

Skeletal and Non-Skeletal Role of Vitamin D: Are We Getting Enough?

Reinhold Vieth, Ph.D., Dip Clin Chem, F.C.A.C.B.

**Associate Professor, Department of Laboratory Medicine and Pathology, University of Toronto,
and Director of Bone and Mineral Lab, Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto.**

Introduction

From the standpoint of public perception, vitamin D only relates to bone health, because of the notion that vitamin D is only needed to help in the absorption of calcium. Vitamin D is also perceived as potentially toxic. It is believed that great caution should be exercised in considering or promoting its consumption. Based on recent evidence these perceptions need to be evaluated.

Recommendations for vitamin D intake were initially intended to prevent rickets in infants. In essence, the infant dose of 400 IU/day was selected because it approximated what was in a teaspoon-full of cod-liver oil. Cod-liver oil had been a folk remedy for almost 200 years, for the vague purpose of helping babies to thrive¹. The dose happens to be appropriate for preventing rickets. Until recently, there has been no objective measure of the quality of vitamin D nutrition in adults. During the past 25 years, the criteria of vitamin D nutritional adequacy for adults has progressed from a vitamin D intake ensuring protection against osteomalacia (adult rickets), to an intake that suppresses parathyroid hormone secretion, and more recently, to prevent osteoporosis^{2,3}. To achieve these latter targets, specific blood levels of 25-hydroxyvitamin D [25(OH)D] must be maintained.

Based on the serum 25(OH)D concentrations of Canadians, there is strong evidence that vitamin D is the one nutrient that we are most deficient in during winter. Despite this fact, supplementing with vitamin D particularly during winter is rarely promoted.

The past decade has seen a rapid growth in knowledge about vitamin D. In 1997, North American nutritional recommendations for calcium and vitamin D were revised². For adults over age 70 years, the recommended intake for vitamin D was tripled, in what is still regarded as the largest ever increase for any nutrient recommendation. Even with that, the amounts of vitamin D consumed by North American adults remain inconsequential in terms of ensuring that circulating 25(OH)D levels are in the desirable range.

The first part of this review summarizes vitamin D nutrition consistent with current guidelines²; the second part presents evidence of how specific vitamin D intakes affect circulating 25(OH)D concentrations and summarizes the effects of vitamin D nutrition that are not related to bone.

PART I Adult Bone Health

On average adults resorb (dissolve away) just under 1% of the skeleton every month, and at the same time put almost that much back.

After about age 35, we only put back about nine tenths of what we take out of the skeleton. The calcium in our bones could be thought of like a retirement bank account where withdrawals exceed deposits. With this analogy, osteoporosis is a form of bankruptcy that pertains to the amount of calcium stored in the skeleton.

Here, depletion results in bones that might no longer withstand some of the normal stresses of everyday living. Consequently, minor falls or unusual movements can result in a fracture. Current treatments for osteoporosis restore bone density by a few percentage points, hence stabilizing the condition.

Bone mass falls faster during the winter months, and during the summer bone density remains fairly stable. The group headed by Bess Dawson-Hughes showed that vitamin D supplements eliminate the faster fall in bone density during winter⁴. And when vitamin D is used along with calcium supplements, it is difficult to tell which is doing more good at the bone, the vitamin D or the calcium^{5,6}. They probably act together by providing calcium, and by suppressing the secretion of parathyroid hormone [PTH].

For the elderly starting to take calcium and vitamin D, the risk of fracture is reduced fairly quickly, even though bone density is not increased by enough to account for the fewer fractures⁶. What is not yet common knowledge, is that vitamin D improves muscle strength and balance -- it is thought that this is what reduces the occurrence of falls that cause fractures⁷.

