CLINICAL PRACTICE

# Vitamin D Insufficiency

Clifford J. Rosen, M.D.

*This* Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A healthy 61-year-old white woman is concerned about a low vitamin D level detected during an assessment of her skeletal health. Her menopause began at 54 years of age. She has no history of falls, and there is no family history of hip fracture. She takes no medications or supplements. Her height is 157.5 cm (5 ft 2 in.), and her weight 59.1 kg (130 lb). The results of a physical examination are unremarkable, and the findings on laboratory studies are normal. The T score for bone mineral density at the hip is –1.5, and the serum level of 25-hydroxyvitamin D is 21 ng per milliliter (53 nmol per liter). What do you advise?**

## THE CLINICAL PROBLEM

From the Maine Medical Center Research Institute, Scarborough. Address reprint requests to Dr. Rosen at Maine Medical Center Research Institute, 81 Research Dr., Scarborough, ME 04074, or at rosenc@mmc.org.

N Engl J Med 2011;364:248-54.


*An audio version of this article is available at NEJM.org*

Whereas frank vitamin D deficiency (serum level of 25-hydroxyvitamin D below 10 ng per milliliter [25 nmol per liter]) has long been recognized as a medical condition characterized by muscle weakness, bone pain, and fragility fractures, vitamin D "insufficiency," characterized as a serum level of 25-hydroxyvitamin D of 10 to 30 ng per milliliter (25 to 75 nmol per liter), without overt clinical symptoms, has recently become a concern on the part of physicians and patients.[1] Increased attention to this new "syndrome" and its potential complications has led to a substantial increase in testing for the metabolite 25-hydroxyvitamin D, the best clinical measure of vitamin D stores. The number of 25-hydroxyvitamin D assays performed by one major reference laboratory increased by 50% in the fourth quarter of 2009 as compared with the same quarter in 2008, and it is expected that several million tests will be performed this year.[2]

The implications of vitamin D levels that are below the normal reference range but not markedly reduced and the value of supplementation are incompletely understood. Vitamin D is critical for skeletal mineralization, and numerous observational studies have linked low levels of 25-hydroxyvitamin D to fractures.[3-7] Therefore it is not surprising that most observational and randomized, placebo-controlled trials concerning vitamin D insufficiency have focused on skeletal health outcomes. In the past several years, attention has turned to nonskeletal effects of vitamin D insufficiency, particularly in relation to cardiovascular disease, diabetes mellitus, cancer, and immune dysfunction.[8-11] This review summarizes the current understanding and uncertainties regarding vitamin D insufficiency and the effects of vitamin D supplementation on health outcomes.

## STRATEGIES AND EVIDENCE

### DEFINING VITAMIN D INSUFFICIENCY

Interpreting the import of a serum level of 25-hydroxyvitamin D in the "insufficient" range (i.e., 10 to 30 ng per milliliter) is challenging for several reasons. First, most reference laboratories have raised the lower boundary of the normal range to

