Early release, published at www.cmaj.ca on July 19, 2010. Subject to revision.

CMAJ REVIEW

Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada

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∞∞ See also the summary article by Hanley and colleagues

The 2002 guidelines for the management of osteoporosis published by Osteoporosis Canada[1] identified adequate vitamin D status, in addition to calcium from diet or supplements, as essential for the prevention of osteoporosis. Recent large clinical trials and meta-analyses have expanded our knowledge of the role of vitamin D in fractures, falls and other health outcomes, as well as its effect on disorders such as diabetes mellitus, autoimmune and infectious diseases, malignancies and cardiovascular disease.

Current Canadian recommendations for "adequate intake" and "tolerable upper level" of vitamin D, which are more than 10 years old, were derived mainly from early nutritional science estimates of the minimal intake necessary to prevent florid deficiency states (rickets or osteomalacia). However, these levels have never been supported by adequately conducted dose-finding studies.[2]

This review is an update to the 2002 recommendations on vitamin D and is specific for adults, excluding times of pregnancy and lactation.

Key points

- Adequate vitamin D is an essential factor in the prevention of osteoporosis and may reduce the risk of other medical disorders unrelated to bone and mineral metabolism.
- To most consistently improve clinical outcomes such as fracture risk, an optimal serum level of 25-hydroxyvitamin D is probably above 75 nmol/L; for most Canadians, supplementation is needed to achieve this level.
- The recommended vitamin D intake is 10–25 μg (400–1000 IU) daily for low-risk adults under 50 years of age and 20–50 μg (800–2000 IU) for high-risk and older adults, with potential for consideration of higher doses.
- Doses up to 50 μg (2000 IU) are safe and do not require monitoring, but if higher doses are sometimes needed, monitoring is appropriate.

Methods

We systematically searched the MEDLINE database, for the period 1996 to June 30, 2008, and the Cochrane Library using the terms "vitamin D," "vitamin D deficiency," "25-hydroxyvitamin D," "meta-analysis" and "systematic review." We identified 168 potentially relevant papers. Of these, 16 relevant systematic reviews remained after removal of duplicates and screening of abstracts by two reviewers (including A.C.). We included systematic reviews of randomized controlled trials and observational studies that assessed fractures, falls, death or extraskeletal outcomes. We used the Assessment of Multiple Systematic Reviews instrument[3] to evaluate the methodologic quality of systematic reviews published between the cutoff date for literature reviewed in the 2002 clinical practice guidelines[1] until June 30, 2008 (Appendices 1 and 2, available at www.cmaj.ca/cgi/content/full/cmaj.080663/DC1). A multidisciplinary expert panel consisting of the authors of this paper reviewed the abstracted articles and quality measures. Following this review, we formulated summary statements based upon the highest level of evidence and developed graded recommendations. All authors contributed to this process, reaching consensus through a series of in-person meetings, teleconferences and electronic communications. Levels of evidence and grading of recommendations followed the same system as used in 2002 (Table 1).[1] The Guidelines Committee and the Executive Committee of Osteoporosis Canada's Scientific Advisory Council approved the recommendations.

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CMAJ 2010. DOI:10.1503/cmaj.080663

DOI:10.1503/cmaj.080663

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Assessment of vitamin D

Measurement and assay

After synthesis in the skin or dietary ingestion, vitamin D is removed from the bloodstream into various tissues, including the liver, adipose tissue and muscle. Its biologic half-life is about 60 days,[4] and it is eventually converted to 25-hydroxyvitamin D in the hepatocytes.[4,5] Vitamin D_3 (cholecalciferol) is the molecule synthesized in the skin in response to ultraviolet B radiation, whereas vitamin D_2 (ergocalciferol) is derived from irradiation of certain fungi. Both vitamin D_2 and vitamin D_3 create 1,25-dihydroxyvitamin D, the active form, although there is some evidence that vitamin D_2 may not be used in the body as efficiently as vitamin D_3.[6] In Canada, most vitamin D supplements consist of vitamin D_3, but high-dose preparations, available by prescription, are vitamin D_2. In this paper we use the term "vitamin D" to refer to both forms, unless a distinction is warranted.

The serum concentration of 25-hydroxyvitamin D_3 is the best indicator of the nutritional and functional status of vitamin D.[2] A nonfasting sample taken at any time of day is suitable for measurement of 25-hydroxyvitamin D (level 2 evidence). Circulating calcitriol (1α,25-dihydroxyvitamin D_3 or 1,25-dihydroxycholecalciferol) is the vitamin D hormone regulating intestinal calcium and phosphate absorption, but it is *not* an appropriate indicator of clinical vitamin D status,[5] the exception being in patients with abnormalities of calcitriol synthesis (e.g., sarcoidosis) or rare disorders of phosphate or vitamin D metabolism (level 4 evidence, grade D recommendation).

