

## Too little vitamin D in premenopausal women: why should we care?<sup>1,2</sup>

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Nesby-O'Dell et al (1) report compelling data that provide irrefutable evidence that vitamin D deficiency is a major unrecognized epidemic in adult women of childbearing age (15–49 y). Not surprisingly, the prevalence of vitamin D deficiency was 42% in African American women and 4.2% in white women. It is likely that the prevalences would have been much higher if the survey had also been performed in the winter for both groups of women in the North. Tangpricha et al (2) reported that 36% of healthy men and women in Boston aged 18–29 y were vitamin D insufficient, with 25-hydroxyvitamin D [25(OH)D] < 50 nmol/L (20 ng/mL). Thus, although Nesby-O'Dell et al studied only females, it is likely that vitamin D deficiency is equally prevalent among males of the same age. Nesby-O'Dell et al note that the third National Health and Nutrition Examination Survey (which provided the data for their study) did not measure either parathyroid hormone (PTH) or the active metabolite of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D]. It was unfortunate that the PTH concentrations were not measured because PTH is the most sensitive indicator of calcium homeostasis and vitamin D deficiency (3–5). It would not have been helpful, however, to have had 1,25(OH)<sub>2</sub>D concentrations, which are often misleading because they can be low, normal, or even elevated in vitamin D deficiency as a result of secondary hyperparathyroidism (3).

Nesby-O'Dell et al chose a 25(OH)D cutoff of 37.5 nmol/L (15 µg/L). Most studies that have evaluated 25(OH)D concentrations have correlated them with blood concentrations of PTH. 25(OH)D concentrations of ≥50 nmol/L and as high as 85 nmol/L are required before PTH concentrations are at their normal baseline values (2–6). Provocative testing for PTH changes is probably the best method to determine vitamin D adequacy. Malabanan et al (6) gave 50000 IU vitamin D once a week for 8 wk to 35 healthy adults who had “normal” blood concentrations of 25(OH)D of 27.5–60 nmol/L. PTH concentrations declined on average 55% and 35% in those with 25(OH)D concentrations of 27.5–39.5 and 40.0–49.9 nmol/L, respectively, with no significant change in PTH concentrations in those whose 25(OH)D concentrations were >50 nmol/L. On the basis of these data, 50 nmol/L (20 µg/L) should be the minimum cutoff for vitamin D sufficiency. The normal range for 25(OH)D is the mean ± 2 SDs of a presumed healthy population. However, the data of Nesby-O'Dell et al suggest that the so-called healthy population were vitamin D deficient. Thus, the normal range likely significantly underestimates vitamin D deficiency.

Even if vitamin D deficiency is common among healthy young female adults, why should we care, given that their skeletons have matured and there is no evidence of significant osteoporosis

in this age group? Are there other, more insidious consequences of vitamin D deficiency for this age group? Vitamin D is essential to maximize skeletal health from birth until death. Vitamin D as 1,25(OH)<sub>2</sub>D accomplishes this by increasing the efficiency of intestinal calcium and phosphorus transport. Vitamin D deficiency causes a mineralization defect that results in growth retardation and rickets in growing children. The effect is more subtle in adults. Vitamin D deficiency causes osteomalacia, which is associated with nonspecific isolated or generalized bone pain, muscle aches, and muscle weakness, ie, symptoms similar to fibromyalgia. Indeed, it was suggested that a majority of Danish women with symptoms of fibromyalgia had severe vitamin D deficiency and osteomalacia (7). Vitamin D deficiency also causes secondary hyperparathyroidism, which can precipitate and exacerbate osteoporosis by increasing mobilization of mineral and matrix from the skeleton (3–5).