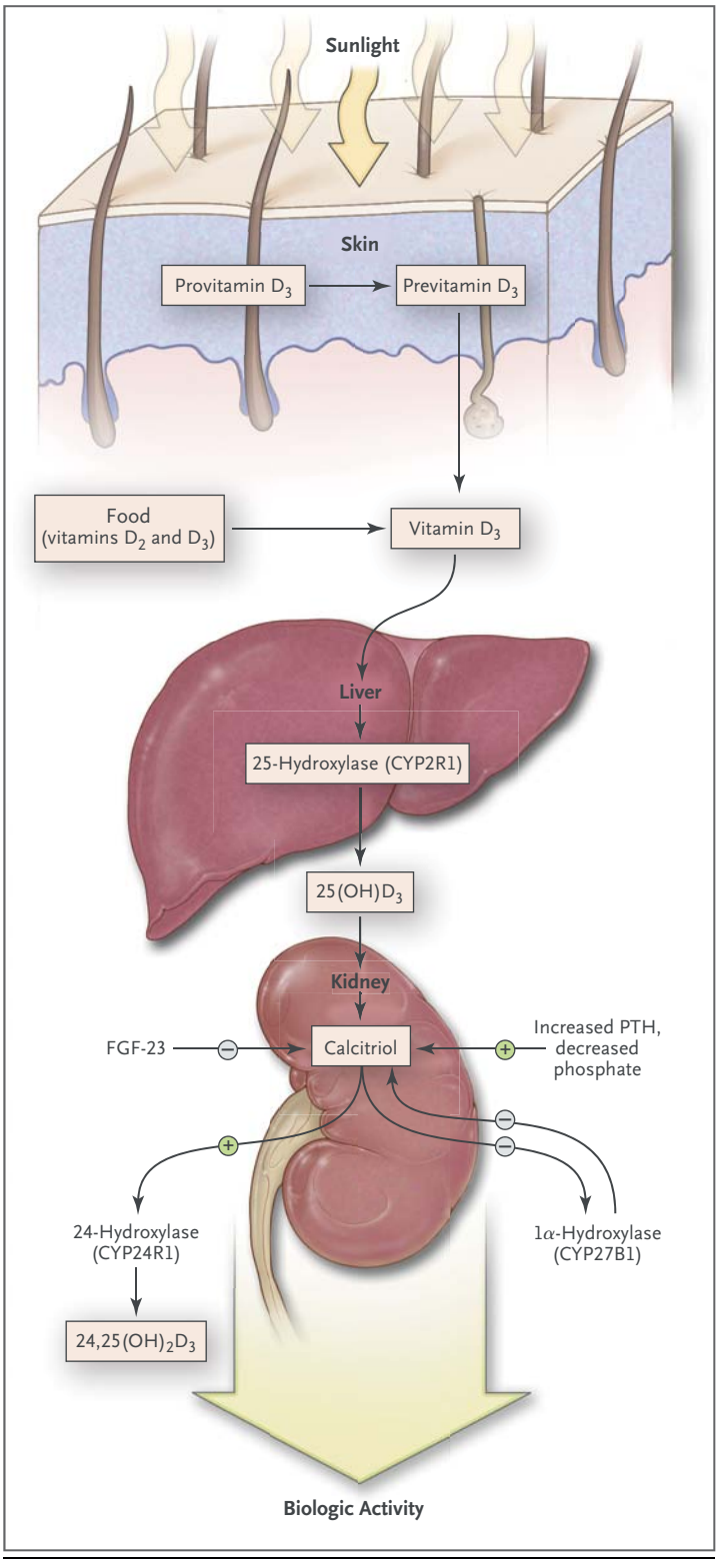


**Figure 1. Synthesis and Metabolism of Vitamin D.**

Vitamin D is initially generated in the skin from the nonenzymatic conversion of provitamin $D_3$ to previtamin $D_3$. Dietary intake of vitamin D is usually relatively limited, since few foods, with the exception of certain kinds of fish, contain sizable amounts; supplements are commonly used. Vitamin D is either stored in adipose tissue or converted in the liver by the enzyme 25-hydroxylase to 25-hydroxyvitamin $D_3$ (25[OH]$D_3$), the form that circulates in the highest concentration and reflects solar and dietary exposure. It is converted to the active metabolite, 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), or calcitriol, in the kidney, although other tissues have 1α-hydroxylase enzymatic activity. The synthesis of calcitriol is enhanced (+) by increasing levels of parathyroid hormone (PTH), which rise in response to lower levels of serum calcium. Reduced levels of serum phosphate can also increase (+) the production of calcitriol. Its synthesis is suppressed (–) by the production of fibroblast growth factor 23 (FGF-23), which is secreted by osteocytes in the bone matrix. Calcitriol inhibits the activity of 1α-hydroxylase (CYP27B1) and stimulates the activity of 24-hydroxylase (CYP24R1), an enzyme that promotes production of 24,25$(OH)_2D_3$, a vitamin D product that is not biologically active. In CYP2R1, CYP27B1, and CYP24R1, CYP denotes cytochrome P.