Many techniques are widely available for measuring 25-hydroxyvitamin D.[7–9] These assays all perform reasonably well in identifying clinically important low levels (Table 2), but methods other than high-performance liquid chromatography may misclassify about 20% of low values.[7–9] However, the data used to define current clinical decision values for 25-hydroxyvitamin D concentrations were obtained by means of immunoassays. Variability in measurements of serum 25-hydroxyvitamin D make it imperative that clinical laboratories participate in external laboratory proficiency testing programs,[7–9] such as the Vitamin D External Quality Assessment Scheme.[10] External proficiency testing should be a mandatory component of accreditation for laboratories that measure 25-hydroxyvitamin D (level 2 evidence).

Monitoring of serum 25-hydroxyvitamin D

There has been a marked increase in the clinical use of 25-hydroxyvitamin D assays.[11] However, serum 25-hydroxyvitamin D should be measured only if deficiency is suspected or would affect the person's response to therapy (e.g., in cases of impaired intestinal absorption, such as celiac disease, or osteoporosis requiring pharmacologic therapy). In treating deficiency, serum 25-hydroxyvitamin D will indicate the effectiveness of vitamin D therapy. The half-life of 25-hydroxyvitamin D in the body is 15–20 days.[4] With standard-dose supplementation, serum 25-hydroxyvitamin D plateaus after three to four months.[12] Therefore, serum 25-hydroxyvitamin D should be checked no sooner than three months after standard-dose treatment is initiated (level 2 evidence, grade B recommendation). After high-dose oral or parenteral vitamin D replacement is administered (e.g., 500 000 IU), the peak 25-hydroxyvitamin D level may be achieved in one month.[13] Patients taking daily doses above Health Canada's "tolerable upper intake level" (currently set at 50 μg [2000 IU]) should undergo monitoring of serum 25-hydroxyvitamin D (level 4 evidence, grade D recommendation). For healthy Canadians, the dose recommendations for routine supplementation in this paper should result in adequate blood levels. Monitoring of routine supplement use and routine testing of

Table 1: Levels of evidence and grading system*

Level or grade	Criteria
Evidence	
1+	Systematic overview or meta-analysis of randomized controlled trials
1	Randomized controlled trial with adequate power
2+	Randomized controlled trial that does not meet level 1 criteria
3	Nonrandomized clinical trial or cohort study
4	Before–after study, cohort study with noncontemporaneous controls, case–control study
5	Case series with controls
6	Case series without controls
Recommendation	
A	Supported by level 1 or 1+ evidence plus consensus
B	Supported by level 2 or 2+ evidence plus consensus
C	Supported by level 3 evidence plus consensus
D	Any lower level of evidence supported by consensus

*Identified articles were reviewed, and the summary statements developed from these articles were assigned a level of evidence (from 1 = highest to 4 = lowest). Recommendations were assigned a grade, according to a system that incorporated both level of evidence and expert consensus (from A = highest to D = lowest).

Table 2: Classification of vitamin D status by serum level of 25-hydroxyvitamin D (25-OH-D)

Serum 25-OH-D, nmol/L*†	Category	Level of evidence
< 25	Vitamin D deficiency	3
25–75	Vitamin D insufficiency‡	2
> 75	Desirable vitamin D status	3
> 250	Potential adverse effects	2

*Assumes that serum 25-OH-D is measured by a clinical laboratory participating in an external quality assurance program.
†2.5 nmol/L = 1 ng/mL.
‡"Insufficiency" is a milder form of deficiency and should preferably be termed "suboptimal vitamin D status."

otherwise healthy individuals as a screening procedure are not indicated (grade D recommendation).

Vitamin D status

Vitamin D deficiency should be regarded as a continuum, encompassing past definitions of "deficiency" and "insufficiency" (Table 2). The term "deficiency" was previously used to describe the advanced clinical effects of chronically low vitamin D: malabsorption of calcium and phosphate with resultant hypocalcemia, hypophosphatemia and secondary hyperparathyroidism, as well as proximal myopathy and impaired growth-plate development (rickets) and bone mineralization (osteomalacia)[5] (level 3 evidence). Vitamin D "insufficiency" described a milder form of deficiency in which reduced absorption of calcium and resultant mild secondary hyperparathyroidism might increase bone loss. Vitamin D insufficiency commonly occurs in patients with osteoporosis and could contribute to their clinical presentation of low bone density, fractures and falls[5] (level 2 evidence; see "Traditional roles," later in this article).

