CHAPTER **3**

VITAMIN D DEFICIENCY

Stephan J. LaPointe, DPM, PhD

Vitamin D is commonly known as a fat soluble vitamin. In truth it is a prohormone produced in the human body and in most animals by the skin when exposed to sunlight. There are multiple forms of the vitamin and the real form is vitamin D3 since this is what is found in the skin (chemical name cholecalciferol). Vitamin D3 supplements are derived from lanolin or cod liver oil and this form is what should be used to treat vitamin D deficiency. Vitamin D2 or ergocalciferol is derived from fungal sources. There are also pharmaceutical versions of vitamin D metabolites. Both the D2 and pharamaceutical versions should not be used to treat vitamin D deficiency.

Vitamin D3 is metabolized in the body into 25-hydroxy-vitamin D (25(OH)D) or calcidiol and a second metabolite 1,25-dihydroxyvitamin D or 1,25(OH)2D3. Calcidiol is made in the liver and is a prehormone. When blood levels are evaluated, this is the form that is measured and is the storage form of the vitamin. Calctriol is synthesized from calcidiol in the kidneys. It is the most important steroid in the body and is unique in that there is not a negative feedback loop to stop production. It controls the expression of genes in human DNA.

Vitamin D levels less than10 ng/ml are found in rickets and the adult form osteomalacia. Levels between 10 and 20 ng/ml are insufficient for parathyroid homeostasis. Prior to studying vitamin D, the accepted normal levels were determined by measuring levels in the individual's sun rich geographic locations. Then the commonly accepted level for adequate bone health is 32 ng/ml (1). However, this level has been brought into question and it is now believed that 50 ng/ml is the minimum level for optimum bone and general health and reduces the risks of certain forms of cancer (2-4). The recommended daily allowance (RDA) of vitamin D is 600 to 800 IU. As a rule of thumb, an increase of 100 IU of vitamin D per day results in an increase of 1 ng/ml. The current recommendation is to get a vitamin D level and adjust the dosage of supplementation until levels are between 50 and 80 ng/ml. Otherwise timed tanning booth exposure in colder climates or sun exposure during the midday sun for 20 to 30 minutes for fair skinned and up to six times longer for dark skinned individuals is recommended (5-8). In addition to vitamin D, there several co-factors that are required for proper efficacy that include magnesium, vitamin A and K, zinc, and boron.

Vitamin D is synthesized in the skin when exposed to the sun's UVB wavelength spectrum (9). Factors affecting the efficacy of vitamin D production include angle of the sun's rays, which favors the midday sun (10). Latitude is a factor since in the winter high latitudes do not get enough UVB to produce vitamin D. In Boston from about October to March the sun is not strong enough to produce vitamin D (9). The darker the skin pigmentation, the more exposure is required to produce Vitamin D, six times the amount for the former under the same conditions (5, 11-13). Sunblock with an SPF as low as 8, can block 95% of the production of vitamin D. Tanning booths have been used to successfully treat vitamin D deficiency (7, 8). The few foodstuffs including fortified milk have not been shown adequate for treatment of vitamin D deficiency (14, 15).

One study performed in southern Arizona found that during the winter months 33% and during summer months 9% of the adult population were deficient using a very low cut off of 20ng/ml as their standard. Hispanics and blacks had a higher percentage as a function of their skin pigmentation(16). A similar study performed in southern Florida using the same cut off for deficiency found that winter climes resulted in a 38% and summer a 13% level of deficiency (17). These percentages would have been significantly higher using the accepted 30 ng/ml and now 50 ng/ml for normal health.

Vitamin D toxicity does not occur due to sun exposure because the skin converts it to an inactive form after over exposure. Toxic dosing of vitamin D requires an oral intake of over 40,000 IU per day (18). The toxic threshold limit has been set to 200 to 250 ng/ml (500 to 750 nmol/L) with an upper limit of 100 ng/ml (250 nmol/L) showing a wide therapeutic index since twice the normal limit has not been associated with toxicity (19). Males use 4,000 IU of vitamin D per day and at 40,000 IU/day the therapeutic index is 40,000/4,000 = 10. In comparison we need 8 glasses of water per day and toxic levels are 40 glasses for a therapeutic index of 40/8 = 5. The therapeutic index for vitamin D is twice that of water.

Vitamin D is safe when taken in appropriate doses. Symptoms of vitamin D toxicity include nausea, vomiting, poor appetite, weakness, weight loss, tingling in the mouth, constipation, confusion, and heart arrhythmias. Should these symptoms appear, treatment should include checking for

vitamin D levels. If toxic, avoid sun exposure, decrease any intake including food stuffs with vitamin D, restrict calcium intake, and drink eight glasses of water daily. If not toxic, rule out hypercalcemia and its underlying causes and magnesium deficiency.

Vitamin D deficiency has been linked to osteoporosis and increased fractures especially in the elderly (20-23). One study found that 80% of 81 patients with osteoporotic hip fractures had low levels of Vitamin D (24).

