. If taken in very high doses there is risk of toxicity and hypercalcemia. Those with chronic kidney disease, hyperparathyroidism or sarcoidosis are at higher risk for toxicity. There are reports of daytime sleepiness in those who take vitamin D supplementation.

When vitamin D deficiency is diagnosed, a common way to treat it is with prescription strength vitamin D. It is dosed 50,000 IU once a week for 8-12 weeks. Typically, a vitamin D level is drawn after treatment to assure adequate replacement and then the patient is placed on a maintenance dose of vitamin D.

Drug to Vitamin and Vitamin to Vitamin Interactions

Some medications and other vitamins can interact with vitamin D.

- When magnesium is combined with vitamin D there is a risk of elevated levels of magnesium, especially in those with chronic renal insufficiency.
- Anti-seizure drugs (phenytoin and phenobarbital) may lower the levels of vitamin D.
- Orlistat (Xenical/Alli), cholestyramine (Questran) and colestipol (Colestid) can reduce absorption of vitamin D. This effect can be minimized if vitamin D and the above medications are taken at separate times.
- Stimulant laxatives and mineral oil may reduce the absorption of vitamin D.
- Chronic use of corticosteroids may increase the needs of vitamin D and calcium.
- Rifampin reduces the level of vitamin D in the blood.

Breastfeeding and Vitamin D

For years breast milk was considered the perfect food for infants. Recently, vitamin D deficiency has been noticed in infants that are exclusively breastfed.

The American Academy of Pediatrics recommends that 400 IU of vitamin D is supplemented in breast fed infants beginning the first few days of life (31). Even children who are formula fed should be supplemented with vitamin D until they are taking in one liter of vitamin D fortified formula per day.

Only select infants should have their levels checked. This includes those who take anticonvulsants and those who have disorders of malabsorption. Ideal levels are unclear in infants and children, but less than 20 ng/ml is often used in children as a marker of deficiency.

Mothers who breast feed should take a multivitamin. Most multivitamins contain 400IU of vitamin D and this will in most cases maintain an adequate vitamin D level in mothers.

Maintaining adequate vitamin D levels in breastfed infants involves making sure that the mother has adequate vitamin D levels.

Conclusion

Vitamin D is a hot topic in the medical literature and has been linked to many diseases and many conditions. Low levels of vitamin D may be associated with osteoporosis, multiple types of cancer, diabetes, heart disease, neurological disease and muscle pain.

Many people are afflicted with low vitamin D levels and getting adequate amounts often requires the help of supplementation or getting extra sunlight.

More research will be done in regard to vitamin D. Further research will help define the benefits of vitamin D including looking at the long term benefits of vitamin D supplementation and which mode of getting vitamin D is most beneficial – supplementation, natural food or sunlight.

References

1. Kulie T, Groff A, Redmer J. et al. Vitamin D: An Evidence-Based Review. *The Journal of the American Board of Family Medicine* 2009; 22 (6): 698-706.
2. Wolf M, Shah A, Gutierrez O, et al. Vitamin D levels and early mortality among incident hemodialysis patients. *Kidney International* 2007; 72: 1004–13.
3. Inaguma D, Nagaya H, Hara K, et al. Relationship between serum 1,25-dihydroxyvitamin D and mortality in patients with pre-dialysis chronic kidney disease. *Clinical and Experimental Nephrology* 2008; 12: 126–31.
4. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Archives of Internal Medicine* 2008; 168: 1340–9.