Vitamin D does not necessarily have to be at the stomach at the same time as the calcium. Vitamin D is the raw material needed to make a hormone, through a 2-step process. After vitamin D enters the blood via the skin or the diet, the liver automatically converts it to 25(OH)D within a day or two⁸. This compound has a half-life of about two months, and conventional dogma regards 25(OH)D as having no activity by itself. However, 25(OH)D is the best measure of vitamin D nutritional status, and it is the main criterion for diagnosing nutritional rickets or osteomalacia. The kidney functions as an endocrine gland, using 25(OH)D to make the hormone 1,25-dihydroxyvitamin D [1,25(OH)2D, or calcitriol]. Synthesis of 1,25(OH)2D is greatest when calcium supplies are lowest. The hormone induces the active transport of calcium through intestinal mucosa. The minimal supplies of vitamin D needed to normalize 1,25(OH)2D synthesis are not enough to prevent rickets or osteomalacia. Further increases in vitamin D will not increase 1,25(OH)2D levels⁹⁻¹². As kidney function deteriorates, its endocrine capability also declines, and thus a low 1,25(OH)2D level reflects impaired renal function, not poor nutrition¹³.

Current Nutritional Recommendations

Nutritional recommendations specify 200 IU of vitamin D per day for infants and for adults under age 50. For those between 51 - 70 years age, the recommended intake is 400 IU of vitamin D per day; and for adults over 70 years, 600 IU per day².

In Canada, it is a legal requirement that dairy milk for drinking must contain vitamin D. Other products produced from milk, like butter, ice cream, and yogurt cannot contain vitamin D. Conventional, milk-containing North American diets provide about 200 IU per day (100 IU per glass), but close to half of the population does not drink milk at all. There is some vitamin D in ocean fish like cod and salmon, but since we do not eat these regularly, their contribution to vitamin D intake of Canadians is limited. Nutritional legislation assumes that we get at least 200 units from the sun, and that occasional exposure of the face and hands to sunlight is enough.

PART II The RDA for Vitamin D

The working definition of recommended dietary allowance [RDA] is to ensure "levels of intake of essential nutrients considered... to be adequate to meet the known nutritional needs of practically all healthy persons"¹⁴. From this, one should assume that if the recommended intakes of vitamin D are maintained, they will protect adults from vitamin D insufficiency, the definition of which now involves suppression of PTH^{15,16}. Our own data, based on nutritional questionnaires and measurement of 25(OH)D show no connection between the biochemical measurement, and subjects' stated vitamin D intake. Likewise, two recent studies cast doubt on the current RDA value for vitamin D beyond childhood. In immigrant women in Denmark, Glerup et al could not uncover any prevention of 25(OH)D < 40 nmol/L when 5-15 µg/d (200-600 IU) was taken¹⁷. In Finland, 10 µg/d (400 IU) vitamin D was given to 9 to 15-year-old girls to test whether this would protect from developing 25(OH)D concentrations below 37.5 nmol/L during winter. There was no protective effect¹⁸.

Non-bone Effects of Vitamin D

The level of evidence needed to make a health claim involves direct intervention, the controlled administration of the agent to many healthy people, and showing an effect that stands up to statistical analysis. The evidence for following is based on cross-sectional studies. Although the effects described here are statistically significant, the cross-sectional nature of such studies would regard the quality of evidence implicating vitamin D as still

circumstantial. Epidemiological studies show that higher serum 25(OH)D, or environmental ultraviolet exposure is associated with lower rates of cancer, particularly of the breast, ovary, prostate, and colon¹⁹⁻²⁶. Multiple sclerosis is more prevalent in populations having lower levels of vitamin D nutrition or ultraviolet exposure^{24,27}, and it has been proposed that vitamin D intake, ranging from 1,300 to 3,800 IU per day, helps prevent the disease²⁷.

Established osteoarthritis progresses more slowly (i.e. less severe) in adults with higher vitamin D nutritional status; McAlindon recommends serum 25(OH)D exceed 75 nmol/L for adults with osteoarthritis^{28,29}. Hypertension is more prevalent with distance, north or south, from the equator³⁰. Blood pressure goes down in subjects whose 25(OH)D levels are raised to over 100 nmol/L by tanning³¹. Vitamin D deficiency impairs immune function in animals³². In children there is a strong association between pneumonia and nutritional rickets³³. If any of these non-traditional effects of vitamin D were taken into account, they would result in a substantial upward revision of the RDA for vitamin D.

Vitamin D Toxicity

Like anything that has an effect on living things, vitamin D can be harmful if it is taken in excess. It is probable that the reason vitamin D is thought of as toxic, is that daily ingestion in the milligram range has caused harm. This toxic intake exceeds by four times the amount of vitamin D adults acquire naturally through sunshine. Conversely, the current RDA for adults under age 50 represents only about 2% of what they could be making if they regularly spent 20 min with skin exposed to summer sun.