30 ng per milliliter. Second, although there are several ways to measure 25-hydroxyvitamin D (radioimmunoassays, enzyme-linked assays, and liquid chromatography with mass spectrometry), the precision and accuracy of the assays, especially in nonreference laboratories, remain problematic.[12] Third, 25-hydroxyvitamin D levels change with the seasons, exposure to sunlight, and dietary intake. For example, in northern latitudes, serum levels of 25-hydroxyvitamin D decline by 20% from late summer to midwinter, whereas 30 minutes of full-body exposure to the sun during the summer rapidly generates vitamin D. Regular exposure to sunlight (depending on its strength) can increase the serum level of 25-hydroxyvitamin D.[3]

What does a serum 25-hydroxyvitamin D level represent? Vitamin D is produced by the nonenzymatic conversion of provitamin D to previtamin D in the skin during exposure to sunlight emitting ultraviolet radiation in the narrow band of 290 to 315 nm (Fig. 1). Some vitamin D also comes from food sources (between 100 and 200 IU per day). Vitamin D is converted in the liver to 25-hydroxyvitamin D, a partially water-soluble form with a shorter half-life than vitamin D that circulates bound to vitamin D–binding protein. About 40 to 50% of circulating 25-hydroxyvitamin D is derived from skin conversion.[1,3] The active form of vitamin D is 1,25-dihydroxyvitamin D, which is generated primarily in the kidney. It circulates in lower concentrations than

25-hydroxyvitamin D but has much greater affinity for the vitamin D receptor and is biologically more potent. Low levels of 1,25-dihydroxyvitamin D do not reflect low levels of 25-hydroxyvitamin D but result from other causes, most commonly renal insufficiency and less frequently oncogenic osteomalacia.

The serum 25-hydroxyvitamin D level is the best indicator of overall vitamin D status because this measurement reflects total vitamin D from dietary intake and sunlight exposure, as well as the conversion of vitamin D from adipose stores in the liver.[13,14] According to the National Health and Nutrition Evaluation Survey (NHANES), in the United States, the average dietary intake of vitamin D (including supplements) may be as low as 200 IU per day (with differences according to age).[15] Skin-derived synthesis of vitamin D is quite variable, depending on pigmentation, latitude, season, clothing, age, sunscreen use, and local weather conditions. Levels of 25-hydroxyvitamin D are considerably lower among blacks than among whites because of greater pigmentation in blacks. In healthy whites, serum levels of 25-hydroxyvitamin D may vary according to environmental, hormonal, genetic, and nutritional factors.[3,14] The body-mass index (BMI), for example, is inversely related to the serum 25-hydroxyvitamin D level, and obese patients typically have levels in the range of 10 to 20 ng per milliliter (25 to 50 nmol per liter); these differences may be due in part to lower levels of exercise and sunlight exposure in obese persons than lean persons. Several conditions cause very low serum levels of 25-hydroxyvitamin D (i.e., below 10 ng per milliliter), including poor dietary intake of vitamin D coupled with negligible sun exposure; malabsorption due to inflammatory bowel disease, gluten enteropathy, gastric surgery, biliary disease, or intestinal overgrowth; use of antiseizure medications (e.g., phenobarbital or phenytoin); and long-term use of glucocorticoids.[1,3]

Defining a level of serum 25-hydroxyvitamin D as low or insufficient depends on the level that is defined as normal. Previously, according to the World Health Organization, levels below 10 ng per milliliter were considered deficient and levels below 20 ng per milliliter were classified as insufficient.[16] However, with the recent changes in laboratory reference ranges, a normal level is now typically defined as a serum level of 30 to 76 ng per milliliter (75 to 190 nmol per liter). When that range is used, the estimated prevalence of vitamin D insufficiency is as high as 50 to 80% in the general population.[17,18] According to the NHANES for 2005 and 2006, the mean 25-hydroxyvitamin D level among several age groups was 24 ng per milliliter (60 nmol per liter), a level considered to be insufficient according to some standards.[15]

There are two rationales for setting the low end of the normal range for 25-hydroxyvitamin D at 30 ng per milliliter: one, put forward in studies published in the past several years, suggests that levels of parathyroid hormone (PTH) rise when levels of 25-hydroxyvitamin D fall below 30 ng per milliliter[3,13,19]; the other, proposed in earlier studies, suggests that active calcium absorption is optimal when the level of 25-hydroxyvitamin D is 30 ng per milliliter.[20] However, both tenets are now being questioned.[14] Data indicate that the relationship of PTH and 25-hydroxyvitamin D is not curvilinear, and there is substantial variation in PTH levels when 25-hydroxyvitamin D levels are between 20 and 30 ng per milliliter. There is no absolute threshold level of serum 25-hydroxyvitamin D at which PTH levels rise.[13,19] Furthermore, although the information derived from dual isotope analysis is the most accurate measure of calcium absorption, there are too few studies to establish an absolute cutoff for levels of 25-hydroxyvitamin D above which calcium absorption is not enhanced. Generally, peak absorption of calcium occurs at levels between 20 and 30 ng per milliliter.