In rickets and osteomalacia, serum levels of 25-hydroxyvitamin D are usually below 20–25 nmol/L, whereas levels of vitamin D in "insufficiency" are below the desirable range but above 20–25 nmol/L. The lower limit of the desirable (optimal) range is debatable, but available evidence supports setting this at 75–80 nmol/L[12–17] (level 3 evidence). Setting an optimal level of 75 nmol/L makes certain the person has reached the point at which, with increasing vitamin D intake, serum parathyroid hormone, intestinal calcium absorption[15] and muscle function in the lower extremities[14] have reached a plateau and at which, according to one meta-analysis,[16] fracture prevention is consistently seen.

Factors associated with vitamin D deficiency

Many factors are associated with vitamin D deficiency, some causative (e.g., marked avoidance of ultraviolet radiation, malabsorption), and others being conditions in which vitamin D deficiency or insufficiency is reported frequently (e.g., chronic renal failure)[17,18] (mostly level 4 evidence).

Vitamin D deficiency should be considered in patients with osteoporosis, particularly if there is no response to therapy.[19] Elderly patients living in institutions are at high risk for vitamin D deficiency because of lack of exposure to sunlight.[20] Absolute avoidance of sunlight increases the risk of vitamin D deficiency, and vitamin D supplementation is needed in this situation (level 3 evidence, grade C recommendation). Sunscreens lower the rate of vitamin D synthesis[21] but have not been associated with vitamin D deficiency and should not be avoided out of fear of such a deficiency.[22,23]

Summary statements

1. Measurement of 25-hydroxyvitamin D in the serum (with no restrictions on the timing of collection) is the best indicator of vitamin D sufficiency[24] (level 2 evidence).
2. In the absence of external laboratory proficiency testing, serum 25-hydroxyvitamin D values from different clinical laboratories cannot be assumed to be comparable[7,9,25] (level 2 evidence).
3. Monitoring of routine vitamin D supplementation by measurement of serum 25-hydroxyvitamin D is unnecessary (level 4 evidence). Monitoring of high-risk patients and those with osteoporosis should not be performed before three months of standard supplementation (20–50 μg [800–2000 IU daily])[12] (level 2 evidence). Patients taking daily doses above Health Canada's "tolerable upper intake level" (currently set at 50 μg [2000 IU]) should undergo monitoring of serum 25-hydroxyvitamin D (level 4 evidence).

Sources of vitamin D

Exposure to the sun

Ultraviolet B radiation (wavelength 290–315 nm) promotes synthesis of vitamin D from 7-dehydrocholesterol in the skin.[24] The amount of exposure needed to achieve adequate vitamin D status depends on latitude, altitude, time of year and day, weather, other aspects of the environment, age, skin pigmentation type, clothing, activity and the amount of skin irradiated.[21] To obtain 25 μg (1000 IU) of vitamin D3 from moderate exposure to ultraviolet B radiation, a young white person needs exposure at one-quarter of the minimal erythemal dose (4 minutes) to 25% of the body surface (arms and most of the legs), whereas an older person or a person with darker skin may need as long as 18 minutes[26,27] (level 2 evidence). Unfortunately, many detrimental effects of ultraviolet B radiation are cumulative, and one-quarter of the minimal erythemal dose per day would result in a significant amount of ultraviolet B radiation exposure over a summer. For that reason, dermatologists recommend that the safest course is to avoid exposure to the sun and to take vitamin D supplements.

The effects of latitude on vitamin D synthesis may be related to fractures: for each 10° change in latitude away from the equator, the probability of hip fracture increases by 0.6%.[28] In wintertime, above 35° North latitude, sunlight does not contain adequate ultraviolet B radiation for production of vitamin D_3.[29] Therefore, Canadians are at risk for seasonal vitamin D insufficiency or deficiency.[30–32] Although 25-hydroxyvitamin D levels in summer may reach or exceed 75 nmol/L, in winter they can fall by half[33] (level 3 evidence).

Food sources

The influence of diet on vitamin D status is minimal (accounting for 3.7–5.9 μg or 148–236 IU daily), and most circulating vitamin D is derived from exposure to sunlight.[34] The major dietary sources of vitamin D come from Canada's mandatory fortification of margarine, milk (both fluid and powdered forms) and plant-based beverages and from optional fortification of fruit juices and yogurts[35] (level 2 evidence).

Supplements

The 2007 Canada Food Guide recommendation that all adults over the age of 50 years take a daily vitamin D supplement of 10 μg (400 IU)[36] should ensure that older Canadians meet the 1997 dietary recommendations from the Institute of Medi-

cine.[2] However, this level of intake does not meet the previous recommendation of Osteoporosis Canada of 20 μg (800 IU), which was based on data suggesting that this is the minimum dose consistently associated with prevention of fractures[1,17] (level 1+ evidence).