Lifeguards and farmers acquire the equivalent of at least 10 000 IU/day (250 micrograms, or 0.25 milligrams per day)¹. The current safety limit for vitamin D supplements is 2000 IU/day², but review of the literature shows that the lowest dose of vitamin D proven to cause toxicity is 40,000 IU/day¹. This translates to 1000 micrograms, or 1 milligram, taken daily for many months. If a Canadian consumer wanted to achieve the toxic dose, he or she would need to take forty of the

1000 IU pills (the highest dose available without a prescription) every day for many months.

Concluding Comments

The adult recommended dietary intake for vitamin D was based on an educated guess made in the 1960's, before there were objective criteria for adequacy. Furthermore, the dietary recommendations were aimed at preventing rickets in children with no consideration for its requirement in adults. Long-standing, mild insufficiency of vitamin D is now regarded as a cause of osteoporosis. We can now quantify vitamin D nutrition by testing circulating 25(OH)D concentrations. The blind guesses about vitamin D requirements, made almost 40 years ago are turning out to be so inadequate particularly for adults. Our current dietary and

nondietary vitamin D intake is inadequate in predicting a person's 25(OH)D status. Another complication entering the vitamin D picture is our cultural response toward sunlight. We are avoiding the sun more because of fear of skin cancer, and for many Canadians there is a cultural preference to prevent skin from tanning. For older adults, sunlight is more harmful than for the young. For older adults, less vitamin D is produced when skin is exposed to the sun.

The solution to the problem of diminished vitamin D nutrition from sunshine, is to supplement with more vitamin D than we have been - with at least 1000 IU (25 µg)/day not just during winter, but all year. Vitamin D is safe, inexpensive, it is effective in terms of bone disease. In addition, there is growing evidence that Vitamin D intake is beneficial for other conditions.

Table 1. Clinical interpretation of serum 25(OH)D levels and the estimated intakes of vitamin D needed to ensure these levels (1 µg = 40 IU)

	Deficiency (rickets and Osteomalacia)	Insufficiency (increased PTH secretion, osteoporosis)	Sufficiency	Desirable (suppress PTH)	Toxic/Therapy (could increase urine and serum calcium)
Serum 25(OH)D nmol/L	0-25	25-40	40-100	75-160	>220
Vitamin D ₃ µg/day needed to reach the 25(OH)D above:					
Dietary guidelines	0 µg/d	5-10	5-20	not stated	≥95
From evidence reviewed	0-5 µg/d	10-15	25-100	100-250	>1000 (> 40000 IU)

The Whitehall-Robins Report is a Whitehall-Robins publication that focuses on current issues on the role of vitamins and minerals in health promotion and disease prevention. Complimentary copies are distributed to Canadian health care professionals active or with a special interest in nutrition. Each issue is written and/or reviewed by independent health care professionals with expertise in the chosen topic.

Editor: Whitehall-Robins Inc.

If you have any comments about the Whitehall-Robins

Report or would like to be added to the mailing list, please write to:

The Editor: The Whitehall-Robins Report,
5975 Whittle Road, Mississauga, ON L4Z 3M6



© 2001-February. May be reproduced without permission provided source is recognized.