### VITAMIN D AND BONE HEALTH

Although recent attention has focused on the nonskeletal effects of vitamin D, it is well established that vitamin D is critical for bone mineralization.[1,8-11] Therefore, it is not surprising that most studies of vitamin D have assessed outcomes for skeletal health.

Several observational studies of the associations between serum levels of 25-hydroxyvitamin D and skeletal health have had conflicting results. A report from Ottawa on 15 studies (3 prospective cohort studies and 12 case–control studies) concluded that associations between serum 25-hydroxyvitamin D concentrations and fractures, falls, and performance measures (tests of gait, stability, and activity) among postmenopausal women or elderly men were inconsistent.[21] A more recent report from the Agency for Healthcare Research and Quality (AHRQ) and Tufts Medical

Center, analyzing the same observational studies, concluded that there was fair, or reasonable, evidence of an association between lower serum concentrations of 25-hydroxyvitamin D and an increased risk of falls among institutionalized elderly persons.[22]

Randomized, controlled trials of vitamin D supplementation have addressed its effects on skeletal outcomes, but most of these trials involved supplementation with both vitamin D and calcium, making it impossible to separate out the effects attributable specifically to vitamin D. The results of a 2007 meta-analysis of 29 trials of supplementation with both calcium and vitamin D or with calcium alone suggested that daily supplementation with 1200 mg of calcium and at least 800 IU of vitamin D resulted in reduced rates of fracture and a modest increase in bone mineral density, but the relationship between serum 25-hydroxyvitamin D levels and skeletal outcomes was not assessed.[23] A 2009 Cochrane meta-analysis of 10 trials testing the effects of vitamin D supplementation alone and 8 trials testing the effects of vitamin D plus calcium showed no significant relationship between vitamin D supplementation alone and a reduction in the risk of fracture.[24] However, the study confirmed the conclusion of the 2007 meta-analysis that calcium plus vitamin D was marginally effective in reducing the risk of fracture in older persons as compared with no supplementation (odds ratio, 0.89; 95% confidence interval, 0.80 to 0.99).

Despite the observational data suggesting an inverse association between serum levels of 25-hydroxyvitamin D and the risk of falls among institutionalized elderly persons, the evidence is inconsistent, with some studies showing a benefit and others showing no effect of vitamin D supplementation on the risk of fractures or falls in various populations.[22,25] Similarly, a randomized study conducted by the Women's Health Initiative showed a nonsignificant reduction in hip fractures among women receiving a total of 700 IU of vitamin D and more than 2000 mg of calcium per day.[26] However, the high baseline intake of calcium (an average of 1100 to 1200 mg per day) and vitamin D (approximately 300 IU per day) in the placebo group may have limited the ability of the investigators to detect effects of supplementation. Subgroup analyses of women over 60 years of age and of those who adhered to their supplementation regimen showed a significant reduction in hip fractures with supplementation, but these results must be interpreted with caution. Randomized trials of supplementation with vitamin $D_2$ or $D_3$ (with daily doses ranging from 400 to 822 IU) published after the AHRQ–Tufts analysis also failed to show significant effects of vitamin D supplementation on the risk of fracture or falls in older populations.[27,28] However, in one of those trials, vitamin D supplementation at a dose of 400 IU daily improved gait speed and reduced body sway.[27]