When supplements are used to treat vitamin D insufficiency, the amount should be great enough to increase 25-hydroxyvitamin D to desirable levels. Daily doses over 50 μg (2000 IU) can safely be administered under medical supervision.[2] Assuming that the patient can absorb an orally administered dose, severe deficiency (rickets or osteomalacia) requires doses as high as 1250 μg (50 000 IU) daily for two to four weeks, then weekly or biweekly, with monitoring of serum 25-hydroxyvitamin D at one month and three months. Less severe deficiency can be managed with lower doses.[5] A clinically useful estimate is 1 nmol/L for each microgram of vitamin D;[12,37,38] for example, vitamin D_3 1 μg (40 IU) daily raises serum 25-hydroxyvitamin D by 0.7–2.0 nmol/L. If diet and a background of moderate sun exposure during summer is assumed to achieve a mean serum 25-hydroxyvitamin D level of 50 nmol/L, then a further 25 μg (1000 IU) per day of dietary vitamin D_3 may be needed to exceed 75 nmol/L. Some individuals, particularly those deprived of sunlight and those who are elderly, may need greater intake (level 2 evidence).

Safety and toxicity of vitamin D supplementation

Because of the long half-life of vitamin D accumulation in the tissues, excessive intake of vitamin D has the potential to cause chronic toxic effects, which present as hypercalcemia and renal damage. Most countries have set the "tolerable upper intake level" for vitamin D (the highest daily intake presenting no risk of adverse health effects in almost all individuals in the general population) at 50 μg (2000 IU) for adults.[2] However, this intake level was set without adequate studies of dose–response relationships or toxicity. Small studies have shown that hypercalcemia or hypercalciuria cannot be elicited in healthy adults who consume up to 250 μg (10 000 IU) daily over long periods.[12,39] Recent reviews have recommended that the tolerable upper intake level be raised to 250 μg (10 000 IU) daily,[4,39] but more studies are needed.[39] If the desirable serum level of 25-hydroxyvitamin D is at least 75 nmol/L, daily intakes greater than 20–50 μg (800–1000 IU) and as high as 125 μg (5000 IU) may be required in some cases[40] (level 2 and 4 evidence).

There is no convincing evidence of adverse effects of daily intakes up to 125 μg (5000 IU). Although the Women's Health Initiative, which used 10 μg (400 IU) daily, found an increased incidence of nephrolithiasis, there was no evidence of elevated 25-hydroxyvitamin D in the small number of participants tested, and calciuria was not assessed.[41]

Diseases like sarcoidosis sometimes feature hypercalcemia and/or hypercalciuria, and calcium levels should be monitored in affected patients, particularly in summer.[42] The vitamin D intake of patients with primary hyperparathyroidism should not be restricted. Vitamin D insufficiency is common in this condition, and repletion may have beneficial effects[43,44] (level 3 evidence).

There is no evidence that increasing the recommended vitamin D intake for the general population to 20–50 μg (800–2000 IU) would cause any medical problems. At this level of vitamin D intake, there is no need to monitor calcium in the serum or urine or to monitor renal function[2,40] (level 2 evidence, grade B recommendation).

Summary statements

1. In Canada, some vitamin D is obtained with safe exposure to the sun during the summer months,[26,27,45] (level 1 evidence), but exposure to sunlight and dietary intake are insufficient to maintain average serum 25-hydroxyvitamin D concentration above 75 nmol/L throughout the year[12,31,32] (level 2 evidence).
2. A daily intake of 25 μg vitamin D_3 (1000 IU) — a safe, commonly available dose — will raise the average serum level of 25-hydroxyvitamin D by 15–25 nmol/L[12,37] (level 2 evidence).
3. The upper level for safe vitamin D_3 intake has not been well defined but is probably as high as 250 μg (10 000 IU) daily[12,39] (level 2 evidence). In clinical practice, supplementation with this dose of vitamin D is rarely required (level 4 evidence).

Traditional roles of vitamin D

Effect on bone mineral density

Vitamin D deficiency is associated with low bone mineral density, a key risk factor for osteoporotic fracture.[1] Observational studies have shown a positive association between serum 25-hydroxyvitamin D (range 40–90 nmol/L) and higher bone density.[46–48]

In older women (> 65 years), daily vitamin D_3 17.5 or 20 μg (700 or 800 IU) resulted in small but significant increases in bone mineral density in the lumbar spine and femoral neck relative to placebo.[49,50] Similarly, the Women's Health Initiative found, in a subgroup of 2431 women taking vitamin D and calcium supplements, a 1.06% increase in total hip density ($p < 0.001$)[41] (level 1 evidence).