REFERENCES 1. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety [see comments]. *Am J Clin Nutr.* 1999; 69: 842-856. 2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes.: Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academy Press, 1997. 3. Heaney, R. P. Vitamin D: How much do we need, and how much is too much? *Osteoporos.Int.* 11, (in press) 4. Dawson-Hughes B, Dallal GE, Krall EA, Harris S, Sokoll LJ, Falconer G: Effect of vitamin D supplementation on winter-time and overall bone loss in healthy postmenopausal women. *Ann Intern Med* 1991; 115: 505-512. 5. Chapuy MC, Arlot ME, Duboeuf F, et al: Vitamin D₃ and calcium to prevent hip fractures in the elderly women. *N Engl J Med.* 1992; 327: 1637-1642. 6. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med.* 1997; 337: 670-676. 7. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res.* 2000; 15: 1113-1118. 8. Haddad JG, Matsuoka LY, Hollis BW, Hu YZ, Wortsman J. Human plasma transport of vitamin D after its endogenous synthesis. *J Clin Invest* 1993; 91: 2552-2555. 9. Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK. Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency. *Am J Clin Nutr.* 1987; 45: 755-763. 10. Himmelstein S, Clemens TL, Rubin A, Lindsay R. Vitamin D supplementation in elderly nursing home residents increases 25(OH)D but not 1,25(OH)2D. *Am J Clin Nutr* 1990; 52: 701-706. 11. Landin-Wilhelmsen K, Wilhelmsen L, Wilske J, et al. Sunlight increases serum 25(OH) vitamin D concentration whereas 1,25(OH)2D₃ is unaffected. Results from a general population study in Goteborg, Sweden (The WHO MONICA Project). *Eur J Clin Nutr.* 1995; 49: 400-407. 12. Need AG, Horowitz M, Morris HA, Nordin BC. Vitamin D status: effects on parathyroid hormone and 1,25-dihydroxyvitamin D in postmenopausal women. *Am J Clin Nutr.* 2000; 71: 1577-1581. 13. Ishimura E, Nishizawa Y, Inaba M, et al. Serum levels of 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, and 25-hydroxyvitamin D in nondialyzed patients with chronic renal failure. *Kidney Int.* 1999; 55: 1019-1027. 14. Yates AA. Process and development of dietary reference intakes: basis, need, and application of recommended dietary allowances. *Nutr Rev.* 1998; 56: S5-S9. 15. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos.Int.* 1997; 7: 439-443. 16. Kinyamu HK, Gallagher JC, Rafferty KA, Balhorn KE. Dietary calcium and vitamin D intake in elderly women: effect on serum parathyroid hormone and vitamin D metabolites. *Am J Clin Nutr.* 1998; 67: 342-348. 17. 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; 247: 260-268. 18. Lehtonen-Veromaa M, Mottonen T, Irjala K, et al. Vitamin D intake is low and hypovitaminosis D common in healthy 9 to 15 year old adolescents. *Eur J Clin Nutr.* 1999; 53: 746-751. 19. Lefkowitz ES, Garland CF. Sunlight, vitamin D, and ovarian cancer mortality rates in US women. *Int J Epidemiol.* 1994; 23: 1133-1136. 20. Martinez ME, Giovannucci EL, Colditz GA, et al. Calcium, vitamin D, and the occurrence of colorectal cancer among women. *J Natl Cancer Inst.* 1996; 88: 1375-1382. 21. Tangrea J, Helzlsouer K, Pietinen P, et al. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. *Cancer Causes Control.* 1997; 8: 615-625. 22. Garland CF, Garland FC, Gorham ED. Can colon cancer incidence and death rates be reduced with calcium and vitamin D? *Am J Clin Nutr.* 1991; 54: 193S-201S. 23. Emerson JC, Weiss NS. Colorectal cancer and solar radiation. *Cancer Causes Control* 1992; 3: 95-99. 24. Schwartz GG. Multiple sclerosis and prostate cancer: what do their similar geographies suggest? *Neuroepidemiology* 1992; 11: 244-254. 25. Hanchette CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer* 1992; 70: 2861-2869. 26. Ainsleigh HG. Beneficial effects of sun exposure on cancer mortality. *Preventive Medicine* 1993; 22: 132-140. 27. Hayes CE, Cantorna MT, DeLuca HF. Vitamin D and multiple sclerosis. *Proc Soc Exp Biol Med.* 1997; 216: 21-27. 28. McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham Study. *Ann Intern Med.* 1996; 125: 353-359. 29. Lane NE, Gore LR, Cummings SR, et al. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum.* 1999; 42: 854-860. 30. Rostand SG. Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 1997; 30: 150-156. 31. Krause R, Buhning M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure. *Lancet* 1998; 352: 709-710. 32. McMurray DN, Bartow RA, Mintzer CL, Hernandez-Frontera E. Micronutrient status and immune function in tuberculosis. *Annals of the New York Academy of Sciences* 1990; 587: 59-69. 33. Muhe L, Lulseged S, Mason KE, Simoes EA. Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet* 1997; 349: 1801-1804.