Several large observational studies have addressed the question of whether there is a threshold level of 25-hydroxyvitamin D below which adverse skeletal outcomes are more likely to occur. In one study of elderly men, levels below 16 ng per milliliter (40 nmol per liter) were associated with a greater risk of fracture, whereas in another study, men with levels below 20 ng per milliliter had greater rates of femoral bone loss than men with higher levels.[29,30] In a longitudinal study, Osteoporotic Fractures in Men (MrOs), older men with serum levels of 25-hydroxyvitamin D that were less than 20 ng per milliliter had a higher risk of hip fracture than men with higher levels.[31] In a prospective study of older women, 25-hydroxyvitamin D levels between 24 and 26 ng per milliliter (60 to 65 nmol per liter) were associated with the lowest risk of hip fracture; no additional risk reduction was noted above that level.[32] However, in a study of older New Zealand women, levels of 25-hydroxyvitamin D below 20 ng per milliliter were not associated with an increased risk of fracture during 5 years of follow-up.[33]

### VITAMIN D AND OTHER HEALTH EFFECTS

Observational studies in large cohorts have shown significant associations between low levels of 25-hydroxyvitamin D (i.e., below 20 ng per milliliter) and an increased risk of metabolic, neoplastic, and immune disorders such as type 1 diabetes mellitus and multiple sclerosis.[7-11] The two conditions most often connected with low levels of vitamin D are atherosclerosis and diabetes mellitus.[34-36] For example, a significantly increased risk of type 2 diabetes has been reported among persons with levels of vitamin D that are insufficient (below 30 ng per milliliter), even after adjustment for BMI and percentage of body fat.[8,35] Similarly, another prospective study showed that levels of serum 25-hydroxyvitamin D below 20 ng

per milliliter were associated with an increased risk of cardiovascular disease.[10] However, there are not enough data from large, randomized, controlled trials to assess whether vitamin D supplementation reduces the risk of chronic diseases other than osteoporosis.

## AREAS OF UNCERTAINTY

The dynamics of vitamin D storage and reentry into the circulation remain poorly understood, particularly in obese persons.[37] Optimal dosage regimens for vitamin D remain uncertain. In general, for every 100 IU of vitamin D taken in, there is an increase of roughly 1 ng per milliliter (3 nmol per liter) in the serum level of 25-hydroxyvitamin D; the lower the baseline level of 25-hydroxyvitamin D, the greater the rise with vitamin D supplementation. Most trials assessing the association between 25-hydroxyvitamin D levels and the risk of fractures and falls have used daily doses of vitamin D between 400 and 1000 IU. Data are scarce on the effects of long-term supplementation with doses greater than 1000 IU per day. In a recently published randomized, placebo-controlled trial involving elderly persons not living in institutions, those who received an oral dose of 500,000 IU of vitamin D once a year for 3 years had a significantly increased rate of falls and fractures, as compared with those who received placebo, particularly in the first 3 months after dosing.[38] These results suggest that high intermittent doses of vitamin D, as compared with daily doses, may be metabolized and used differently. Finally, data are lacking from large randomized, controlled trials designed to determine whether vitamin D supplementation reduces the risk of other major diseases, such as colon cancer, for which there are observational data suggesting a reduction in risk with supplementation. The ongoing Vitamin D and Omega-3 Trial (VITAL; ClinicalTrials.gov number, NCT01169259), a 5-year, randomized, placebo-controlled trial involving 20,000 U.S. men and women is examining vitamin D supplementation (2000 IU per day), with or without supplementation of n–3 fatty acids, for the primary prevention of cancer and cardiovascular disease.

Toxicity from vitamin D supplementation is rare and consists principally of acute hypercalcemia, which usually results from doses that exceed 10,000 IU per day; associated serum levels of 25-hydroxyvitamin D are well above 150 ng per milliliter (375 nmol per liter).[39] The tolerable upper level of daily vitamin D intake recently set by the Institute of Medicine (IOM) is 4000 IU.[14] The long-term effects of supplementation at doses above 4000 IU per day are not known, and risks cannot be ruled out. Recent observational studies have suggested associations between serum levels of 25-hydroxyvitamin D above 60 ng per milliliter (150 nmol per liter) and increased risks of pancreatic cancer, vascular calcification, and death from any cause,[34,40,41] but the observational nature of these studies precludes an assessment of cause and effect. More longitudinal studies and controlled trials are needed.