Effect on fractures

Low 25-hydroxyvitamin D concentrations have been associated with fracture. Higher serum 25-hydroxyvitamin D levels were observed in randomized trials that reported a significant reduction in fractures.[49,51–53] However, the treatment effect varied across these trials,[49,51,54–58] possibly because of compliance issues (< 80%) and incomplete assessment of vitamin D status. In their meta-analysis, Bischoff-Ferrari and colleagues[16] combined data from five trials (n = 9829) that used 17.5 or 20 μg (700 or 800 IU) of vitamin D_3 and reported a 23% reduction in nonvertebral fractures. The reduction in risk of fracture was most strongly associated with those doses, provided serum 25-hydroxyvitamin D levels exceeded 75 nmol/L.[16]

The importance of adequate calcium intake and the primary role of vitamin D in the absorption of dietary calcium were highlighted by a meta-analysis[59] showing that the combined relative risk (RR) of fracture from 6 trials (n = 45 509) of vitamin D_3 (10–20 μg [400–800 IU]) combined with cal-

cium was 0.82 (95% confidence interval [CI] 0.71–0.94). Similarly, a recent cumulative meta-analysis found that calcium intake above 1200 mg daily in combination with 20 μg (800 IU) vitamin D provided reduction in fracture risk and prevention of bone loss superior to effects seen with lower calcium intake and 10 μg (400 IU) vitamin D,[60] especially for elderly patients living in institutions, where adherence is assured through supervision of medications.[58]

Vitamin D_3 at daily doses of at least 20 μg (800 IU) in combination with calcium (1000 mg) reduces the risk of hip and nonvertebral fractures, especially for elderly patients living in institutions.[16,60] Clinical trial evidence for the efficacy of vitamin D_3 and calcium in reducing fracture risk in community-dwelling individuals is less strong,[57] but poor compliance was a major factor in the negative studies.[41,52] Although 20 μg (800 IU) is the lowest dose consistently associated with a bone benefit, it is likely that, for a sizeable minority of individuals, this dose would not be effective. Because higher doses are within the current definition of tolerable upper level, it seems reasonable to recommend 20–50 μg (800–2000 IU) for patients at risk for osteoporosis (level 2–4 evidence, grade B–D recommendation).

Effect on falls

Vitamin D may reduce falls through improvements in muscle strength and lower-extremity function.[14,61] A meta-analysis of five trials that adequately defined and ascertained falls showed that vitamin D significantly reduced the risk (by 22%), but this was not the case when the analysis was restricted to the three randomized controlled trials (odds ratio 0.83, 95% CI 0.65–1.06).[62] The inconsistent effect of vitamin D in trials may be related to differences in population, dose and method of capturing data on falls.[55,61–67] There is reasonable evidence that vitamin D_3 at a daily dose of 20 μg (800 IU) reduces the risk of falls, particularly from trials that adequately ascertained falls[62] (level 2 evidence).

Summary statements

1. Supplementation with vitamin D_3 and calcium increases bone density in postmenopausal women and in men over age 50 years[41,46–50,68,69] (level 1 evidence).
2. Vitamin D_3 at daily doses of 20 μg (800 IU), in combination with calcium (1000 mg), reduces the risk of hip and nonvertebral fractures in elderly people living in institutions[16] (level 1 evidence). The evidence for community-dwelling individuals is less strong[16,70] (level 2 evidence).
3. There is evidence that supplementation with 20 μg (800 IU) vitamin D_3 daily reduces the risk of falls, particularly from trials with adequate ascertainment of falls[62] (level 2 evidence).

Nontraditional roles of vitamin D

Since the publication of the previous Osteoporosis Canada guidelines in 2002, a wide variety of previously unsuspected biological roles for vitamin D have been explored. Vitamin D (calcitriol) receptors and the enzymes involved in calcitriol synthesis (1α-hydroxylase, cytochrome P450 27B1 isozyme) and catabolism (24-hydroxylase, cytochrome P450 24 isozyme) are expressed in many tissues, including the skin, colon, prostate, breast, pancreas and heart, as well as the immune system (monocytes, macrophages and lymphocytes).[5] Calcitriol produced in these tissues is not normally released into the circulation and is not regulated by serum calcium, phosphate or parathyroid hormone.[5] Calcitriol may lower blood pressure by downregulating renin production, it may stimulate insulin production and secretion by pancreatic β cells, and it may modulate immune function through actions on lymphocytes and macrophages.[5]

Significant antiproliferative and prodifferentiation properties have been demonstrated in laboratory studies.[71] A systematic review of the PubMed database yielded 63 observational studies of vitamin D status in relation to cancer risk,[72] the majority of which found that lower cancer risk was associated with sufficient vitamin D status. Systematic reviews for colorectal cancer have also found that vitamin D may reduce the risk.[73,74] In a small randomized trial, daily supplementation with calcium 1400–1500 mg and vitamin D_3 27.5 μg (1100 IU) reduced the risk of all cancers (excluding skin cancer).[75]

In the Women's Health Initiative study, there was no benefit of 10 μg (400 IU) with respect to risk of colorectal cancer, but in a nested case–control substudy, low levels of 25-hydroxyvitamin D were associated with higher risk of cancer.[76] Low serum level of 25-hydroxyvitamin D was associated with colon cancer in the Third National Health and Nutrition Examination study[34] (level 3 evidence).