Vitamin D receptors exist in the intestine and bone for regulating calcium and bone metabolism and are also present in a wide variety of other tissues and organs, including the brain, pancreas, skin, gonads, stomach, colon, breast, mononuclear cells, and activated T and B lymphocytes (3). 1,25(OH)<sub>2</sub>D is one of the most potent inhibitors of cellular proliferation and inducers of cellular maturation and has important immunomodulatory activities on B and T lymphocytes (3). Are these biological functions of vitamin D relevant for human health? There is an inverse association of increased risk of dying from breast, colon, ovarian, and prostate cancer with latitude and with decreased synthesis of vitamin D (3, 8, 9). It is now recognized that cells in the colon, prostate, breast, and skin have the enzymatic machinery [ie, the 25(OH)D-1α-hydroxylase (EC 1.14.13.13)] to convert 25(OH)D into 1,25(OH)<sub>2</sub>D (3). Thus, the cellular production of 1,25(OH)<sub>2</sub>D<sub>3</sub> may be essential for the regulation of cellular health, thereby decreasing the risk of developing some cancers. African Americans, who are chronically vitamin D deficient, have a higher incidence and more aggressive forms of many cancers, including breast and prostate cancer (3). Men who are exposed to more sunlight can delay the onset of prostate cancer by >5 y (10). Children receiving vitamin D supplementation from age 1 y on had an 80% decreased risk of developing type 1 diabetes (11).

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What is a healthy concentration of 25(OH)D? Garland et al (8) reported that when 25(OH)D concentrations were  $\geq 50$  nmol/L, adults had a 50% decreased risk of developing colon cancer later in life.

How is it possible in this new millennium that vitamin D deficiency, a disease that plagued our ancestors from the 17th through 19th centuries, should still be a problem? Why is vitamin D deficiency so prevalent? Casual everyday exposure to sunlight provides us with our vitamin D requirement (3). There are very few foods that naturally contain vitamin D. It would be necessary to eat fatty fish such as salmon and mackerel 3–4 times/wk to satisfy the body's vitamin D requirement. How much is an adequate intake? The 1997 recommendations by the Institute of Medicine (12) are probably too low. They make an important contribution by at least recognizing that an adequate intake of vitamin D needs to be 400 IU in middle-aged adults (50–70 y) and 600 IU in older adults ( $\geq 71$  y). The committee's charge was to make these recommendations on the basis of the literature. Unfortunately, few studies have looked at the consequences of 25(OH)D concentrations and vitamin D deficiency in most age groups, including premenopausal women. It is likely that in the absence of exposure to sunlight, the adequate intake for vitamin D should be  $\geq 800$ –1000 IU vitamin D/d. Can you get too much vitamin D from exposure to sunlight or the diet? There has never been a reported case of vitamin D intoxication from excessive exposure to sunlight. The safe upper intake of vitamin D for ages above 1 y is 2000 IU/d (12).

Therefore, increasing our vitamin D intake or casual exposure to sunlight may decrease the risk of some of the most common cancers, type 1 diabetes, and possibly multiple sclerosis. The only way to know a person's vitamin D status is to measure 25(OH)D. Thus, it is reasonable for everyone to have his or her 25(OH)D concentration measured once a year. 

## REFERENCES

1. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr* 2002; 76:187–92.
2. Tangpricha V, Pearce EN, Chen TC, Holick MF. Vitamin D insufficiency among free-living adults. *Am J Med* (in press).
3. Holick MF. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. *Curr Opin Endocrinol Diabetes* 2002;9:87–98.
4. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. *Endocr Rev* 2000;22:477–501.
5. Harris SS, Soteriades E, Stina Coolidge JA, et al. Vitamin D insufficiency and hyperparathyroidism in a low income, multiracial, elderly population. *J Clin Endocrinol Metab* 2001;85:4125–30.
6. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. *Lancet* 1998;351:805–6.
7. Glerup H, Mikkelsen K, Poulsen L, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med* 2000;66:419–24.
8. Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet* 1989;2:1176–8.
9. Grant WB. An ecologic study of dietary and solar ultraviolet-B links to breast carcinoma mortality rates. *Cancer* 2002;94:272–81.
10. Luscombe CJ, Fryer AA, French ME, et al. Exposure to ultraviolet radiation: association with susceptibility and age at presentation with prostate cancer. *Lancet* 2001;358:641–2.
11. Hyponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *Lancet* 2001;358:1500–3.
12. Institute of Medicine. Dietary reference intakes for calcium phosphorus, magnesium, vitamin D, and fluoride Washington, DC: National Academy Press, 1997.