Several studies have suggested that vitamin D supplementation may be most effective in reducing fractures and falls in institutionalized elderly persons, in whom serum levels of 25-hydroxyvitamin D are often below 20 ng per milliliter.[42-44] Yet the optimal replacement dose in this population is still not known. A large, long-term, randomized trial is warranted to examine the effects of several different doses of vitamin D on physical performance measures and the incidence of falls and fractures in the institutionalized elderly population.

## GUIDELINES FROM PROFESSIONAL SOCIETIES

At an international workshop on vitamin D held in 2007, there was agreement that most of the world's population is not getting an amount of vitamin D sufficient to maintain healthy bone mass and minimize the risk of fracture. The workshop members also agreed that vitamin D insufficiency decreases muscle strength and increases the risk of falls.[45] The recommendation from that group, made on the basis of available observational data, was that the minimum desirable serum level of 25-hydroxyvitamin D is 20 ng per milliliter. Three years later, Osteoporosis Canada issued a report stating that the 25-hydroxyvitamin D level should be at least 30 ng per milliliter and that vitamin D insufficiency should be defined as a level of 10 to 29 ng per milliliter.[46] In 2010, the International Osteoporosis Foundation issued a position statement on vitamin D status, also based on observational data, recommending a target serum level of 25-hydroxyvitamin D of 30 ng per milliliter in all elderly persons and

stating that vitamin D intakes as high as 2000 IU per day may be necessary to attain the recommended level in some persons.[47] In contrast, the IOM report, based on evidence from observational studies and recent randomized trials, suggests that a serum level of 20 ng per milliliter of 25-hydroxyvitamin D would protect 97.5% of the population against adverse skeletal outcomes such as fractures and falls.[14]

## CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette is a healthy postmenopausal woman with slightly low bone mineral density and a 25-hydroxyvitamin D level of 21 ng per milliliter. Although the laboratory that performed the measurement, and many other laboratories, would label that level as insufficient, she is certainly not deficient in vitamin D. According to the Fracture Risk Assessment Tool (FRAX) developed by the World Health Organization, the probability that she will sustain a hip fracture over the next 10 years is less than 1%. Moreover, she is not at high risk for falls and is unlikely to have osteomalacia.[48] Hence, for patients such as this one, I would recommend an exercise program and a total calcium intake of 1200 mg per day. There remains uncertainty about whether vitamin D supplementation is appropriate for her, and if so, what the dose should be, although the recent IOM guidelines recommend 600 IU daily for a postmenopausal woman who is not at high risk for fractures or falls and 800 IU daily for persons who have a very high risk of osteoporosis or who are older than 70 years of age.[14] I would explain that despite the recent focus in the media on the potential role of vitamin D in reducing the risk of various chronic diseases, this hypothesis requires testing in large, randomized, controlled trials, and vitamin D cannot currently be recommended for the purpose of reducing the risk of heart disease or cancer.

Dr. Rosen reports serving as an unpaid consultant for Lexicon Genetics and serving on the Vitamin D Subcommittee for the IOM, for which he received reimbursement for travel expenses. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

## REFERENCES

1. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80:Suppl:1689S-1696S.
2. Parker-Pope T. The miracle of vitamin D: sound science or hype? New York Times, Feb. 1, 2010.
3. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
4. Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. Am J Clin Nutr 2008;88:537S-540S.
5. van Schoor NM, Visser M, Pluijm SM, Kuchuk N, Smit JH, Lips P. Vitamin D deficiency as a risk factor for osteoporotic fractures. Bone 2008;42:260-6.
6. Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. J Am Geriatr Soc 2003;51:1762-7.
7. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003;326:469.
8. 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. J Clin Endocrinol Metab 2007;92:2017-29.
9. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98:451-9.
10. 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. Arch Intern Med 2008;168:1340-9.
11. Hewison M. Vitamin D and innate immunity. Curr Opin Investig Drugs 2008;9:485-90.
12. Binkley N, Krueger D, Lensmeyer G. 25-Hydroxyvitamin D measurement 2009: a review for clinicians. J Clin Densitom 2009;12:417-27.
13. Heaney RP. The vitamin D requirement in health and disease. J Steroid Biochem Mol Biol 2005;97:13-9.
14. IOM report on calcium and vitamin D. Washington, DC: Institute of Medicine, 2010. (http://www.iom.edu/vitaminD.)
15. National Health and Nutrition Examination Survey. What we eat in America, 2005-2006. (http://www.ars.usda.gov/ba/bhnrc/fsrg.)
16. WHO Scientific Group on the Prevention and Management of Osteoporosis. Prevention and management of osteoporosis: report of a WHO scientific group. Geneva: World Health Organization, 2003.
17. Holick MF, Siris ES, Binkley N, et al. Prevalence of vitamin D inadequacy among North American postmenopausal women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005;90:3215-24.
18. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med 2009;169:626-32.
19. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 2005;294:2336-41.
20. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997;7:439-43.
21. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. Evidence report/technology assessment no. 158. Rockville, MD: Agency for Healthcare Research and Quality, 2007.
22. Chung M, Balk E, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence report/technology assessment no. 183. Rockville, MD: Agency for Healthcare Research and Quality, 2009.
23. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D

supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370:657-66.
**24.** 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;2:CD000227.
**25.** Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of vitamin D on falls: a meta-analysis. JAMA 2004;291:1999-2006.
**26.** Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669-83. [Erratum, N Engl J Med 2006;354:1102.]
**27.** Bunout D, Barrera G, Leiva L, et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. Exp Gerontol 2006;41:746-52.
**28.** Salovaara K, Tuppurainen M, Karkkainen M, et al. Effect of vitamin D3 and calcium on fracture risk in 65- to 71-year-old women: a population based 3-year randomized controlled trial — the OSTPRE-FPS. J Bone Miner Res 2010;25:1487-95.
**29.** Melhus H, Snellman G, Gedeborg R, et al. Plasma 25-hydroxyvitaminD levels and fracture risk in a community-based cohort of elderly men in Sweden. J Clin Endocrinol Metab 2010;95:2637-45.
**30.** Ensrud KE, Taylor BC, Paudel ML, et al. Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab 2009;94:2773-80.
**31.** Cauley JA, Parimi N, Ensrud KE, et al. Serum 25-hydroxyvitamin D and the risk of hip and nonspine fractures in older men. J Bone Miner Res 2010;25:545-53.
**32.** Cauley JA, Lacroix AZ, Wu L, et al. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. Ann Intern Med 2008;149:242-50.
**33.** Bolland MJ, Bacon CJ, Horne AM, et al. Vitamin D insufficiency and health outcomes over 5 y in older women. Am J Clin Nutr 2010;91:82-9.
**34.** Wang TJ, Pencina MJ, Booth SL. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503-11.
**35.** Pittas AG, Harris SS, Stark PC, Dawson-Hughes B. The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in non diabetic adults. Diabetes Care 2007;30:980-6.
**36.** Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-Hydroxyvitamin D and risk of myocardial infarction in men. Arch Intern Med 2008;168:1174-80.
**37.** Koch TR, Finelli FC. Postoperative metabolic and nutritional complications of bariatric surgery. Gastroenterol Clin North Am 2010;39:109-24.
**38.** Sanders KM, Stuart AL, Williamson EJ, et al. Annual high dose vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815-22. [Erratum, JAMA 2010;303:2357.]
**39.** Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008;88:582S-586S.
**40.** Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, et al. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Am J Epidemiol 2010;172:81-93.
**41.** Melamed ML, Michos ED, Post W, Astor B. 25-Hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008;168:1629-37.
**42.** Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin $D_3$ and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992;327:1637-42.
**43.** Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomized double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int 2007;18:811-8.
**44.** LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. JAMA 1999;281:1505-11.
**45.** Norman AW, Bouillon R, Whiting SJ, Veith R, Lips P. 13th Workshop consensus for vitamin D nutritional guidelines. J Steroid Biochem Mol Biol 2007;103:204-5.
**46.** Hanley DA, Cranney A, Jones G, et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. CMAJ 2010;182(12):E610-E618.
**47.** Dawson-Hughes B, Mithal A, Bonjour J-P, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 2010;21:1151-4.
**48.** Priemel M, von Domarus C, Klatte TO, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 2010;25:305-12.