Vitamin D deficiency, which impairs the synthesis and secretion of insulin in animal models of diabetes mellitus,[77] has been linked to the risk of diabetes. Epidemiologic studies have suggested a link between vitamin D deficiency in early life and later onset of type 1 diabetes.[78] One meta-analysis supported an association between vitamin D deficiency and type 2 diabetes.[79]

Although studies of vitamin D in multiple sclerosis have been small, have lacked controls or have included confounding by other variables, high circulating levels of vitamin D have been associated with a lower risk of this condition, and supplementation has been associated with reduced risk.[80,81]

Vitamin D appears to be required in the immune response that leads to killing of intracellular *Mycobacterium tuberculosis,* which perhaps explains why populations with a high prevalence of vitamin D insufficiency also have susceptibility to microbial infections.[82] A recent systematic review found fair evidence that vitamin D has a role in modifying the body's response to infection (especially tuberculosis, influenza and viral upper respiratory tract illnesses), but further research is needed.[83]

Despite the appearance of interesting potential benefits of nontraditional actions of vitamin D in observational studies, no adequately powered or dosed intervention studies have been performed to test these hypotheses. The US Agency for Healthcare Research and Quality has recently released a systematic review of the evidence for vitamin D affecting health outcomes, which found little or weak evidence supporting the nontraditional actions of vitamin D and could make no recommendations other than that more research is needed.[84]

Box 1: Recommendations for vitamin D supplementation*

1. Adequate vitamin D status, in addition to calcium from diet or supplements, is essential for the prevention of osteoporosis (level 1 evidence, grade A recommendation).
2. Administration of vitamin D and calcium should not be used as the sole treatment for osteoporosis (level 1 evidence, grade A recommendation).
3. The optimal level of serum 25-hydroxyvitamin D for musculoskeletal benefits is at least 75 nmol/L (level 2 evidence, grade B recommendation).
4. Laboratories performing 25-hydroxyvitamin D testing should take part in external proficiency surveys and should demonstrate that values reported for shared samples approximate the consensus of values reported by others (level 4 evidence, grade D recommendation).
5. In healthy adults at low risk for vitamin D deficiency (i.e., under age 50, without osteoporosis or conditions affecting vitamin D absorption or action), routine vitamin D supplementation (10–25 μg [400–1000 IU] daily) is recommended. Serum 25-hydroxyvitamin D should not be measured (level 5 evidence, grade D recommendation).
6. Adults over 50 years of age are at moderate risk for vitamin D deficiency. Supplementation with at least 20–25 μg (800–1000 IU) of vitamin D_3 daily is recommended. To achieve optimal vitamin D status (> 75 nmol/L), many individuals may require supplementation at greater than 25 μg (1000 IU) daily. Doses up to 50 μg (2000 IU) are safe and do not require monitoring (level 3 evidence, grade C recommendation).
7. For individuals receiving pharmacologic therapy for osteoporosis, measurement of serum 25-hydroxyvitamin D should follow three to four months of adequate supplementation and should not be repeated if the optimal level is achieved (grade D recommendation).
8. Measurement of serum 25-hydroxyvitamin D is recommended for individuals with recurrent fractures, bone loss despite osteoporosis treatment or comorbid conditions that affect vitamin D absorption or action (grade D recommendation). Dose requirements above Health Canada's current tolerable upper intake level (50 μg [2000 IU]) may be needed, in which case monitoring of serum 25-hydroxyvitamin D levels is required (level 4 evidence, grade D recommendation).
9. Exposure to natural sunlight, when used in moderation (avoiding sunburn) and individualized to the person's skin type, can contribute to summertime vitamin D sufficiency (level 2 evidence, grade B recommendation).
10. Research is needed to better define the minimum required daily dose and the optimal dose for musculoskeletal and other health benefits and to better establish the tolerable upper level for vitamin D supplementation (grade D recommendation).

*Levels of evidence and grades of recommendation are explained in Table 1.

Summary statements

1. Vitamin D insufficiency has been associated with malignancies[72] (especially colorectal cancer[73]), diabetes mellitus,[78] multiple sclerosis[81] and impaired immune response[82] (level 3 evidence).
2. The benefits of vitamin D for these nontraditional roles are associated with 25-hydroxyvitamin D levels above 75 nmol/L[37,72] (level 3 evidence).