5. Autier P, Gandini S. Vitamin D supplementation and total mortality. *Archives of Internal Medicine* 2007; 167: 1730–7.
6. Cranney A, Weiler HA, O'Donnell S, Puil L. Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health. *American Journal of Clinical Nutrition* 2008; 88(Suppl): 513S–9S.
7. Broe KE, Chen TC, Weinberg J, et al. A higher dose of vitamin D reduces the risk of falls in nursing home residents: a randomized multiple-dose study. *Journal of the American Geriatric Society* 2007; 55: 234–9.
8. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. *JAMA* 2004; 291: 1999–2006.
9. Martini LA & Wook RJ. Vitamin D and blood pressure connection: update on epidemiological, clinic, and mechanistic evidence. *Nutrition Reviews* 2008; 66(5): 291-297.
10. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008; 117: 503-511.
11. Giovannucci E, Liu Y, Hollis BW & Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: A Prospective Study. *Archives of Internal Medicine* 2008; 168(11): 1174-1180.
12. Pilz S, Dobnig H, Fischer JE et al. Low vitamin D levels predict stroke in patients referred to coronary angiography. *Stroke* 2008; 39(9): 2611-2613.
13. Sloka S, Grant M & Newhook LA. The geospatial relation between UV solar radiation and type 1 diabetes in Newfoundland. *Acta Diabetology* 2010; 47(1): 73-78.
14. Danescu LG, Levy S & Levy J. Vitamin D and diabetes mellitus. *Endocrine* 2009; 35: 11-17.

15. Pittas AG, Lau J, Hu FB & Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *Journal of Clinical Endocrinology Metabolism* 2007; 92: 2017-2029.
16. Giovannucci E, Liu Y, Rimm EB et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *National Cancer Institute* 2006; 98: 451–459.
17. Freedman DM, Looker AC, Chang SC & Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. *Journal of the National Cancer Institute* 2007; 99: 1594-602.
18. Gorham ED, Garland CR, Garland FC et al. Optimal vitamin D status for colorectal cancer prevention: A quantitative meta analysis. *American Journal of Preventative Medicine* 2007; 32(3); 210-216.
19. Garland CF, Gorham ED, Mohr SB, et al. Vitamin D and prevention of breast cancer: Pooled analysis. *Journal of Steroid Biochemistry and Molecular Biology* 2007; 103(3-5): 708-711.
20. Lappe JM, Travers-Gustafson, D, Davies KM, et al. Vitamin D and calcium supplementation reduced cancer risk: Results of a randomized trial. *American Journal of Clinical Nutrition* 2007; 32(3): 210-216.
21. Kampman MT, Wilsgaard T & Mellgren SI. Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. *Journal of Neurology* 2007; 254: 471-477.
22. Munger KL, Levin LI, Hollis BW, et. al.. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis *JAMA* 2006; 296: 2832–8.

23. van der Mei IAF, Ponsonby A, Dwyer T, et al. Vitamin D levels in people with multiple sclerosis and community controls in Tasmania, Australia. *Journal of Neurology* 2007; 254: 581–90.
24. Munger KL, Zhang S.M, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology* 2004; 62: 60–5.
25. Smolders J, Damoiseaux J, Menheere P & Hupperts R. Vitamin D as an immune modulator in multiple sclerosis, a review. *Journal of Neuroimmunology* 2008; 194: 7–17.
26. Grant WB. Does vitamin D reduce the risk of dementia? *Journal of Alzheimer's Disease* 2009; 17(1): 151-159.
27. Buell JS & Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing "D"ecline. *Molecular Aspects of Medicine* 2008; 29: 415–22.
28. Heath KM, Elovic EP. Vitamin D deficiency: implications in the rehabilitation setting. *American Journal of Physical Medicine and Rehabilitation* 2003; 85: 916–23.
29. Holick MF. *Comprehensive Look at Benefits of Vitamin D*. Audio-Digest Family Practice Volume 57 Issue 12. 2009.
30. National Institute of Health. *Dietary Supplement Fact Sheet: Vitamin D*. 2009. Retrieved on March 31, 2010. Available at: http://dietary-supplements.info.nih.gov/factsheets/VitaminD_pf.asp 11/13/2009
31. Wagner CL, Greer FR, American Academy of Pediatrics Section on Breastfeeding, American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008; 122: 1142–52.