Relative to nonunions, Brinker et al (25) performed a study on 683 consecutive patients diagnosed with nonunion over a 7 year span in a tertiary orthopedic referral center. They screened the cases based on three criteria: unexplained nonunion despite adequate reduction and stabilization and no other cause for the nonunion; history of multiple low energy fractures with at least one progressing to a nonunion; and nonunion of nondisplaced pubic rami or sacral ala fracture. Of those 683 patients, 37 were included in the study to have a full endocrine work up by one of two independent endocrinologists. This work up included adrenocortictrophic hormone (ACTH), cortisol, 24 hour cortisol, growth hormone, dehydroepiandrosterone (DHEA-S), growth hormone (GH), insulin-like growth factor-1 (IGF-1), intact parathyroid (iPTH), follicle stimulating hormone, luteinizing hormone, total estrogen, estradiol (E2), testosterone, free testosterone, prolactin, thyroid function test, serum protein electrophoresis and immunofixation electrophoresis, calcium, calcium 24 hour urine, magnesium, phosphorous, alkaline phosphatase, 25-hydroxy vitamin D, and 1,25-dihydroxy vitamin D. Of the 37 patients, 31 had an endocrine disorder. Vitamin D deficiency was found in 25 of the 37 or 68% (or 81% of those with metabolic disorder). Other disorders included abnormal calcium in 13 (35%), thyroid dysfunction in 9 (24%), reproductive hormone in 8 (22%), and alkaline phosphatase in 6 (16%).

Thirty of the 31 fractures healed within 9.6 months after the underlying endocrine abnormality was treated. Of these, 8 did not have surgery and had bony union in 7.6 months. Brinker et al recommend that all patients diagnosed with a nonunion that meet their criteria should be referred to endocrine for a full work up before proceeding with care.

REFERENCES

1. Heaney RP. The Vitamin D requirement in health and disease. J Steroid Biochem Mol Biol 2005;97:13-9.
2. Davis W, Rockway S, Kwasny M. Effect of a combined therapeutic approach of intensive lipid management, omega-3 fatty acid supplementation, and increased serum 25 (OH) vitamin D on coronary calcium scores in asymptomatic adults. Am J Ther 2009;16:326-32.
3. Seki T, Yamamoto M, Ohwada R, et al. Successful treatment of post-surgical hypoparathyroidism by intramuscular injection of vitamin D3 in a patient associated with malabsorption syndrome due to multiple abdominal surgeries. J Bone Miner Metab 2010;28:227-32.
4. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. Am J Public Health 2006;96:252-61.
5. Ladizesky M, Lu Z, Oliveri B, et al. Solar ultraviolet B radiation and photoproduction of vitamin D3 in central and southern areas of Argentina. J Bone Miner Res 1995;10:545-9.
6. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988;67:373-8.
7. Koutkia P, Lu Z, Chen TC, Holick MF. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. Gastroenterology 2001;121:1485-8.
8. Tangpricha V, Turner A, Spina C, Decastro S, Chen TC, Holick MF. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. Am J Clin Nutr 2004;80:1645-9.
9. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. J Bone Miner Res 2007;22 Suppl 2:V28-33.
10. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr 1995;61(3 Suppl): 638S-645S.
11. Pettifor JM, Moodley GP, Hough FS, et al. The effect of season and latitude on in vitro vitamin D formation by sunlight in South Africa. S Afr Med J 1996;86:1270-2.
12. Webb AR, DeCosta BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. J Clin Endocrinol Metab 1989;68:882-7.
13. Webb AR, Holick MF. The role of sunlight in the cutaneous production of vitamin D3. Annu Rev Nutr 1988;8:375-99.
14. Chan J, Jaceldo-Siegl K, Fraser GE. Serum 25-hydroxyvitamin D status of vegetarians, partial vegetarians, and nonvegetarians: the Adventist Health Study-2. Am J Clin Nutr 2009;89:1686S-692S.
15. Valimaki VV, Loyttyniemi E, Valimaki MJ. Vitamin D fortification of milk products does not resolve hypovitaminosis D in young Finnish men. Eur J Clin Nutr 2007;61:493-7.
16. Jacobs ET, Alberts DS, Foote JA, et al. Vitamin D insufficiency in southern Arizona. Am J Clin Nutr 2008;87:608-13.
17. Levis S, Gomez A, Jimenez C, et al. Vitamin d deficiency and seasonal variation in an adult South Florida population. J Clin Endocrinol Metab 2005;90:1557-62.
18. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999;69:842-56.
19. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008;88:582S-6S.
20. Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2009:CD000227.
21. Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2005:CD000227.
22. Barrios C, Brostrom LA, Stark A, Walheim G. Healing complications after internal fixation of trochanteric hip fractures: the prognostic value of osteoporosis. J Orthop Trauma 1993;7:438-42.
23. Nakamura K, Iki M. Efficacy of optimization of vitamin D in preventing osteoporosis and osteoporotic fractures: A systematic review. Environ Health Prev Med 2006;11:155-70.
24. Simonelli C. The role of vitamin D deficiency in osteoporosis and fractures. Minn Med 2005;88:34-6.
25. Brinker MR, O'Connor DP, Monla YT, Earthman TP. Metabolic and endocrine abnormalities in patients with nonunions. J Orthop Trauma 2007;21:557-70.