Approach to supplementation

There are major deficits in our knowledge of vitamin D, and more research, including well-conducted randomized controlled trials, is needed to define optimal intake levels. Nonetheless, the consensus position of Osteoporosis Canada is that the available evidence of safety and the potential benefits for adults justify recommending that optimal vitamin D status represents a serum 25-hydroxyvitamin D level of at least 75 nmol/L. In Canada, exposure to sunlight and dietary intake are insufficient to maintain this level, and use of vitamin D supplementation is therefore indicated for most adults.[30–32]

The clinical approach can take into account three "settings," based on suspicion for vitamin D insufficiency and its complications.

People with low risk for vitamin D insufficiency are adults below age 50 years without comorbid conditions affecting vitamin D absorption or action. For these people, supplementation at 10–25 μg (400–1000 IU) is appropriate, and serum 25-hydroxyvitamin D should not be measured (level 3 evidence, grade D recommendation).

People with moderate risk for vitamin D insufficiency are adults 50 years of age or older, with or without osteoporosis, but without comorbid conditions that affect vitamin D absorption or action. For these people, routine supplementation with vitamin D is appropriate, and this should be at a dose of 20–50 μg (800–2000 IU) daily (level 2 evidence, grade B recommendation). Serum 25-hydroxyvitamin D should not be measured routinely in initial assessment of these individuals, but if pharmacologic therapy for osteoporosis is prescribed, 25-hydroxyvitamin D should be measured after three to four months of an adequate supplementation dose (level 3–5 evidence, grade D recommendation).

People at high risk for adverse outcomes from vitamin D insufficiency include those with recurrent fractures or bone loss despite osteoporosis treatment and/or comorbid conditions that affect vitamin D absorption or action. In these cases, serum 25-hydroxyvitamin D should be measured as part of the initial assessment, and supplementation with vitamin D should be based on the measured value. Supplementation dose requirements above the current definition of tolerable upper intake level (50 μg [2000 IU]) may be identified by measuring serum 25-hydroxyvitamin D levels (grade B recommendation).

Vitamin D_3 is the preferred supplementary form for humans, with vitamin D_2 being available for large-dose preparations. Calcitriol and its analogs are prescription products with narrow margins of safety. They are not synonymous with vitamin D and are not advised for prevention or routine treatment of osteoporosis. For most adults given a supplement, an initial dose of vitamin D_3 of 20–25 μg (800–1000 IU) daily, is likely to raise serum 25-hydroxyvitamin D by approximately 15–30 nmol/L.[12,37] To achieve desirable vitamin D status (> 75 nmol/L) many individuals will require doses greater than this minimum dose.

A weekly dose of 250 μg (10 000 IU) vitamin D_3 may be more convenient for some patients if available. Some practitioners use vitamin D_2 at a dose of 1250 μg (50 000 IU) monthly or more frequently as needed.

Table 3: Key changes to the vitamin D guidelines in the 2002 guidelines for the management of osteoporosis

2002 guidelines[1]	Changes in the current guidelines*
Recommended vitamin D intake from all sources† • Men and women < 50 yr: 400 IU (10 μg)/day • Men and women ≥ 50 yr: 800 IU (20 μg)/day	For most healthy adults, regardless of age, the recommended vitamin D_3 intake is 800–1000 IU (20–25 μg) per day. For individuals at high risk for vitamin D deficiency, supplementation at doses between 800 and 2000 IU (20–50 μg) per day is recommended, with potential for higher doses.
Measurement of serum 25-OH-D not recommended	For individuals receiving pharmacologic therapy for osteoporosis, vitamin D deficiency should be considered and serum 25-OH-D measured, either at initial assessment if the person is already taking recommended supplementation or after 3 months of vitamin D supplementation.

Note: 25-OH-D = 25-hydroxyvitamin D.
*Additional new guidelines are presented in Box 1.
†The term "all sources" refers to the total of dietary intake and supplementation.

Our recommendations for the use of vitamin D are presented in Box 1. Changes from the 2002 guidelines are related most specifically to dose recommendations and are presented in Table 3. A summary of this guideline is also available.[85]

Knowledge gaps

These guideline recommendations are limited by the fact that most studies in the traditional areas of bone health are flawed by use of low doses and poor adherence. With respect to the effects of vitamin D outside the musculoskeletal system, adequately powered randomized clinical trials of a properly defined effective dose of vitamin D have never been done. The upper margins of dose safety for vitamin D have not been determined by trials using adequate numbers of participants and appropriate durations of dosing, but they are undoubtedly much higher than the current national recommendations.

Despite the inadequacy of clinical trial evidence, we suggest that the low cost of vitamin D supplements, the wide therapeutic window and the favourable risk–benefit ratio justify our recommendations. A daily supplement of 25 μg (800 IU) should now be regarded as the minimum dose. Canadians can safely take daily vitamin D supplements up to the current definition of tolerable upper intake level (50 μg [2000 IU]), but doses above that require medical supervision. Research is needed to better define the minimum required daily dose, the optimal dose and the tolerable upper limit of vitamin D for musculoskeletal and other health benefits.

This article has been peer reviewed.

Competing interests: The authors constituted the Vitamin D Working Group of the Guidelines Committee of the Scientific Advisory Council of Osteoporosis Canada. David A. Hanley has been an investigator in clinical trials, participated in advisory boards or received speaking honoraria from the following companies: Amgen, Merck Frosst Canada, Proctor and Gamble Canada (now Warner-Chilcott), Sanofi-Aventis, Novartis, NPS Pharmaceuticals, Eli Lilly Canada, Pfizer, Wyeth-Ayerst, Roche, Servier, Abbott Laboratories and Nycomed. Glenville Jones serves on the scientific advisory board of the not-for-profit Vitamin D External Quality Assessment Scheme. He is also on the advisory board and has received a research grant from Cytochroma Inc. and is a member of the Genzyme speakers' bureau. Susan J. Whiting is a member of the International Institute for Nutrition and Bone Health, an educational initiative sponsored by Yoplait. She has received current or recent funding in the form of grants and contracts from the Canadian Institutes of Health Research and the Canadian Foundation for Dietetic Research. She is a nutrition consultant to Osteoporosis Canada. She has presented talks with sponsorship from the Dairy Farmers of Canada, the International Alliance of Dietary/Food Supplement Associations, the Vitamin D Society, GlaxoSmithKline and Amway/Nutrilite. William D. Leslie has received speaker fees and unrestricted research grants from Merck Frosst Canada Ltd; unrestricted research grants from Sanofi-Aventis, Procter and Gamble Pharmaceuticals Canada, Novartis, Amgen Pharmaceuticals Canada and Genzyme Canada; and has served on advisory boards for Genzyme Canada, Novartis and Amgen Pharmaceuticals Canada. Robert G. Josse has received speaking honoraria and/or research grants from and/or sits on advisory boards for the following companies: Eli Lilly Canada, Merck Frosst Canada, Warner Chilcott, Novartis Canada, GlaxoSmithKline, Sanofi-Aventis and Amgen Canada. None declared for Ann Cranney, David E.C. Cole, Stephanie A. Atkinson, Sidney Feldman, Gregory A. Kline and Cheryl Rosen.

Contributors: All authors are members of the Vitamin D Working Group of the Guidelines Committee of the Scientific Advisory Council of Osteoporosis Canada. All authors participated in the conception and design of the vitamin D guideline project. David Hanley oversaw the writing project, recruited committee members, and edited and revised all section submissions. Ann Cranney wrote the Methods section and the section entitled "Traditional roles of vitamin D" and was one of the reviewers of the abstracts identified in the literature search. Glenville Jones wrote the section entitled "Assessment of vitamin D," Susan Whiting wrote the section entitled "Sources of vitamin D" and William Leslie wrote the section entitled "Nontraditional roles of vitamin D." All authors contributed to the review and revision of the entire manuscript and approved the final version submitted for publication.

Acknowledgements: The document was reviewed and approved by the Guidelines Committee of the Scientific Advisory Council of Osteoporosis Canada (chaired by William D. Leslie): Angela Cheung, Kerry Siminoski, Alexandra Papaioannou, Sophie Jamal, Anthony Hodsman and Jacques Brown. The assistance of Loretta Hillier in editing and abridging this document is greatly appreciated.

Funding: Osteoporosis Canada received a grant from the Ontario Ministry of Health and Long-Term Care to develop these guidelines as a part of a larger project to develop guidelines for the investigation and management of osteoporosis.

Endorsements: Canadian Association of Clinical Chemists, Canadian Association of Nuclear Medicine, Canadian Cancer Society, Canadian Geriatric Society, Canadian Orthopaedic Association, Canadian Society of Endocrinology and Metabolism, Dietitians of Canada, Ontario Association of Radiologists, Society of Obstetricians and Gynaecologists of Canada.

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This full review and guideline of vitamin D in adult health and disease was prepared by a committee of authors chosen by the Guidelines Committee of the Scientific Advisory Council of Osteoporosis Canada. The guideline is an update of the vitamin D section of the complete osteoporosis clinical practice guidelines of Osteoporosis Canada, published in 2002. A summary of this article is available online at www.cmaj.ca.